

Recent program changes will not be reflected in this report.

PS01-01

Feasibility and oncological safety of targeted axillary dissection or sentinel lymph node biopsy in patients with clinically node-positive disease after neoadjuvant chemotherapy in the prospective MF-1803 NEOSENTITURK-study

Presenting Author(s) and Co-Author(s):

- N. Cabioğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Bakırköy, Istanbul, Turkey
- H. Karanlık. Istanbul University Institute of Oncology, Department of Surgical Oncology, Istanbul, Turkey
- M. Gulcelik. University of Health Sciences, Gulhane Hospital, Department of Surgery, Turkey
- H. Kocer. Sakarya University, Department of Surgery, Turkey
- M. Muslumanoğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey
- A. İgci. American Hospital, Department of Surgery, Istanbul, Turkey
- M. Tukenmez. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey
- C. Uras. Acibadem University, School of Medicine, Department of Surgery, United States
- E. Ozkurt. Department of Surgery, Florence Nightingale Hospital, Istanbul, Turkey
- G. Akgul. University of Health Sciences, Gulhane Hospital, Department of Surgery, Turkey
- S. Emiroglu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey
- S. Bademler. Istanbul University Institute of Oncology, Department of Surgical Oncology, Istanbul, Turkey
- A. Dağ. Mersin University, Faculty of Medicine, Department of Surgery, Turkey
- D. Trabulus. Bahcesehir University, Department of Surgery, Turkey
- N. Yıldırım. American Hospital, Department of Surgery, Turkey
- G. Karadeniz Cakmak. Zonguldak Bulent Ecevit University, Department of Surgery, Turkey
- E. Sen Oran. Basaksehir State Hospital, Department of Surgery, Istanbul, Turkey
- H. Kara. Acibadem University, School of Medicine, Istanbul, Turkey
- G. Basaran. Acibadem University School of Medicine, Altunizade Hospital Breast Health Center, Turkey
- A. Altinok. Medical Park Hospital, Department of Radiation Oncology, Istanbul, Turkey
- M. Ugurlu. Marmara University School of Medicine, Department of Surgery, Istanbul, Turkey
- K. Senol. Uludag University, Faculty of Medicine, Department of Surgery, Turkey
- B. Zengel. University of Health Sciences, İzmir Bozyaka Hospital, Department of Surgery, United States
- N. Karaman. Ankara Oncology Hospital, Department of Surgery, Turkey
- E. Varol. Department of General Surgery, Faculty of Medicine, Kocaeli University Turkey University, Turkey
- E. Dilege. Koç University, Faculty of Medicine, Department of Surgery, Turkey
- Y. Bolukbasi. Department of Radiation Oncology, Faculty of Medicine, Koc University, Istanbul, Turkey
- A. Akcan. Department of Surgery, Faculty of Medicine, Erciyes University, Kayseri, Turkey

- Y. Ersoy. Bezmialem Vakıf University, Department of Surgery, Turkey
- A. Soyder. Acibadem University, Faculty of Medicine, Department of Surgery, Turkey
- S. Ozbas. Breast Health Working Group International, United States
- M. Velidedeoglu. Istanbul University Cerrahpasa Faculty of Medicine, Department of Surgery, Turkey
- B. Ozcinar. Istanbul University Istanbul Medical Faculty, Turkey
- N. Utkan. Kocaeli University, Faculty of Medicine, Department of Surgery, Turkey
- B. Citgez. Atasehir Memorial Hospital, Istanbul, United States
- B. Celik. Department of General Surgery, Faculty of Medicine, Koc University, Turkey
- L. Zer. Department of Surgery, Atasehir Florence Nightingale Hospital, Istanbul Turkey, Koc University, Istanbul, Turkey
- G. Sakman. Department of General Surgery, Faculty of Medicine, Cukurova University Adana Turkey, Turkey
- L. Yeniay. Ege University, Faculty of Medicine, Department of Surgery, Izmir, Turkey
- L. Dogan. Breast Health Working Group International, United States
- M. Dogan. Department of Medical Oncology, Ankara Oncology Hospital, Ankara, United States
- F. Eroozen. Health Sciences University, Haseki Hospital, Department of Surgery, Turkey
- B. GOKTEPE. Ege University, Medical Faculty, Department of General Surgery, Izmir, Turkey
- O. Agcaoglu. Department of Surgery, Faculty of Medicine, Koc University, Istanbul, Turkey
- T. Kivilcim. Department of General Surgery, Faculty of Medicine, Okan University Istanbul, Istanbul, Turkey
- F. Balci. Department of General Surgery, Sisli Memorial Hospital, Istanbul, Turkey
- B. Gulluoglu. Marmara University School of Medicine, Department of Surgery, Istanbul, Turkey
- A. Polat. Ondokuz Mayıs University, Faculty of Medicine, Department of Surgery, Samsun, Turkey
- K. Ibis. Istanbul University, Istanbul Faculty of Medicine, Department of Radiation Oncology, Istanbul, Turkey
- V. Ozmen. Florence Nightingale Sisli Hospital, Department of Surgery, Istanbul, Turkey

Background: Previous prospective studies reported decreased false negative rates in patients presenting with T1-3/cN1 disease, with the removal of 2 or more sentinel lymph nodes (SLNs), using combined technique for SLN biopsy (SLNB), and by targeted axillary dissection (TAD) in initially clinically node-positive patients after neoadjuvant chemotherapy (NAC). The aim of this prospective study is to compare the feasibility and the oncological safety of TAD with SLNB in patients with cN-positive/ycN0 breast cancer following NAC in a prospective study. **Methods:** This study included patients with a cT1-4N1-3M0 disease from the prospective multicenter MF1803 NEOSENTITURK registry study who were treated either SLNB- or TAD-alone without ALND. TAD included removing the biopsy-proven positive LN marked mostly with a clip as SLN or non-SLN. All patients had nodal and regional irradiation. **Results:** Between 2019 to 2021, 976 patients with cT1-4N1-3M0 disease from 37 centers underwent either SLNB-alone (n=620) or TAD-alone (n=356). Patients with TAD (median age: 46, range: 24-76) and SLNB (median age:46, range: 21-80) have shown a similar age distribution. The median number (range, 25%-75%) of SLNs and total LNs and total metastatic LNs removed were 3 (2-4), 4(3-6), and 1 (1-2), respectively. Patients with TAD were more likely to have cT1-2 disease (91.9% vs 78.7%, p< 0.001), cN1 disease (85.7% vs 78.5%, p< 0.006), a breast conservative surgery (66.0% vs

51.3%, $p < 0.001$), the combined technique for mapping (44.1% vs 22.3%, $p < 0.0001$), and a decreased median (IQR) lymph node ratio as calculated by the total positive lymph node number to the total lymph node number (0.29:0.20-0.40 vs 0.33: 0.20-0.50; $p=0.033$). Of note, there was a trend for the decreased non-sentinel lymph node positivity in the TAD-group compared to the SLNB-group that did not reach the statistical significance (TAD: 10% vs SLNB: 19%, $p=0.07$). However, no significant difference could be found in pathological characteristics including tumor type, breast pCR, non-luminal disease such as HER2-positivity or triple negative disease or presence of low volume metastatic disease (ITC or micrometastasis), and extracapsular extension (Table 1). Of note, patients with ypN-positive disease ($n=351$) were more likely to have SLNs (ypN+, 3.7 ± 1.7 vs ypN0, 3.4 ± 1.7 , $p=0.008$) or total LNs (ypN+, 4.7 ± 1.9 vs ypN0, 3.4 ± 1.9 , $p=0.001$) removed compared to those with ypN0 ($n=635$). Among those with ypN0 disease, patients with TAD were more likely to have LNs removed compared to those with SLNB (TAD, 4.2 ± 1.9 vs 3.9 ± 1.9 , $p=0.034$) (Table 2). Of those with ypN+, patients with TAD were more likely to have SLNs compared to those with SLNB (TAD, 3.9 ± 1.7 vs 3.5 ± 1.7 , $p=0.062$), whereas patients with SLNB were more likely to have non-SLNs removed compared to those with TAD (TAD, 2.3 ± 1.4 vs 2.9 ± 1.5 , $p=0.028$). At a mean follow-up of 28.8 months (± 12.1), the ipsilateral axillary and locoregional recurrence rates were 0.2% ($n=2$) and 0.4% ($n=4$) in the TAD-group and SLNB_group, respectively. Of note, no significant difference could be found in ipsilateral axillary, locoregional, and systemic recurrences between cohorts treated with TAD-alone vs SLNB-alone (Table 3). Conclusion: Our findings suggest that TAD might be more feasible in ypN+ patients which resulted in a decreased lymph node ratio and decreased non-SLN positivity. In ypN0 patients, TAD may contrary cause unnecessary lymph node removal that might be important in arm function and lymphedema development. Furthermore, our findings with short-term follow-up indicate that axillary and locoregional recurrences were observed at very low rates in a selected group of ycN0 patients treated with SLN- or TAD without ALND. Therefore, omission of ALND could be safely considered for patients with limited nodal involvement (<2 LNs) as long as <3 LNs removed and nodal radiotherapy provided.

Table 1. Clinicopathologic Characteristics According to the Axillary Surgery: Targeted Axillary Dissection (=TAD) versus Sentinel Lymph Node Biopsy (=SLNB)

Characteristics	Total (n=976) n(%)	TAD (n=356) n(%)	SLNB (n=620) n(%)	p-Value
Median follow-up (months, median IQR)	27(18-38)	28(18-39)	27(19-37)	
Mean follow-up (months, \pm SD)	28.8 \pm 12.1	29.3 \pm 15.5	28.6 \pm 11.9	
Median age (minimum-maximum)	46(24-80)	46(24-76)	46(21-80)	0.835 ^a
Clinical T stage				<0.001^{ba}
cT1/2	815(83.5)	327(91.9)	488(78.7)	
cT3/4	161(16.5)	29(8.1)	132(21.3)	
Clinical N stage				0.006^{ba}
cN1	792(81.1)	305(85.7)	487(78.5)	
cN2-3	184(18.9)	51(14.3)	133(21.5)	
Type of Breast Surgery				<0.001^{ba}
Breast Conserving Therapy	553(56.7)	235(66)	318(51.3)	
Mastectomy	423(43.3)	121(34)	302(48.7)	
pCR (breast)				0.927 ^b
Complete	445(45.6)	163(45.8)	282(45.5)	
Partial	531(54.4)	193(54.2)	338(54.5)	
pCR (axilla)				0.062 ^b
Complete	635(65.1)	245(68.8)	390(62.9)	
Partial	341(34.9)	111(31.2)	230(37.1)	
pCR (breast+axilla)				0.258 ^b
Complete	391(40.1)	151(42.4)	240(38.7)	
Partial	585(59.9)	205(57.6)	380(61.3)	
Tumor Subtype (by immunohistochemistry)				0.557 ^b
Luminal	672(68.9)	249(69.9)	423(68.2)	
Non-luminal	304(31.1)	107(30.1)	197(31.8)	
Sentinel Lymph Node (SLN) Methodology				<0.001^{ba}
Blue Dye or radioisotope	681(69.8)	199(55.9)	482(77.7)	
Combined (Blue dye and radioisotope)	295(30.2)	157(44.1)	138(22.3)	
Characteristics of metastatic LNs removed (n=341)				0.807 ^b
Isolated tumor cellsµmetastasis	163(47.8)	52(46.8)	111(48.3)	
Macrometastasis	178(52.2)	59(53.2)	115(51.7)	
No	289(84.8)	95(85.6)	194(84.3)	
Non-SLN positivity (n=294)				0.073 ^b
Yes	48(16.3)	14(11.7)	34(19.5)	
No	246(83.7)	106(88.3)	148(80.5)	
Number of SLNs (median IQR)				0.180
Number of metastatic SLNs (median IQR)	1(1-2)	1(1-2)	1(1-2)	0.551
Number of non-SLNs (median IQR) (n=294)	2(1-3)	2(1-3)	2(1-4)	0.320
Number of metastatic non-SLNs (median IQR) (n=48)	1(1-2)	1(1-1)	1(1-2)	0.092
Number of total LNs (median IQR)	4(3-6)	4(3-6)	4(3-6)	0.085
Number of total metastatic LNs (median IQR)	1(1-2)	1(1-2)	1(1-2)	0.222
Lymph Node Ratio (LNR), median(IQR)	0.33(0.2-0.5)	0.29(0.2-0.4)	0.33(0.2-0.5)	0.033^{ba}

a: Mann-Whitney U Test. b: Chi-Square Tests. * $p < 0.05$; IQR (P₂₅-P₇₅): Inter Quartile Range

Table 2. Clinicopathologic Characteristics According to the Pathological Nodal Status

Table 2. Clinicopathologic Characteristics According to the Pathological Nodal Status

Characteristics	All	ypN		p-value	
		ypN0 (n=635)	ypN(+) (n=341)		
Number of sentinel lymph nodes (SLNs) (median IQR)	3(2-4)	3(2-4)	3(2-5)	0.008*	
mean± SD	3.5±1.7	3.4±1.7	3.7±1.7		
Number of non-SLNs (median IQR) (n=294)	2(1-3)	2(1-3)	2(2-3)	0.090	
mean± SD	2.5±1.5	2.4±1.5	2.7±1.5		
Number of total lymph nodes (LNs) (median IQR)	4(3-6)	4(3-5)	5(3-6)	<0.001*	
mean± SD	4.2±1.9	3.4±1.9	4.7±1.9		
		ypN0			
		All	TAD (n=245)	SLNB (n=390)	p-value
Number of SLNs (median IQR)	3(2-4)	3(2-4)	3(2-4)	3(2-4)	0.590
mean± SD	3.4±1.7	3.4±1.8	3.4±1.7	3.4±1.7	
Number of non-SLNs (n=154)	2(1-3)	2(1-3)	2(1-3)	2(1-3)	0.358
mean± SD	2.4±1.5	2.5±1.5	2.4±1.5	2.4±1.5	
Number of total LN	4(3-5)	4(3-5)	4(2-5)	4(2-5)	0.034*
mean± SD	4.0±1.9	4.2±1.9	3.9±1.9	3.9±1.9	
		ypN+			
		All	TAD (n=111)	SLNB (n=230)	p-value
Number of SLNs	3(2-5)	4(3-5)	3(2-5)	3(2-5)	0.062
mean± SD	3.7±1.7	3.9±1.7	3.5±1.7	3.5±1.7	
Number of metastatic SLNs	1(1-2)	1(1-2)	1(1-2)	1(1-2)	0.519
mean± SD	1.4±0.8	1.4±0.8	1.4±0.8	1.4±0.8	
Number of non-SLNs (n=140)	2(2-3)	2(1-3)	2(2-4)	2(2-4)	0.028*
mean± SD	2.7±1.5	2.3±1.4	2.9±1.5	2.9±1.5	
Number of metastatic non-SLNs (n=48)	1(1-2)	1(1-1)	1(1-2)	1(1-2)	0.092
mean± SD	1.6±1.1	1.3±0.8	1.7±1.1	1.7±1.1	
Number of total LNs	5(3-6)	5(4-6)	5(3-6)	5(3-6)	0.265
mean± SD	4.7±1.9	4.9±1.7	4.7±1.9	4.7±1.9	
Number of total metastatic LNs	1(1-2)	1(1-2)	1(1-2)	1(1-2)	0.212
mean± SD	1.6±0.9	1.5±0.9	1.6±0.9	1.6±0.9	

Table 3. Locoregional and systemic recurrences in cT1-4N1-3 patients treated with Targeted Axillary Dissection (=TAD) or Sentinel Lymph Node Biopsy (=SLNB) (N=976)

Table 3. Locoregional and systemic recurrences in cT1-4N1-3 patients treated with Targeted Axillary Dissection (=TAD) or Sentinel Lymph Node Biopsy (=SLNB) (N=976)

Variables	All (n=976) n(%)	TAD (n=356) n(%)	SLNB (n=620) n(%)	p-value*	ypN0 (n=635) n(%)	ypN(+) (n=341) n(%)	p-value*
Locoregional recurrence				0.999			0.999
Yes	4(0.4)	1(0.3)	3(0.5)		3(0.5)	1(0.3)	
No	972(99.6)	355(99.7)	617(99.5)		632(99.5)	340(99.7)	
Ipsilateral Axillary recurrence				0.999			0.545
Yes	2(0.2)	1(0.3)	1(0.2)		2(0.3)	0(0)	
No	974(99.8)	355(99.7)	619(99.8)		633(99.7)	341(100)	
Systemic recurrence				0.121			0.225
Yes	38(3.9)	9(2.5)	29(4.7)		21(3.3)	17(5)	
No	938(96.1)	347(97.5)	591(95.3)		614(96.7)	324(95)	
Mortality				0.999			0.700
Yes	7(0.7)	2(0.6)	5(0.8)		4(0.6)	3(0.9)	
No	969(99.3)	354(99.4)	615(99.2)		631(99.4)	338(99.1)	

*Fisher's Exact Test
locoregional recurrence=axillary, peripheral lymphatic, mammaria interna and contralateral axillary.

PS01-02

Long-term outcomes of sentinel lymph node biopsy following neoadjuvant chemotherapy for initially node-positive breast cancer: A systematic review and meta-analysis.

Presenting Author(s) and Co-Author(s):

M. Rana. University of Saskatchewan, Canada, Regina, Saskatchewan, Canada

A. Weiss. Division of Surgical Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States

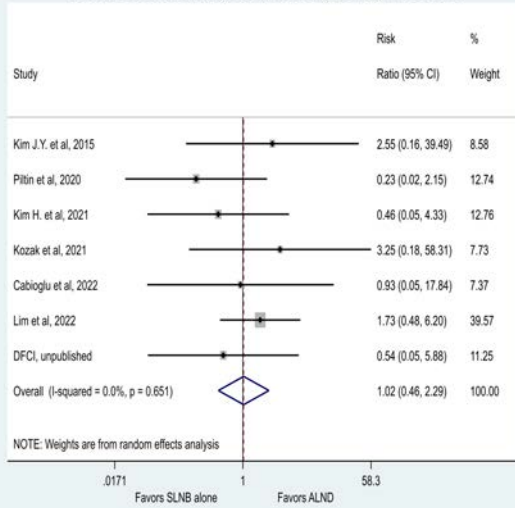
A. Laws. Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, United States

C. Mita. Harvard Medical School, Harvard University, Boston, Massachusetts, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

Background: Sentinel lymph node biopsy (SLNB) alone is now frequently offered to women with initially node-positive breast cancer who convert to pathologically node negative (nodal pCR) following neoadjuvant chemotherapy (NAC), despite limited long-term data regarding the oncologic safety of this approach. The aim of this meta-analysis was to evaluate the long-term oncologic outcomes associated with SLNB alone following NAC for initially node-positive breast cancer. **Methods:** A systematic review and meta-analysis was conducted according to PRISMA guidelines. Medline (Ovid), Embase, and Cochrane Central Registry were systematically searched for studies comparing women undergoing SLNB or ALND following NAC for initially clinically node-positive breast cancer. Included studies reported one of the following outcomes: axillary recurrence (AR), locoregional recurrence (LRR), disease-free survival (DFS) or overall survival. A random effects meta-analysis was used to calculate weighted pooled effect estimates (risk ratios, RR) for all outcomes. Variability across studies due to heterogeneity was estimated using I^2 statistics. Subgroup analysis was performed by length of follow-up for each study. Risk of bias within studies was assessed using the Newcastle-Ottawa Scale (NOS). **Results:** Data for participants undergoing treatment between 2004 and 2022 was captured across studies. The median age of women treated with NAC for initially node-positive breast cancer ranged from 46 to 60 years. The median follow-up time ranged from 19.5 to 108 months across included studies. Nine observational studies were eligible for meta-analysis. No studies were excluded from the analysis on the basis of quality: Newcastle-Ottawa Scale scores ranged from 6 to 9 (maximum possible score of 9). Rates of axillary recurrence (AR) were low across all included studies (range 0.0% to 5.6%). For AR, data for 2,882 patients from 7 studies was quantitatively synthesized (SLNB=1,964; ALND=917). For LRR, data for 2,629 patients from 7 studies was quantitatively synthesized (SLNB=1,857; ALND=771). No significant differences were observed in AR between patients undergoing SLNB alone versus ALND following NAC for initially node-positive breast cancer: pooled RR 1.02 (95% CI: 0.46-2.29, $I^2=0.0\%$). Similarly, no significant differences were observed in LRR (RR 0.70, 95% CI: 0.45-1.10, $I^2=0.0\%$), DFS (RR 0.77, 95% CI: 0.55-1.08, $I^2=0.0\%$), nor overall mortality (RR 0.66, 95% CI: 0.33-1.33, $I^2=0.0\%$) between the SLNB and ALND groups. **Conclusions:** Among patients who convert to node-negative following NAC, this meta-analysis suggests that SLNB alone does not result in significantly different oncologic outcomes compared to ALND, and that de-escalation of axillary surgery to SLNB alone in this context may be safely considered in this patient population.

Relative Risk of Axillary Recurrence by Axillary Procedure



PS01-03

What to expect from the No axillary surgical treatment for lymph node-negative patients after ultra-sonography [NAUTILUS] trial (KBCSG-21): Clinicopathologic characteristics and axillary lymph node status of enrolled patients

Presenting Author(s) and Co-Author(s):

J. Ryu. Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam, Ulsan-gwangyoksi, Republic of Korea

H. Lee. Seoul National University Hospital, United States

S. Ahn. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

I. Chung. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

S. Lee. National Cancer Center, Goyang, Republic of Korea

S. Park. Yonsei University college of medicine, United States

W. Lim. Department of Surgery, Ewha Womans University School of Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

J. Lee. Samsung Medical Center, Seoul, Republic of Korea

E. Kang. Seoul National Univ. Hospital, Surgery, Republic of Korea

J. Chang. Department of Radiation Oncology, Seoul National University Hospital, Seoul, Republic of Korea

J. Chang. Department of Radiology, Seoul National University College of Medicine, United States

W. Moon. Department of Radiology, Seoul National University College of Medicine, Seoul, South Korea

W. Han. Seoul National University Hospital, Seoul, Republic of Korea

E. Kim. Seoul National University Bundang Hospital, Seoul National University College of Medicine, United States

Purpose: The primary role of sentinel lymph node biopsy (SLNB) for early breast cancer (BC) is axillary staging. In terms of clearance of axillary disease or prevention of recurrence, its role may be limited considering the low axillary recurrence rate of less than 2% even though false-negative rates are 5-10% and the 25% additional axillary lymph node (ALN) detection in the ALND arms of the ACOSOG Z0011 and AMAROS trials. The NAUTILUS trial (NCT04303715) randomized cT1-2/N0 BC patients planned for breast-conserving surgery to evaluate the non-inferiority of omitting SLNB regarding 5-year invasive disease-free survival. The secondary endpoints are overall survival, distant metastasis-free survival, axillary recurrence rate, and quality of life of the patients. We aimed to investigate the clinicopathologic characteristics and ALN status of the subjects enrolled in the NAUTILUS trial. **Methods:** NAUTILUS trial randomized 1,734 subjects into SLNB or no-SLNB arms from September 2020 to October 2022. Axillary ultrasonography was mandatory to determine clinical N0, defined as no suspicious ALN or no tumor on ultrasound-guided biopsy of suspicious ALN. Clinicopathologic variables and the ALN status of the SLNB arm were analyzed. **Results:** Among 1,734 enrolled subjects, 828 (50.3%) and 818 (49.7%) subjects in the SLNB and no-SLNB arms, respectively,

were included for analysis. Clinical and pathologic T stage, hormonal receptor/HER2 status, histologic grade, age, menopausal status, and Ki-67 were evenly distributed between the two groups (p = 0.554, 0.350, 0.056, 0.369, 0.623, 0.725 and 0.214, respectively). Median age was 55.3 (range, 48.0-62.0) years, and 661 (40.2%) were premenopausal. Overall, 30 (1.8%), 1,382 (84.0%), and 229 (13.9%) subjects were pTmic, pT1, and pT2, respectively, and median tumor size was 1.3 cm (range, 0.1-5.0). In the SLNB group, 94 (11.4%) had ALN metastasis, of which 9 (1.1%), 78 (9.4%), and 5 (0.6%) were pN1mic, pN1, and pN2-3, respectively (Table 1). According to pathologic tumor size, 5.8% (16/279), 11.4% (48/421), and 23.8% (30/126) were ALN positive for ≤ 1.0 cm, >1.0cm & ≤ 2.0 cm, and > 2.0 & ≤ 5.0 cm, respectively. The clinical and pathologic tumor size distribution among subjects with ALN metastasis were 23 (24.5%), 43 (45.7%), 9 (9.6%) and 16 (17.0%), 48 (51.1%), 30 (31.9%), respectively, for ≤ 1.0 cm, >1.0cm & ≤ 2.0 cm, and > 2.0 & ≤ 5.0 cm (Table 2). Among them, 12 (12.8%) received subsequent ALND. There was no difference in ALN metastasis rate according to molecular subtype, histologic grade, age, menopausal status, and Ki-67 (p= 0.812, 0.204, 0.671, and 0.101, respectively). Conclusions: The NAUTILUS trial completed enrollment of 1,734 subjects, among which 1,646 are available to analyze basic clinicopathologic characteristics. The trial included 229 (13.9%) pT2 and 661 (40.2%) premenopausal subjects and is expected to show the impact of SLNB omission in these subgroups. Data lock is expected in October 2027.

Patients characteristics

	SLNB, n (%)	Non-SLNB, n (%)	p-value	T-tumor, n (%)
Age				
Median age (range)	55.3 (48.0-62.0)	54.0 (48.0-62.0)	0.552	55.3 (48.0-62.0)
			0.823	55.3 (48.0-62.0)
			0.325	
Menopausal status				
Premenopausal	229 (13.9%)	229 (13.9%)	0.725	229 (13.9%)
Postmenopausal	432 (26.1%)	432 (26.1%)		432 (26.1%)
Unknown	105 (6.3%)	105 (6.3%)		105 (6.3%)
Primary history				
Total mastectomy	1100 (65.9%)	1100 (65.9%)	0.328	1100 (65.9%)
Breast conserving surgery	218 (12.9%)	218 (12.9%)		218 (12.9%)
Unknown	7 (0.4%)	7 (0.4%)		7 (0.4%)
LVI				
Yes	589 (35.2%)	589 (35.2%)	0.543	589 (35.2%)
No	1205 (72.5%)	1205 (72.5%)		1205 (72.5%)
Unknown	1 (0.1%)	1 (0.1%)		1 (0.1%)
Pathologic T stage				
≤ 1.0	4859 (29.2%)	4859 (29.2%)	0.218	4859 (29.2%)
> 1.0 & ≤ 2.0	502 (30.1%)	502 (30.1%)		502 (30.1%)
> 2.0 & ≤ 5.0	327 (19.9%)	327 (19.9%)		327 (19.9%)
Unknown	89 (5.4%)	89 (5.4%)		89 (5.4%)
Pathologic N stage				
≤ 1.0	352 (21.3%)	352 (21.3%)	0.385	352 (21.3%)
> 1.0 & ≤ 2.0	4842 (29.0%)	4842 (29.0%)		4842 (29.0%)
> 2.0 & ≤ 5.0	1483 (89.7%)	1483 (89.7%)		1483 (89.7%)
Unknown	103 (6.2%)	103 (6.2%)		103 (6.2%)
Molecular Subtype				
ER+/PR+/HER2-	1100 (65.9%)	1100 (65.9%)	0.088	1100 (65.9%)
ER+/PR+/HER2+	368 (22.3%)	368 (22.3%)		368 (22.3%)
ER+/PR-/HER2-	152 (9.2%)	152 (9.2%)		152 (9.2%)
ER+/PR-/HER2+	223 (13.5%)	223 (13.5%)		223 (13.5%)
Unknown	65 (3.9%)	65 (3.9%)		65 (3.9%)
HER2				
+	3159 (192.5%)	3159 (192.5%)	0.274	3159 (192.5%)
-	5929 (357.5%)	5929 (357.5%)		5929 (357.5%)
Unknown	12 (0.7%)	12 (0.7%)		12 (0.7%)
Clinical T stage				
≤ 1.0	2552 (153.2%)	2552 (153.2%)	0.554	2552 (153.2%)
> 1.0 & ≤ 2.0	3427 (206.1%)	3427 (206.1%)		3427 (206.1%)
> 2.0 & ≤ 5.0	1511 (90.7%)	1511 (90.7%)		1511 (90.7%)
Unknown	1388 (84.6%)	1388 (84.6%)		1388 (84.6%)
Median tumor size, mm (range)	1.3 (0.1-5.0)	1.3 (0.1-5.0)	0.511	1.3 (0.1-5.0)
Pathologic T stage				
≤ 1.0	148 (8.9%)	148 (8.9%)	0.389	148 (8.9%)
> 1.0 & ≤ 2.0	4859 (29.2%)	4859 (29.2%)		4859 (29.2%)
> 2.0 & ≤ 5.0	327 (19.9%)	327 (19.9%)		327 (19.9%)
Unknown	89 (5.4%)	89 (5.4%)		89 (5.4%)
Pathologic N stage				
≤ 1.0	352 (21.3%)	352 (21.3%)	<0.001	352 (21.3%)
> 1.0 & ≤ 2.0	4842 (29.0%)	4842 (29.0%)		4842 (29.0%)
> 2.0 & ≤ 5.0	1483 (89.7%)	1483 (89.7%)		1483 (89.7%)
Unknown	103 (6.2%)	103 (6.2%)		103 (6.2%)
Pathologic M stage				
Stage I	644 (39.4%)	644 (39.4%)	0.034	644 (39.4%)
Stage II	1046 (63.0%)	1046 (63.0%)		1046 (63.0%)
Stage III	35 (2.1%)	35 (2.1%)		35 (2.1%)
Unknown	22 (1.3%)	22 (1.3%)		22 (1.3%)
Primary Surgery				
Total mastectomy	1100 (65.9%)	1100 (65.9%)	<0.001	1100 (65.9%)
Breast conserving surgery	218 (12.9%)	218 (12.9%)		218 (12.9%)
Unknown	7 (0.4%)	7 (0.4%)		7 (0.4%)
Axillary Surgery				
Yes (SLNB)	94 (5.7%)	94 (5.7%)	<0.001	94 (5.7%)
SLNB	3189 (192.5%)	3189 (192.5%)		3189 (192.5%)
ALND	12 (0.7%)	12 (0.7%)		12 (0.7%)
Other	0 (0.0%)	0 (0.0%)		0 (0.0%)

SLNB, sentinel lymph node biopsy; LVI, lymphovascular invasion; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HER2, anti-human epidermal growth factor-2; BCS, breast conserving surgery; TM, total mastectomy; ALND, axillary lymph node dissection

Basic characteristics for sentinel lymph node biopsy group

	No ALN metastasis, n (%)	ALN metastasis, n (%)	p-value	Total, n(%)
Number, %	734 (88.6%)	94 (11.4%)		
Clinical tumour size, cm			0.083	
≤ 1.0	269 (36.6%)	23 (24.5%)		292 (35.3%)
>1.0 and ≤ 2.0	304 (41.4%)	43 (45.7%)		347 (41.9%)
>2.0 and ≤ 5.0	42 (5.7%)	9 (9.6%)		51 (6.2%)
Unknown	119 (16.2%)	19 (20.2%)		138 (16.7%)
Suspicious LN group^a			0.119	
Yes	22 (3.0%)	6 (6.4%)		28 (3.4%)
No	712 (97.0%)	88 (9.4%)		800 (96.6%)
Age			0.671	
<35	10 (1.4%)	0 (0.0%)		10 (1.2%)
35-50	255 (34.7%)	31 (33.0%)		286 (34.5%)
>50	469 (63.9%)	63 (67.0%)		532 (64.3%)
Menopausal status			0.798	
Premenopause	291 (39.6%)	34 (36.2%)		325 (39.3%)
Postmenopause	430 (58.6%)	58 (61.7%)		488 (58.9%)
unknown	13 (1.8%)	2 (2.1%)		15 (1.8%)
Nuclear grade			0.519	
Low	29 (4.0%)	3 (3.2%)		32 (3.9%)
Intermediate	564 (76.8%)	78 (83.0%)		642 (77.5%)
High	135 (18.4%)	13 (13.8%)		148 (17.9%)
Unknown	6 (0.8%)	0 (0.0%)		6 (0.7%)
Histologic grade			0.204	
Low	158 (21.5%)	14 (14.9%)		172 (20.8%)
Intermediate	473 (64.4%)	70 (74.5%)		543 (65.6%)
High	93 (12.7%)	10 (10.6%)		103 (12.4%)
Unknown	10 (1.4%)	0 (0.0%)		10 (1.2%)
Pathologic tumour size, cm			<0.001	
≤ 1.0	258 (35.1%)	16 (17.0%)		274 (33.1%)
>1.0 and ≤ 2.0	373 (50.8%)	48 (51.1%)		421 (50.8%)
>2.0 and ≤ 5.0	96 (13.1%)	30 (31.9%)		126 (15.2%)
Unknown	7 (1.0%)	0 (0.0%)		7 (0.8%)
Molecular Subtype			0.812	
Hormone receptor(+)/HER(-)	636 (86.6%)	83 (88.3%)		719 (86.8%)
Hormone receptor(+)/HER(+)	51 (6.9%)	7 (7.4%)		58 (7.0%)
Hormone receptor(-)/HER(+)	12 (1.6%)	0 (0.0%)		12 (1.4%)
Hormone receptor(-)/HER(-)	30 (4.1%)	3 (3.2%)		33 (4.0%)
unknown	4 (0.5%)	1 (1.1%)		6 (0.7%)
Ki-67			0.101	
≥ 10%	275 (37.5%)	44 (46.8%)		319 (38.5%)
< 10%	459 (62.5%)	50 (53.2%)		509 (61.5%)

a revealed no lymph node metastasis by fine needle aspiration or gun biopsy
ALN, axillary lymph node; LN, lymph node

PS01-04

To dissect or not to dissect? The surgeon's perspective on the prediction of ≥ 4 axillary lymph node metastasis in cN0 T1-2 breast cancer: A comparative analysis of the per-protocol population of the SINODAR-ONE clinical trial.

Presenting Author(s) and Co-Author(s):

D. Gentile. IRCCS Humanitas Research Hospital, Milan, Lombardia, Italy
W. Gatzemeier. IRCCS Humanitas Research Hospital, United States
A. Sagona. IRCCS Humanitas Research Hospital, United States
E. Barbieri. IRCCS Humanitas Research Hospital, United States
A. Bottini. IRCCS Humanitas Research Hospital, United States
A. Testori. IRCCS Humanitas Research Hospital, United States
V. Errico. IRCCS Humanitas Research Hospital, United States
S. Di Maria Grimaldi. IRCCS Humanitas Research Hospital, United States
G. Caraceni. IRCCS Humanitas Research Hospital, United States
S. Darwish. IRCCS Humanitas Research Hospital, United States
G. Canavese. IRCCS Humanitas Research Hospital, United States
C. Tinterri. IRCCS Humanitas Research Hospital, United States

Objectives The role of axillary surgery in the management of breast cancer (BC) has evolved considerably over the past decades, with only a few routine indications for axillary lymph node dissection (ALND) remaining in clinical practice. However, de-escalation of axillary surgery, especially in BC patients with 1-3 positive sentinel lymph nodes (SLNs) challenges the recently established criteria for adjuvant treatment (i.e., combination therapy with abemaciclib, endocrine therapy, and chemotherapy in patients with ≥ 4 positive nodes). The question remains as to whether these patients should undergo further ALND to determine whether ≥ 4 nodes are positive. To further investigate the latest controversies in axillary management of BC patients and predict the presence of ≥ 4 axillary lymph node metastasis, we evaluated and compared patients ≥ 4 positive nodes in the per-protocol population of the SINODAR-ONE clinical trial. Patients in the standard arm (ALND) of the per-protocol population were evaluated, and a comparison of characteristics between patients with ≥ 4 metastatic lymph nodes versus patients with 1-3 metastatic lymph nodes was performed. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Multivariable analysis was performed using a logistic regression model to identify independent predictors of ≥ 4 axillary lymph node metastasis. **Results:** Overall, 403 cN0 T1-2 BC patients in the per-protocol population were randomized to receive ALND. Of these, 65 and 338 patients presented with ≥ 4 or 1-3 axillary lymph node metastasis, respectively. Invasive lobular BC (26.2% versus 14.5% if other histology, odds ratio (OR)=4.185, 95% confidence interval (95%CI)= 1.284-1.443, $p=0.041$), G3 (38.5% versus 21.3% if G1-2, OR=5.930, 95%CI= 2.134-2.289, $p=0.015$), pT2 (46.2% versus 30.5% if pT1, OR=5.260, 95%CI= 15.330-16.346, $p=0.022$), and 2 positive SLNs (32.3% versus 13.6% if 1 positive SLN, OR=13.188, 95%CI= 1.179-1.280, $p<0.0001$) were found to significantly increase the probability to present ≥ 4 axillary lymph node metastasis at definitive histopathological evaluation. **Conclusions:** The introduction of abemaciclib and other combination therapies has the potential to impact the surgical management of the axilla. Our results suggest that a minority of cN0 T1-2 BC patients may be understaged if ALND is not performed. However, the improvements and increasing effectiveness of combination therapies may sufficiently control and treat the axillary tumor-burden left behind, potentially reducing the

need for extensive axillary surgery, as demonstrated by the promising 3-year oncological outcomes of the SINODAR-ONE trial. Although ALND may still be considered, after multidisciplinary team discussion, in individual patients presenting with specific risk factors for additional axillary disease (lobular, G3, pT2 BC with 2 positive SLNs), our suggestion is that routine ALND is not indicated for systemic therapy decision-making in the upfront surgical setting.

PS01-06

The relationship between margin status of < 2mm and local recurrence in DCIS patients

Presenting Author(s) and Co-Author(s):

S. Alsafi. Asan Medical Center, Republic of Korea. Al Adan Hospital, Ministry of Health, Kuwait, Bayan, Hawalli, Kuwait

T. Yoo. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

S. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

J. Kim. Asan Medical Center, United States

I. Chung. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

H. Kim. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

B. Ko. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

J. Lee. Asan Medical Center, United States

B. Son. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

H. Lee. University of Ulsan College of Medicine, Asan Medical Center, United States

G. Gong. Asan Medical Center, United States

Background: There has been controversial evidence regarding adequate margin in breast conserving surgery (BCS) for ductal carcinoma in situ (DCIS). However, the consensus is a surgical margin distance of 2 mm. Moreover, recent recommendations advised on "clinical judgement" approach to re-excision in cases of margin distance < 2mm. The ongoing controversy in DCIS margin compared to invasive cancer margin is due to the differences in post operative management. This is important as margin status is one of the modifiable risk factor for local regional recurrence in DCIS. In our study we evaluated margin distance in patient diagnosed with DCIS who underwent BCS on local recurrence **Methods:** Patients who underwent breast conserving surgery between February 2000 and December 2018 at Asan Medical Center were retrospectively reviewed. Patients with involved resection margins were excluded. Kaplan-Meier survival analysis and Cox proportional hazard models were applied to determine the relationship between negative margin width and local recurrence. **Results:** A total of 1,858 patients were included in the study. Almost half of the patients had a tumor size of 1cm or smaller (n=876, 47.1%). Only 98 (5.3%) patients did not undergo radiation therapy. A negative margin width of < 1mm, < 2mm, < 5mm were all not associated with local recurrence (log-rank test p-value 0.1, 0.1, 0.078, respectively). For patients who underwent radiation therapy, a negative margin of any width was not related to local recurrence. Whereas, for patients who did not undergo radiation therapy, those with margins ≤ 2 mm were significantly more likely to develop local recurrence than those with margins < 2mm (10-yr local recurrence rate, 16.4% vs 5.5%, respectively; hazard ratio, 5.709; 95% CI, 1.106-29.46, p=0.038). **Conclusion:** A negative margin is not related to local recurrence in DCIS patients who undergo breast conserving surgery with radiation therapy. Routine additional surgery for wider negative margin may only be needed for patients who do not undergo radiation therapy.

PS01-07

Impact of Race and Ethnicity on Recurrence Risk in Patients with Ductal Carcinoma in Situ Treated with Breast-Conserving Surgery

Presenting Author(s) and Co-Author(s):

N. Polidoro. Memorial Sloan Kettering Cancer Center, New York, New York, United States

V. Jones. Memorial Sloan Kettering Cancer Center, United States

V. Sevilimedu. Memorial Sloan Kettering Cancer Center, United States

M. Morrow. Memorial Sloan Kettering Cancer Center, New York, New York, United States

K. Van Zee. Memorial Sloan Cancer Center, New York, New York, United States

A. Barrio. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Among women with invasive breast cancer, clinical presentation, tumor biology and survival vary by race and ethnicity. However, the impact of race and ethnicity on clinical presentation and recurrence risk in women with ductal carcinoma in situ (DCIS) treated with breast-conserving surgery (BCS) has not been well studied. We sought to compare rates of recurrence in women with DCIS across racial and ethnic groups and identify factors associated with recurrence. **Methods:** Patients with DCIS treated with BCS from 1978 to 2016 at a single institution were identified. Patients were grouped and analyzed based on self-reported race and ethnicity as: Asian, Hispanic, non-Hispanic Black (Black), non-Hispanic White (White). Individuals with undefined ethnicity were classified by race, while those lacking both race and ethnicity data were excluded. Clinicopathologic characteristics were compared across racial and ethnic groups. The association of race and ethnicity on recurrence risk was analyzed using Kaplan–Meier methods, competing risk analysis and multivariable analysis. **Results:** Overall, 4207 cases were included, of which 6% (n = 261) were Asian, 9% (n = 358) Black, 5% (n = 226) Hispanic and 80% (n = 3362) White. Median age was 57 years (IQR 49, 67), 56% received radiotherapy (RT) and 26% received endocrine therapy. Black women with DCIS were older; Asian women were younger (median age: 60 vs 53 respectively, $p < 0.001$). Black women were more likely to have a clinical presentation ($p = 0.006$), and Black and Hispanic women were more likely to require ≥ 3 excisions ($p = 0.006$). The use of RT was most common among Hispanic women ($p = 0.02$). At a median follow-up of 8.8 years, 602 (14%) had local recurrence (LR) (315 [52%] DCIS; 284 [47%] invasive and 3 [$< 1\%$] unknown). The 10-year rate of LR was 15% and was lower in those treated with RT than without (11% vs 20%, respectively; $p < 0.0001$), despite those receiving RT having more high-risk characteristics. Rates of LR varied significantly by race and ethnicity, with the highest 10-year rate in Black women (25%) compared with Asian (11%), Hispanic (15%) and White (14%) women ($p = 0.03$). This statistically significant difference persisted among the no RT cohort (10-year rate: 31% [Black], 13% [Asian], 25% [Hispanic], 19% [White], $p = 0.043$), but did not reach significance in the RT cohort (21% [Black], 9% [Asian], 9% [Hispanic] and 11% [White], $p = 0.3$). Using competing risk analysis, the risk of invasive recurrence was similar or lower than DCIS recurrence in each racial group with or without RT. After adjusting for other factors on multivariable analysis, there remained a higher risk of LR among Black women (hazard ratio [HR] 1.48, 95% CI 1.12-1.95, $p = 0.01$). Older age ($p < 0.001$), radiologic presentation ($p = 0.02$), margins ≥ 2 mm ($p < 0.001$), the use of endocrine therapy ($p < 0.001$) and the use of RT ($p < 0.001$) were associated with lower rates of LR (Table). Sixteen women (0.4%) developed distant disease, with similar rates among Asian (0%), Black (0.8%), Hispanic (0.9%) and White (0.3%) women ($p = 0.2$). **Conclusion:** Compared with Asian, Hispanic and White women, Black women with DCIS had a significantly higher rate of LR after BCS, even after adjusting for known clinicopathologic risk

factors. Rates of distant recurrence were low, and similar across racial groups. These higher rates of LR should be considered when making decisions about adjuvant therapy. Table. Factors associated with local recurrence in women with ductal carcinoma in situ treated with breast-conserving surgery.

	Univariate analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, years			< 0.001			< 0.001
≤ 49	Ref	—		Ref	—	
50-79	0.71	0.60 – 0.85		0.66	0.56 – 0.79	
≥ 80	1.20	0.72 – 1.99		0.72	0.42 – 1.25	
Presentation			< 0.001			0.02
Clinical	Ref	—		Ref	—	
Radiological	0.66	0.53 – 0.82		0.75	0.59 – 0.95	
Race/Ethnicity			0.04			0.01
White	Ref	—		Ref	—	
Asian	0.77	0.52 – 1.14		0.71	0.47 – 1.07	
Black	1.43	1.09 – 1.87		1.48	1.12 – 1.95	
Hispanic	1.08	0.74 – 1.57		1.07	0.73 – 1.58	
Year of diagnosis			0.005			0.8
≤ 1998	Ref	—		Ref	—	
≥ 1999	0.77	0.65 – 0.92		0.98	0.80 – 1.19	
Family history			0.3			
No	Ref	—		—	—	
Yes	1.10	0.93 – 1.29				
Grade			0.3			
High	Ref	—		—	—	
Low/intermediate	0.92	0.77 – 1.09				
Necrosis			0.4			
Absent	Ref	—		—	—	
Present	1.08	0.91 – 1.30				
Number of excisions			0.08			
≤ 2	Ref	—		—	—	
≥ 3	1.32	0.98 – 1.78				
Margin status			< 0.001			< 0.001
< 2 mm	Ref	—		Ref	—	
≥ 2 mm	0.65	0.53 – 0.80		0.61	0.49 – 0.74	
Endocrine therapy			< 0.001			< 0.001
No	Ref	—		Ref	—	
Yes	0.46	0.37 – 0.58		0.51	0.41 – 0.65	
Radiotherapy			< 0.001			< 0.001
No	Ref	—		Ref	—	
Yes	0.59	0.50 – 0.69		0.58	0.49 – 0.69	

HR, hazard ratio; CI confidence interval; Ref, referent.

PS01-08

Management of ipsilateral breast tumor recurrence following breast conservation surgery for ductal carcinoma in situ – a data-free zone

Presenting Author(s) and Co-Author(s):

B. Diskin. Memorial Sloan Kettering Cancer Center, New York, New York, United States

V. Sevilimedu. Memorial Sloan Kettering Cancer Center, United States

K. Van Zee. Memorial Sloan Cancer Center, New York, New York, United States

M. Morrow. Memorial Sloan Kettering Cancer Center, New York, New York, United States

H. Cody. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Management of ipsilateral breast tumor recurrence following breast conservation surgery for ductal carcinoma in situ – a data-free zone Brian Diskin, Varadan Sevilimedu, Monica Morrow, Kimberly J. Van Zee, Hiram S Cody III Background: Breast-conserving surgery (BCS) is well established for the management of ductal carcinoma in situ (DCIS). Although a growing body of data support re-conservation therapy (RBCS) for ipsilateral breast tumor recurrence (IBTR) following BCS in invasive cancer, neither randomized trials nor guidelines address management of IBTR following BCS for DCIS. Here we aim to compare the outcomes of mastectomy vs RBCS for a large series of DCIS patients with IBTR. Methods: We identified women treated with BCS for DCIS at MSKCC who developed IBTR as a first event. Between those treated with mastectomy vs RBCS, we compared the clinicopathologic characteristics for the initial and recurrent tumors, the use of adjuvant RT (both upfront (“primary RT”) and post IBTR (“secondary RT”)) and/or tamoxifen, the rate of third events (local, regional, distant), breast cancer specific (BCSS) and overall survival (OS). Results: From our service databases among 3001 women treated with BCS for DCIS (1978-2010), we found 383 who developed an IBTR as a first event and were treated at our institution between 1983-2023, 186 (49%) with RBCS and 197 (51%) with mastectomy. RBCS was more frequent over time and comprised 56% of patients treated between 2014 and 2023. Among those treated with mastectomy, the initial tumors were significantly more likely to have necrosis (74% vs 59%), high grade (47% vs 28%), comedo histology (38% vs 20%), and to have received primary RT at the time of BCS (61% vs 21%). Between those who underwent mastectomy vs RBCS, there were no significant differences in disease-free interval, in the pathologic characteristics of their IBTR, or in the proportion of invasive vs in situ disease. For patients treated with RBCS, 11 (5.9%) received both primary and secondary RT and 77 (41.3%) received neither (Table 1a). For patients treated with a mastectomy only 8.5% had secondary RT (Table 1b). At a median follow-up of 5.1 years post-IBTR, third local events in total were more frequent for RBCS vs mastectomy (16.1% vs 3.0%, 0.001), but there were no differences in BCSS or OS. Among RBCS patients, third local events (breast re-recurrence) were least frequent among those who received primary and secondary RT, and comparable between with who did vs did not receive secondary RT (16% (13/82) vs 16% (117/104), Table 2). Conclusions: Our data show that for women with isolated IBTR following BCS for DCIS and treated by mastectomy vs RBCS, 1) treatment with mastectomy was associated with less favorable initial pathology and more frequent use of primary RT, 2) re-recurrence was more frequent with RBCS, and 3) BCSS and OS were comparable. In an era of increasing surgical de-escalation, our data suggest a wider role for RBCS and – as for patients having RBCS for IBTR following invasive cancer – further study of

the relationship between secondary RT and the rate of third breast events.

Table 1a
Receipt of primary vs secondary RT
in RBCS

RCT (n=186)		2° irradiation?	
		Yes	No
1° irradiation?	Yes	11 (5.9%)	27 (14.5%)
	No	71 (38.1%)	77 (41.3%)

Table 1b
Receipt of primary vs secondary RT
in mastectomy

Mastectomy (n=197)		2° irradiation?	
		Yes	No
1° irradiation?	Yes	9 (4.5%)	107 (54.3%)
	No	8 (4.0%)	73 (37.0%)

Table 2
Frequency of breast re-recurrence by receipt
of primary vs secondary RT for RBCS

2 nd LRR after RBCS (n=186)		Receipt of 2° irradiation	
		Yes	No
Receipt of 1° irradiation	Yes	1/11 (9%)	6/27 (22%)
	No	12/71 (17%)	11/77 (14%)

PS01-09

Early Results of a Phase I Pre-Operative Single Fraction Ablative Trial for Early Stage Breast Cancer

Presenting Author(s) and Co-Author(s):

- A. Rahimi. University of Texas Southwestern Medical Center, Dallas, Texas, United States
- A. Leitch. University of Texas Southwestern Medical Center, Texas, United States
- B. Dogan. UT Southwestern Medical Center, Dallas, Texas, United States
- P. Alluri. UTSW, United States
- D. Farr. UT Southwestern Medical Center, United States
- M. Arbab. UTSW, United States
- S. Seiler. UTSW, United States
- N. Kim. VUMC, United States
- R. Wooldridge. UTSW, United States
- N. Unni. University of Texas Southwestern Medical Center, Dallas, Texas, United States
- C. Nwachukwu. University of Texas Southwestern Medical Center, United States
- I. Patel. University of Texas Southwestern Medical Center, United States
- Y. Zhang. University of Texas Southwestern Medical Center, United States
- D. Parsons. Medical Artificial Intelligence and Automation (MAIA) Lab, Department of Radiation Oncology, UT Southwestern Medical Center, United States
- A. Nguyen. University of Texas Southwestern Medical Center, United States
- H. Morgan. University of Texas Southwestern Medical Center, United States
- H. McArthur. UT Southwestern, Dallas, Texas, United States
- S. Sahoo. University of Texas Southwestern Medical Center, United States
- R. Timmerman. UTSW, United States

Objective(s): To explore the impact of pre-operative single fraction stereotactic ablative partial breast irradiation (SPBI) dose escalation (30, 34, or 38Gy) on toxicity and tumor response for early-stage hormone receptor (HR)+ breast cancer in an interim analysis of an expanded cohort phase I dose escalation study (NCT04040569). Methods: Eligible patients (pts) have < 3 cm, HR+, Her2 -, cN0 invasive breast carcinomas not requiring chemotherapy. Patients are treated on either MR LINAC, robotic radiosurgery, or cobalt stereotactic breast units. Endocrine therapy is started two weeks after SPBI. Surgery is completed 2-12 months after SPBI. The primary objective is to escalate single fraction SPBI to an ablative dose without exceeding maximum tolerable dose (MTD). Secondary endpoints include pathologic complete response (pCR), local control, toxicity, cosmesis, and distant disease-free survival. Near complete response (nCR) is defined as RCB 1 and Miller-Payne 4/5. Dose limiting toxicity (DLT) is defined as grade ≥ 3 toxicity or any grade 4/5 toxicity attributed to SPBI. Each dose cohort enrolls 7-15 pts. Dose escalation is permitted if 0/7, 2/9, $\leq 3/12$, or $\leq 4/15$ patients experienced a DLT within 90 days of SPBI. MTD is exceeded if more DLTs occur in any cohort. Results: From 12/2019 to 6/2023, 11 and 15 pts were treated with 30Gy and 34Gy, respectively. Rates of pCR/nCR are 37.5% for 30Gy versus 92.8% 34 Gy ($p=0.01$). At 30Gy, 8/11 pts (73%) underwent surgery with a median 4.3 (range 2.8-5.9) month interval from SPBI to surgery: 0/8 (0%) had a pCR and 3/8 (37.5%) had a nCR. At dose level 34Gy, 14/15 pts (93%) underwent surgery with a median 7.3 (range

5.9-12) month interval from SPBI to surgery: 6/14 (42.8%) had a pCR while 7/14 (50%) had a nCR. Of the 8 pts with a nCR, 50% had only 1-3mm of residual disease. The mean ki67 for the entire cohort was 12.0% +/- 6.9% at diagnosis and decreased to 1.4 +/-2.3% at surgery. 13/14 (92.8%) pts with residual disease had a ki67 < 3% after surgery and SPBI. There were 33 acute grade 1; 2 acute grade 2 (breast pain and dermatitis); and 10 late grade 1 [1 grade 2 (breast pain), and 1 grade 3 (slow healing wound) in an uncontrolled diabetic] toxicities. Conclusion: First study to show pre-operative SPBI up to 34Gy in a single fraction was safe and effective for early-stage HR+ breast cancer. Escalating the dose has achieved a dramatic improvement in pCR/nCR (92.8%) suggesting this is an exciting approach for potentially eliminating tumor with radiation/endocrine therapy alone in early stage breast cancer and potentially paving a path towards non-surgical management in highly selected patients.

PS01-10

Surgical margins in breast conserving surgery (BCS) for ductal carcinoma in-situ (DCIS) and clinical outcomes: significant associations with increased recurrence and overall survival.

Presenting Author(s) and Co-Author(s):

J. Robertson. University of Nottingham, Nottingham, UK; University Hospitals of Derby and Burton, Derby, England, United Kingdom

D. Sibbering. University Hospital of Derby & Burton, United States

S. Ndebele-Mahati. The Institute of Cancer Research, Clinical Trials and Statistics Unit, London, England, United Kingdom

O. Kearins. NHS England, United States

S. Pinder. School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom

A. Gandhi. Division of Cancer Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester Academic Health Science Centre & Manchester University Hospitals Trust, Manchester, United Kingdom

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

L. Kilburn. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

Background: Optimal surgical margin in breast conserving surgery (BCS) for DCIS are not established, largely due to an absence of accurate margin data. A margin width of 2mm was adopted by the American College of Surgeons (ACS). The UK Association of Breast Surgery (ABS) recommended a 1mm margin. Conducting a randomized controlled trial to answer this question is unfeasible; therefore we used retrospective histological margin data from available datasets to assess whether there is an association between margin width and time to recurrence (TTR). **Methods:** Patients were included if aged >18 years with a new diagnosis of DCIS alone, between 2003-2014, within UK NHS Breast Screening Programme (BSP). Primary treatment included BCS and a minimum histological excision margin width recorded. Exclusion criteria included: i) prior history of DCIS; ii) prior history of invasive cancer or its diagnosis within 3 months of initial surgical treatment for DCIS. Data was extracted from English Cancer Registries (CR), ABS and Sloane audits. TTR was defined as time from diagnosis to local or distant recurrence. Cox regression was used to compare TTR by surgical margin width utilising a range of thresholds, with focus on < 1mm vs ≥1mm; < 2mm vs ≥2mm and ≥1- < 2mm vs ≥2mm. Patients with 0mm margin or where categorized as "clear/not stated" were excluded from these analyses. Models were adjusted for age group, DCIS grade and size, ER status, number of BCSs, radiotherapy (RT) received, diagnosis year and CR centre. Overall survival (OS) was a secondary endpoint. **Results:** 17,260 patients diagnosed with DCIS having BCS as definitive surgery were identified between 2003-2014; 679 (5%), 2105 (15%), 1339 (10%) and 9744 (70%) with recorded margins of >0- < 1mm, ≥1- < 2mm, ≥2- < 3mm and ≥3mm, respectively. 10,253 (59%) patients received RT and in 7,007 (41%) RT receipt was unknown. Overall, 14,004 (81%), 3,052 (18%) and 201 (1%) patients had one, two and ≥3 BCSs respectively; there was no significant change in these percentages over time (p=0.2 Cuzick test). Median follow-up time for the cohort was 8.2 years (IQR: 6.1-11.2). 2221 (13%) patients had a subsequent event: 1741/2221 (78%) invasive recurrence and 480/2221 (22%) DCIS alone. The annual event rate over 15 years of follow-up was relatively consistent at 1.2% per

annum (pa) for margins ≥ 2 mm versus 1.8% pa for margins < 2 mm. A shorter TTR was observed for patients with surgical margins < 1 mm vs ≥ 1 mm (adjusted HR=1.30; 95%CI: 1.05-1.62; $p=0.02$); < 2 mm vs ≥ 2 mm (adjusted HR=1.20; 95%CI: 1.06-1.36; $p=0.004$) and $\geq 1- < 2$ mm vs ≥ 2 mm (adjusted HR=1.20; 95%CI: 1.04-1.40; $p=0.02$). Margins > 2 mm did not appear to significantly improve TTR (adjusted HR=0.96; 95%CI: 0.85-1.08; $p=0.50$ for ≥ 5 mm vs $\geq 2- < 5$ mm). Models also showed that risk of recurrence increased as the number of BCSs increased (adjusted HR=1.25; 95%CI: 1.10-1.43; $p < 0.001$ for 2 vs 1 and adjusted HR=2.03; 95%CI: 1.36-3.03; $p < 0.001$ for 3+ vs 1). In total, 1552 (9%) patients had died. OS appeared reduced for patients with surgical margins < 2 mm vs ≥ 2 mm (adjusted HR=1.25 (1.07-1.45); $p=0.005$) and for $\geq 1- < 2$ mm vs ≥ 2 mm (adjusted HR=1.28 (1.07-1.54); $p=0.008$). Margins < 2 mm did not appear to significantly improve OS further (adjusted HR=1.06; 95%CI: 0.92-1.21; $p=0.43$ for ≥ 5 mm vs $\geq 2- < 5$ mm). Conclusion: Patients with DCIS with histological margins of < 2 mm, adjusted for other clinical factors, have significantly worse TTR and OS rates compared to margins ≥ 2 mm; the increased annual event rate is consistent out to 15 years. More than 1 BCS is also associated with an increased risk of recurrence. These findings are important for the treatment of patients with DCIS.

PS02-01

Efficacy, safety, and quality of life with ribociclib + endocrine therapy in elderly patients with HR+/HER2– advanced breast cancer across the MONALEESA-2, -3, and -7 trials

Presenting Author(s) and Co-Author(s):

L. Hart. Atrium Health/Wake Forest Baptist Comprehensive Cancer Center , Fort Myers, Florida, United States

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

B. Sousa. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

G. Freyer. Oncology Department, Hôpital Lyon Sud, Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL) and Université de Lyon, France

T. Decker. Oncology Ravensburg, Ravensburg, Germany

K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

A. Thuerigen. Novartis Pharma AG, Basel, Switzerland

M. Gao. Novartis Pharma AG, Basel, Switzerland

H. Hu. Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

Background: Ribociclib (RIB) + endocrine therapy (ET) showed statistically significant progression-free survival (PFS) and overall survival (OS) benefits in MONALEESA-2, -3, and -7 in patients (pts) with HR+/HER2– advanced breast cancer (ABC). Here, we report efficacy, safety, and quality of life (QOL) with RIB + ET in elderly pts in the MONALEESA trials.

Methods: Data were pooled from the MONALEESA-2, -3, and -7 trials of pre- and postmenopausal pts with HR+/HER2– ABC treated with first-line RIB + ET or placebo (PBO) + ET. The tamoxifen cohort in MONALEESA-7 and pts with early relapse were excluded from this analysis. PFS, OS, and time to first chemotherapy (TTC) were analyzed in pts <65 y, 65- <75 y, and ≥75 y using Kaplan-Meier methods. Time to definitive deterioration (TTD) by ≥10 points in global health status (GHS) was analyzed across age subgroups using Kaplan-Meier methods.

Results: Of the 1229 pts included in this analysis, 773 (62.9%) were <65 y, 335 (27.3%) were 65- <75 y, and 121 (9.8%) were ≥75 y. There were minor differences in baseline characteristics between the age groups: slightly higher % of pts in the ≥75 y group with a ECOG status of 1 and slightly higher % of de novo disease in the <65 y group (Table). Regardless of age, a PFS and OS benefit was seen with RIB + ET vs PBO + ET (Table). RIB + ET also delayed the median TTC in all age groups. In the RIB + ET group, the most common first subsequent antineoplastic treatment was hormonal therapy alone (<65 y, 26.3%; 65- <75 y, 41.6%; ≥75 y, 38.1%). In the ≥75 y subgroup, pts in the RIB + ET arm (6.3%) less frequently used chemotherapy alone as the first subsequent antineoplastic treatment vs the PBO + ET (24.5%) arm. In pts <65 y, safety results were consistent with those in the overall trial population. In pts 65- <75 y and ≥75 y, the most common any grade adverse events (AEs) with RIB + ET vs PBO + ET were neutropenia (67.6% vs 5.4% and 52.9% vs 3.8%), nausea (52.7% vs 32.0% and

52.9% vs 40.4%), fatigue (42.0% vs 38.1% and 36.8% vs 21.2%), and diarrhea (39.9% vs 30.6% and 48.5% vs 32.7%). For RIB + ET vs PBO + ET, rates of grade 3/4 febrile neutropenia (<65 y, 1.2% vs 0.3%; 65- <75 y, 1.1% vs 0; ≥75 y, 2.9% vs 0), all grade interstitial lung disease (<65 y, 1.0% vs 0.6%; 65- <75 y, 2.7% vs 0.7%; ≥75 y, 7.4% vs 0), and all grade QT prolongation (<65 y, 9.1% vs 2.9%; 65- <75 y, 11.2% vs 4.1%; ≥75 y, 16.2% vs 1.9%) were numerically higher in pts 65- <75 y and ≥75 y than in pts <65 y. Rates of discontinuation due to AEs with RIB + ET vs PBO + ET were 14.6% vs 3.1% in pts <65 y, 19.7% vs 6.8% in pts 65- <75 y, and 41.2% vs 7.7% in pts ≥75 y. In pts who discontinued treatment due to AEs, the percentage of pts without prior dose reduction was 34.4% in pts <65 y, 40.5% in pts 65- <75 y, and 50.0% in pts ≥75 y. TTD in GHS was prolonged with RIB + ET vs PBO + ET in pts <65 y. In pts 65- <75 y and ≥75 y, TTD was generally similar with RIB + ET vs PBO + ET (Table). Conclusions: This pooled analysis of the MONALEESA-2, -3, and -7 trials demonstrated PFS and OS benefits with RIB + ET in elderly pts consistent with those observed in younger pts. Across age subgroups, treatment with RIB + ET also delayed TTC. Overall, RIB was well tolerated in elderly pts, with a safety profile consistent with what is anticipated for an older patient population. Additionally, there was no difference in TTD in GHS with RIB + ET vs PBO + ET in pts 65- <75 y and pts ≥75 y.

Table.

		<65 y		65-<75 y		≥75 y	
		RIB+ET n=419	PBO+ET n=354	RIB+ET n=188	PBO+ET n=147	RIB+ET n=68	PBO+ET n=53
Age, mean, y		50.6	51.0	68.7	69.0	79.2	78.1
ECOG, % ^a	0	68.7	68.6	53.7	61.2	54.4	50.9
	1	31.0	31.1	46.3	38.8	45.6	49.1
De novo, %		43.4	42.9	37.8	36.7	38.2	35.8
mPFS, mo		31.8	16.4	35.7	19.2	31.1	19.3
HR (95% CI)		0.56 (0.47-0.66)		0.55 (0.42-0.73)		0.54 (0.34-0.86)	
mOS, mo		67.6	51.7	72.6	59.8	62.1	52.8
HR (95% CI)		0.69 (0.56-0.84)		0.79 (0.58-1.07)		0.75 (0.46-1.21)	
mTTC, mo		58.0	40.2	NE	48.3	80.3	42.3
HR (95% CI)		0.67 (0.55-0.83)		0.64 (0.47-0.89)		0.48 (0.27-0.87)	
TTD in GHS HR (95% CI)		0.61 (0.47-0.80)		0.90 (0.57-1.42)		1.26 (0.57-2.80)	

^aFor the <65 y age group, 1 patient in each arm had unknown ECOG status.

ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; GHS, Global Health Status; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib; TTC, time to chemotherapy; TTD; time to definitive deterioration.

PS02-02

Patient-reported outcomes from the Phase 3 CAPitello-291 trial investigating capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR-positive/HER2-negative advanced breast cancer

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

S. Howell. The University of Manchester, Manchester, England, United Kingdom

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

X. Hu. Shanghai Cancer Center, Fudan University, Shanghai, China

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

P. Krivorotko. N.N. Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russia

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

M. Okera. Adelaide Cancer Centre, Adelaide, Australia

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

E. Tokunaga. National hospital organization Kyushu Cancer Center, Fukuoka, Japan

M. Toi. Graduate School of Medicine, Kyoto University, Kyoto, Japan

S. Yousef. Emek Medical Center, Afula, Israel

L. Zhukova. Loginov Moscow Clinical Scientific Center, Moscow, Russia

M. Fulford. Oncology R&D, AstraZeneca, Warsaw, Poland

H. Andrews. Oncology R&D, AstraZeneca, Gaithersburg, Maryland, United States

I. Wadsworth. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. D'Cruz. Oncology R&D, AstraZeneca, Waltham, Massachusetts, United States

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background: In the Phase 3 CAPitello-291 trial, adding capivasertib (C), a pan-AKT inhibitor, to fulvestrant (F) in patients (pts) with aromatase inhibitor-resistant, HR+/HER2- (HER2- defined as IHC 0, or 1+ or IHC2+/ISH-) advanced breast cancer significantly improved PFS vs placebo (P) + F in the overall (HR 0.60, 95% CI 0.51, 0.71, $p < 0.001$) and AKT pathway-altered populations (HR 0.50, 95% CI 0.38, 0.65, $p < 0.001$). The safety profile of C-F was manageable;

diarrhea (mostly grade 1) was the most frequent adverse event. Global health status (GHS)/health-related quality of life (HRQoL) was maintained from baseline in both arms; time to deterioration (TTD) favored C-F. We report results from additional patient-reported outcomes (PRO). Methods: Pts were randomized 1:1 to receive F (500 mg IM on days 1 and 15 of cycle 1 and day 1 of each subsequent 28-day cycle) with either P or C (400 mg BID; 4 days on, 3 days off). PRO measures assessed HRQoL, disease-related symptoms, functioning, and patient-reported treatment tolerability using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), EORTC QLQ Breast Cancer 23 items (EORTC QLQ-BR23), PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), and Patient Global Impression of Treatment Tolerability (PGI-TT). PROs were assessed at pre-specified timepoints. Change from baseline was assessed using Mixed Model Repeat Measures (on-treatment scores) for EORTC QLQ-C30 and summarized for EORTC QLQ-BR23; TTD was assessed using the stratified log-rank test for both. Results: Overall, 708 pts were randomized to C-F (n=355) or P-F (n=353). Overall compliance rates with EORTC QLQ-C30 and PGI-TT were 84.5% and 80.6% with C-F and 81.8% and 81.7% with P-F, respectively. Baseline compliance rates with the EORTC QLQ-C30 and PGI-TT were 88.2% and 82.8% with C-F and 87.3% and 83.1% with P-F, respectively. Mean changes from baseline in EORTC QLQ-C30 functional and symptom domain scores were maintained with C-F and P-F, except for diarrhea in the C-F arm, where scores worsened by >10 points (table). TTD analysis showed that HRs favored C-F vs P-F for all functional and symptom domains, except diarrhea (HR 2.75; 95% CI 2.01, 3.81), which favored P-F (table). Median TTD of diarrhea was shorter with C-F vs P-F in line with the C-F safety profile. Diarrhea with C-F was generally manageable, and discontinuations due to diarrhea were low (2.0%; n=7/355). For PGI-TT, most pts reported that they were 'not at all' or 'a little bit' bothered by the side effects of cancer therapy. Over the first 6 months, the proportion of pts reporting to be 'somewhat', 'quite a bit', or 'very much' bothered by side effects was higher for C-F vs P-F, with between-arm differences being highest in the first 2 cycles. Results from EORTC QLQ-BR23 domains will be presented at the meeting. Conclusions: Pts treated with C-F maintained HRQoL for longer than pts treated with P-F on all EORTC QLQ-C30 functional and symptom domain scores, except diarrhea. Worsening of diarrhea was observed with C-F, consistent with the safety profile of C, but events appeared tolerable and did not negatively impact GHS/HRQoL. Together with the clinical efficacy and manageable safety profile of C-F, the PRO results from the CAPItello-291 trial further support a positive benefit–risk profile of the combination in this population. <https://clinicaltrials.gov/>: NCT04305496. Funding: CAPItello-291 is sponsored by AstraZeneca. Editorial acknowledgment: AstraZeneca-funded medical writing support was provided by Suzanne Patel, Ph.D., from BOLDSCIENCE Inc. Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

EORTC QLQ-C30 domains	LS mean change from baseline (95% CI)*		LS mean difference (95% CI)**	Median TTD, months		HR (95% CI)***
	C+F	P+F		C+F	P+F	
GHS/HRQoL	-2.52 (-4.49, -0.55)	-5.62 (-7.86, -3.37)	3.10 (0.21, 5.98)	24.9	12.0	0.70 (0.53, 0.92)
Functional domains						
Physical functioning	-2.72 (-4.20, -1.23)	-2.30 (-3.97, -0.63)	-0.42 (-2.53, 1.70)	22.1	14.7	0.80 (0.60, 1.06)
Role functioning	-5.61 (-8.08, -3.14)	-5.96 (-8.74, -3.17)	0.35 (-3.22, 3.91)	14.7	11.1	0.76 (0.59, 0.99)
Cognitive functioning	-2.17 (-3.81, -0.53)	-4.05 (-5.91, -2.18)	1.87 (-0.48, 4.23)	17.5	12.8	0.67 (0.51, 0.88)
Emotional functioning	-0.56 (-2.74, 1.62)	-3.05 (-5.50, -0.60)	2.49 (-0.67, 5.65)	NR	16.7	0.81 (0.59, 1.10)
Social functioning	-4.45 (-6.48, -2.41)	-5.39 (-7.64, -3.13)	0.94 (-1.93, 3.80)	14.8	13.0	0.89 (0.69, 1.17)
Symptom domains						
Fatigue	4.26 (1.93, 6.59)	5.61 (2.98, 8.23)	-1.34 (-4.73, 2.04)	11.9	7.7	0.84 (0.66, 1.06)
Pain	0.37 (-1.62, 2.55)	5.88 (3.38, 8.37)	-5.51 (-8.65, -2.37)	21.1	13.0	0.77 (0.58, 1.01)
Nausea and vomiting	3.01 (1.77, 4.25)	2.28 (0.85, 3.71)	0.73 (-1.04, 2.50)	17.4	22.0	0.88 (0.65, 1.19)
Dyspnea	3.72 (1.21, 6.23)	6.45 (3.60, 9.30)	-2.73 (-6.40, 0.94)	22.1	18.4	0.85 (0.62-1.16)
Insomnia	-2.99 (-5.52, -0.45)	-1.21 (-4.12, 1.70)	-1.78 (-5.48, 1.93)	23.0	23.9	0.73 (0.52, 1.02)
Appetite loss	4.11 (1.96, 6.26)	0.90 (-1.54, 3.34)	3.21 (0.15, 6.27)	NR	25.7	0.94 (0.70, 1.28)
Constipation	-5.89 (-8.01, -3.78)	3.48 (1.01, 5.96)	-9.38 (-12.50, -6.25)	NR	NR	0.43 (0.28, 0.64)
Diarrhea	21.24 (18.80, 23.67)	2.75 (-0.04, 5.55)	18.49 (14.96, 22.01)	11.2	23.0	2.75 (2.01, 3.81)
<p>*Calculated using Mixed Model Repeat Measures (on-treatment scores). For functional scales and global health status/QoL score, a positive change from baseline indicates improvement in functioning and health status. For symptom scales, a negative change from baseline indicates improvement. A clinically meaningful change was defined as an absolute change from baseline of ≥ 10.</p> <p>**For functional scales and global health status/QoL score, LS mean difference > 0 indicates a change potentially favoring C+F. For symptom scales, LS mean difference < 0 indicates a change potentially favoring C+F.</p> <p>***HR< 1 indicates a change potentially favoring C+F.</p> <p>LS, least squares; NR, not reached.</p>						

PS02-03

Is de-escalation of treatment by omission of radiotherapy associated with fear of cancer recurrence and health-related quality of life in women with early breast cancer? An exploratory study

Presenting Author(s) and Co-Author(s):

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

M. Sinclair. Royal Women's Hospital, Melbourne, VIC, Australia

P. Butow. University of Sydney, United States

J. Hughes. RMH, United States

A. Park. Royal Melbourne Hospital, Melbourne, VIC, Australia

L. Gilham. BCT, United States

A. Rose. RMH, United States

L. Stafford. RMH, United States

Background: There is growing interest in treatment optimization in early breast cancer (EBC). PROSPECT (ANZ-1002) provided compelling evidence that a combination of pre-operative MRI and pathological features could identify a substantial group of patients with localised EBC in whom radiotherapy (RT) could be safely omitted. The patient experience of de-escalation or its association with health-related quality of life (HRQoL) and fear of cancer recurrence (FCR), was not examined in PROSPECT but is a key consideration of treatment decision-making. We conducted a retrospective, mixed methods, cross-sectional study to explore this association. **Methods:** Psychometrically validated measures including the Fear of Cancer Recurrence Inventory Short-Form, Depression Anxiety Stress Scale, Breast Cancer Treatment Outcomes Scale, EORTC QLQ-C30 and its breast-specific module, the BR23, and the Decision Regret Scale were completed by three groups of women with early EBC: Women in the PROSPECT clinical trial who underwent pre-surgical MRI and omitted RT (A), women who underwent pre-surgical MRI and received RT (B); and women who received usual care (no MRI, received RT; C). Between group differences were analysed with ANOVA or equivalent non-parametric tests. A subset from each group participated in a semi-structured interview. These data (n=44) were analysed with directed content analysis. **Results:** Data from 400 women were analysed. Median age was 65 years, and median time since diagnosis was 4.4 years. There were no group differences in neuroticism, mental health, age, medical comorbidities, parity, or time since diagnosis. Significantly lower FCR was observed in Group A (n=125) than in Group B (n=102; p=.002) or Group C (n=173; p=.001), and when participants were categorized by RT status (omitted RT vs received RT; p< .001). The proportion of women with normal FCR was significantly (p< .05) larger in Group A (62%) than in Group B (35%) or Group C (40%). There were no differences between groups on depression and anxiety. Women in Group A had fewer breast symptoms than in Group B (p=.003) and Group C (p< .001), fewer arm symptoms than in Group B (p=.004) and Group C (p=.011), and better body image than Group C (p=.041). Compared to Groups B and C, Group A performed better on cosmetic (both p< .001), functional (A vs C: p=.011) and breast-specific pain measures (both p< .001). Pre-operative MRI and omission of RT were highly acceptable and decision regret was low. A secondary analysis was conducted to eliminate any potential impact of disease severity on the analysis. All cases (n=126) with any positive nodes, a Grade 3 tumour and tumour size >20mm were removed. The remaining sample comprised 274 women. The results were similar to the primary analysis. Qualitative analysis showed that women who omitted RT viewed this as appropriate treatment, not undertreatment. Women considered RT toxic but endured it as a necessity, if prescribed.

Few women experienced ongoing negative effects from RT but there was a tendency to minimize RT treatment burden. Women managed their FCR by having trust in their treatment and faith in the medical advice they received. Conclusions: In the setting of the PROSPECT trial, treatment de-escalation via omitting RT was associated with less FCR, better HRQoL and functional and cosmetic outcomes and was highly acceptable. Clinicians should consider the potential for preserved HRQoL associated with omission of RT in treatment decision-making. Positive perceptions about tailored care, lower treatment burden, and trust in clinicians appear to be protective against FCR. Future studies should include prospective collection of FCR and HRQoL measures.

PS02-04

Associations of sleep health with quality of life among women with newly diagnosed breast cancer: baseline results from the AMBER cohort study

Presenting Author(s) and Co-Author(s):

L. Yang. Alberta Health Services, Calgary, Alberta, Canada
Q. Wang. Alberta Health Services, Calgary, Alberta, Canada
J. McNeil. University of North Carolina Greensboro, United States
C. Matthews. National Cancer Institute, United States
L. Dickau. Alberta Health Services, United States
J. Vallance. Athabasca University, United States
M. McNeely. University of Alberta, Edmonton, Alberta, Canada
S. Culos-Reed. University of Calgary, United States
K. Kopciuk. Alberta Health Services, United States
K. Courneya. University of Alberta, Edmonton, Alberta, Canada
C. Friedenreich. University of Calgary, United States

Background High incidence, ageing, and advancements in early detection and clinical treatment have led to a growing breast cancer survivor population, particularly in developed countries. Sleep problems are common and persist in this population, affecting over 50% of breast cancer survivors. Good sleep health is characterized by sleep duration, sleep timing and sleep quality, and these three dimensions do not necessarily correlate with each other. This analysis aimed to investigate the associations of sleep health, characterized by sleep duration, sleep timing, and a range of metrics for sleep quality (latency, efficiency, disturbance, medication, daytime dysfunction) with physical and mental well-being in women with newly diagnosed breast cancer. **Methods** Newly diagnosed breast cancer patients, with early-stage disease were recruited between 2012-2019 in Edmonton and Calgary, Canada, and completed the Pittsburgh Sleep Quality Index (PSQI) to assess the habitual sleep duration and timing, as well as sleep latency, efficiency, disturbance, medication and daytime dysfunction. To measure quality of life, participants completed the SF-36 version-2 to assess their physical and mental well-being. Multivariable linear regressions were used to estimate the association of sleep characteristics with physical and mental well-being, adjusting for socio-demographic, disease, clinical and lifestyle behaviour factors. **Results** Among 1409 breast cancer survivors, 41% reported short or long sleep duration (< 6 or ≥9 h/d), 41% reported habitual bedtimes after 11pm, 56% reported sleep efficiency being < 85%, 80% reported fairly good (vs. very good) sleep disturbance, 35% reported taking sleep medication in the past month, and 71% reported fairly good, fairly bad or very bad (vs. very good) daytime function. In the multivariable model, short sleep (≤6/d) was associated with worse mental well-being (-3.6, 95%CI: -4.7,-2.4) but not physical well-being (-1.5, 95%CI: -2.3,-0.7). No clinically meaningful differences in quality of life were found for sleep timing. Metrics characterizing suboptimal sleep quality were associated with poorer physical and mental well-being, with stronger associations observed for mental health well-being. Notably, only 20% and 29% women were classified as “very good” in sleep disturbance and daytime dysfunction measures, respectively. Nevertheless, even “fairly good” sleep disturbance and daytime dysfunction were associated with statistically and clinically meaningful significant poorer physical (-3, 95%CI: -3.8,-2.2) and mental (-8, 95%CI: -9,-7) well-being. **Conclusion** Sleep timing does not appear to affect the quality of life in a clinically meaningful manner in women newly diagnosed with breast cancer. In contrast, short sleep duration and worse sleep

quality were strongly associated with poorer mental well-being in these women. Targeted interventions to improve sleep may lead to improvements in the quality of life among women with newly diagnosed breast cancer.

Table 1. Association of Sleep Characteristics with SF-36 Measured Quality of Life, Physical Well-Being.

	Mean (SD)	Beta-coefficient (95% CI)		
		Age-adjusted ^a	MV model 1 ^{a,b}	MV model 2 ^{a,b,c}
Sleep duration				
6-9 h/d	50.1 (7.2)	0 [reference]	0 [reference]	0 [reference]
≤ 6 h/d	48.0 (7.7)	-2.0 (-2.9 to -1.1)	-1.6 (-2.4 to -0.8)	-1.5 (-2.3 to -0.7)
≥ 9 h/d	48.7 (8.2)	-1.3 (-2.6 to -0.2)	-1.0 (-2.5 to 0.2)	-1.0 (-2.2 to 0.2)
Sleep timing				
< 10 pm	49.5 (7.4)	0 [reference]	0 [reference]	0 [reference]
10-<11 pm	49.5 (7.4)	0 (-1.1 to 1.1)	-0.2 (-1.2 to 0.9)	-0.3 (-1.3 to 0.7)
11-<12 pm	49.4 (7.6)	-0.1 (-1.2 to 1.0)	0.2 (-0.9 to 1.3)	0.2 (-0.8 to 1.3)
≥ 12 pm	47.7 (8.1)	-1.8 (-3.4 to -0.3)	-0.3 (-1.8 to 1.2)	-0.2 (-1.6 to 1.3)
Sleep latency				
< 15 min	50.3 (7.3)	0 [reference]	0 [reference]	0 [reference]
16-30 min	49.5 (7.2)	-0.8 (-1.7 to 0.1)	-0.7 (-1.5 to -0.2)	-0.7 (-1.6 to 0.1)
31-60 min	48.1 (7.9)	-2.1 (-3.2 to -1.1)	-1.9 (-2.8 to -0.8)	-1.7 (-2.7 to -0.7)
≥ 60 min	45.6 (7.5)	-4.6 (-6.4 to -2.9)	-3.7 (-5.4 to -2.0)	-3.6 (-5.3 to -2.0)
Sleep efficiency				
≥ 85%	50.5 (7.3)	0 [reference]	0 [reference]	0 [reference]
75-84%	49.3 (7.5)	-1.2 (-2.2 to -0.2)	-1.0 (-1.9 to -0.1)	-1.0 (-1.9 to -0.1)
65-74%	48.0 (7.6)	-2.5 (-3.6 to -1.3)	-2.1 (-3.2 to -1.0)	-2.0 (-3.1 to -1.0)
<65%	47.0 (7.3)	-3.5 (-4.7 to -2.3)	-2.9 (-4.0 to -1.7)	-2.7 (-3.8 to -1.5)
Sleep disturbance				
Very good	51.5 (6.9)	0 [reference]	0 [reference]	0 [reference]
Fairly good	48.7 (7.6)	-2.8 (-3.7 to -1.8)	-2.4 (-3.3 to -1.5)	-2.2 (-3.1 to -1.3)
Sleep medication				
Not during the past month	50.0 (7.5)	0 [reference]	0 [reference]	0 [reference]
Less than once a week	48.9 (6.8)	-1.1 (-2.4 to 0.2)	-1.2 (-2.4 to 0)	-0.9 (-2.2 to 0.3)
Once or twice a week	48.5 (7.4)	-1.6 (-3.0 to -0.2)	-1.6 (-2.9 to -0.3)	-1.2 (-2.5 to 0.1)
Three or more times a week	47.0 (7.7)	-3.1 (-4.2 to -2.0)	-2.8 (-3.8 to -1.7)	-2.2 (-3.3 to -1.2)
Day time dysfunction				
Very good	52.2 (6.4)	0 [reference]	0 [reference]	0 [reference]
Fairly good	48.7 (7.5)	-3.6 (-4.4 to -2.7)	-3.1 (-3.9 to -2.3)	-3.0 (-3.8 to -2.2)
Fairly bad	45.5 (7.3)	-6.8 (-8.2 to -5.4)	-6.0 (-7.4 to -4.6)	-5.6 (-7.0 to -4.2)
Very bad	41.4 (6.5)	-10.8 (-13.8 to -7.8)	-9.2 (-12.2 to -6.3)	-8.5 (-11.5 to -5.6)

^a Adjusted for age (years)

^b Multivariable (MV) model additionally adjusted study location (Edmonton, Calgary), marital status (married or common-law, widowed/separated/divorced, single/never married), ethnicity (White, non-white), education attainment (high school or below, college, university, graduate school), annual family income (<\$50,000, 50-100k, 100-150k, >150k), body mass index (kg/m²), total caloric intake (kcal/day), moderate to vigorous intensity physical activity (minutes/day), alcohol consumed (g/day), smoking (never smoker, past smoker, current smoker), disease stage (I, II, III), tumor grade (1, 2, 3), surgery status (pre-surgery [neoadjuvant therapy], lumpectomy, mastectomy)

^c Additionally adjusted for comorbidity score (0-8)

Table 2. Association of Sleep Characteristics with SF-36 Measured Quality of Life, Mental Well-Being.

	Mean (SD)	Beta-coefficient (95% CI)		
		Age-adjusted ^a	MV model 1 ^{a,b}	MV model 2 ^{a,b,c}
Sleep duration				
6-9 h/d	49.3 (9.4)	0 [reference]	0 [reference]	0 [reference]
≤ 6 h/d	45.4 (10.6)	-3.7 (-4.8 to -2.5)	-3.7 (-4.7 to -2.5)	-3.6 (-4.7 to -2.4)
≥ 9 h/d	46.8 (10.6)	-2.0 (-3.7 to -0.4)	-1.9 (-3.6 to -0.3)	-1.9 (-3.6 to -0.2)
Sleep timing				
< 10 pm	47.2 (10.2)	0 [reference]	0 [reference]	0 [reference]
10-<11 pm	48.0 (10.0)	0.8 (-0.6 to 2.2)	0.6 (-0.8 to 2.0)	0.6 (-0.8 to 2.0)
11-<12 pm	48.3 (9.6)	0.9 (-0.6 to 2.4)	0.8 (-0.7 to 2.3)	0.8 (-0.6 to 2.3)
≥ 12 pm	46.6 (11.3)	-0.9 (-2.9 to 1.1)	-0.6 (-2.7 to 1.4)	-0.6 (-2.6 to 1.5)
Sleep latency				
< 15 min	50.4 (9.1)	0 [reference]	0 [reference]	0 [reference]
16-30 min	47.5 (9.9)	-2.7 (-3.8 to -1.5)	-2.7 (-3.9 to -1.5)	-2.7 (-3.9 to -1.6)
31-60 min	44.6 (10.3)	-5.7 (-7.1 to -4.4)	-5.6 (-6.9 to -4.2)	-5.5 (-6.8 to -4.1)
≥ 60 min	43.7 (11.5)	-6.4 (-8.7 to -4.1)	-6.3 (-8.6 to -3.9)	-6.2 (-8.5 to -3.9)
Sleep efficiency				
≥ 85%	49.2 (10.0)	0 [reference]	0 [reference]	0 [reference]
75-84%	48.1 (9.5)	-1.4 (-2.6 to -0.1)	-1.5 (-2.7 to -0.2)	-1.5 (-2.7 to -0.2)
65-74%	46.5 (9.7)	-2.9 (-4.3 to -1.4)	-2.8 (-4.3 to -1.3)	-2.8 (-4.3 to -1.3)
<65%	44.5 (10.9)	-4.8 (-6.2 to -3.0)	-4.4 (-5.9 to -2.8)	-4.3 (-5.8 to -2.7)
Sleep disturbance				
Very good	51.1 (8.4)	0 [reference]	0 [reference]	0 [reference]
Fairly good	47.0 (10.3)	-4.6 (-5.8 to -3.3)	-4.5 (-5.7 to -3.2)	-4.4 (-5.7 to -3.1)
Sleep medication				
Not during the past month	48.8 (9.9)	0 [reference]	0 [reference]	0 [reference]
Less than once a week	47.2 (9.5)	-1.8 (-3.4 to -0.1)	-1.7 (-3.4 to 0.1)	-1.7 (-3.4 to 0)
Once or twice a week	46.4 (10.4)	-2.8 (-4.7 to -1.0)	-3.1 (-4.9 to -1.2)	-2.9 (-4.8 to -1.0)
Three or more times a week	44.9 (10.2)	-4.0 (-5.4 to -2.6)	-3.8 (-5.2 to -2.4)	-3.6 (-5.1 to -2.2)
Day time dysfunction				
Very good	54.5 (6.8)	0 [reference]	0 [reference]	0 [reference]
Fairly good	46.4 (9.2)	-7.9 (-8.9 to -6.9)	-8.0 (-9.1 to -7.0)	-8.0 (-9.0 to -7.0)
Fairly bad	38.2 (10.5)	-15.5 (-17.2 to -13.8)	-15.6 (-17.3 to -13.9)	-15.5 (-17.2 to -13.8)
Very bad	35.3 (10.4)	-18.7 (-22.3 to -15.1)	-19.0 (-22.7 to -15.3)	-18.9 (-22.7 to 15.2)

^a Adjusted for age (years)

^b Multivariable (MV) model additionally adjusted study location (Edmonton, Calgary), marital status (married or common-law, widowed/separated/divorced, single/never married), ethnicity (White, non-white), education attainment (high school or below, college, university, graduate school), annual family income (<\$50,000, 50-100k, 100-150k, >150k), body mass index (kg/m²), total caloric intake (kcal/day), moderate to vigorous intensity physical activity (minutes/day), alcohol consumed (g/day), smoking (never smoker, past smoker, current smoker), disease stage (I, II, III), tumor grade (1, 2, 3), surgery status (pre-surgery [neoadjuvant therapy], lumpectomy, mastectomy)

^c Additionally adjusted for comorbidity score (0-8)

PS02-05

Trajectories and predictors of peripheral neuropathy after neoadjuvant chemotherapy in a prospective cohort of 11,014 patients with early breast cancer

Presenting Author(s) and Co-Author(s):

- Y. Drouet. Centre Léon Bérard, Lyon, France
- E. Thomas. Centre Léon Bérard, Lyon, France
- F. Lerebours. Institut Curie, United States
- B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France
- O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France
- C. Jouannaud. Institut Godinot, Reims, France
- M. Fournier. institut Bergonié, Bordeaux, France
- P. Rouanet. L'Institut du Cancer de Montpellier, Montpellier, France
- L. Vanlemmens. Centre Oscar Lambret, Lille, France
- C. COUTANT. Centre Georges-François Leclerc, France
- A. Dhaini Merimeche. Centre lexis Vautrin, Nancy, France
- B. Sauterey. Institut de cancérologie de l'Ouest, Angers, France
- C. Levy. Centre François Baclesse, Caen, Basse-Normandie, France
- M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France
- C. Tarpin. Institut Paoli Calmettes, Marseille, United States
- M. Mouret-Reynier. Centre Jean Perrin, United States
- O. Rigal. Centre Henri Becquerel, Rouen, France
- T. Petit. Centre Paul Stauss, Strasbourg, France
- S. Guillermet. Centre Eugène Marquis, Rennes, France
- A. Arnaud. Institut Sainte Catherine, Avignon, France
- M. Ibrahim. CHU La Source, Orléans, United States
- S. Giacchetti. Hôpital Saint Louis, Paris, France
- F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France
- J. Wassermann. CHU Pitié Salpêtrière, Paris, France
- O. Arsène. Centre Hospitalier de Blois, Blois, France
- A. Darut-Jouve. Clinique du Parc Devron, Dijon, France
- S. Everhard. Unicancer, Paris, France, United States
- I. Vaz Luis. Gustave Roussy, Villejuif, France
- A. Martin. Unicancer, Paris, France, United States
- F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France
- J. Deleuze. Centre National de Génotypage, United States
- A. Viari. INRIA, France, United States
- m. Carton. institut curie, United States
- P. Cottu. Institut Curie, Paris, Paris, Ile-de-France, France

Background Peripheral neuropathy (PN) is a debilitating adverse event in patients with early breast cancer (BC) receiving (neo)adjuvant chemotherapy (CT). We harnessed the CANTO cohort study to detail clinical trajectories and explore clinical and genetic predictors of PN. Methods CANTO (CANcer TOxicities - NCT01993498) prospectively enrolled invasive stage I-III BC patients (pts) of 26 French comprehensive cancer centers. Pts were assessed at diagnosis, 3-6 (M6), 12 (M12), 36 (M36), and 60 (M60) months after treatment, defined as completion of surgery, CT or radiotherapy, whichever comes last. At each time point, PN events including paresthesia, sensory and motor neuropathy were collected according to NCI-CTC v4.0 criteria. A genome-wide association study (GWAS) was conducted to identify genetic predictors of PN, using Illumina GSA BeadChips. Minimac4/1000G was used to impute additional single nucleotide polymorphisms (SNPs). After stringent quality control measures, 1,894,475 SNPs with a minor allele frequency (MAF) >0.05 were evaluated. Longitudinal trajectories of PN events were descriptively examined. Statistical associations between each SNP and PN events measured at different time points, and between SNPs and trajectories, were performed with logistic regression assuming a log-additive genetic model. All analyses were adjusted for key clinical parameters and the first ten axes of principal component analysis of the genetic data to control for population stratification. Results Of 12,012 included pts (data lock Aug. 2022), 11,014 (91.7%) were analyzed. Age was < 50 and >65 in 3407 and 2759 pts (31% and 25%, respectively). Overweight/obesity and diabetes were recorded in 5328 (48%) and 458 pts (4%). A neurologic history was observed in 1360 pts (13%). Stage 0-I and II-III were observed in 5356 (49%) and 5512 pts (51%), and 4011 pts had an axillary dissection (37%). CT was administered in 5790 pts (53%), including a taxane (tax) in 5542 pts (96%). Shortly, all grade and grade 2+ PN was observed in 29% and 12%; 27% and 10%; 20% and 10%; 13% and 10% of pts at M6, M12, M36 and M60, respectively. We derived 5 trajectories of overall PN, deemed “never”, “always”, “appears”, “transient” and “disappears”, in respectively 54%, 10%, 9%, 7% and 19% of the pts. Similar trajectories were built for the 3 categories of PN events. We built 9 predictive nomograms including key clinical parameters and time of analysis. E.g., grade 2+ PN at M6 was independently predicted by a medical history of carpal tunnel syndrome, past neurologic history and exposure to tax. Grade 2+ PN at M36 was predicted by past neurologic history and exposure to tax, and largely by previous PN at M6 or M12. The GWAS analysis included 7633 pts (84%). Four independent SNPs adding predictive value to the clinical nomograms were identified at a suggestive level of association ($p < 1e-6$), including one SNP in the NCAM1 gene (involved in neurogenesis) for M6 PN (OR=1.40, 95%CI 1.23-1.60, $p=4.8e-7$, see table) and one SNP in the CLDN11 gene (regulates oligodendrocytes) for M12 sensory PN (OR=1.32; 95%CI 1.17-1.49, $p=7.5e-6$). For rare (< 5%) toxicities, 10 independent suggestive SNPs were identified, including one SNP in the NELL1 gene (neural cell growth regulation and differentiation) for the “always” trajectory (OR=1.61, 95%CI 1.31-1.99, $p=7.6e-6$) and one SNP in the KCNIP1 gene (neuronal sensor) for M36 motor PN (OR=1.5, 95%CI 1.7-3.5, $p=3.1e-07$). Conclusions Risk of early peripheral neuropathy is associated with previous neurological history and taxane exposure. Patients with PN at M6 or M12 are highly exposed to long-term PN. Some key SNPs may add independent predictive value for specific PN endpoints. Exploratory results of interest were produced for rarer toxicities and typical clinical trajectories. Detailed results will be presented at the meeting.

all PN, M6

All PN, M6	Clinical model		Integrative model	
	OR	P	OR	p
Obesity	1.17	.013	1.1	.32
Carpal tunnel	1.44	<.001	1.49	1.1e-05
Neurol. History	2.26	<.001	2.14	6.2e-20
Taxane	3.08	<.001	3.0	4.4e-56
<i>NCAM1</i>	-	-	1.40	4.8e-7

Multivariate analyses of the risk of peripheral neuropathy, all grades, at M6, without and with GWAS input.

PS02-07

Effectiveness of 24-week mobile application based human coaching program for controlling weight, BMI and body composition in overweight/obese breast cancer survivors: Single-arm prospective cohort study

Presenting Author(s) and Co-Author(s):

S. Jung. National Cancer Center, Goyang, Republic of Korea

E. Lee. National Cancer Center, United States

D. Lee. National Cancer Center, United States

J. Kim. National Cancer Center, United States

J. Han. National Cancer Center, United States

S. Lee. National Cancer Center, Goyang, Republic of Korea

H. Kang. National Cancer Center, United States

E. Lee. National Cancer Center, Goyang-si, Gyeonggi-do, Republic of Korea

H. Chae. National Cancer Center, United States

S. Sim. National Cancer Center, United States

K. Lee. Center for Breast Cancer, National Cancer Center, Goyang, Republic of Korea

J. Lee. Noom, New York, New York, United States

Background: Overweight/obesity has been known as a prognostic factor for breast cancer recurrence and breast cancer related death. However, weight control is hard in breast cancer survivors because of menopause, chemotherapy, anti-hormonal therapy, and psychologic issues. This study aimed to develop 24-week mobile application based human coaching program with Noom and evaluate its efficacy in overweight/obese breast cancer survivors. **Methods** In this single-arm prospective cohort study, 130 breast cancer survivors with BMI ≥ 25 were enrolled and received 24-week program including diet-, exercise-, and psychology-based contents with trained human coach in Noom during 2019-2021. For hyperactive group who joined more than 16 weeks, we evaluated weight, BMI, lipid level, bioimpedance, and Quality of Life (QoL) at baseline, 6 month and 12month follow-up. **Results** Among 130 breast cancer survivor, 101 participants (77.7%) and 93 participants (71.5%) completed 6 month and 12 month follow-up, respectively. In hyperactive group (68/101, 67%), body weight and BMI reduced significantly (mean difference: -1.97 kg, 95% CI (confidence interval):-2.65- -1.26, $P < 0.001$ and -0.86, 95% CI:-1.15- -0.56, $P < 0.001$, respectively) at 6 month and maintained at 12 month without the yo-yo effect. Among the lipid panel, triglycerides level decreased significantly (-34.13, 95% CI:-58.09- -10.17, $P=0.006$) and maintained at 12 month. In the aspect of bioimpedance components, skeletal muscle mass (SMM, kg), body fat mass (BFM, kg), percent body fat (PBF, %), waist-hip ratio (WHR), and visceral fat area (VFA, cm^2) were improved for first 6 months. However, WHR and VFA increased during next 6months. Based on the EORTC QLQ C30 and BR 23, nausea/vomiting, constipation, body image, arm and breast symptoms showed significant improvement during the first 6months. **Conclusions** This study demonstrated that 24-week mobile application based human coaching program is beneficial for controlling body weight, BMI, TG and body composition in bioimpedance for overweight/obese breast cancer survivors. [ClinicalTrials.gov NCT05506189](https://clinicaltrials.gov/NCT05506189); <https://clinicaltrials.gov/ct2/show/NCT05506189>. IRB: NCC2019-0098

PS02-08

The Effect of a Digital Health Coaching Program on Patient Reported Outcomes of Women with Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Whisenant. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

E. Hacker. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

L. Williams. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Dains. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

B. Fellman. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Isaac. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

V. Shelton. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Barr. Pack Health, United States

C. Harty. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Rasulnia. Pack Health, United States

K. Brassil. Pack Health, United States

Background Understanding the impact of a digital health coaching (DHC) program on patient-reported outcomes in women with breast cancer is imperative as web-based platforms and mobile phone applications to address health care needs flood the marketplace. This study evaluated the effect of a DHC program on patient-reported outcomes, including global health (primary outcome), symptom burden, quality of life, healthcare utilization, and financial toxicity among women undergoing active treatment for breast cancer. **Methods** English-speaking adult women undergoing active treatment for breast cancer were randomized to receive usual care or a 6-month DHC program, consisting of weekly telephone calls from a Health Advisor, unlimited patient-initiated communication via phone, text, or email, and digital delivery of additional health-behavior content. Patient-reported outcomes (PROs) were collected using validated measures at baseline, and 1, 3, and 6 months. Summary statistics were used to describe participant characteristics. Linear mixed models were used to assess the effect of the intervention on outcomes. **Results** Participants (n=254, planned enrollment=440) were enrolled from August 2019 to December 2022 and randomized equally to the control and intervention groups (n=127 each). Demographic data are presented in Table 1. Participants had a mean age of 48 (SD =10.15) years; 74% were White; 19.7% were Hispanic. In both groups, several PRO scores changed over time with some improving (quality of life and symptom severity) and others worsening (symptom interference and financial toxicity) compared to baseline (time effects). Of those enrolled in the intervention group 69% were retained in the DHC program, with an overall average of 4.6 months of engagement for all participants. There were no significant group (intervention versus control) effects or group by time interaction effects observed. Trends within and between groups are presented in Table 2. Though not statistically significant, there were fewer ER visits in the intervention group at each timepoint. **Conclusions:** While differential improvements in the DHC group were not observed, interesting trends in PROs over the 6-month enrollment period were observed in both groups. Participants reported

improvements in quality of life and worsening of financial toxicity. Interestingly, slight improvements in symptom severity over time were observed in both groups while symptom interference worsened. Potential reasons for failure to detect a treatment effect for DHC may include ineffectiveness of DHC on the selected outcomes, the intervention not being strong enough as currently delivered to detect a treatment effect, varying uptake of DHC in the intervention group, heterogeneity of the sample, or the study being underpowered due to COVID restrictions affecting enrollment.

Table 1. Demographic and clinical characteristics of the study population (n = 254)

Table 1. Demographic and clinical characteristics of the study population (n = 254)

Characteristic	Control (n = 127)	Intervention (n = 127)	p-value
	Mean (SD)	Mean (SD)	
Age at diagnosis			
Mean (SD)	48.17 (9.74)	48.60 (10.59)	0.737
	N (%)		
Employment			0.165
Employed	95 (76.0)	85 (70.3)	
Race			>0.999
White or Caucasian	94 (74.0)	94 (74.0)	
Black or African American	20 (15.8)	21 (16.5)	
Asian	6 (4.7)	6 (4.7)	
Other	6 (4.7)	6 (4.7)	
American Indian or Alaska Native	1 (0.8)	0 (0.0)	
Ethnicity			>0.999
Hispanic or Latino	25 (19.7)	25 (19.7)	
Prior Breast Cancer Treatment			
Surgery	126 (99.2)	120 (94.5)	0.066
Radiation	106 (83.5)	109 (85.8)	0.602
Chemotherapy	124 (97.6)	126 (99.2)	0.622
Hormone therapy	37 (29.1)	49 (38.6)	0.112
Immunotherapy	4 (3.2)	3 (2.4)	>0.999

Table 2. Trends in Patient Reported Outcomes and Healthcare Utilization

Table 2. Trends in Patient Reported Outcomes and Healthcare Utilization

Measure	Cohort	Baseline	Month 3		Month 6		
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
PROMIS Physical	Control	36.59 (7.52)	37.93 (5.74)	36.46 (8.19)			
	Intervention	36.92 (6.76)	37.47 (6.29)	35.08 (5.64)			
PROMIS Mental	Control	36.97 (10.15)	34.63 (9.27)	35.26 (9.74)			
	Intervention	36.31 (11.14)	37.32 (10.16)	36.11 (11.06)			
MDASI Severity	Control	2.69 (1.81)	2.10 (1.57)	1.78 (1.39)			
	Intervention	2.51 (1.91)	1.86 (1.28)	1.75 (1.31)			
MDASI Interference	Control	1.67 (1.37)	1.85 (1.44)	1.87 (1.47)			
	Intervention	1.54 (1.46)	1.74 (1.33)	2.07 (1.60)			
FACT-G	Control	75.13 (17.38)	78.71 (16.24)	79.80 (16.74)			
	Intervention	76.42 (16.99)	80.03 (14.49)	81.03 (15.70)			
COST	Control	23.75 (11.21)	26.10 (10.61)	27.26 (9.87)			
	Intervention	24.82 (11.10)	28.16 (10.54)	28.15 (11.16)			
Healthcare Utilization (n)		Baseline	Mo. 1	Mo. 2	Mo. 3	Mo. 4	Mo 6
ER Visit	Control	17	14	21	7	7	5
	Intervention	8	12	10	5	3	3
Hospitalization	Control	4	5	6	3	5	2
	Intervention	4	5	3	1	4	2

COST, Comprehensive Score for financial Toxicity (lower score represents worse financial toxicity); ER, Emergency Room; FACT-G, Functional Assessment of Cancer Therapy-General (Higher scores represent better quality of life); MDASI, M.D. Anderson Symptom Inventory (Higher score represents more of the concept of measure); PROMIS, Patient Reported Outcomes Measurement Information System (Higher scores represent better health).

PS02-09

Nurse-led individualized follow-up versus regular physician-led visits after early breast cancer (MyHealth) - a randomized, controlled trial

Presenting Author(s) and Co-Author(s):

- L. Saltbæk. Zealand University Hospital, Ballerup, Hovedstaden, Denmark
- P. Bidstrup. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- R. Karlsen. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- B. Høeg. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- T. Horsboel. National Institute of Public Health, University of Southern Denmark, Copenhagen, Hovedstaden, Denmark
- F. Belmonte. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- E. Andersen. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- V. Zoffmann. University of Copenhagen, Copenhagen, Hovedstaden, Denmark
- A. Friberg. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- M. Svendsen. Zealand University Hospital, Roskilde, Sjælland, Denmark
- H. Christensen. Zealand University Hospital, Roskilde, Sjælland, Denmark
- V. Glavicic. Zealand University Hospital, Naestved, Sjælland, Denmark
- D. Nielsen. Copenhagen University Hospital, Herlev and Gentofte, Herlev, Hovedstaden, Denmark
- S. Dalton. Survivorship and Inequality in Cancer, Danish Cancer Society Research Center, Copenhagen, Denmark
- C. Johansen. Copenhagen University Hospital, Rigshospitalet, Copenhagen, Hovedstaden, Denmark

Background: Follow-up after breast cancer with regular specialist-led visits has failed to prove superiority over other strategies in terms of recurrence detection and survival, but it is still a cornerstone in breast cancer follow-up in many healthcare systems. Follow-up provided by the general practitioner or a specialist nurse has been reported more cost-effective and non-inferior in terms of patient-reported health-related quality of life (HRQoL) and in meeting the needs of breast cancer survivors. However, no follow-up strategies have demonstrated indisputable superiority over other strategies. **Methods:** In this randomized controlled trial (MyHealth), patients who recently completed surgery, and chemo-/radiotherapy if indicated, for stage I–II breast cancer were randomly assigned to intervention or control follow-up at Zealand University Hospital, Denmark. The nurse-led intervention comprised three to five individual self-management sessions during the first six months, and regular reporting of symptoms with nurse navigation to relevant healthcare services during three years of follow-up. The control comprised outpatient visits with oncologist every six months for three years. The primary outcome was breast cancer-specific HRQoL measured by the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) summary score of the Functional Assessment of Cancer Therapy-Breast (FACT-B) two years after randomization. Secondary outcomes were fear of recurrence, anxiety, depression, and healthcare utilization. **Results:** From January 2017 to January 2019, 503 patients were randomly assigned to intervention (n=251) or control (n=252) follow-up. At two years, patients in the intervention group reported a significantly higher HRQoL (mean 75·69 (SD 12·27)) than patients in the control group (mean 71·26 (SD 14·08)), a mean difference of 5·05 (95% CI; 3·30–6·79), which is considered clinically relevant. The intervention

group also reported significantly less fear of recurrence, anxiety, and depression as shown in Table 1. Furthermore, patients in the intervention group had fewer physician consultations but more nurse contacts, and an unchanged diagnostic imaging pattern as shown in Table 2. The effect on all outcomes was stable through three years of follow up. Conclusions: The MyHealth study suggests a new strategy for follow-up after early breast cancer providing significant improvements in HRQoL, fear of recurrence, anxiety, and depression without inflicting extra expenses to the healthcare system. (Funded by the Danish Cancer Society, Region Zealand and Copenhagen University Hospital; Clinicaltrials.gov number; NCT02949167.)

Table 1: Outcome findings by study group at baseline, 6, 12, 24, and 36 months

	Time point	Control n = 252	Intervention n = 251	Estimate for difference	95% CI	p- value	Overall p-value	Cohen's d
Quality of life	0	67.26 (13.99)	66.37 (14.40)					
	6	69.95 (13.62)	73.06 (13.37)	4.37	(2.67; 6.08)	< 0.001	< 0.001	0.31
	12	70.59 (14.37)	74.44 (13.13)	4.71	(3.00; 6.42)	< 0.001		0.34
	24	71.26 (14.08)	75.69 (12.27)	5.05	(3.30; 6.79)	< 0.001		0.36
	36	72.60 (13.54)	76.65 (12.90)	4.91	(3.13; 6.70)	< 0.001		0.35
Fear of recurrence	0	13.74 (9.21)	14.56 (10.13)					
	6	13.11 (9.38)	9.76 (8.13)	-4.07	(-5.39; -2.76)	< 0.001	< 0.001	0.44
	12	12.13 (9.20)	9.61 (8.52)	-3.10	(-4.42; -1.78)	< 0.001		0.34
	24	11.10 (9.00)	8.57 (7.99)	-3.19	(-4.54; -1.83)	< 0.001		0.35
	36	11.21 (8.52)	9.17 (8.00)	-2.81	(-4.19; -1.44)	< 0.001		0.31
Anxiety	0	3.69 (4.03)	4.21 (4.40)					
	6	3.81 (4.09)	3.16 (3.86)	0.74	(0.62; 0.88)	< 0.001	< 0.001	0.17
	12	3.64 (3.80)	2.94 (3.74)	0.72	(0.60; 0.86)	< 0.001		0.18
	24	4.02 (4.58)	2.86 (3.30)	0.66	(0.55; 0.78)	< 0.001		0.24
	36	3.27 (3.70)	2.48 (3.08)	0.68	(0.56; 0.82)	< 0.001		0.18
Depression	0	5.78 (4.71)	6.12 (5.01)					
	6	4.92 (4.51)	4.43 (4.35)	0.84	(0.74; 0.96)	0.011	< 0.001	0.13
	12	5.15 (4.47)	4.11 (4.20)	0.75	(0.66; 0.86)	< 0.001		0.22
	24	5.15 (4.90)	3.78 (3.60)	0.70	(0.61; 0.81)	< 0.001		0.27
	36	4.51 (3.84)	3.99 (3.99)	0.83	(0.72; 0.96)	0.011		0.14

Data are mean (SD) unless otherwise stated. The effect estimates are based on the mixed model assuming no difference between groups at baseline. The QoL and fear of recurrence variables are continuous, and the estimates describe the mean difference in score between patients in the two groups. For anxiety and depression, data were zero-inflated. These estimates describe the exponential coefficients of anxiety and depression scores in the intervention group compared to the control group. Cohen's d is a measure of effect size, and interpreted as small for Cohen's d = 0.2, medium for Cohen's d = 0.5, and large for Cohen's d = 0.8

Table 2: Number of contacts and diagnostic imaging examinations during the first three years of follow-up by study group

	Control n = 252		Intervention n = 251		p-value
	n	Mean (SD)	n	Mean (SD)	
Outpatient visit with physician	1326	5.26 (2.32)	370	1.47 (1.81)	< 0.001
Telephone contact with physician	294 ¹	1.17 (1.12)	252	1.00 (1.34)	0.140
Outpatient visit with nurse	12	0.05 (0.23)	101	0.40 (0.65)	< 0.001
Telephone contact with nurse	125	0.50 (1.14)	904	3.60 (2.71)	< 0.001
Mammography	522	2.07 (0.95)	500	1.99 (1.09)	0.384
CT scan	212	0.84 (1.55)	165	0.66 (1.06)	0.122
MR scan	118	0.47 (0.89)	133	0.53 (0.87)	0.431
Bone scintigraphy	43	0.17 (0.43)	49	0.20 (0.42)	0.514
PET CT scan	13	0.05 (0.22)	12	0.05 (0.25)	0.857
All diagnostic imaging	908	3.60 (2.50)	859	3.42 (2.07)	0.377

Data are numbers and mean (SD) per patient during the first three years of follow-up. 1 Most telephone consultations were scheduled as outpatient visits according to the protocol, but changed to telephone consultations due to the COVID-19 pandemic

PS03-01

Single cell analysis of paired lymph nodes and primary tumors in breast cancer patients

Presenting Author(s) and Co-Author(s):

M. Fjørtoft. Institute for Cancer Research, Oslo University Hospital, Oslo, Oslo, Norway

I. Rye. Institute for Cancer Research, Oslo University Hospital, United States

K. Huse. Institute for Cancer Research, Oslo University Hospital, United States

J. Myklebust. Institute for Cancer Research, Oslo University Hospital, United States

H. Russnes. Institute for Cancer Research, Oslo University Hospital, United States

M. Riis. Division of Clinical Medicine, Oslo University Hospital, United States

O. Lingjærde. Institute for Informatics, University of Oslo, United States

□. Garred. Oslo University Hospital, Oslo, Norway

K. Lande. Institute for Cancer Research, Oslo University Hospital, United States

I. Bergheim. Institute for Cancer Research, Oslo University Hospital, United States

E. Schlichting. Oslo University Hospital, Oslo, Norway

A sentinel lymph node (SN) is the primary node draining the tumor and is assumed to be affected early in the metastatic process. The sentinel node holds a key position in the immune response against tumor in breast, and represents a unique connection between the tumor and the host immune response. We hypothesize that the immune profile in the primary tumor and the paired lymph node (LN) is different during tumor progression. 3.7 million single cells from paired primary tumor and lymph nodes from 33 breast cancer patients (Oslo2 cohort) was analyzed by single cell mass cytometry (CyTOF) with a 47 antibody immune panel and characterized by a semi-automatic gating approach (FlowSOM). Tumor cells were found in 11 LN. When analyzing the leucocytes from LN we identified a significant difference in immune cell type skewing towards higher abundance of memory CD4 and CD8 T cells expressing an exhausted phenotype in LN with metastasis. In addition, a higher abundance of activated Tregs and significantly lower abundance of resting Tregs was found in the metastatic LNs compared to the sentinel lymph nodes. The change in immune composition and exhaustion was correlated to the metastatic tumor burden. The skewing towards an exhausted immune profile was also found in larger primary tumors compared to smaller primary tumors. We further analyzed tumor cells from 8 patients with paired primary tumor and LN. No differences were identified in the primary tumor when stratified by LN status, but LNs with smaller metastasis expressed lower levels of epithelial markers essential in the Epithelial-to-Mesenchymal Transition such as E-cadherin, Pan Cytokeratin and EpCAM – this in contrast to the LN with manifested metastasis in the axilla which expressed higher levels of epithelial markers and lower levels of mesenchymal markers such as Vimentin and CD44. We identified a skewing in the immune profile from a naive phenotype towards a memory and exhausted phenotype in CD8 and CD4 T cell population in LN with manifested metastasis, as well as in larger primary tumors. We also identified that tumor cells in smaller metastatic tumors resembled a “mesenchymal like” phenotype compared to in the larger manifested tumors. These results suggest that the immune suppression is correlated with the tumor burden.

PS03-02

Single-cell metabolic profiling uncovers new precision immunotherapy strategy in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

Y. Xu. Fudan University Shanghai Cancer Center, United States

Y. Xiao. Fudan University Shanghai Cancer Center, United States

H. Wang. Fudan University Shanghai Cancer Center, United States

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China (People's Republic)

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Background: Immunotherapy has emerged as a novel cornerstone in the treatment of triple-negative breast cancer (TNBC), while its benefits have been observed in only a limited subset of patients. The intricate metabolic interplay between cancer cells and microenvironmental cells remodels the tumor microenvironment and exerts a significant influence on the responses to immunotherapy. However, there is still a lack of clarity regarding the strategies to target this metabolic crosstalk in order to predict efficacy and enhance sensitivity for immunotherapy. Methods: We conducted single-cell RNA sequencing (scRNA-seq) analysis on a cohort of 27 patients with TNBC receiving either immunotherapy combination regimen or chemotherapy alone. Building upon this foundation, we embarked on a comprehensive investigation of the single-cell metabolic landscape from three distinct perspectives: metabolic genes, metabolic pathways, and metabolic flux, represented by the flux balance analysis (FBA) algorithm Compass. Furthermore, we identified crucial cell subgroups that exhibited a strong correlation with immunotherapy efficacy and elucidated their metabolic characteristics to postulate potential metabolic crosstalk. Then, we employed the *in vitro*, *in vivo*, and patient-derived models to unravel the underlying mechanisms of metabolic crosstalk and proposed the translational strategies. Results: Utilizing newly-developed single-cell FBA method, we illustrated that different cell types have distinct metabolic features. Specifically, tumor cells and macrophages had more active metabolic reprogramming and higher metabolic heterogeneity. Furthermore, we illustrated that a subset of tumor cells having active antioxidant metabolism (featured by the upregulation of GSTP1) and macrophage subset depending on glutamine metabolism (characterized by CCL3⁺) were negatively and positively predictive of immunotherapy responses, respectively. Mechanistically, GSTP1-mediated excessive consumption of glutamine by tumor cells competitively restrained the intake of glutamine into CCL3⁺ macrophages to promote their ferroptosis and reduce their infiltration. Clinically, we demonstrated that targeting the GSTP1, which is specifically expressed in tumor cells, remodeled immune-metabolic microenvironment and enhanced immunotherapy efficacy. Furthermore, we established the utility of plasma CCL3 abundance, GSTP1 protein abundance, and CCL3 protein abundance, as robust predictors of response to immunotherapy, in several independent immunotherapy cohorts. Conclusion: Our study presented a comprehensive and multidimensional analysis of the single-cell metabolic landscape. Identifying the crucial metabolic crosstalk remodeling the immune microenvironment, our promising finding highlights the potential significance of modulating cell-cell metabolic interactions in sensitizing TNBC to immunotherapy, providing valuable insights for future therapeutic interventions.

PS03-03

The spatially resolved single-cell atlas of the tumor immune architecture revealed the central role of IFN-alpha and plasmacytoid dendritic cells in triple-negative breast cancer in the Mayo Clinic cohort and FinXX trial

Presenting Author(s) and Co-Author(s):

S. Chumsri. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

Y. Liu. Mayo Clinic, United States

Y. Ma. Mayo Clinic, United States

J. Carter. University of Alberta, Edmonton, Alberta, Canada

M. Gregory. NanoString Technologies, United States

S. Church. NanoString Technologies, United States

J. Reeves. NanoString Technologies, United States

H. Brauer. NanoString Technologies, United States

S. Warren. NanoString Technologies, United States

H. Joensuu. Helsinki University Hospital and University of Helsinki, United States

E. Perez. Mayo, United States

R. Leon-Ferre. Mayo Clinic, Rochester, Minnesota, United States

D. Hillman. Mayo Clinic, Rochester, Minnesota, United States

J. Boughey. Division of Breast and Melanoma Surgical Oncology, Department of Surgery, Mayo Clinic, Rochester, Minnesota, United States

J. Ingle. Mayo Clinic, Rochester, Minnesota, United States

K. Kalari. Mayo Clinic, Rochester, Minnesota, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

K. Knutson. Mayo Clinic, United States

E. Thompson. Mayo Clinic, United States

Background: Multiple studies have confirmed the central role of preexisting immune response measured by stromal tumor-infiltrating lymphocytes (sTILs) in triple-negative breast cancer (TNBC). Emerging studies showed that not only the number of TILs but also the location of TILs is important. There are 3 distinct immune architectures described based on the amount and locations of TILs, namely immune enriched (IN), immune excluded (IE), and immune desert (ID). Here we evaluated outcomes and characteristics associated with each immune landscape. Methods: NanoString Digital Spatial Profiling (DSP) and CosMx, a spatial multi-omics single-cell imaging platform, were performed in 75 samples from the Mayo Clinic (MC) TNBC cohort (Leon-Ferre BCRT 2018). NanoString IO360 was performed in 114 samples from the FinXX trial (NCT00114816). Firstly, tumors with sTIL quantified by H&E $\leq 30\%$ were classified as ID. The rest of the tumors with high sTIL $> 30\%$ were categorized according to the intratumoral CD8 protein expression by DSP, with IE having intratumoral CD8 in the lower median and IN having intratumoral CD8 in the upper median. Chi-square test, gene set enrichment, Cox regression, and Kaplan-Meier analysis were used. Differential expression listed as log 2-fold change (FC) was estimated from the linear mixed model with significance defined as two-sided $p < 0.05$. Results: ID is associated with low Ki67 $< 5\%$ (23.3% vs. 9.6% ID, $p 0.02$) as well as

apocrine (11/13, 84.6%) and metaplastic histology (10/12, 83%). In both univariate and multivariate analysis, patients with IN had significantly improved recurrence-free survival (RFS) compared to those with ID (HR 0.37, 95%CI 0.18-0.74, p 0.005). Despite having high sTILs, IE had poor outcomes similar to ID (HR 0.84, 95%CI 0.36-1.98). Strikingly, we identified that IE patients had significantly lower plasmacytoid dendritic cells (pDCs) compared to IN (mean 0 vs. 0.26 /100 tumor cells, 95%CI 0.08-0.43 , p 0.01). Using Gene Set Enrichment Analysis to evaluate differential hallmarks between IN and IE, we identified IFN α and IFN γ (FDR < 0.001) responses as significantly enriched in IN group, consistent with the function of pDCs, which are a subset of dendritic cells specialized in secreting high levels of type I interferon. To validate this finding, we further evaluated the 11 leading edge gene IFN α signature in the FinXX trial. A high IFN α signature score was associated with significantly improved outcomes in the FinXX trial (HR 0.21, 95%CI 0.09-0.51 , p < 0.001). Similar findings were observed using Kaplan-Meier analysis in the FinXX trial with significantly improved RFS (p 0.0006) and overall survival (p 0.0001) in patients with high IFN α signature scores. Furthermore, we evaluated the differential gene expression unique to IN tumors in the Mayo cohort. Expressions of MHC class I and class II in tumor cells, including HLA-A, HLA-B, HLA-C, HLA-DRA, HLA-DRB1, HLA-DPA1, and HLA-E, were associated with IN and significantly improved outcomes (p < 0.05) compared to ID and IE. Conclusions: Highlighting the importance of spatial context, we identified that patients with IE tumors had poor outcomes despite having high TILs. Moreover, using an in-depth analysis with spatially defined context, we identified the central role of pDC and the significance of IFN α in TNBC. Support: Breast Cancer Research Foundation, Mayo Clinic Breast Cancer SPORE (P50CA116201-17) W81XWH-15-1-0292, P50CA015083, R35CA253187

PS03-04

Tumor immune microenvironment modulates resistance to estrogen suppression in ER+ breast cancer

Presenting Author(s) and Co-Author(s):

F. Napolitano. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

Y. Wang. Division of Gastroenterology, Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

D. Sudhan. UT Southwestern medical center, United States

P. Gonzalez-Ericsson. Vanderbilt University Medical Center, United States

L. Formisano. Department of Clinical Medicine and Surgery, University of Naples "Federico II", United States

L. Guo. UT Southwestern Medical Center, United States

M. Chica-Parrado. University of Texas Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, United States

C. Lin. University of Texas Southwestern Simmons Comprehensive Cancer Center, United States

K. Lee. Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, USA; Department of Life Sciences, College of Natural Science, Hanyang University, Seoul, Republic of South Korea., United States

H. Ma. Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon, United States

N. Evans. Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; Division of Bioinformatics & Computational Biology, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, Oregon, United States

A. Servetto. Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, USA; Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy., United States

S. Mendiratta. UT Southwestern Simmons Comprehensive Cancer Center, United States

S. Barnes. Lyda Hill Department of Bioinformatics, University of Texas Southwestern Medical Center, Dallas, Texas, United States

Y. Fang. University of Texas Southwestern Medical Center, United States

L. Xu. UT Southwestern, United States

J. Balko. Vanderbilt University Medical Center, Nashville, Tennessee, United States

G. Mills. Knight Cancer Institute, Oregon Health & Science University, United States

M. Labrie. Department of Immunology and Cell Biology, Université de Sherbrooke, Sherbrooke, QC, Canada; Department of Obstetrics and Gynecology, Université de Sherbrooke, Sherbrooke, Quebec, Canada

A. Hanker. UT Southwestern Medical Center, Dallas, Texas, United States

C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

Despite major advances in the treatment of estrogen receptor positive (ER+) breast cancer (BC), advanced disease continues to be the main cause of death from this disease. The role of the tumor immune microenvironment (TIME) in the progression of ER+ BC and its response to treatment is not completely understood. The aim of this study was to elucidate the role the TIME in the response of ER+ tumors to estrogen deprivation (ED). We collected samples from 215 postmenopausal patients with stage I-III ER+ BC, treated with letrozole for 2-4 weeks, to induce ED. We used AQUA on pre-treatment biopsies and on-treatment surgical biopsies to assess ER, PR, HER2, and Ki67. Then, we categorized the patients' response to ED based on the Ki67 score in on-treatment samples: ED-sensitive (ED-S) if natural log (ln) of the Ki67 score ≤ 1.0 or $\leq 2.7\%$ Ki67+ cells vs. ED-resistant (ED-R) if $\ln \geq 2.0$ or $\geq 7.4\%$ Ki67+ cells. Firstly, we assessed TIME composition by investigating stromal tumor-infiltrating lymphocytes (sTILs) in H&E-stained FFPE of on-treatment tumor sections. ED-R tumors exhibited a significantly higher stromal TILs score ($p=0.0001$) relative to ED-S tumors. We next prepared tissue microarrays from 227 (on-treatment) surgical sections and subjected them to cyclic immunofluorescence (CyclIF) with 38 antibodies to examine their intra-tumoral immune cell infiltration. From each tumor core, we segmented single cells and labeled them as immune, cancer, or stromal cells based on expression of a set of markers. Briefly, cells that stained strongly for CD45 (leukocyte marker), and/or CD4 (T lymphocyte marker), or CD68 (macrophage marker) were labeled immune cells. CD45/CD4/CD68-negative cells were categorized as tumor if E-cadherin and/or cytokeratin-positive, or stromal cells if -negative. Next, we assessed cell specific spatial enrichment by quantifying the expression of immune markers in the area immediately adjacent to each tumor cell. Immune-suppressive T-reg (FOXP3+) cells were enriched in the ED-S tumors ($p=0.0004$), as well as PD1+ (exhausted) T cells ($p=0.0004$), and CD68+ cells ($p < 0.0001$) compared to ED-R tumors. ED-R tumors exhibited higher CD20+ B cells ($p < 0.0001$), higher CD8+ T cells ($p=0.0329$), in addition to higher CD45+ cells ($p < 0.0001$), compared to ED-S tumors. RNA-sequencing of the same surgical samples showed a higher T cells cytolytic score in ED-R relative to ED-S ($p=0.0058$), suggesting enhanced CD8+ T cells activity, in addition to their higher infiltration. We are currently analyzing letrozole-induced changes in TIME composition using Geomix digital spatial profiler in paired pre- and on-treatment biopsies from ED-R and ED-S tumors and will be presented at the meeting. Consistent with the CyclIF findings, GSEA of hallmark gene signatures from bulk RNA-sequencing of treated tumors revealed that immune-related gene sets, such as "IFN α response", "IFN γ response", and "allograft rejection" were upregulated in ED-R vs. ED-S cancers. ED-R tumors showed enrichment of CXCL9, CXCL10, and CXCL11 chemokines and their receptor, CXCR3. Publicly available datasets of patients with ER+ breast cancers showed that higher expression CXCL9 (HR 1.36; $p=0.016$), CXCL10 (HR 1.71; $p < 0.0001$), and CXCL11 (HR 1.5; $p=0.0016$) are predictive of shorter relapse-free survival on antiestrogen therapy. We are currently investigating whether these chemokines play a causal role in resistance to ED, and if this is phenocopied by co-cultures of ER+ BC cells and CD8+ T-cells. Conclusions ED-resistant tumors are enriched with stromal TILs and exhibit higher immune cell intra-tumoral infiltration and CD8+T cells cytolytic activity compared to ER+ tumors sensitive to estrogen suppression. In contrast, ED-S tumors showed a more immunosuppressed milieu. The role of CXCL9, CXCL10 and CXCL11 in inducing resistance to ED warrants further investigation.

PS03-06

Clinical implementation of artificial-intelligence-assisted detection of breast cancer metastases in sentinel lymph nodes: saving costs and time (the CONFIDENT-B trial)

Presenting Author(s) and Co-Author(s):

R. Flach. University Medical Centre Utrecht, Utrecht, Netherlands

N. ter Hoeve. University Medical Centre Utrecht, Utrecht, Netherlands

C. Vreuls. University Medical Centre Utrecht, Utrecht, Netherlands

R. Goldschmeding. University Medical Centre Utrecht, Utrecht, Netherlands

J. Freund. University Medical Centre Utrecht, Utrecht, Netherlands

P. Pham. University Medical Centre Utrecht, Utrecht, Netherlands

T. Nguyen. University Medical Centre Utrecht, Utrecht, Netherlands

E. Van der Wall. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

G. Frederix. University Medical Centre Utrecht, Utrecht, Netherlands

N. Stathonikos. University Medical Centre Utrecht, Utrecht, Netherlands

P. Van Diest. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

C. van Dooijeweert. University Medical Centre Utrecht, Utrecht, Utrecht, Netherlands

Background Metastases in sentinel lymph nodes (SN) of breast cancer (BC) patients are strongly associated with a worse survival and consequently guide treatment. If metastases are absent upon pathologist' assessment of the regular hematoxylin and eosin (HE)-slide, additional immunohistochemistry (IHC)-stains are performed to ensure that no metastases are missed. However, these stains come at high additional costs, which may exceed specimen reimbursement. Fortunately, digital pathology is becoming more common, thereby creating an avenue of opportunities for artificial intelligence (AI) assistance. Although the number of studies on (promising) AI-algorithms increases exponentially, studies on actual clinical implementation are lacking. In this single-center prospective trial, we investigated to which extent an artificial intelligence (AI)-assisted clinical workflow for the detection of SN-metastases reduces IHC-use, while maintaining current diagnostic safety standards. Methods We enrolled 190 SN-specimens of 182 patients with invasive or in situ BC from September 2022 to May 2023. SN-specimens were allocated bi-weekly to either the control-arm (n=90) or the intervention-arm (n=100). In the control-arm, SN-specimens were digitally assessed according to the current clinical workflow, while pathologists in the intervention-arm assessed the SN-specimen with the output the 'Metastasis-Detection-App' (Visiopharm©) available. In both groups, IHC was performed in all morphologically negative cases. Main outcome was the relative risk (RR) of IHC-use per detected case of SN-metastases. Case-mix adjustment was performed by log-binomial regression. Results Overall, 59 SN-specimens contained metastases (31.1%). AI-assistance resulted in a significantly lower risk of IHC-use per detected case of SN-metastases (adjusted RR: 0.680, 95% CI: 0.347-0.878). Besides preventing IHC-use, thereby reducing costs, AI-assisted pathologists also spent significantly less time on their assessment of the SN-specimen (3m:41s vs. 6m:04s, $p = 0.028$). Furthermore, the sensitivity of AI-assisted pathologists was up to 30% higher. The AI-assisted pathologists missed two cases of micro-metastases in the intervention arm, one of which was in retrospect highlighted by the algorithm, while in the other case the tumor cells were located in a heavily cauterized area of the HE-slide and therefore only visible on the (serial) IHC-slides. In the control arm, the algorithm in retrospect picked up all micro- and macro-metastases and nearly half of the isolated tumor cells (ITC). In addition, all participating pathologists stated that AI was easy to use, that they felt confident using AI, and

that besides saving them time, AI made their work more enjoyable. Cost reductions on IHC by AI-assistance depend on laboratory policy (i.e. when and on how many levels IHC is performed), but, at a cost of €25,- per IHC-stain, range from €1.500 to €3.500 per 100 SN's in a scenario where IHC is performed in all morphologically negative cases. In a scenario where IHC is only performed in patients in whom finding ITC has clinical consequences (i.e. patients who received neoadjuvant treatment), cost savings on IHC range from €7.500-€12.500 per 100 SNs, depending on laboratory policy. Conclusion AI-implementation for the detection of SN-metastases in BC-patients leads to a significant reduction of IHC-use and subsequent costs, while saving pathologists time and making their work more enjoyable. Importantly, AI-implementation during this trial was safe and patients were not at risk of an inferior diagnosis. By doing this trial alone, an estimated €3,000 on IHC-use was saved. Such tangible cost savings are crucial to build a viable business case for AI implementation in diagnostic pathology.

PS03-07

Morphometric signature identifies ductal carcinoma in situ of the breast with low risk of progression to invasive breast cancer

Presenting Author(s) and Co-Author(s):

M. Sobral-Leite. Netherlands Cancer Institute, Amsterdam, Noord-Holland, Netherlands

S. Castillo. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Vonk. Netherlands Cancer Institute, Amsterdam, Netherlands

X. Melillo. Netherlands Cancer Institute, Amsterdam, Netherlands

N. Lam. Netherlands Cancer Institute, Amsterdam, Netherlands

B. de Bruijn. Netherlands Cancer Institute, Amsterdam, Netherlands

Y. Hagos. The Institute of Cancer Research, London, United Kingdom

J. Sanders. Netherlands Cancer Institute, Amsterdam, Netherlands

M. Almekinders. Netherlands Cancer Institute, Amsterdam, Netherlands

L. Visser. Netherlands Cancer Institute, Amsterdam, Netherlands

E. Groen. Netherlands Cancer Institute, Amsterdam, Netherlands

C. Van der Borden. Netherlands Cancer Institute, Amsterdam, Netherlands

P. Kristel. Netherlands Cancer Institute, Amsterdam, Netherlands

E. Caner. University Hospital Basel, Basel, Switzerland

L. Azarang. Netherlands Cancer Institute, Amsterdam, Netherlands

Y. Yuan. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

R. Menezes. Netherlands Cancer Institute, Amsterdam, Netherlands

E. Lips. Netherlands Cancer Institute, Amsterdam, Netherlands

J. Wesseling. Netherlands Cancer Institute, Amsterdam, Netherlands

G. PRECISION Consortium. Netherlands Cancer Institute, Amsterdam, Netherlands

Background. Ductal carcinoma in situ (DCIS) is a frequently found precursor of invasive breast cancer (IBC). However, the majority of DCIS will never progress to IBC. As we cannot distinguish yet which DCIS will remain indolent ('harmless') from those that might progress in the future to IBC, almost all women with DCIS are intensively treated by surgery, often followed by radiotherapy. This brings an urgent clinical need to learn distinguishing harmless from potentially progressive DCIS to save many women with indolent DCIS the burden of unnecessary overtreatment. **Aim.** We aimed to investigate if the geometry and spatial configuration of DCIS ducts in Hematoxylin-Eosin (H&E) stained tissue sections are related to the risk of progression of DCIS to ipsilateral IBC (iIBC). **Methods.** We obtained data from a population-based cohort of women diagnosed with primary DCIS between 1989 and 2004 in the Netherlands, treated with breast conserving surgery (BCS) only and a median follow-up time of 12 years. A nested case-control study (n=689) was designed in which patients diagnosed with iIBC recurrences during follow-up were considered as "cases" (n= 226) and those with no subsequent iIBC as "controls" (n=463). The DCIS and stroma regions were digitally annotated on H&E-stained whole slide images (WSIs) by a pathologist as ground truth for the deep learning neural network of HALO AI module (IndicaLabs). We developed a computational pipeline to automatically detect and measure stroma areas, DCIS ducts, and the nucleus of

their cells. We validated the accuracy of DCIS detection in H&Es WSIs from an external study, in which DCIS regions were digitally annotated by an independent pathologist (Translational Breast Cancer Research Consortium, TBCRC). We classified cases and controls according to morphological measurements using logistic ridge regression with double-loop cross-validation, followed by hierarchical clustering. The risk of subsequent iIBC after primary DCIS diagnosis was evaluated by multivariate Cox proportional hazards models. Results. The accuracy of DCIS detection performed by the computational pipeline was compared with pathologist annotations in 20 slides from the TBCRC study. Results showed a satisfactory DCIS overlap area agreement of 0.76 (0.68 – 0.83). We applied the DCIS computational pipeline on the case-control series. We obtained 15 morphological measurements for each DCIS duct, such as duct area, cell density, distance between ducts, average nucleus area, etc. We calculated 8 distribution parameters from each measurement in each WSI, including median and range. After leaving out redundant variables, 55 unique morphometric variables were obtained, representing the heterogeneity of DCIS ducts per WSI. The c lassifier revealed a median area-under the curve (AUC) of 0.66 (0.55-0.77) to predict 5-years free of iIBC, 0.59 (0.50-0.67) to predict 10-years and 0.60 (0.52-0.68) to predict 15-years. The 30 variables with the highest association with outcome were used to build four morphometric signatures. Signature number 1, which is characterized by lesions with small-sized ducts, a lower number of cells and a lower DCIS/stroma area ratio, showed a significant lower risk of developing iIBC compared to the other three signatures in a multivariate Cox regression model including grade, ER, COX-2 and HER2 expression: HR = 0.56 (0.28-0.78 95%CI). Conclusion. We developed a computational pipeline able to detect and measure DCIS ducts in H&E WSIs with high accuracy and reproducibility. DCIS lesions presenting the morphometric signature of small-sized DCIS ducts have a very low chance to progress to invasive breast cancer. After successful validation, our morphometric method will serve as a robust and easy to implement biomarker for de-escalation strategies in DCIS, and as such, could limit unnecessary overtreatment in the near future.

PS03-08

Spatial biomechanics determines fate in breast cancer

Presenting Author(s) and Co-Author(s):

S. Nizzero. Houston Methodist Research Institute, Houston, Texas, United States

M. Pelaez Soni. Houston Methodist Research Institute/Rice University, United States

G. Zaugg. Artidis, United States

M. Gachechiladze. Artidis, United States

Y. Xu. Houston Methodist Research Institute, United States

L. Zhang. Houston Methodist Research Institute, United States

J. Zheng. Houston Methodist Research Institute, United States

B. Menegaz. Baylor College of Medicine, United States

L. Jordan. University of Dundee/NHS Tayside, United States

C. Purdie. University of Dundee/NHS Tayside, United States

P. Quinlan. University of Nottingham, United Kingdom

C. Nagi. Baylor College of Medicine, United States

K. Sepulveda. Baylor College of Medicine, Texas, United States

P. Oertle. Artidis, United States

T. Appenzeller. Artidis, United States

M. Loparic. Artidis, United States

Z. Wang. Houston Methodist Research Institute, United States

S. Chen. Houston Methodist Research Institute, United States

V. Cristini. Houston Methodist Research Institute, United States

M. Plodinec. Artidis, United States

A. Thompson. Baylor College of Medicine, Houston, Texas, United States

Background: With the recent advancements of spatial omics, it has become increasingly recognized that spatial analysis of tumor architecture is key to decipher the heterogeneous intratumoral relationships between different tumor components and provide better understanding of cancer therapy resistance, as well as help to identify potential targets for personalized therapy. The challenge of the discovery and implementation of such biomarkers still lays in the technological and methodological difficulties, and their translation into clinical practice. In parallel a major advancement in cancer research has been the recognition of the importance of cancer biomechanical properties in cancer progression, metastasis, and therapy response. Methods: We developed a new computational platform to identify biomechanical drivers of cancer outcome from spatial omics data. We used it to identify recurring spatial patterns of these markers within the tumor microenvironment, and define the spatial scale of heterogeneity of such patterns. Our dataset consists in 700 primary breast cancer baseline samples analyzed with two 30-marker imaging mass cytometry panels to identify cancer, immune, and stromal cells and structures and their biomechanical states. Our patient cohort includes 20+ years of follow up, with up to 6 samples per patient from 64 patients alive 12 years post diagnosis, and 49 patients lost to breast cancer deaths. Patients were treated with surgery, radiation, chemotherapy, endocrine therapy, or combinations of these post-surgery. Based on this approach, we derived a new three-parameter quantitative metric of preferential spatial co-

localization between different cells or structures, and we use this metric to stratify patients into responders and non-responders with the aid of single and multivariate survival analysis. Finally, we include a correlation with Atomic Force Microscopy to identify the mechanical signature of these driving patterns in breast cancer. Results: Our work enabled the identification of tumor-immune-stromal spatial patterns that drive breast cancer outcome and their spatial scale. Among our results, we were able to further define spatial regions of hypoxia-driven EMT. We found these regions to be usually on the scale of 50 μ m radius, and enriched in presence of unspecified immune cells. They are also more frequent in ER+ areas, with high NaKATPase activity. Our analysis also shed light on the controversy on the role of fibroblasts. We have found that the presence of a strong, spatially structured stroma, in fibroblast-rich regions is a strong predictor of positive outcome. Similarly, in our analysis collagen cross-linking emerges as a positive control factor in Vimentin-rich microenvironments, offering new interpretation to the role of the ECM structure. Importantly, our first principle approach allows for the identification of driving structures beyond heterogeneity, and thus enables easy extension to additional datasets. Finally, when correlating these patterns with Atomic force microscopy measurements, we can clearly see that patterns predictive of poor survival present a clear heterogeneous stiffness signature, as opposed to a very homogenous good survival pattern signature. Conclusion: These results confirm the importance of spatial distribution of biomechanical drivers in cancer, offering new avenues of physics-based therapeutic targets. Our results also offer a solid base to inform machine learning algorithms on how to significantly parametrize spatial patterns in breast cancer for clinical significance. Furthermore, we demonstrate for the first time the use of Atomic Force Microscopy as a single biomarker for these patterns in breast cancer with a direct correlation based on pathology matching.

PS03-09

Age-related normal breast tissue features differ in women with germline BRCA1/2 mutations

Presenting Author(s) and Co-Author(s):

A. Grigoriadis. King's College London, Comprehensive Cancer Centre, Faculty of Life Sciences and Medicine, London; School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom

M. Parreno-Centeno. King's College London, United States

S. Chen. King's College London, United States

G. Verghese. King's College London, United States

E. Lips. NCI, United States

C. Gillett. King's Health Partners Cancer Biobank, King's College London, United States

L. Jones. Barts Cancer Institute, United States

S. Pinder. School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom

Ageing, a breast cancer risk factor, can be reflected in histologically normal breast tissue (NBT). However, the relationship between age-related histological features and cancer risk is not fully understood. We propose that biological and microscopic features can be identified in seemingly histologically NBT in gBRCA1/2m carriers that are indicative of the earliest tissue changes of breast cancer, potentially as a result of accelerated tissue ageing. To study NBT, we have put in place a unique and scalable repository, named OASIS, storing currently >2,000 digitised whole slide images (WSI) of H&E-stained NBT from individuals with long clinical follow-up. These tissues are from individuals with a spectrum of risk for developing breast cancer and derived from reduction surgery from non-gBRCA1/2m carriers, risk reducing mastectomies, and from contralateral and peri-tumoural NBT from gBRCA1/2m carriers and women with breast cancer. Across 6 NBT resources, 70 selected WSIs were manually annotated for epithelial cells, fibrous stroma and adipocytes, resembling the "ground truth". Extensive comparisons of different tile sizes, tile overlapping ratios, stain normalisation techniques and deep learning (DL) feature extractors were conducted to implement a Tissue-Classifer, which achieved 95% accuracy in 3-fold cross-validation. Based on the MobileNet architecture, a DL-framework achieved a sensitivity of 81.2% and specificity of 81.8% (84.7% AUC) in predicting Tissue-Age based on discernible histological patterns in healthy women. In gBRCA1/2m carriers, we discovered features of accelerated tissue ageing (e.g. degree of lobule involution), indicating that the biological NBT age differs from their chronological age. Our DL-based framework robustly captured histological patterns to predict tissue components and age. The global organisation of these patterns showed variations in WSIs of women with different risks of developing breast cancers, which may provide new insights into premalignant alterations in NBT.

PS01-01

Feasibility and oncological safety of targeted axillary dissection or sentinel lymph node biopsy in patients with clinically node-positive disease after neoadjuvant chemotherapy in the prospective MF-1803 NEOSENTITURK-study

Presenting Author(s) and Co-Author(s):

- N. Cabioğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Bakırköy, Istanbul, Turkey
- H. Karanlık. Istanbul University Institute of Oncology, Department of Surgical Oncology, Istanbul, Turkey
- M. Gulcelik. University of Health Sciences, Gulhane Hospital, Department of Surgery, Turkey
- H. Kocer. Sakarya University, Department of Surgery, Turkey
- M. Muslumanoğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey
- A. İgci. American Hospital, Department of Surgery, Istanbul, Turkey
- M. Tukenmez. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey
- C. Uras. Acibadem University, School of Medicine, Department of Surgery, United States
- E. Ozkurt. Department of Surgery, Florence Nightingale Hospital, Istanbul, Turkey
- G. Akgul. University of Health Sciences, Gulhane Hospital, Department of Surgery, Turkey
- S. Emiroglu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey
- S. Bademler. Istanbul University Institute of Oncology, Department of Surgical Oncology, Istanbul, Turkey
- A. Dağ. Mersin University, Faculty of Medicine, Department of Surgery, Turkey
- D. Trabulus. Bahcesehir University, Department of Surgery, Turkey
- N. Yıldırım. American Hospital, Department of Surgery, Turkey
- G. Karadeniz Cakmak. Zonguldak Bulent Ecevit University, Department of Surgery, Turkey
- E. Sen Oran. Basaksehir State Hospital, Department of Surgery, Istanbul, Turkey
- H. Kara. Acibadem University, School of Medicine, Istanbul, Turkey
- G. Basaran. Acibadem University School of Medicine, Altunizade Hospital Breast Health Center, Turkey
- A. Altinok. Medical Park Hospital, Department of Radiation Oncology, Istanbul, Turkey
- M. Ugurlu. Marmara University School of Medicine, Department of Surgery, Istanbul, Turkey
- K. Senol. Uludag University, Faculty of Medicine, Department of Surgery, Turkey
- B. Zengel. University of Health Sciences, İzmir Bozyaka Hospital, Department of Surgery, United States
- N. Karaman. Ankara Oncology Hospital, Department of Surgery, Turkey
- E. Varol. Department of General Surgery, Faculty of Medicine, Kocaeli University Turkey University, Turkey
- E. Dilege. Koç University, Faculty of Medicine, Department of Surgery, Turkey
- Y. Bolukbasi. Department of Radiation Oncology, Faculty of Medicine, Koc University, Istanbul, Turkey
- A. Akcan. Department of Surgery, Faculty of Medicine, Erciyes University, Kayseri, Turkey

- Y. Ersoy. Bezmialem Vakıf University, Department of Surgery, Turkey
- A. Soyder. Acibadem University, Faculty of Medicine, Department of Surgery, Turkey
- S. Ozbas. Breast Health Working Group International, United States
- M. Velidedeoglu. Istanbul University Cerrahpasa Faculty of Medicine, Department of Surgery, Turkey
- B. Ozcinar. Istanbul University Istanbul Medical Faculty, Turkey
- N. Utkan. Kocaeli University, Faculty of Medicine, Department of Surgery, Turkey
- B. Citgez. Atasehir Memorial Hospital, Istanbul, United States
- B. Celik. Department of General Surgery, Faculty of Medicine, Koc University, Turkey
- L. Zer. Department of Surgery, Atasehir Florence Nightingale Hospital, Istanbul Turkey, Koc University, Istanbul, Turkey
- G. Sakman. Department of General Surgery, Faculty of Medicine, Cukurova University Adana Turkey, Turkey
- L. Yeniay. Ege University, Faculty of Medicine, Department of Surgery, Izmir, Turkey
- L. Dogan. Breast Health Working Group International, United States
- M. Dogan. Department of Medical Oncology, Ankara Oncology Hospital, Ankara, United States
- F. Eroozen. Health Sciences University, Haseki Hospital, Department of Surgery, Turkey
- B. GOKTEPE. Ege University, Medical Faculty, Department of General Surgery, Izmir, Turkey
- O. Agcaoglu. Department of Surgery, Faculty of Medicine, Koc University, Istanbul, Turkey
- T. Kivilcim. Department of General Surgery, Faculty of Medicine, Okan University Istanbul, Istanbul, Turkey
- F. Balci. Department of General Surgery, Sisli Memorial Hospital, Istanbul, Turkey
- B. Gulluoglu. Marmara University School of Medicine, Department of Surgery, Istanbul, Turkey
- A. Polat. Ondokuz Mayıs University, Faculty of Medicine, Department of Surgery, Samsun, Turkey
- K. Ibis. Istanbul University, Istanbul Faculty of Medicine, Department of Radiation Oncology, Istanbul, Turkey
- V. Ozmen. Florence Nightingale Sisli Hospital, Department of Surgery, Istanbul, Turkey

Background:

Previous prospective studies reported decreased false negative rates in patients presenting with T1-3/cN1 disease, with the removal of 2 or more sentinel lymph nodes (SLNs), using combined technique for SLN biopsy (SLNB), and by targeted axillary dissection (TAD) in initially clinically node-positive patients after neoadjuvant chemotherapy (NAC). The aim of this prospective study is to compare the feasibility and the oncological safety of TAD with SLNB in patients with cN-positive/ycN0 breast cancer following NAC in a prospective study.

Methods:

This study included patients with a cT1-4N1-3M0 disease from the prospective multicenter MF1803 NEOSENTITURK registry study who were treated either SLNB- or TAD-alone without ALND. TAD included removing the biopsy-proven positive LN marked mostly with a clip as SLN or non-SLN. All patients had nodal and regional irradiation.

Results:

Between 2019 to 2021, 976 patients with cT1-4N1-3M0 disease from 37 centers underwent

either SLNB-alone (n=620) or TAD-alone (n=356). Patients with TAD (median age: 46, range: 24-76) and SLNB (median age:46, range: 21-80) have shown a similar age distribution. The median number (range, 25%-75%) of SLNs and total LNs and total metastatic LNs removed were 3 (2-4), 4(3-6), and 1 (1-2), respectively.

Patients with TAD were more likely to have cT1-2 disease (91.9% vs 78.7%, $p < 0.001$), cN1 disease (85.7% vs 78.5%, $p < 0.006$), a breast conservative surgery (66.0% vs 51.3%, $p < 0.001$), the combined technique for mapping (44.1% vs 22.3%, $p < 0.0001$), and a decreased median (IQR) lymph node ratio as calculated by the total positive lymph node number to the total lymph node number (0.29:0.20-0.40 vs 0.33: 0.20-0.50; $p=0.033$). Of note, there was a trend for the decreased non-sentinel lymph node positivity in the TAD-group compared to the SLNB-group that did not reach the statistical significance (TAD: 10% vs SLNB: 19%, $p=0.07$). However, no significant difference could be found in pathological characteristics including tumor type, breast pCR, non-luminal disease such as HER2-positivity or triple negative disease or presence of low volume metastatic disease (ITC or micrometastasis), and extracapsular extension (Table 1).

Of note, patients with ypN-positive disease (n=351) were more likely to have SLNs (ypN+, 3.7 ± 1.7 vs ypN0, 3.4 ± 1.7 , $p=0.008$) or total LNs (ypN+, 4.7 ± 1.9 vs ypN0, 3.4 ± 1.9 , $p=0.001$) removed compared to those with ypN0 (n=635). Among those with ypN0 disease, patients with TAD were more likely to have LNs removed compared to those with SLNB (TAD, 4.2 ± 1.9 vs 3.9 ± 1.9 , $p=0.034$) (Table 2). Of those with ypN+, patients with TAD were more likely to have SLNs compared to those with SLNB (TAD, 3.9 ± 1.7 vs 3.5 ± 1.7 , $p=0.062$), whereas patients with SLNB were more likely to have non-SLNs removed compared to those with TAD (TAD, 2.3 ± 1.4 vs 2.9 ± 1.5 , $p=0.028$).

At a mean follow-up of 28.8 months (± 12.1), the ipsilateral axillary and locoregional recurrence rates were 0.2% (n=2) and 0.4% (n=4) in the TAD-group and SLNB_group, respectively. Of note, no significant difference could be found in ipsilateral axillary, locoregional, and systemic recurrences between cohorts treated with TAD-alone vs SLNB-alone (Table 3).

Conclusion:

Our findings suggest that TAD might be more feasible in ypN+ patients which resulted in a decreased lymph node ratio and decreased non-SLN positivity. In ypN0 patients, TAD may contrary cause unnecessary lymph node removal that might be important in arm function and lymphedema development. Furthermore, our findings with short-term follow-up indicate that axillary and locoregional recurrences were observed at very low rates in a selected group of ypN0 patients treated with SLN- or TAD without ALND. Therefore, omission of ALND could be safely considered for patients with limited nodal involvement (<2 LNs) as long as <3 LNs removed and nodal radiotherapy provided.

Table 1. Clinicopathologic Characteristics According to the Axillary Surgery: Targeted Axillary Dissection (=TAD) versus Sentinel Lymph Node Biopsy (=SLNB)

Table 1. Clinicopathologic Characteristics According to the Axillary Surgery: Targeted Axillary Dissection (=TAD) vs Sentinel Lymph Node Biopsy (=SLNB)

Characteristics	Total (n=976) n(%)	TAD (n=356) n(%)	SLNB (n=620) n(%)	p-Value
Median follow-up (months, median IQR)	27(18-38)	28(18-39)	27(19-37)	
Mean follow-up (months, ±SD)	28.8±12.1	29.3±15.5	28.6±11.9	
Median age (minimum-maximum)	46(24-80)	46(24-76)	46(21-80)	0.835 ^a
Clinical T stage				<0.001 ^{ba}
cT1/2	815(83.5)	327(91.9)	488(78.7)	
cT3/4	161(16.5)	29(8.1)	132(21.3)	
Clinical N stage				0.006 ^{ba}
cN1	792(81.1)	305(85.7)	487(78.5)	
cN2-3	184(18.9)	51(14.3)	133(21.5)	
Type of Breast Surgery				<0.001 ^{ba}
Breast Conserving Therapy	553(56.7)	235(66)	318(51.3)	
Mastectomy	423(43.3)	121(34)	302(48.7)	
pCR (breast)				0.927 ^b
Complete	445(45.6)	163(45.8)	282(45.5)	
Partial	531(54.4)	193(54.2)	338(54.5)	
pCR (axilla)				0.062 ^b
Complete	635(65.1)	245(68.8)	390(62.9)	
Partial	341(34.9)	111(31.2)	230(37.1)	
pCR (breast+axilla)				0.255 ^b
Complete	391(40.1)	151(42.4)	240(38.7)	
Partial	585(59.9)	205(57.6)	380(61.3)	
Tumor Subtype (by immunohistochemistry)				0.557 ^b
Luminal	672(68.9)	249(69.9)	423(68.2)	
Non-luminal	304(31.1)	107(30.1)	197(31.8)	
Sentinel Lymph Node (SLN) Methodology				<0.001 ^{ba}
Blue Dye or radioisotope	681(69.8)	199(55.9)	482(77.7)	
Combined (Blue dye and radioisotope)	295(30.2)	157(44.1)	138(22.3)	
Characteristics of metastatic LNs removed (n=341)				0.807 ^b
Isolated tumor cellsµmetastasis	163(47.8)	52(46.8)	111(48.3)	
Macrometastasis	178(52.2)	59(53.2)	119(51.7)	
No	289(84.8)	95(85.6)	194(84.3)	
Non-SLN positivity(n=294)				0.073 ^b
Yes	48(16.3)	14(11.7)	34(19.5)	
No	246(83.7)	106(88.3)	140(80.5)	
Number of SLNs (median IQR)	3(2-4)	3(2-5)	3(2-4)	0.180
Number of metastatic SLNs (median IQR)	1(1-2)	1(1-2)	1(1-2)	0.551
Number of non-SLNs (median IQR) (n=294)	2(1-3)	2(1-3)	2(1-4)	0.320
Number of metastatic non-SLNs (median IQR) (n=48)	1(1-2)	1(1-1)	1(1-2)	0.092
Number of total LNs (median IQR)	4(3-6)	4(3-6)	4(3-6)	0.085
Number of total metastatic LNs (median IQR)	1(1-2)	1(1-2)	1(1-2)	0.222
Lymph Node Ratio(LNR), median(IQR)	0.33(0.2-0.5)	0.29(0.2-0.4)	0.33(0.2-0.5)	0.033 ^{ba}

a: Mann-Whitney U Test, b: Chi-Square Tests. *p<0.05; IQR (P₂₅-P₇₅): Inter Quantile Range

Table 2. Clinicopathologic Characteristics According to the Pathological Nodal Status

Table 2. Clinicopathologic Characteristics According to the Pathological Nodal Status

Characteristics	ypN			p-value
	All	ypN0 (n=635)	ypN+ (n=341)	
Number of sentinel lymph nodes (SLNs) (median IQR)	3(2-4)	3(2-4)	3(2-5)	0.008*
mean±SD	3.5±1.7	3.4±1.7	3.7±1.7	
Number of non-SLNs (median IQR) (n=294)	2(1-3)	2(1-3)	2(2-3)	0.090
mean±SD	2.5±1.5	2.4±1.5	2.7±1.5	
Number of total lymph nodes (LNs) (median IQR)	4(3-6)	4(3-5)	5(3-6)	<0.001*
mean±SD	4.2±1.9	3.4±1.9	4.7±1.9	
		ypN0		
	All	TAD (n=245)	SLNB (n=390)	p-value
Number of SLNs (median IQR)	3(2-4)	3(2-4)	3(2-4)	0.590
mean±SD	3.4±1.7	3.4±1.8	3.4±1.7	
Number of non-SLNs (n=154)	2(1-3)	2(1-3)	2(1-3)	0.358
mean±SD	2.4±1.5	2.5±1.5	2.4±1.5	
Number of total LN	4(3-5)	4(3-5)	4(2-5)	0.034*
mean±SD	4.0±1.9	4.2±1.9	3.9±1.9	
		ypN+		
	All	TAD (n=111)	SLNB (n=230)	p-value
Number of SLNs	3(2-5)	4(3-5)	3(2-5)	0.062
mean±SD	3.7±1.7	3.9±1.7	3.5±1.7	
Number of metastatic SLNs	1(1-2)	1(1-2)	1(1-2)	0.519
mean±SD	1.4±0.8	1.4±0.8	1.4±0.8	
Number of non-SLNs (n=140)	2(2-3)	2(1-3)	2(2-4)	0.028*
mean±SD	2.7±1.5	2.3±1.4	2.9±1.5	
Number of metastatic non-SLNs (n=48)	1(1-2)	1(1-1)	1(1-2)	0.092
mean±SD	1.6±1.1	1.3±0.8	1.7±1.1	
Number of total LNs	5(3-6)	5(4-6)	5(3-6)	0.265
mean±SD	4.7±1.9	4.9±1.7	4.7±1.9	
Number of total metastatic LNs	1(1-2)	1(1-2)	1(1-2)	0.212
mean±SD	1.6±0.9	1.5±0.9	1.6±0.9	

Table 3. Locoregional and systemic recurrences in cT1-4N1-3 patients treated with Targeted Axillary Dissection (=TAD) or Sentinel Lymph Node Biopsy (=SLNB) (Nf976)

Table 3. Locoregional and systemic recurrences in cT1-4N1-3 patients treated with Targeted Axillary Dissection (=TAD) or Sentinel Lymph Node Biopsy (=SLNB) (N=976)

Variables	All (n=976) n(%)	TAD (n=356) n(%)	SLNB (n=620) n(%)	p-value*	ypN0 (n=635) n(%)	ypN(+) (n=341) n(%)	p-value*
Locoregional recurrence				0.999			0.999
Yes	4(0.4)	1(0.3)	3(0.5)		3(0.5)	1(0.3)	
No	972(99.6)	355(99.7)	617(99.5)		632(99.5)	340(99.7)	
Ipsilateral Axillary recurrence				0.999			0.545
Yes	2(0.2)	1(0.3)	1(0.2)		2(0.3)	0(0)	
No	974(99.8)	355(99.7)	619(99.8)		633(99.7)	341(100)	
Systemic recurrence				0.121			0.225
Yes	38(3.9)	9(2.5)	29(4.7)		21(3.3)	17(5)	
No	938(96.1)	347(97.5)	591(95.3)		614(96.7)	324(95)	
Mortality				0.999			0.700
Yes	7(0.7)	2(0.6)	5(0.8)		4(0.6)	3(0.9)	
No	969(99.3)	354(99.4)	615(99.2)		631(99.4)	338(99.1)	

*Fisher's Exact Test
 locoregional recurrence=axillary, peripheric lymphatic, mammaria interna and contralateral axillary.

Disclosure(s):

Neslihan Cabrioğlu: No financial relationships to disclose

Poster Spotlight Session 1: Less is More: Minimizing Surgical Treatment in Patients with Early Stage Breast Cancer

Presenting Author(s) and Co-Author(s):

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

Disclosure(s):

Tari A. King, MD: Consulting Fees (e.g., advisory boards): Exact Sciences (Genomic Health) (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Exact Sciences (Genomic Health) (Ongoing)

PS01-02

Long-term outcomes of sentinel lymph node biopsy following neoadjuvant chemotherapy for initially node-positive breast cancer: A systematic review and meta-analysis.

Presenting Author(s) and Co-Author(s):

M. Rana. University of Saskatchewan, Canada, Regina, Saskatchewan, Canada

A. Weiss. Division of Surgical Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States

A. Laws. Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, United States

C. Mita. Harvard Medical School, Harvard University, Boston, Massachusetts, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

Background:

Sentinel lymph node biopsy (SLNB) alone is now frequently offered to women with initially node-positive breast cancer who convert to pathologically node negative (nodal pCR) following neoadjuvant chemotherapy (NAC), despite limited long-term data regarding the oncologic safety of this approach. The aim of this meta-analysis was to evaluate the long-term oncologic outcomes associated with SLNB alone following NAC for initially node-positive breast cancer.

Methods:

A systematic review and meta-analysis was conducted according to PRISMA guidelines. Medline (Ovid), Embase, and Cochrane Central Registry were systematically searched for studies comparing women undergoing SLNB or ALND following NAC for initially clinically node-positive breast cancer. Included studies reported one of the following outcomes: axillary recurrence (AR), locoregional recurrence (LRR), disease-free survival (DFS) or overall survival. A random effects meta-analysis was used to calculate weighted pooled effect estimates (risk ratios, RR) for all outcomes. Variability across studies due to heterogeneity was estimated using I^2 statistics. Subgroup analysis was performed by length of follow-up for each study. Risk of bias within studies was assessed using the Newcastle-Ottawa Scale (NOS).

Results:

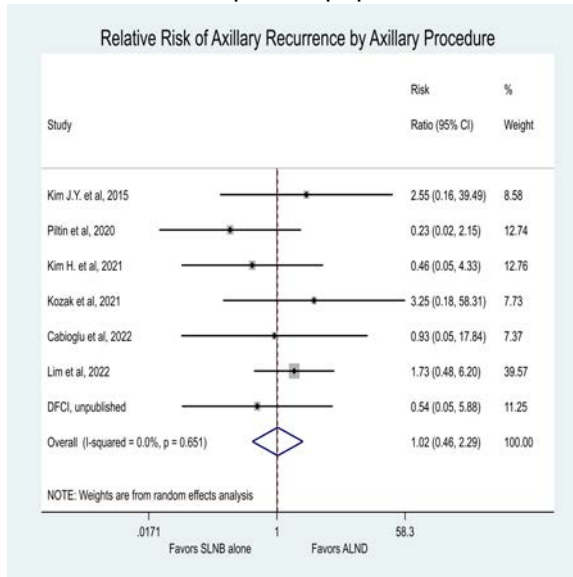
Data for participants undergoing treatment between 2004 and 2022 was captured across studies. The median age of women treated with NAC for initially node-positive breast cancer ranged from 46 to 60 years. The median follow-up time ranged from 19.5 to 108 months across included studies. Nine observational studies were eligible for meta-analysis. No studies were excluded from the analysis on the basis of quality: Newcastle-Ottawa Scale scores ranged from 6 to 9 (maximum possible score of 9).

Rates of axillary recurrence (AR) were low across all included studies (range 0.0% to 5.6%). For AR, data for 2,882 patients from 7 studies was quantitatively synthesized (SLNB=1,964; ALND=917). For LRR, data for 2,629 patients from 7 studies was quantitatively synthesized (SLNB=1,857; ALND=771). No significant differences were observed in AR between patients undergoing SLNB alone versus ALND following NAC for initially node-positive

breast cancer: pooled RR 1.02 (95% CI: 0.46-2.29, $I^2=0.0\%$). Similarly, no significant differences were observed in LRR (RR 0.70, 95% CI: 0.45-1.10, $I^2=0.0\%$), DFS (RR 0.77, 95% CI: 0.55-1.08, $I^2=0.0\%$), nor overall mortality (RR 0.66, 95% CI: 0.33-1.33, $I^2=0.0\%$) between the SLNB and ALND groups.

Conclusions:

Among patients who convert to node-negative following NAC, this meta-analysis suggests that SLNB alone does not result in significantly different oncologic outcomes compared to ALND, and that de-escalation of axillary surgery to SLNB alone in this context may be safely considered in this patient population.



Disclosure(s):

Mariam Rana, BSc MBBS FRCSC: No financial relationships to disclose

Tari A. King, MD: Consulting Fees (e.g., advisory boards): Exact Sciences (Genomic Health) (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Exact Sciences (Genomic Health) (Ongoing)

PS01-03

What to expect from the No axillary surgical treatment for lymph node-negative patients after ultra-sonography [NAUTILUS] trial (KBCSG-21): Clinicopathologic characteristics and axillary lymph node status of enrolled patients

Presenting Author(s) and Co-Author(s):

J. Ryu. Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam, Ulsan-gwangyoksi, Republic of Korea

H. Lee. Seoul National University Hospital, United States

S. Ahn. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

I. Chung. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

S. Lee. National Cancer Center, Goyang, Republic of Korea

S. Park. Yonsei University college of medicine, United States

W. Lim. Department of Surgery, Ewha Womans University School of Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

J. Lee. Samsung Medical Center, Seoul, Republic of Korea

E. Kang. Seoul National Univ. Hospital, Surgery, Republic of Korea

J. Chang. Department of Radiation Oncology, Seoul National University Hospital, Seoul, Republic of Korea

J. Chang. Department of Radiology, Seoul National University College of Medicine, United States

W. Moon. Department of Radiology, Seoul National University College of Medicine, Seoul, South Korea

W. Han. Seoul National University Hospital, Seoul, Republic of Korea

E. Kim. Seoul National University Bundang Hospital, Seoul National University College of Medicine, United States

Purpose:

The primary role of sentinel lymph node biopsy (SLNB) for early breast cancer (BC) is axillary staging. In terms of clearance of axillary disease or prevention of recurrence, its role may be limited considering the low axillary recurrence rate of less than 2% even though false-negative rates are 5-10% and the 25% additional axillary lymph node (ALN) detection in the ALND arms of the ACOSOG Z0011 and AMAROS trials. The NAUTILUS trial (NCT04303715) randomized cT1-2/N0 BC patients planned for breast-conserving surgery to evaluate the non-inferiority of omitting SLNB regarding 5-year invasive disease-free survival. The secondary endpoints are overall survival, distant metastasis-free survival, axillary recurrence rate, and quality of life of the patients. We aimed to investigate the clinicopathologic characteristics and ALN status of the subjects enrolled in the NAUTILUS trial.

Methods:

NAUTILUS trial randomized 1,734 subjects into SLNB or no-SLNB arms from September 2020 to October 2022. Axillary ultrasonography was mandatory to determine clinical N0, defined as

no suspicious ALN or no tumor on ultrasound-guided biopsy of suspicious ALN. Clinicopathologic variables and the ALN status of the SLNB arm were analyzed.

Results:

Among 1,734 enrolled subjects, 828 (50.3%) and 818 (49.7%) subjects in the SLNB and no-SLNB arms, respectively, were included for analysis. Clinical and pathologic T stage, hormonal receptor/HER2 status, histologic grade, age, menopausal status, and Ki-67 were evenly distributed between the two groups (p = 0.554, 0.350, 0.056, 0.369, 0.623, 0.725 and 0.214, respectively). Median age was 55.3 (range, 48.0-62.0) years, and 661 (40.2%) were premenopausal. Overall, 30 (1.8%), 1,382 (84.0%), and 229 (13.9%) subjects were pTmic, pT1, and pT2, respectively, and median tumor size was 1.3 cm (range, 0.1-5.0). In the SLNB group, 94 (11.4%) had ALN metastasis, of which 9 (1.1%), 78 (9.4%), and 5 (0.6%) were pN1mic, pN1, and pN2-3, respectively (Table 1). According to pathologic tumor size, 5.8% (16/279), 11.4% (48/421), and 23.8% (30/126) were ALN positive for ≤ 1.0 cm, >1.0cm & ≤ 2.0 cm, and > 2.0 & ≤ 5.0 cm, respectively. The clinical and pathologic tumor size distribution among subjects with ALN metastasis were 23 (24.5%), 43 (45.7%), 9 (9.6%) and 16 (17.0%), 48 (51.1%), 30 (31.9%), respectively, for ≤ 1.0 cm, >1.0cm & ≤ 2.0 cm, and > 2.0 & ≤ 5.0 cm (Table 2). Among them, 12 (12.8%) received subsequent ALND. There was no difference in ALN metastasis rate according to molecular subtype, histologic grade, age, menopausal status, and Ki-67 (p= 0.812, 0.204, 0.671, and 0.101, respectively).

Conclusions:

The NAUTILUS trial completed enrollment of 1,734 subjects, among which 1,646 are available to analyze basic clinicopathologic characteristics. The trial included 229 (13.9%) pT2 and 661 (40.2%) premenopausal subjects and is expected to show the impact of SLNB omission in these subgroups. Data lock is expected in October 2027.

Patients characteristics

	SLNB, n (%)	No-SLNB, n (%)	p-value	95% CI
Demographics				
Age, years	55.3 (48.0-62.0)	55.3 (48.0-62.0)	0.554	54.9 (48.0-62.0)
Menopausal status			0.350	
Premenopausal	332 (40.1%)	329 (40.1%)		
Perimenopausal	152 (18.2%)	152 (18.2%)		
Postmenopausal	344 (41.7%)	337 (41.7%)		
Unknown	0 (0.0%)	0 (0.0%)		
Total	828 (100.0%)	818 (100.0%)		
95% CI	828 (100.0%)	818 (100.0%)		
Pathologic T stage				
pTmic	30 (3.6%)	30 (3.7%)	0.725	2.9 (3.6-4.3)
pT1	1352 (163.4%)	1352 (163.4%)		
pT2	229 (27.7%)	229 (27.7%)		
Unknown	0 (0.0%)	0 (0.0%)		
Total	1611 (194.3%)	1611 (194.3%)		
95% CI	1611 (194.3%)	1611 (194.3%)		
Pathologic N stage				
pN0	1517 (182.1%)	1517 (182.1%)	0.812	1517 (182.1%)
pN1mic	9 (1.1%)	9 (1.1%)		
pN1	78 (9.4%)	78 (9.4%)		
pN2-3	5 (0.6%)	5 (0.6%)		
Unknown	0 (0.0%)	0 (0.0%)		
Total	1609 (193.2%)	1609 (193.2%)		
95% CI	1609 (193.2%)	1609 (193.2%)		
Pathologic tumor size, mm (range)				
≤ 1.0	16 (1.9%)	16 (1.9%)	0.204	16 (1.9%)
> 1.0 & ≤ 2.0	48 (5.8%)	48 (5.8%)		
> 2.0 & ≤ 5.0	30 (3.6%)	30 (3.6%)		
Unknown	0 (0.0%)	0 (0.0%)		
Total	94 (11.3%)	94 (11.3%)		
95% CI	94 (11.3%)	94 (11.3%)		
Pathologic tumor size, mm (range)				
≤ 1.0	23 (2.8%)	23 (2.8%)	0.101	23 (2.8%)
> 1.0 & ≤ 2.0	43 (5.2%)	43 (5.2%)		
> 2.0 & ≤ 5.0	30 (3.6%)	30 (3.6%)		
Unknown	0 (0.0%)	0 (0.0%)		
Total	96 (11.6%)	96 (11.6%)		
95% CI	96 (11.6%)	96 (11.6%)		
Receptor status				
ER	828 (100.0%)	828 (100.0%)	0.204	828 (100.0%)
PR	828 (100.0%)	828 (100.0%)		
HER2	828 (100.0%)	828 (100.0%)		
Unknown	0 (0.0%)	0 (0.0%)		
Total	828 (100.0%)	828 (100.0%)		
95% CI	828 (100.0%)	828 (100.0%)		
Pathologic tumor size, mm (range)				
≤ 1.0	16 (1.9%)	16 (1.9%)	0.671	16 (1.9%)
> 1.0 & ≤ 2.0	48 (5.8%)	48 (5.8%)		
> 2.0 & ≤ 5.0	30 (3.6%)	30 (3.6%)		
Unknown	0 (0.0%)	0 (0.0%)		
Total	94 (11.3%)	94 (11.3%)		
95% CI	94 (11.3%)	94 (11.3%)		

SLNB, sentinel lymph node biopsy; LVI, lymphovascular invasion; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HER2, anti-human epidermal growth factor-2; BCS, breast conserving surgery; TM, total mastectomy; ALND, axillary lymph node dissection

Basic characteristics for sentinel lymph node biopsy group

	No ALN metastasis, n (%)	ALN metastasis, n (%)	p-value	Total, n(%)
Number, %	734 (88.6%)	94 (11.4%)		
Clinical tumour size, cm			0.083	
≤ 1.0	269 (36.6%)	23 (24.5%)		292 (35.3%)
>1.0 and ≤ 2.0	304 (41.4%)	43 (45.7%)		347 (41.9%)
>2.0 and ≤ 5.0	42 (5.7%)	9 (9.6%)		51 (6.2%)
Unknown	119 (16.2%)	19 (20.2%)		138 (16.7%)
Suspicious LN group^a			0.119	
Yes	22 (3.0%)	6 (6.4%)		28 (3.4%)
No	712 (97.0%)	88 (9.4%)		800 (96.6%)
Age			0.671	
<35	10 (1.4%)	0 (0.0%)		10 (1.2%)
35-50	255 (34.7%)	31 (33.0%)		286 (34.5%)
>50	469 (63.9%)	63 (67.0%)		532 (64.3%)
Menopausal status			0.798	
Premenopause	291 (39.6%)	34 (36.2%)		325 (39.3%)
Postmenopause	430 (58.6%)	58 (61.7%)		488 (58.9%)
unknown	13 (1.8%)	2 (2.1%)		15 (1.8%)
Nuclear grade			0.519	
Low	29 (4.0%)	3 (3.2%)		32 (3.9%)
Intermediate	564 (76.8%)	78 (83.0%)		642 (77.5%)
High	135 (18.4%)	13 (13.8%)		148 (17.9%)
Unknown	6 (0.8%)	0 (0.0%)		6 (0.7%)
Histologic grade			0.204	
Low	158 (21.5%)	14 (14.9%)		172 (20.8%)
Intermediate	473 (64.4%)	70 (74.5%)		543 (65.6%)
High	93 (12.7%)	10 (10.6%)		103 (12.4%)
Unknown	10 (1.4%)	0 (0.0%)		10 (1.2%)
Pathologic tumour size, cm			<0.001	
≤ 1.0	258 (35.1%)	16 (17.0%)		274 (33.1%)
>1.0 and ≤ 2.0	373 (50.8%)	48 (51.1%)		421 (50.8%)
>2.0 and ≤ 5.0	96 (13.1%)	30 (31.9%)		126 (15.2%)
Unknown	7 (1.0%)	0 (0.0%)		7 (0.8%)
Molecular Subtype			0.812	
Hormone receptor(+)/HER(-)	636 (86.6%)	83 (88.3%)		719 (86.8%)
Hormone receptor(+)/HER(+)	51 (6.9%)	7 (7.4%)		58 (7.0%)
Hormone receptor(-)/HER(+)	12 (1.6%)	0 (0.0%)		12 (1.4%)
Hormone receptor(-)/HER(-)	30 (4.1%)	3 (3.2%)		33 (4.0%)
unknown	4 (0.5%)	1 (1.1%)		6 (0.7%)
Ki-67			0.101	
≥ 10%	275 (37.5%)	44 (46.8%)		319 (38.5%)
< 10%	459 (62.5%)	50 (53.2%)		509 (61.5%)

a revealed no lymph node metastasis by fine needle aspiration or gun biopsy
ALN, axillary lymph node; LN, lymph node

Disclosure(s):

Jai Min Ryu, MD, PhD: No financial relationships to disclose

PS01-04

To dissect or not to dissect? The surgeon's perspective on the prediction of ≥ 4 axillary lymph node metastasis in cN0 T1-2 breast cancer: A comparative analysis of the per-protocol population of the SINODAR-ONE clinical trial.

Presenting Author(s) and Co-Author(s):

D. Gentile. IRCCS Humanitas Research Hospital, Milan, Lombardia, Italy
W. Gatzemeier. IRCCS Humanitas Research Hospital, United States
A. Sagona. IRCCS Humanitas Research Hospital, United States
E. Barbieri. IRCCS Humanitas Research Hospital, United States
A. Bottini. IRCCS Humanitas Research Hospital, United States
A. Testori. IRCCS Humanitas Research Hospital, United States
V. Errico. IRCCS Humanitas Research Hospital, United States
S. Di Maria Grimaldi. IRCCS Humanitas Research Hospital, United States
G. Caraceni. IRCCS Humanitas Research Hospital, United States
S. Darwish. IRCCS Humanitas Research Hospital, United States
G. Canavese. IRCCS Humanitas Research Hospital, United States
C. Tinterri. IRCCS Humanitas Research Hospital, United States

Objectives

The role of axillary surgery in the management of breast cancer (BC) has evolved considerably over the past decades, with only a few routine indications for axillary lymph node dissection (ALND) remaining in clinical practice. However, de-escalation of axillary surgery, especially in BC patients with 1-3 positive sentinel lymph nodes (SLNs) challenges the recently established criteria for adjuvant treatment (i.e., combination therapy with abemaciclib, endocrine therapy, and chemotherapy in patients with ≥ 4 positive nodes). The question remains as to whether these patients should undergo further ALND to determine whether ≥ 4 nodes are positive. To further investigate the latest controversies in axillary management of BC patients and predict the presence of ≥ 4 axillary lymph node metastasis, we evaluated and compared patients ≥ 4 positive nodes in the per-protocol population of the SINODAR-ONE clinical trial.

Patients in the standard arm (ALND) of the per-protocol population were evaluated, and a comparison of characteristics between patients with ≥ 4 metastatic lymph nodes versus patients with 1-3 metastatic lymph nodes was performed. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Multivariable analysis was performed using a logistic regression model to identify independent predictors of ≥ 4 axillary lymph node metastasis.

Results:

Overall, 403 cN0 T1-2 BC patients in the per-protocol population were randomized to receive ALND. Of these, 65 and 338 patients presented with ≥ 4 or 1-3 axillary lymph node metastasis, respectively. Invasive lobular BC (26.2% versus 14.5% if other histology, odds ratio (OR)=4.185, 95% confidence interval (95%CI)= 1.284-1.443, $p= 0.041$), G3 (38.5% versus 21.3% if G1-2, OR=5.930, 95%CI= 2.134-2.289, $p= 0.015$), pT2 (46.2% versus 30.5% if pT1, OR=5.260, 95%CI= 15.330-16.346, $p= 0.022$), and 2 positive SLNs (32.3% versus 13.6% if 1 positive SLN, OR=13.188, 95%CI= 1.179-1.280, $p< 0.0001$) were found to significantly increase the probability to present ≥ 4 axillary lymph node metastasis at definitive histopathological

evaluation.

Conclusions:

The introduction of abemaciclib and other combination therapies has the potential to impact the surgical management of the axilla. Our results suggest that a minority of cN0 T1-2 BC patients may be understaged if ALND is not performed. However, the improvements and increasing effectiveness of combination therapies may sufficiently control and treat the axillary tumor-burden left behind, potentially reducing the need for extensive axillary surgery, as demonstrated by the promising 3-year oncological outcomes of the SINODAR-ONE trial. Although ALND may still be considered, after multidisciplinary team discussion, in individual patients presenting with specific risk factors for additional axillary disease (lobular, G3, pT2 BC with 2 positive SLNs), our suggestion is that routine ALND is not indicated for systemic therapy decision-making in the upfront surgical setting.

Disclosure(s):

Damiano Gentile: No financial relationships to disclose

PS01-06

The relationship between margin status of <2mm and local recurrence in DCIS patients

Presenting Author(s) and Co-Author(s):

S. Alsafi. Asan Medical Center, Republic of Korea. Al Adan Hospital, Ministry of Health, Kuwait, Bayan, Hawalli, Kuwait

T. Yoo. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

S. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

J. Kim. Asan Medical Center, United States

I. Chung. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

H. Kim. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

B. Ko. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

J. Lee. Asan Medical Center, United States

B. Son. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

H. Lee. University of Ulsan College of Medicine, Asan Medical Center, United States

G. Gong. Asan Medical Center, United States

Background:

There has been controversial evidence regarding adequate margin in breast conserving surgery (BCS) for ductal carcinoma in situ (DCIS). However, the consensus is a surgical margin distance of 2 mm. Moreover, recent recommendations advised on "clinical judgement" approach to re-excision in cases of margin distance < 2mm. The ongoing controversy in DCIS margin compared to invasive cancer margin is due to the differences in post operative management. This is important as margin status is one of the modifiable risk factor for local regional recurrence in DCIS. In our study we evaluated margin distance in patient diagnosed with DCIS who underwent BCS on local recurrence

Methods:

Patients who underwent breast conserving surgery between February 2000 and December 2018 at Asan Medical Center were retrospectively reviewed. Patients with involved resection margins were excluded. Kaplan-Meier survival analysis and Cox proportional hazard models were applied to determine the relationship between negative margin width and local recurrence.

Results:

A total of 1,858 patients were included in the study. Almost half of the patients had a tumor size of 1cm or smaller (n=876, 47.1%). Only 98 (5.3%) patients did not undergo radiation therapy. A negative margin width of < 1mm, < 2mm, < 5mm were all not associated with local recurrence (log-rank test p-value 0.1, 0.1, 0.078, respectively). For patients who underwent radiation therapy, a negative margin of any width was not related to local recurrence. Whereas, for patients who did not undergo radiation therapy, those with margins ≤ 2 mm were significantly more likely to develop local recurrence than those with margins < 2mm (10-yr local recurrence

rate, 16.4% vs 5.5%, respectively; hazard ratio, 5.709; 95% CI, 1.106-29.46, p=0.038).

Conclusion:

A negative margin is not related to local recurrence in DCIS patients who undergo breast conserving surgery with radiation therapy. Routine additional surgery for wider negative margin may only be needed for patients who do not undergo radiation therapy.

Disclosure(s):

Sarah Alsafi, MD: No financial relationships to disclose

PS01-07

Impact of Race and Ethnicity on Recurrence Risk in Patients with Ductal Carcinoma in Situ Treated with Breast-Conserving Surgery

Presenting Author(s) and Co-Author(s):

N. Polidorio. Memorial Sloan Kettering Cancer Center, New York, New York, United States

V. Jones. Memorial Sloan Kettering Cancer Center, United States

V. Sevilimedu. Memorial Sloan Kettering Cancer Center, United States

M. Morrow. Memorial Sloan Kettering Cancer Center, New York, New York, United States

K. Van Zee. Memorial Sloan Cancer Center, New York, New York, United States

A. Barrio. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background:

Among women with invasive breast cancer, clinical presentation, tumor biology and survival vary by race and ethnicity. However, the impact of race and ethnicity on clinical presentation and recurrence risk in women with ductal carcinoma in situ (DCIS) treated with breast-conserving surgery (BCS) has not been well studied. We sought to compare rates of recurrence in women with DCIS across racial and ethnic groups and identify factors associated with recurrence. Methods:

Patients with DCIS treated with BCS from 1978 to 2016 at a single institution were identified. Patients were grouped and analyzed based on self-reported race and ethnicity as: Asian, Hispanic, non-Hispanic Black (Black), non-Hispanic White (White). Individuals with undefined ethnicity were classified by race, while those lacking both race and ethnicity data were excluded. Clinicopathologic characteristics were compared across racial and ethnic groups. The association of race and ethnicity on recurrence risk was analyzed using Kaplan–Meier methods, competing risk analysis and multivariable analysis. Results:

Overall, 4207 cases were included, of which 6% (n= 261) were Asian, 9% (n = 358) Black, 5% (n = 226) Hispanic and 80% (n = 3362) White. Median age was 57 years (IQR 49, 67), 56% received radiotherapy (RT) and 26% received endocrine therapy. Black women with DCIS were older; Asian women were younger (median age: 60 vs 53 respectively, $p < 0.001$). Black women were more likely to have a clinical presentation ($p = 0.006$), and Black and Hispanic women were more likely to require ≥ 3 excisions ($p = 0.006$). The use of RT was most common among Hispanic women ($p = 0.02$).

At a median follow-up of 8.8 years, 602 (14%) had local recurrence (LR) (315 [52%] DCIS; 284 [47%] invasive and 3 [$< 1\%$] unknown). The 10-year rate of LR was 15% and was lower in those treated with RT than without (11% vs 20%, respectively; $p < 0.0001$), despite those receiving RT having more high-risk characteristics. Rates of LR varied significantly by race and ethnicity, with the highest 10-year rate in Black women (25%) compared with Asian (11%), Hispanic (15%) and White (14%) women ($p = 0.03$). This statistically significant difference persisted among the no RT cohort (10-year rate: 31% [Black], 13% [Asian], 25% [Hispanic], 19% [White], $p = 0.043$), but did not reach significance in the RT cohort (21% [Black], 9% [Asian], 9% [Hispanic] and 11% [White], $p = 0.3$). Using competing risk analysis, the risk of invasive recurrence was similar or lower than DCIS recurrence in each racial group with or without RT.

After adjusting for other factors on multivariable analysis, there remained a higher risk of LR among Black women (hazard ratio [HR] 1.48, 95% CI 1.12-1.95, $p = 0.01$). Older age ($p <$

0.001), radiologic presentation ($p = 0.02$), margins ≥ 2 mm ($p < 0.001$), the use of endocrine therapy ($p < 0.001$) and the use of RT ($p < 0.001$) were associated with lower rates of LR (Table). Sixteen women (0.4%) developed distant disease, with similar rates among Asian (0%), Black (0.8%), Hispanic (0.9%) and White (0.3%) women ($p = 0.2$). Conclusion: Compared with Asian, Hispanic and White women, Black women with DCIS had a significantly higher rate of LR after BCS, even after adjusting for known clinicopathologic risk factors. Rates of distant recurrence were low, and similar across racial groups. These higher rates of LR should be considered when making decisions about adjuvant therapy.

Table. Factors associated with local recurrence in women with ductal carcinoma in situ treated with breast-conserving surgery.

	Univariate analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, years			< 0.001			< 0.001
≤ 49	Ref	—		Ref	—	
50-79	0.71	0.60 – 0.85		0.66	0.56 – 0.79	
≥ 80	1.20	0.72 – 1.99		0.72	0.42 – 1.25	
Presentation			< 0.001			0.02
Clinical	Ref	—		Ref	—	
Radiological	0.66	0.53 – 0.82		0.75	0.59 – 0.95	
Race/Ethnicity			0.04			0.01
White	Ref	—		Ref	—	
Asian	0.77	0.52 – 1.14		0.71	0.47 – 1.07	
Black	1.43	1.09 – 1.87		1.48	1.12 – 1.95	
Hispanic	1.08	0.74 – 1.57		1.07	0.73 – 1.58	
Year of diagnosis			0.005			0.8
≤ 1998	Ref	—		Ref	—	
≥ 1999	0.77	0.65 – 0.92		0.98	0.80 – 1.19	
Family history			0.3			
No	Ref	—		—	—	
Yes	1.10	0.93 – 1.29		—	—	
Grade			0.3			
High	Ref	—		—	—	
Low/intermediate	0.92	0.77 – 1.09		—	—	
Necrosis			0.4			
Absent	Ref	—		—	—	
Present	1.08	0.91 – 1.30		—	—	
Number of excisions			0.08			
≤ 2	Ref	—		—	—	
≥ 3	1.32	0.98 – 1.78		—	—	
Margin status			< 0.001			< 0.001
< 2 mm	Ref	—		Ref	—	
≥ 2 mm	0.65	0.53 – 0.80		0.61	0.49 – 0.74	
Endocrine therapy			< 0.001			< 0.001
No	Ref	—		Ref	—	
Yes	0.46	0.37 – 0.58		0.51	0.41 – 0.65	
Radiotherapy			< 0.001			< 0.001
No	Ref	—		Ref	—	
Yes	0.59	0.50 – 0.69		0.58	0.49 – 0.69	

HR, hazard ratio; CI confidence interval; Ref, referent.

Disclosure(s):

Natalia Polidoro, MD, PhD: No financial relationships to disclose

Monica Morrow, MD: No financial relationships to disclose

Andrea V. Barrio, MD, FACS: No financial relationships to disclose

PS01-08

Management of ipsilateral breast tumor recurrence following breast conservation surgery for ductal carcinoma in situ – a data-free zone

Presenting Author(s) and Co-Author(s):

B. Diskin. Memorial Sloan Kettering Cancer Center, New York, New York, United States

V. Sevilimedu. Memorial Sloan Kettering Cancer Center, United States

K. Van Zee. Memorial Sloan Cancer Center, New York, New York, United States

M. Morrow. Memorial Sloan Kettering Cancer Center, New York, New York, United States

H. Cody. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Management of ipsilateral breast tumor recurrence following breast conservation surgery for ductal carcinoma in situ – a data-free zone

Brian Diskin, Varadan Sevilimedu, Monica Morrow, Kimberly J. Van Zee, Hiram S Cody III

Background:

Breast-conserving surgery (BCS) is well established for the management of ductal carcinoma in situ (DCIS). Although a growing body of data support re-conservation therapy (RBCS) for ipsilateral breast tumor recurrence (IBTR) following BCS in invasive cancer, neither randomized trials nor guidelines address management of IBTR following BCS for DCIS. Here we aim to compare the outcomes of mastectomy vs RBCS for a large series of DCIS patients with IBTR.

Methods:

We identified women treated with BCS for DCIS at MSKCC who developed IBTR as a first event. Between those treated with mastectomy vs RBCS, we compared the clinicopathologic characteristics for the initial and recurrent tumors, the use of adjuvant RT (both upfront (“primary RT”) and post IBTR (“secondary RT”)) and/or tamoxifen, the rate of third events (local, regional, distant), breast cancer specific (BCSS) and overall survival (OS).

Results:

From our service databases among 3001 women treated with BCS for DCIS (1978-2010), we found 383 who developed an IBTR as a first event and were treated at our institution between 1983-2023, 186 (49%) with RBCS and 197 (51%) with mastectomy. RBCS was more frequent over time and comprised 56% of patients treated between 2014 and 2023. Among those treated with mastectomy, the initial tumors were significantly more likely to have necrosis (74% vs 59%), high grade (47% vs 28%), comedo histology (38% vs 20%), and to have received primary RT at the time of BCS (61% vs 21%). Between those who underwent mastectomy vs RBCS, there were no significant differences in disease-free interval, in the pathologic characteristics of their IBTR, or in the proportion of invasive vs in situ disease.

For patients treated with RBCS, 11 (5.9%) received both primary and secondary RT and 77 (41.3%) received neither (Table 1a). For patients treated with a mastectomy only 8.5% had secondary RT (Table 1b).

At a median follow-up of 5.1 years post-IBTR, third local events in total were more frequent for RBCS vs mastectomy (16.1% vs 3.0%, 0.001), but there were no differences in BCSS or OS.

Among RBCS patients, third local events (breast re-recurrence) were least frequent among those who received primary and secondary RT, and comparable between with who did vs did

not receive secondary RT (16% (13/82) vs 16% (117/104), Table 2).

Conclusions:

Our data show that for women with isolated IBTR following BCS for DCIS and treated by mastectomy vs RBCS, 1) treatment with mastectomy was associated with less favorable initial pathology and more frequent use of primary RT, 2) re-recurrence was more frequent with RBCS, and 3) BCSS and OS were comparable. In an era of increasing surgical de-escalation, our data suggest a wider role for RBCS and – as for patients having RBCS for IBTR following invasive cancer – further study of the relationship between secondary RT and the rate of third breast events.

Table 1a
Receipt of primary vs secondary RT
in RBCS

RCT (n=186)		2 ^o irradiation?	
		Yes	No
1 ^o irradiation?	Yes	11 (5.9%)	27 (14.5%)
	No	71 (38.1%)	77 (41.3%)

Table 1b
Receipt of primary vs secondary RT
in mastectomy

Mastectomy (n=197)		2 ^o irradiation?	
		Yes	No
1 ^o irradiation?	Yes	9 (4.5%)	107 (54.3%)
	No	8 (4.0%)	73 (37.0%)

Table 2
Frequency of breast re-recurrence by receipt
of primary vs secondary RT for RBCS

2 nd LRR after RBCS (n=186)		Receipt of 2 ^o irradiation	
		Yes	No
Receipt of 1 ^o irradiation	Yes	1/11 (9%)	6/27 (22%)
	No	12/71 (17%)	11/77 (14%)

Disclosure(s):

Brian Diskin, MD: No financial relationships to disclose
Monica Morrow, MD: No financial relationships to disclose
Hiram S. Cody, MD, III: No financial relationships to disclose

PS01-09

Early Results of a Phase I Pre-Operative Single Fraction Ablative Trial for Early Stage Breast Cancer

Presenting Author(s) and Co-Author(s):

- A. Rahimi. University of Texas Southwestern Medical Center, Dallas, Texas, United States
- A. Leitch. University of Texas Southwestern Medical Center, Texas, United States
- B. Dogan. UT Southwestern Medical Center, Dallas, Texas, United States
- P. Alluri. UTSW, United States
- D. Farr. UT Southwestern Medical Center, United States
- M. Arbab. UTSW, United States
- S. Seiler. UTSW, United States
- N. Kim. VUMC, United States
- R. Wooldridge. UTSW, United States
- N. Unni. University of Texas Southwestern Medical Center, Dallas, Texas, United States
- C. Nwachukwu. University of Texas Southwestern Medical Center, United States
- I. Patel. University of Texas Southwestern Medical Center, United States
- Y. Zhang. University of Texas Southwestern Medical Center, United States
- D. Parsons. Medical Artificial Intelligence and Automation (MAIA) Lab, Department of Radiation Oncology, UT Southwestern Medical Center, United States
- A. Nguyen. University of Texas Southwestern Medical Center, United States
- H. Morgan. University of Texas Southwestern Medical Center, United States
- H. McArthur. UT Southwestern, Dallas, Texas, United States
- S. Sahoo. University of Texas Southwestern Medical Center, United States
- R. Timmerman. UTSW, United States

Objective(s):

To explore the impact of pre-operative single fraction stereotactic ablative partial breast irradiation (SPBI) dose escalation (30, 34, or 38Gy) on toxicity and tumor response for early-stage hormone receptor (HR)+ breast cancer in an interim analysis of an expanded cohort phase I dose escalation study (NCT04040569).

Methods:

Eligible patients (pts) have < 3 cm, HR+, Her2 -, cN0 invasive breast carcinomas not requiring chemotherapy. Patients are treated on either MR LINAC, robotic radiosurgery, or cobalt stereotactic breast units. Endocrine therapy is started two weeks after SPBI. Surgery is completed 2-12 months after SPBI.

The primary objective is to escalate single fraction SPBI to an ablative dose without exceeding maximum tolerable dose (MTD). Secondary endpoints include pathologic complete response (pCR), local control, toxicity, cosmesis, and distant disease-free survival. Near complete response (nCR) is defined as RCB 1 and Miller-Payne 4/5.

Dose limiting toxicity (DLT) is defined as grade ≥ 3 toxicity or any grade 4/5 toxicity attributed to

SPBI. Each dose cohort enrolls 7-15 pts. Dose escalation is permitted if 0/7, 2/9, \leq 3/12, or \leq 4/15 patients experienced a DLT within 90 days of SPBI. MTD is exceeded if more DLTs occur in any cohort.

Results:

From 12/2019 to 6/2023, 11 and 15 pts were treated with 30Gy and 34Gy, respectively. Rates of pCR/nCR are 37.5% for 30Gy versus 92.8% 34 Gy ($p=0.01$). At 30Gy, 8/11 pts (73%) underwent surgery with a median 4.3 (range 2.8-5.9) month interval from SPBI to surgery: 0/8 (0%) had a pCR and 3/8 (37.5%) had a nCR. At dose level 34Gy, 14/15 pts (93%) underwent surgery with a median 7.3 (range 5.9-12) month interval from SPBI to surgery: 6/14 (42.8%) had a pCR while 7/14 (50%) had a nCR. Of the 8 pts with a nCR, 50% had only 1-3mm of residual disease. The mean ki67 for the entire cohort was 12.0% +/- 6.9% at diagnosis and decreased to 1.4 +/-2.3% at surgery. 13/14 (92.8%) pts with residual disease had a ki67 < 3% after surgery and SPBI. There were 33 acute grade 1; 2 acute grade 2 (breast pain and dermatitis); and 10 late grade 1 [1 grade 2 (breast pain), and 1 grade 3 (slow healing wound) in an uncontrolled diabetic] toxicities.

Conclusion:

First study to show pre-operative SPBI up to 34Gy in a single fraction was safe and effective for early-stage HR+ breast cancer. Escalating the dose has achieved a dramatic improvement in pCR/nCR (92.8%) suggesting this is an exciting approach for potentially eliminating tumor with radiation/endocrine therapy alone in early stage breast cancer and potentially paving a path towards non-surgical management in highly selected patients.

Disclosure(s):

Asal Rahimi, MD, MS: Ad Board: Accuray (Ongoing); Consulting Fees (e.g., advisory boards): Accuray (Terminated, June 24, 2021), GE Health (Terminated, June 24, 2021); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Accuray (Ongoing)

Heather McArthur, MD, MPH: Consulting Fees (e.g., advisory boards): Crown Bioscience (Ongoing), Daiichi Sankyo |Astrazeneca (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer (Ongoing), Seattle Genetics/Seagen (Ongoing)

PS01-10

Surgical margins in breast conserving surgery (BCS) for ductal carcinoma in-situ (DCIS) and clinical outcomes: significant associations with increased recurrence and overall survival.

Presenting Author(s) and Co-Author(s):

J. Robertson. University of Nottingham, Nottingham, UK; University Hospitals of Derby and Burton, Derby, England, United Kingdom

D. Sibbering. University Hospital of Derby & Burton, United States

S. Ndebele-Mahati. The Institute of Cancer Research, Clinical Trials and Statistics Unit, London, England, United Kingdom

O. Kearins. NHS England, United States

S. Pinder. School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom

A. Gandhi. Division of Cancer Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester Academic Health Science Centre & Manchester University Hospitals Trust, Manchester, United Kingdom

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

L. Kilburn. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

Background:

Optimal surgical margin in breast conserving surgery (BCS) for DCIS are not established, largely due to an absence of accurate margin data. A margin width of 2mm was adopted by the American College of Surgeons (ACS). The UK Association of Breast Surgery (ABS) recommended a 1mm margin. Conducting a randomized controlled trial to answer this question is unfeasible; therefore we used retrospective histological margin data from available datasets to assess whether there is an association between margin width and time to recurrence (TTR).

Methods:

Patients were included if aged >18 years with a new diagnosis of DCIS alone, between 2003-2014, within UK NHS Breast Screening Programme (BSP). Primary treatment included BCS and a minimum histological excision margin width recorded. Exclusion criteria included: i) prior history of DCIS; ii) prior history of invasive cancer or its diagnosis within 3 months of initial surgical treatment for DCIS.

Data was extracted from English Cancer Registries (CR), ABS and Sloane audits. TTR was defined as time from diagnosis to local or distant recurrence. Cox regression was used to compare TTR by surgical margin width utilising a range of thresholds, with focus on < 1mm vs ≥ 1 mm; < 2mm vs ≥ 2 mm and ≥ 1 - < 2mm vs ≥ 2 mm. Patients with 0mm margin or where categorized as "clear/not stated" were excluded from these analyses. Models were adjusted for age group, DCIS grade and size, ER status, number of BCSs, radiotherapy (RT) received, diagnosis year and CR centre. Overall survival (OS) was a secondary endpoint.

Results:

17,260 patients diagnosed with DCIS having BCS as definitive surgery were identified between 2003-2014; 679 (5%), 2105 (15%), 1339 (10%) and 9744 (70%) with recorded margins of >0- <

1mm, ≥ 1 - < 2mm, ≥ 2 - < 3mm and ≥ 3 mm, respectively. 10,253 (59%) patients received RT and in 7,007 (41%) RT receipt was unknown. Overall, 14,004 (81%), 3,052 (18%) and 201 (1%) patients had one, two and ≥ 3 BCSs respectively; there was no significant change in these percentages over time ($p=0.2$ Cuzick test). Median follow-up time for the cohort was 8.2 years (IQR: 6.1-11.2). 2221 (13%) patients had a subsequent event: 1741/2221 (78%) invasive recurrence and 480/2221 (22%) DCIS alone. The annual event rate over 15 years of follow-up was relatively consistent at 1.2% per annum (pa) for margins ≥ 2 mm versus 1.8% pa for margins < 2mm.

A shorter TTR was observed for patients with surgical margins < 1mm vs ≥ 1 mm (adjusted HR=1.30; 95%CI: 1.05-1.62; $p=0.02$); < 2mm vs ≥ 2 mm (adjusted HR=1.20; 95%CI: 1.06-1.36; $p=0.004$) and ≥ 1 - < 2mm vs ≥ 2 mm (adjusted HR=1.20; 95%CI: 1.04-1.40; $p=0.02$). Margins >2mm did not appear to significantly improve TTR (adjusted HR=0.96; 95%CI: 0.85-1.08; $p=0.50$ for ≥ 5 mm vs ≥ 2 - < 5mm). Models also showed that risk of recurrence increased as the number of BCSs increased (adjusted HR=1.25; 95%CI: 1.10-1.43; $p < 0.001$ for 2 vs 1 and adjusted HR=2.03; 95%CI: 1.36-3.03; $p < 0.001$ for 3+ vs 1).

In total, 1552 (9%) patients had died. OS appeared reduced for patients with surgical margins < 2mm vs ≥ 2 mm (adjusted HR=1.25 (1.07-1.45); $p=0.005$) and for ≥ 1 - < 2mm vs ≥ 2 mm (adjusted HR=1.28 (1.07-1.54); $p=0.008$). Margins <2mm did not appear to significantly improve OS further (adjusted HR=1.06; 95%CI: 0.92-1.21; $p=0.43$ for ≥ 5 mm vs ≥ 2 - < 5mm).

Conclusion:

Patients with DCIS with histological margins of < 2mm, adjusted for other clinical factors, have significantly worse TTR and OS rates compared to margins ≥ 2 mm; the increased annual event rate is consistent out to 15 years.

More than 1 BCS is also associated with an increased risk of recurrence.

These findings are important for the treatment of patients with DCIS.

Disclosure(s):

John Robertson, MB ChB BSc MD FRCS: Advisory Committee/Board Member: Carrick Therapeutics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): AstraZeneca (Terminated, October 29, 2023), Takeda (Terminated, October 29, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Carrick Therapeutics (Ongoing), FaHRAS (Ongoing), Oncimmune (Ongoing)

PS02-01

Efficacy, safety, and quality of life with ribociclib + endocrine therapy in elderly patients with HR+/HER2– advanced breast cancer across the MONALEESA-2, -3, and -7 trials

Presenting Author(s) and Co-Author(s):

L. Hart. Atrium Health/Wake Forest Baptist Comprehensive Cancer Center , Fort Myers, Florida, United States

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

B. Sousa. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

G. Freyer. Oncology Department, Hôpital Lyon Sud, Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL) and Université de Lyon, France

T. Decker. Oncology Ravensburg, Ravensburg, Germany

K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

A. Thuerigen. Novartis Pharma AG, Basel, Switzerland

M. Gao. Novartis Pharma AG, Basel, Switzerland

H. Hu. Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

Background:

Ribociclib (RIB) + endocrine therapy (ET) showed statistically significant progression-free survival (PFS) and overall survival (OS) benefits in MONALEESA-2, -3, and -7 in patients (pts) with HR+/HER2– advanced breast cancer (ABC). Here, we report efficacy, safety, and quality of life (QOL) with RIB + ET in elderly pts in the MONALEESA trials.

Methods:

Data were pooled from the MONALEESA-2, -3, and -7 trials of pre- and postmenopausal pts with HR+/HER2– ABC treated with first-line RIB + ET or placebo (PBO) + ET. The tamoxifen cohort in MONALEESA-7 and pts with early relapse were excluded from this analysis. PFS, OS, and time to first chemotherapy (TTC) were analyzed in pts <65 y, 65- <75 y, and ≥75 y using Kaplan-Meier methods. Time to definitive deterioration (TTD) by ≥10 points in global health status (GHS) was analyzed across age subgroups using Kaplan-Meier methods.

Results:

Of the 1229 pts included in this analysis, 773 (62.9%) were <65 y, 335 (27.3%) were 65- <75 y, and 121 (9.8%) were ≥75 y. There were minor differences in baseline characteristics between the age groups: slightly higher % of pts in the ≥75 y group with a ECOG status of 1 and slightly higher % of de novo disease in the <65 y group (Table). Regardless of age, a PFS and OS benefit was seen with RIB + ET vs PBO + ET (Table). RIB + ET also delayed the median TTC in all age groups. In the RIB + ET group, the most common first subsequent antineoplastic treatment was hormonal therapy alone (<65 y, 26.3%; 65- <75 y, 41.6%; ≥75 y, 38.1%). In the

≥75 y subgroup, pts in the RIB + ET arm (6.3%) less frequently used chemotherapy alone as the first subsequent antineoplastic treatment vs the PBO + ET (24.5%) arm. In pts <65 y, safety results were consistent with those in the overall trial population. In pts 65- <75 y and ≥75 y, the most common any grade adverse events (AEs) with RIB + ET vs PBO + ET were neutropenia (67.6% vs 5.4% and 52.9% vs 3.8%), nausea (52.7% vs 32.0% and 52.9% vs 40.4%), fatigue (42.0% vs 38.1% and 36.8% vs 21.2%), and diarrhea (39.9% vs 30.6% and 48.5% vs 32.7%). For RIB + ET vs PBO + ET, rates of grade 3/4 febrile neutropenia (<65 y, 1.2% vs 0.3%; 65- <75 y, 1.1% vs 0; ≥75 y, 2.9% vs 0), all grade interstitial lung disease (<65 y, 1.0% vs 0.6%; 65- <75 y, 2.7% vs 0.7%; ≥75 y, 7.4% vs 0), and all grade QT prolongation (<65 y, 9.1% vs 2.9%; 65- <75 y, 11.2% vs 4.1%; ≥75 y, 16.2% vs 1.9%) were numerically higher in pts 65- <75 y and ≥75 y than in pts <65 y. Rates of discontinuation due to AEs with RIB + ET vs PBO + ET were 14.6% vs 3.1% in pts <65 y, 19.7% vs 6.8% in pts 65- <75 y, and 41.2% vs 7.7% in pts ≥75 y. In pts who discontinued treatment due to AEs, the percentage of pts without prior dose reduction was 34.4% in pts <65 y, 40.5% in pts 65- <75 y, and 50.0% in pts ≥75 y. TTD in GHS was prolonged with RIB + ET vs PBO + ET in pts <65 y. In pts 65- <75 y and ≥75 y, TTD was generally similar with RIB + ET vs PBO + ET (Table).

Conclusions:

This pooled analysis of the MONALEESA-2, -3, and -7 trials demonstrated PFS and OS benefits with RIB + ET in elderly pts consistent with those observed in younger pts. Across age subgroups, treatment with RIB + ET also delayed TTC. Overall, RIB was well tolerated in elderly pts, with a safety profile consistent with what is anticipated for an older patient population. Additionally, there was no difference in TTD in GHS with RIB + ET vs PBO + ET in pts 65- <75 y and pts ≥75 y.

Table.

	<65 y		65-<75 y		≥75 y		
	RIB+ET n=419	PBO+ET n=354	RIB+ET n=188	PBO+ET n=147	RIB+ET n=68	PBO+ET n=53	
Age, mean, y	50.6	51.0	68.7	69.0	79.2	78.1	
ECOG, % ^a	0	68.7	68.6	53.7	61.2	54.4	50.9
	1	31.0	31.1	46.3	38.8	45.6	49.1
De novo, %	43.4	42.9	37.8	36.7	38.2	35.8	
mPFS, mo	31.8	16.4	35.7	19.2	31.1	19.3	
HR (95% CI)	0.56 (0.47-0.66)		0.55 (0.42-0.73)		0.54 (0.34-0.86)		
mOS, mo	67.6	51.7	72.6	59.8	62.1	52.8	
HR (95% CI)	0.69 (0.56-0.84)		0.79 (0.58-1.07)		0.75 (0.46-1.21)		
mTTC, mo	58.0	40.2	NE	48.3	80.3	42.3	
HR (95% CI)	0.67 (0.55-0.83)		0.64 (0.47-0.89)		0.48 (0.27-0.87)		
TTD in GHS HR (95% CI)	0.61 (0.47-0.80)		0.90 (0.57-1.42)		1.26 (0.57-2.80)		

^aFor the <65 y age group, 1 patient in each arm had unknown ECOG status.
ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; GHS, Global Health Status; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib; TTC, time to chemotherapy; TTD; time to definitive deterioration.

Disclosure(s):

Lowell L. Hart, MD FACP: Consulting Fees (e.g., advisory boards): Circulogene (Ongoing), Mirati Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Novartis Pharma GmbH (Ongoing)

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

Kevin Kalinsky, MD, MS: Consulting Fees (e.g., advisory boards): Merck Foundation (Terminated), Takeda Pharmaceuticals, Ltd. (Terminated); spouse is employee: EQRX (Ongoing)

Poster Spotlight Session 2: Improving QOL and Care Delivery for the Breast Cancer Patient

Presenting Author(s) and Co-Author(s):

A. Blaes. University of Minnesota, Minneapolis, Minnesota, United States

Disclosure(s):

Anne Blaes, MD MS: No financial relationships to disclose

PS02-02

Patient-reported outcomes from the Phase 3 CAPitello-291 trial investigating capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR-positive/HER2-negative advanced breast cancer

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

S. Howell. The University of Manchester, Manchester, England, United Kingdom

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

X. Hu. Shanghai Cancer Center, Fudan University, Shanghai, China

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

P. Krivorotko. N.N. Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russia

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

M. Okera. Adelaide Cancer Centre, Adelaide, Australia

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

E. Tokunaga. National hospital organization Kyushu Cancer Center, Fukuoka, Japan

M. Toi. Graduate School of Medicine, Kyoto University, Kyoto, Japan

S. Yousef. Emek Medical Center, Afula, Israel

L. Zhukova. Loginov Moscow Clinical Scientific Center, Moscow, Russia

M. Fulford. Oncology R&D, AstraZeneca, Warsaw, Poland

H. Andrews. Oncology R&D, AstraZeneca, Gaithersburg, Maryland, United States

I. Wadsworth. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. D'Cruz. Oncology R&D, AstraZeneca, Waltham, Massachusetts, United States

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background:

In the Phase 3 CAPItello-291 trial, adding capivasertib (C), a pan-AKT inhibitor, to fulvestrant (F) in patients (pts) with aromatase inhibitor-resistant, HR+/HER2- (HER2- defined as IHC 0, or 1+ or IHC2+/ISH-) advanced breast cancer significantly improved PFS vs placebo (P) + F in the overall (HR 0.60, 95% CI 0.51, 0.71, $p < 0.001$) and AKT pathway-altered populations (HR 0.50, 95% CI 0.38, 0.65, $p < 0.001$). The safety profile of C-F was manageable; diarrhea (mostly grade 1) was the most frequent adverse event. Global health status (GHS)/health-related quality of life (HRQoL) was maintained from baseline in both arms; time to deterioration (TTD) favored C-F. We report results from additional patient-reported outcomes (PRO).

Methods:

Pts were randomized 1:1 to receive F (500 mg IM on days 1 and 15 of cycle 1 and day 1 of each subsequent 28-day cycle) with either P or C (400 mg BID; 4 days on, 3 days off). PRO measures assessed HRQoL, disease-related symptoms, functioning, and patient-reported treatment tolerability using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), EORTC QLQ Breast Cancer 23 items (EORTC QLQ-BR23), PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), and Patient Global Impression of Treatment Tolerability (PGI-TT). PROs were assessed at pre-specified timepoints. Change from baseline was assessed using Mixed Model Repeat Measures (on-treatment scores) for EORTC QLQ-C30 and summarized for EORTC QLQ-BR23; TTD was assessed using the stratified log-rank test for both.

Results:

Overall, 708 pts were randomized to C-F (n=355) or P-F (n=353). Overall compliance rates with EORTC QLQ-C30 and PGI-TT were 84.5% and 80.6% with C-F and 81.8% and 81.7% with P-F, respectively. Baseline compliance rates with the EORTC QLQ-C30 and PGI-TT were 88.2% and 82.8% with C-F and 87.3% and 83.1% with P-F, respectively.

Mean changes from baseline in EORTC QLQ-C30 functional and symptom domain scores were maintained with C-F and P-F, except for diarrhea in the C-F arm, where scores worsened by >10 points (table).

TTD analysis showed that HRs favored C-F vs P-F for all functional and symptom domains, except diarrhea (HR 2.75; 95% CI 2.01, 3.81), which favored P-F (table). Median TTD of diarrhea was shorter with C-F vs P-F in line with the C-F safety profile. Diarrhea with C-F was generally manageable, and discontinuations due to diarrhea were low (2.0%; n=7/355).

For PGI-TT, most pts reported that they were 'not at all' or 'a little bit' bothered by the side effects of cancer therapy. Over the first 6 months, the proportion of pts reporting to be 'somewhat', 'quite a bit', or 'very much' bothered by side effects was higher for C-F vs P-F, with between-arm differences being highest in the first 2 cycles.

Results from EORTC QLQ-BR23 domains will be presented at the meeting.

Conclusions:

Pts treated with C-F maintained HRQoL for longer than pts treated with P-F on all EORTC QLQ-C30 functional and symptom domain scores, except diarrhea. Worsening of diarrhea was observed with C-F, consistent with the safety profile of C, but events appeared tolerable and did

not negatively impact GHS/HRQoL. Together with the clinical efficacy and manageable safety profile of C-F, the PRO results from the CAPItello-291 trial further support a positive benefit–risk profile of the combination in this population.

<https://clinicaltrials.gov/>: NCT04305496.

Funding:

CAPItello-291 is sponsored by AstraZeneca.

Editorial acknowledgment:

AstraZeneca-funded medical writing support was provided by Suzanne Patel, Ph.D., from BOLDSCIENCE Inc.

Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

EORTC QLQ-C30 domains	LS mean change from baseline (95% CI)*		LS mean difference (95% CI)**	Median TTD, months		HR (95% CI)***
	C+F	P+F		C+F	P+F	
GHS/HRQoL	-2.52 (-4.49, -0.55)	-5.62 (-7.86, -3.37)	3.10 (0.21, 5.98)	24.9	12.0	0.70 (0.53, 0.92)
Functional domains						
Physical functioning	-2.72 (-4.20, -1.23)	-2.30 (-3.97, -0.63)	-0.42 (-2.53, 1.70)	22.1	14.7	0.80 (0.60, 1.06)
Role functioning	-5.61 (-8.08, -3.14)	-5.96 (-8.74, -3.17)	0.35 (-3.22, 3.91)	14.7	11.1	0.76 (0.59, 0.99)
Cognitive functioning	-2.17 (-3.81, -0.53)	-4.05 (-5.91, -2.18)	1.87 (-0.48, 4.23)	17.5	12.8	0.67 (0.51, 0.88)
Emotional functioning	-0.56 (-2.74, 1.62)	-3.05 (-5.50, -0.60)	2.49 (-0.67, 5.65)	NR	16.7	0.81 (0.59, 1.10)
Social functioning	-4.45 (-6.48, -2.41)	-5.39 (-7.64, -3.13)	0.94 (-1.93, 3.80)	14.8	13.0	0.89 (0.69, 1.17)
Symptom domains						
Fatigue	4.26 (1.93, 6.59)	5.61 (2.98, 8.23)	-1.34 (-4.73, 2.04)	11.9	7.7	0.84 (0.66, 1.06)
Pain	0.37 (-1.82, 2.55)	5.88 (3.38, 8.37)	-5.51 (-8.65, -2.37)	21.1	13.0	0.77 (0.58, 1.01)
Nausea and vomiting	3.01 (1.77, 4.25)	2.28 (0.85, 3.71)	0.73 (-1.04, 2.50)	17.4	22.0	0.88 (0.65, 1.19)
Dyspnea	3.72 (1.21, 6.23)	6.45 (3.60, 9.30)	-2.73 (-6.40, 0.94)	22.1	18.4	0.85 (0.62-1.16)
Insomnia	-2.99 (-5.52, -0.45)	-1.21 (-4.12, 1.70)	-1.78 (-5.48, 1.93)	23.0	23.9	0.73 (0.52, 1.02)
Appetite loss	4.11 (1.96, 6.26)	0.90 (-1.54, 3.34)	3.21 (0.15, 6.27)	NR	25.7	0.94 (0.70, 1.28)
Constipation	-5.89 (-8.01, -3.78)	3.48 (1.01, 5.96)	-9.38 (-12.50, -6.25)	NR	NR	0.43 (0.28, 0.64)
Diarrhea	21.24 (18.80, 23.67)	2.75 (-0.04, 5.55)	18.49 (14.96, 22.01)	11.2	23.0	2.75 (2.01, 3.81)
*Calculated using Mixed Model Repeat Measures (on-treatment scores). For functional scales and global health status/QoL score, a positive change from baseline indicates improvement in functioning and health status. For symptom scales, a negative change from baseline indicates improvement. A clinically meaningful change was defined as an absolute change from baseline of ≥10.						
**For functional scales and global health status/QoL score, LS mean difference >0 indicates a change potentially favoring C+F. For symptom scales, LS mean difference <0 indicates a change potentially favoring C+F.						
***HR<1 indicates a change potentially favoring C+F.						
LS, least squares; NR, not reached.						

Disclosure(s):

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr

Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

Mafalda Oliveira, MD, PhD: Advisory Committee/Board Member: Astra Zeneca (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Daiichi-Sankyo / AstraZeneca (Ongoing), Gilead (Ongoing), iTeos (Ongoing), Lilly (Ongoing), MSD (Ongoing), Pfizer, Inc. (Ongoing), Pierre-Fabre (Ongoing), Relay Therapeutics (Ongoing), Roche (Ongoing), Seagen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Astra Zeneca (Ongoing), Gilead (Ongoing), Lilly (Ongoing), MSD (Ongoing), Novartis (Ongoing), Roche (Ongoing), Seagen (Ongoing); Independent Contractor: Libbs (Ongoing), Pfizer, Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Terminated), Ayala Pharmaceuticals (Terminated), Boehringer-Ingelheim (Terminated), Genentech (Terminated), Gilead (Terminated), Novartis (Terminated), Pfizer, Inc. (Terminated), Roche (Terminated), Seagen (Terminated), Zenith Epigenetics (Terminated); Travel Grant: Gilead (Terminated), Pierre-Fabre (Terminated)

Sacha J. Howell, MD, PhD, FRCP: Consulting Fees (e.g., advisory boards): Pfizer, Inc. (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Eli Lilly and company (Ongoing), Pfizer, Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Eli Lilly and company (Ongoing)

Javier Cortés, MD, PhD: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), Astrazeneca (Ongoing), Bioasis (Ongoing), BioInvent Pharma (Ongoing), Boehringer Ingelheim (Ongoing), BridgeBio (Ongoing), Clovis Oncology (Ongoing), Daiichi-Sankyo (Ongoing), Ellipses (Ongoing), Expres2ion Biotechnologies (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gemoab (Ongoing), Gilead (Ongoing), HiberCell (Ongoing), Jazz Pharmaceuticals (Ongoing), Leuko (Ongoing), Lilly (Ongoing), Menarini (Ongoing), Merck Sharp&Dhome (Ongoing), Reveal Genomics, S.L. (Ongoing), Scorpion Therapeutics (Ongoing), Seattle genetics (Ongoing), Zymeworks Inc. (Ongoing); honoraria: Lilly (Ongoing), Novartis (Ongoing); honoraria, research funding to the institution, travel and expenses: Astrazeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Europe Ltd. (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Merck Sharp&Dhome (Ongoing), Pfizer, Inc. (Ongoing); honoraria, travel and expenses: Gilead (Ongoing), Steamline Therapeutics (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1 (Ongoing), MAJ3 Capital (Ongoing), Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. (Ongoing); research funding to the institution: Ariad pharmaceuticals (Ongoing), Baxalta GMBH/Servier Affaires (Ongoing), Bayer Pharmaceuticals (Ongoing), Guardant Health Inc. (Ongoing), IQVIA Inc. (Ongoing), Piquor Therapeutics (Ongoing), Queen Mary University of London (Ongoing); stock (relative): Leuko (Ongoing)

Komal Jhaveri, MD, FACP: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), AstraZeneca (Ongoing), Blueprint Medicines (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Jounce Therapeutics (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Menarini/Stemline (Ongoing), Novartis (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing), Sun Pharma Advanced Research Company Ltd (Ongoing), TAIHO Oncology (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Context Therapeutics (Ongoing), Debio Pharmaceuticals (Ongoing),

Genentech/Roche (Ongoing), Gilead (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck Pharmaceuticals (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Puma Biotechnology, Inc (Ongoing), Zymeworks Inc. (Ongoing)

Sibylle Loibl, MD, PhD: Advisory Committee/Board Member: GSK, Pfizer, Novartis (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Consulting Fees (e.g., advisory boards): GSK, Pfizer, Novartis (Ongoing), Menarini/Stemline (Ongoing), MSD Co., Ltd. (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Licences for VM Ki67 Quantifier: VM Scope GmbH (Ongoing); patents pending: EP14153692.0 , EP21152186.9 , EP19808852.8 , (Ongoing)

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Guardant Health (Ongoing), Invitae (Ongoing), Natera (Ongoing), Personalis (Ongoing)

PS02-03

Is de-escalation of treatment by omission of radiotherapy associated with fear of cancer recurrence and health-related quality of life in women with early breast cancer? An exploratory study

Presenting Author(s) and Co-Author(s):

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

M. Sinclair. Royal Women's Hospital, Melbourne, VIC, Australia

P. Butow. University of Sydney, United States

J. Hughes. RMH, United States

A. Park. Royal Melbourne Hospital, Melbourne, VIC, Australia

L. Gilham. BCT, United States

A. Rose. RMH, United States

L. Stafford. RMH, United States

Background:

There is growing interest in treatment optimization in early breast cancer (EBC). PROSPECT (ANZ-1002) provided compelling evidence that a combination of pre-operative MRI and pathological features could identify a substantial group of patients with localised EBC in whom radiotherapy (RT) could be safely omitted. The patient experience of de-escalation or its association with health-related quality of life (HRQoL) and fear of cancer recurrence (FCR), was not examined in PROSPECT but is a key consideration of treatment decision-making.

We conducted a retrospective, mixed methods, cross-sectional study to explore this association.

Methods:

Psychometrically validated measures including the Fear of Cancer Recurrence Inventory Short-Form, Depression Anxiety Stress Scale, Breast Cancer Treatment Outcomes Scale, EORTC QLQ-C30 and its breast-specific module, the BR23, and the Decision Regret Scale were completed by three groups of women with early EBC: Women in the PROSPECT clinical trial who underwent pre-surgical MRI and omitted RT (A), women who underwent pre-surgical MRI and received RT (B); and women who received usual care (no MRI, received RT; C). Between group differences were analysed with ANOVA or equivalent non-parametric tests. A subset from each group participated in a semi-structured interview. These data (n=44) were analysed with directed content analysis.

Results:

Data from 400 women were analysed. Median age was 65 years, and median time since diagnosis was 4.4 years. There were no group differences in neuroticism, mental health, age, medical comorbidities, parity, or time since diagnosis. Significantly lower FCR was observed in Group A (n=125) than in Group B (n=102; p=.002) or Group C (n=173; p=.001), and when participants were categorized by RT status (omitted RT vs received RT; p<.001). The proportion of women with normal FCR was significantly (p<.05) larger in Group A (62%) than in Group B (35%) or Group C (40%). There were no differences between groups on depression and anxiety. Women in Group A had fewer breast symptoms than in Group B (p=.003) and Group C (p<.001), fewer arm symptoms than in Group B (p=.004) and Group C (p=.011), and better body image than Group C (p=.041). Compared to Groups B and C, Group A

performed better on cosmetic (both $p < .001$), functional (A vs C: $p = .011$) and breast-specific pain measures (both $p < .001$). Pre-operative MRI and omission of RT were highly acceptable and decision regret was low. A secondary analysis was conducted to eliminate any potential impact of disease severity on the analysis. All cases ($n = 126$) with any positive nodes, a Grade 3 tumour and tumour size $> 20\text{mm}$ were removed. The remaining sample comprised 274 women. The results were similar to the primary analysis. Qualitative analysis showed that women who omitted RT viewed this as appropriate treatment, not undertreatment. Women considered RT toxic but endured it as a necessity, if prescribed. Few women experienced ongoing negative effects from RT but there was a tendency to minimize RT treatment burden. Women managed their FCR by having trust in their treatment and faith in the medical advice they received.

Conclusions:

In the setting of the PROSPECT trial, treatment de-escalation via omitting RT was associated with less FCR, better HRQoL and functional and cosmetic outcomes and was highly acceptable. Clinicians should consider the potential for preserved HRQoL associated with omission of RT in treatment decision-making. Positive perceptions about tailored care, lower treatment burden, and trust in clinicians appear to be protective against FCR. Future studies should include prospective collection of FCR and HRQoL measures.

Disclosure(s):

Bruce Mann, MBBS, PhD, FRACS: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Prelude corporation (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Prelude corporation (Ongoing)

PS02-04

Associations of sleep health with quality of life among women with newly diagnosed breast cancer: baseline results from the AMBER cohort study

Presenting Author(s) and Co-Author(s):

L. Yang. Alberta Health Services, Calgary, Alberta, Canada
Q. Wang. Alberta Health Services, Calgary, Alberta, Canada
J. McNeil. University of North Carolina Greensboro, United States
C. Matthews. National Cancer Institute, United States
L. Dickau. Alberta Health Services, United States
J. Vallance. Athabasca University, United States
M. McNeely. University of Alberta, Edmonton, Alberta, Canada
S. Culos-Reed. University of Calgary, United States
K. Kopciuk. Alberta Health Services, United States
K. Courneya. University of Alberta, Edmonton, Alberta, Canada
C. Friedenreich. University of Calgary, United States

Background

High incidence, ageing, and advancements in early detection and clinical treatment have led to a growing breast cancer survivor population, particularly in developed countries. Sleep problems are common and persist in this population, affecting over 50% of breast cancer survivors. Good sleep health is characterized by sleep duration, sleep timing and sleep quality, and these three dimensions do not necessarily correlate with each other. This analysis aimed to investigate the associations of sleep health, characterized by sleep duration, sleep timing, and a range of metrics for sleep quality (latency, efficiency, disturbance, medication, daytime dysfunction) with physical and mental well-being in women with newly diagnosed breast cancer.

Methods

Newly diagnosed breast cancer patients, with early-stage disease were recruited between 2012-2019 in Edmonton and Calgary, Canada, and completed the Pittsburg Sleep Quality Index (PSQI) to assess the habitual sleep duration and timing, as well as sleep latency, efficiency, disturbance, medication and daytime dysfunction. To measure quality of life, participants completed the SF-36 version-2 to assess their physical and mental well-being. Multivariable linear regressions were used to estimate the association of sleep characteristics with physical and mental well-being, adjusting for socio-demographic, disease, clinical and lifestyle behaviour factors.

Results

Among 1409 breast cancer survivors, 41% reported short or long sleep duration (< 6 or ≥ 9 h/d), 41% reported habitual bedtimes after 11pm, 56% reported sleep efficiency being $< 85\%$, 80% reported fairly good (vs. very good) sleep disturbance, 35% reported taking sleep medication in the past month, and 71% reported fairly good, fairly bad or very bad (vs. very good) daytime function. In the multivariable model, short sleep (≤ 6 /d) was associated with worse mental well-being (-3.6, 95%CI: -4.7,-2.4) but not physical well-being (-1.5, 95%CI: -2.3,-0.7). No clinically meaningful differences in quality of life were found for sleep timing. Metrics characterizing suboptimal sleep quality were associated with poorer physical and mental well-being, with stronger associations observed for mental health well-being. Notably, only 20% and

29% women were classified as “very good” in sleep disturbance and daytime dysfunction measures, respectively. Nevertheless, even “fairly good” sleep disturbance and daytime dysfunction were associated with statistically and clinically meaningful significant poorer physical (-3, 95%CI: -3.8,-2.2) and mental (-8, 95%CI: -9,-7) well-being.

Conclusion

Sleep timing does not appear to affect the quality of life in a clinically meaningful manner in women newly diagnosed with breast cancer. In contrast, short sleep duration and worse sleep quality were strongly associated with poorer mental well-being in these women. Targeted interventions to improve sleep may lead to improvements in the quality of life among women with newly diagnosed breast cancer.

Table 1. Association of Sleep Characteristics with SF-36 Measured Quality of Life, Physical Well-Being.

	Mean (SD)	Beta-coefficient (95% CI)		
		Age-adjusted ^a	MV model 1 ^{a,b}	MV model 2 ^{a,b,c}
Sleep duration				
6-9 h/d	50.1 (7.2)	0 [reference]	0 [reference]	0 [reference]
≤ 6 h/d	48.0 (7.7)	-2.0 (-2.9 to -1.1)	-1.6 (-2.4 to -0.8)	-1.5 (-2.3 to -0.7)
≥ 9 h/d	48.7 (8.2)	-1.3 (-2.6 to -0.2)	-1.0 (-2.5 to 0.2)	-1.0 (-2.2 to 0.2)
Sleep timing				
< 10 pm	49.5 (7.4)	0 [reference]	0 [reference]	0 [reference]
10-<11 pm	49.5 (7.4)	0 (-1.1 to 1.1)	-0.2 (-1.2 to 0.9)	-0.3 (-1.3 to 0.7)
11-<12 pm	49.4 (7.6)	-0.1 (-1.2 to 1.0)	0.2 (-0.9 to 1.3)	0.2 (-0.8 to 1.3)
≥ 12 pm	47.7 (8.1)	-1.8 (-3.4 to -0.3)	-0.3 (-1.8 to 1.2)	-0.2 (-1.6 to 1.3)
Sleep latency				
< 15 min	50.3 (7.3)	0 [reference]	0 [reference]	0 [reference]
16-30 min	49.5 (7.2)	-0.8 (-1.7 to 0.1)	-0.7 (-1.5 to -0.2)	-0.7 (-1.6 to 0.1)
31-60 min	48.1 (7.9)	-2.1 (-3.2 to -1.1)	-1.9 (-2.8 to -0.8)	-1.7 (-2.7 to -0.7)
≥ 60 min	45.6 (7.5)	-4.6 (-6.4 to -2.9)	-3.7 (-5.4 to -2.0)	-3.6 (-5.3 to -2.0)
Sleep efficiency				
≥ 85%	50.5 (7.3)	0 [reference]	0 [reference]	0 [reference]
75-84%	49.3 (7.5)	-1.2 (-2.2 to -0.2)	-1.0 (-1.9 to -0.1)	-1.0 (-1.9 to -0.1)
65-74%	48.0 (7.6)	-2.5 (-3.6 to -1.3)	-2.1 (-3.2 to -1.0)	-2.0 (-3.1 to -1.0)
<65%	47.0 (7.3)	-3.5 (-4.7 to -2.3)	-2.9 (-4.0 to -1.7)	-2.7 (-3.8 to -1.5)
Sleep disturbance				
Very good	51.5 (6.9)	0 [reference]	0 [reference]	0 [reference]
Fairly good	48.7 (7.6)	-2.8 (-3.7 to -1.8)	-2.4 (-3.3 to -1.5)	-2.2 (-3.1 to -1.3)
Sleep medication				
Not during the past month	50.0 (7.5)	0 [reference]	0 [reference]	0 [reference]
Less than once a week	48.9 (6.8)	-1.1 (-2.4 to 0.2)	-1.2 (-2.4 to 0)	-0.9 (-2.2 to 0.3)
Once or twice a week	48.5 (7.4)	-1.6 (-3.0 to -0.2)	-1.6 (-2.9 to -0.3)	-1.2 (-2.5 to 0.1)
Three or more times a week	47.0 (7.7)	-3.1 (-4.2 to -2.0)	-2.8 (-3.8 to -1.7)	-2.2 (-3.3 to -1.2)
Day time dysfunction				
Very good	52.2 (6.4)	0 [reference]	0 [reference]	0 [reference]
Fairly good	48.7 (7.5)	-3.6 (-4.4 to -2.7)	-3.1 (-3.9 to -2.3)	-3.0 (-3.8 to -2.2)
Fairly bad	45.5 (7.3)	-6.8 (-8.2 to -5.4)	-6.0 (-7.4 to -4.6)	-5.6 (-7.0 to -4.2)
Very bad	41.4 (6.5)	-10.8 (-13.8 to -7.8)	-9.2 (-12.2 to -6.3)	-8.5 (-11.5 to -5.6)

^a Adjusted for age (years)
^b Multivariable (MV) model additionally adjusted study location (Edmonton, Calgary), marital status (married or common-law, widowed/separated/divorced, single/never married), ethnicity (White, non-white), education attainment (high school or below, college, university, graduate school), annual family income (<\$50,000, 50-100k, 100-150k, >150k), body mass index (kg/m²), total caloric intake (kcal/day), moderate to vigorous intensity physical activity (minutes/day), alcohol consumed (g/day), smoking (never smoker, past smoker, current smoker), disease stage (I, II, III), tumor grade (1, 2, 3), surgery status (pre-surgery [neoadjuvant therapy], lumpectomy, mastectomy)
^c Additionally adjusted for comorbidity score (0-8)

Table 2. Association of Sleep Characteristics with SF-36 Measured Quality of Life, Mental Well-Being.

Table 2. Association of Sleep Characteristics with SF-36 Measured Quality of Life, Mental Well-Being.

	Mean (SD)	Beta-coefficient (95% CI)		
		Age-adjusted ^a	MV model 1 ^{a,b}	MV model 2 ^{a,b,c}
Sleep duration				
6-9 h/d	49.3 (9.4)	0 [reference]	0 [reference]	0 [reference]
≤ 6 h/d	45.4 (10.6)	-3.7 (-4.8 to -2.5)	-3.7 (-4.7 to -2.5)	-3.6 (-4.7 to -2.4)
≥ 9 h/d	46.8 (10.6)	-2.0 (-3.7 to -0.4)	-1.9 (-3.6 to -0.3)	-1.9 (-3.6 to -0.2)
Sleep timing				
< 10 pm	47.2 (10.2)	0 [reference]	0 [reference]	0 [reference]
10-<11 pm	48.0 (10.0)	0.8 (-0.6 to 2.2)	0.6 (-0.8 to 2.0)	0.6 (-0.8 to 2.0)
11-<12 pm	48.3 (9.6)	0.9 (-0.6 to 2.4)	0.8 (-0.7 to 2.3)	0.8 (-0.6 to 2.3)
≥ 12 pm	46.6 (11.3)	-0.9 (-2.9 to 1.1)	-0.6 (-2.7 to 1.4)	-0.6 (-2.6 to 1.5)
Sleep latency				
< 15 min	50.4 (9.1)	0 [reference]	0 [reference]	0 [reference]
16-30 min	47.5 (9.9)	-2.7 (-3.8 to -1.5)	-2.7 (-3.9 to -1.5)	-2.7 (-3.9 to -1.6)
31-60 min	44.6 (10.3)	-5.7 (-7.1 to -4.4)	-5.5 (-6.9 to -4.2)	-5.5 (-6.8 to -4.1)
≥ 60 min	43.7 (11.5)	-6.4 (-8.7 to -4.1)	-6.3 (-8.6 to -3.9)	-6.2 (-8.5 to -3.9)
Sleep efficiency				
≥ 85%	49.2 (10.0)	0 [reference]	0 [reference]	0 [reference]
75-84%	48.1 (9.5)	-1.4 (-2.6 to -0.1)	-1.5 (-2.7 to -0.2)	-1.5 (-2.7 to -0.2)
65-74%	46.5 (9.7)	-2.9 (-4.3 to -1.4)	-2.8 (-4.3 to -1.3)	-2.8 (-4.3 to -1.3)
<65%	44.5 (10.9)	-4.6 (-6.2 to -3.0)	-4.4 (-5.9 to -2.8)	-4.3 (-5.8 to -2.7)
Sleep disturbance				
Very good	51.1 (8.4)	0 [reference]	0 [reference]	0 [reference]
Fairly good	47.0 (10.3)	-4.6 (-5.8 to -3.3)	-4.5 (-5.7 to -3.2)	-4.4 (-5.7 to -3.1)
Sleep medication				
Not during the past month	48.8 (9.9)	0 [reference]	0 [reference]	0 [reference]
Less than once a week	47.2 (9.5)	-1.8 (-3.4 to -0.1)	-1.7 (-3.4 to -0.1)	-1.7 (-3.4 to -0)
Once or twice a week	46.4 (10.4)	-2.8 (-4.7 to -1.0)	-3.1 (-4.9 to -1.2)	-2.9 (-4.8 to -1.0)
Three or more times a week	44.9 (10.2)	-4.0 (-5.4 to -2.6)	-3.8 (-5.2 to -2.4)	-3.6 (-5.1 to -2.2)
Day time dysfunction				
Very good	54.5 (6.8)	0 [reference]	0 [reference]	0 [reference]
Fairly good	46.4 (9.2)	-7.9 (-8.9 to -6.9)	-8.0 (-9.1 to -7.0)	-8.0 (-9.0 to -7.0)
Fairly bad	38.2 (10.5)	-15.5 (-17.2 to -13.8)	-15.6 (-17.3 to -13.9)	-15.5 (-17.2 to -13.8)
Very bad	35.3 (10.4)	-18.7 (-22.3 to -15.1)	-19.0 (-22.7 to -15.3)	-18.9 (-22.7 to 15.2)

^a Adjusted for age (years)

^b Multivariable (MV) model additionally adjusted study location (Edmonton, Calgary), marital status (married or common-law, widowed/separated/divorced, single/never married), ethnicity (White, non-white), education attainment (high school or below, college, university, graduate school), annual family income (<\$50,000, 50-100k, 100-150k, >150k), body mass index (kg/m²), total caloric intake (kcal/day), moderate to vigorous intensity physical activity (minutes/day), alcohol consumed (g/day), smoking (never smoker, past smoker, current smoker), disease stage (I, II, III), tumor grade (1, 2, 3), surgery status (pre-surgery [neoadjuvant therapy], lumpectomy, mastectomy)

^c Additionally adjusted for comorbidity score (0-8)

Disclosure(s):

Lin Yang, PhD: No financial relationships to disclose

Kerry S. Courneya, PhD: No financial relationships to disclose

PS02-05

Trajectories and predictors of peripheral neuropathy after neoadjuvant chemotherapy in a prospective cohort of 11,014 patients with early breast cancer

Presenting Author(s) and Co-Author(s):

- Y. Drouet. Centre Léon Bérard, Lyon, France
- E. Thomas. Centre Léon Bérard, Lyon, France
- F. Lerebours. Institut Curie, United States
- B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France
- O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France
- C. Jouannaud. Institut Godinot, Reims, France
- M. Fournier. institut Bergonié, Bordeaux, France
- P. Rouanet. L'Institut du Cancer de Montpellier, Montpellier, France
- L. Vanlemmens. Centre Oscar Lambret, Lille, France
- C. COUTANT. Centre Georges-François Leclerc, France
- A. Dhaini Merimeche. Centre lexis Vautrin, Nancy, France
- B. Sauterey. Institut de cancérologie de l'Ouest, Angers, France
- C. Levy. Centre François Baclesse, Caen, Basse-Normandie, France
- M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France
- C. Tarpin. Institut Paoli Calmettes, Marseille, United States
- M. Mouret-Reynier. Centre Jean Perrin, United States
- O. Rigal. Centre Henri Becquerel, Rouen, France
- T. Petit. Centre Paul Stauss, Strasbourg, France
- S. Guillermet. Centre Eugène Marquis, Rennes, France
- A. Arnaud. Institut Sainte Catherine, Avignon, France
- M. Ibrahim. CHU La Source, Orléans, United States
- S. Giacchetti. Hôpital Saint Louis, Paris, France
- F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France
- J. Wassermann. CHU Pitié Salpêtrière, Paris, France
- O. Arsène. Centre Hospitalier de Blois, Blois, France
- A. Darut-Jouve. Clinique du Parc Devron, Dijon, France
- S. Everhard. Unicancer, Paris, France, United States
- I. Vaz Luis. Gustave Roussy, Villejuif, France
- A. Martin. Unicancer, Paris, France, United States
- F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France
- J. Deleuze. Centre National de Génotypage, United States
- A. Viari. INRIA, France, United States
- m. Carton. institut curie, United States
- P. Cottu. Institut Curie, Paris, Paris, Ile-de-France, France

Background

Peripheral neuropathy (PN) is a debilitating adverse event in patients with early breast cancer (BC) receiving (neo)adjuvant chemotherapy (CT). We harnessed the CANTO cohort study to detail clinical trajectories and explore clinical and genetic predictors of PN.

Methods

CANTO (CANcer TOxicities - NCT01993498) prospectively enrolled invasive stage I-III BC patients (pts) of 26 French comprehensive cancer centers. Pts were assessed at diagnosis, 3-6 (M6), 12 (M12), 36 (M36), and 60 (M60) months after treatment, defined as completion of surgery, CT or radiotherapy, whichever comes last. At each time point, PN events including paresthesia, sensory and motor neuropathy were collected according to NCI-CTC v4.0 criteria. A genome-wide association study (GWAS) was conducted to identify genetic predictors of PN, using Illumina GSA BeadChips. Minimac4/1000G was used to impute additional single nucleotide polymorphisms (SNPs). After stringent quality control measures, 1,894,475 SNPs with a minor allele frequency (MAF) >0.05 were evaluated.

Longitudinal trajectories of PN events were descriptively examined. Statistical associations between each SNP and PN events measured at different time points, and between SNPs and trajectories, were performed with logistic regression assuming a log-additive genetic model. All analyses were adjusted for key clinical parameters and the first ten axes of principal component analysis of the genetic data to control for population stratification.

Results

Of 12,012 included pts (data lock Aug. 2022), 11,014 (91.7%) were analyzed. Age was < 50 and >65 in 3407 and 2759 pts (31% and 25%, respectively). Overweight/obesity and diabetes were recorded in 5328 (48%) and 458 pts (4%). A neurologic history was observed in 1360 pts (13%). Stage 0-I and II-III were observed in 5356 (49%) and 5512 pts (51%), and 4011 pts had an axillary dissection (37%). CT was administered in 5790 pts (53%), including a taxane (tax) in 5542 pts (96%).

Shortly, all grade and grade 2+ PN was observed in 29% and 12%; 27% and 10%; 20% and 10%; 13% and 10% of pts at M6, M12, M36 and M60, respectively. We derived 5 trajectories of overall PN, deemed “never”, “always”, “appears”, “transient” and “disappears”, in respectively 54%, 10%, 9%, 7% and 19% of the pts. Similar trajectories were built for the 3 categories of PN events. We built 9 predictive nomograms including key clinical parameters and time of analysis. E.g., grade 2+ PN at M6 was independently predicted by a medical history of carpal tunnel syndrome, past neurologic history and exposure to tax. Grade 2+ PN at M36 was predicted by past neurologic history and exposure to tax, and largely by previous PN at M6 or M12.

The GWAS analysis included 7633 pts (84%). Four independent SNPs adding predictive value to the clinical nomograms were identified at a suggestive level of association ($p < 1e-6$), including one SNP in the NCAM1 gene (involved in neurogenesis) for M6 PN (OR=1.40, 95%CI 1.23-1.60, $p=4.8e-7$, see table) and one SNP in the CLDN11 gene (regulates oligodendrocytes) for M12 sensory PN (OR=1.32; 95%CI 1.17-1.49, $p=7.5e-6$). For rare (< 5%) toxicities, 10 independent suggestive SNPs were identified, including one SNP in the NELL1 gene (neural cell growth regulation and differentiation) for the “always” trajectory (OR=1.61, 95%CI 1.31-1.99, $p=7.6e-6$) and one SNP in the KCNIP1 gene (neuronal sensor) for M36 motor PN (OR=1.5, 95%CI 1.7-3.5, $p=3.1e-07$).

Conclusions

Risk of early peripheral neuropathy is associated with previous neurological history and taxane exposure. Patients with PN at M6 or M12 are highly exposed to long-term PN. Some key SNPs

may add independent predictive value for specific PN endpoints. Exploratory results of interest were produced for rarer toxicities and typical clinical trajectories. Detailed results will be presented at the meeting.

all PN, M6

All PN, M6	Clinical model		Integrative model	
	OR	P	OR	p
Obesity	1.17	.013	1.1	.32
Carpal tunnel	1.44	<.001	1.49	1.1e-05
Neurol. History	2.26	<.001	2.14	6.2e-20
Taxane	3.08	<.001	3.0	4.4e-56
NCAM1	-	-	1.40	4.8e-7

Multivariate analyses of the risk of peripheral neuropathy, all grades, at M6, without and with GWAS input.

Disclosure(s):

Barbara Pistilli, MD: Advisory Committee/Board Member: LILLY (Ongoing), Novartis Pharma GmbH (Ongoing)

Paul Cottu, MD, PhD: No financial relationships to disclose

PS02-07

Effectiveness of 24-week mobile application based human coaching program for controlling weight, BMI and body composition in overweight/obese breast cancer survivors: Single-arm prospective cohort study

Presenting Author(s) and Co-Author(s):

S. Jung. National Cancer Center, Goyang, Republic of Korea

E. Lee. National Cancer Center, United States

D. Lee. National Cancer Center, United States

J. Kim. National Cancer Center, United States

J. Han. National Cancer Center, United States

S. Lee. National Cancer Center, Goyang, Republic of Korea

H. Kang. National Cancer Center, United States

E. Lee. National Cancer Center, Goyang-si, Gyeonggi-do, Republic of Korea

H. Chae. National Cancer Center, United States

S. Sim. National Cancer Center, United States

K. Lee. Center for Breast Cancer, National Cancer Center, Goyang, Republic of Korea

J. Lee. Noom, New York, New York, United States

Background:

Overweight/obesity has been known as a prognostic factor for breast cancer recurrence and breast cancer related death. However, weight control is hard in breast cancer survivors because of menopause, chemotherapy, anti-hormonal therapy, and psychologic issues. This study aimed to develop 24-week mobile application based human coaching program with Noom and evaluate its efficacy in overweight/obese breast cancer survivors.

Methods

In this single-arm prospective cohort study, 130 breast cancer survivors with BMI ≥ 25 were enrolled and received 24-week program including diet-, exercise-, and psychology-based contents with trained human coach in Noom during 2019-2021. For hyperactive group who joined more than 16 weeks, we evaluated weight, BMI, lipid level, bioimpedance, and Quality of Life (QoL) at baseline, 6 month and 12month follow-up.

Results

Among 130 breast cancer survivor, 101 participants (77.7%) and 93 participants (71.5%) completed 6 month and 12 month follow-up, respectively. In hyperactive group (68/101, 67%), body weight and BMI reduced significantly (mean difference: -1.97 kg, 95% CI (confidence interval): -2.65- -1.26, $P < 0.001$ and -0.86, 95% CI: -1.15- -0.56, $P < 0.001$, respectively) at 6 month and maintained at 12 month without the yo-yo effect. Among the lipid panel, triglycerides level decreased significantly (-34.13, 95% CI: -58.09- -10.17, $P = 0.006$) and maintained at 12 month. In the aspect of bioimpedance components, skeletal muscle mass (SMM, kg), body fat mass (BFM, kg), percent body fat (PBF, %), waist-hip ratio (WHR), and visceral fat area (VFA, cm^2) were improved for first 6 months. However, WHR and VFA increased during next 6months. Based on the EORTC QLQ C30 and BR 23, nausea/vomiting, constipation, body image, arm and breast symptoms showed significant improvement during the first 6months.

Conclusions

This study demonstrated that 24-week mobile application based human coaching program is beneficial for controlling body weight, BMI, TG and body composition in bioimpedance for overweigh/obsess breast cancer survivors.

ClinicalTrials.gov NCT05506189; [https://clinicaltrials.gov/ct2/show/ NCT05506189](https://clinicaltrials.gov/ct2/show/NCT05506189).

IRB: NCC2019-0098

Disclosure(s):

So-Youn Jung, MD PhD: No financial relationships to disclose

PS02-08

The Effect of a Digital Health Coaching Program on Patient Reported Outcomes of Women with Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Whisenant. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

E. Hacker. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

L. Williams. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Dains. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

B. Fellman. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Isaac. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

V. Shelton. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Barr. Pack Health, United States

C. Harty. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Rasulnia. Pack Health, United States

K. Brassil. Pack Health, United States

Background

Understanding the impact of a digital health coaching (DHC) program on patient-reported outcomes in women with breast cancer is imperative as web-based platforms and mobile phone applications to address health care needs flood the marketplace. This study evaluated the effect of a DHC program on patient-reported outcomes, including global health (primary outcome), symptom burden, quality of life, healthcare utilization, and financial toxicity among women undergoing active treatment for breast cancer.

Methods

English-speaking adult women undergoing active treatment for breast cancer were randomized to receive usual care or a 6-month DHC program, consisting of weekly telephone calls from a Health Advisor, unlimited patient-initiated communication via phone, text, or email, and digital delivery of additional health-behavior content. Patient-reported outcomes (PROs) were collected using validated measures at baseline, and 1, 3, and 6 months. Summary statistics were used to describe participant characteristics. Linear mixed models were used to assess the effect of the intervention on outcomes.

Results

Participants (n=254, planned enrollment=440) were enrolled from August 2019 to December 2022 and randomized equally to the control and intervention groups (n=127 each). Demographic data are presented in Table 1. Participants had a mean age of 48 (SD =10.15) years; 74% were White; 19.7% were Hispanic. In both groups, several PRO scores changed over time with some improving (quality of life and symptom severity) and others worsening (symptom interference and financial toxicity) compared to baseline (time effects). Of those enrolled in the intervention group 69% were retained in the DHC program, with an overall

average of 4.6 months of engagement for all participants. There were no significant group (intervention versus control) effects or group by time interaction effects observed. Trends within and between groups are presented in Table 2. Though not statistically significant, there were fewer ER visits in the intervention group at each timepoint.

Conclusions:

While differential improvements in the DHC group were not observed, interesting trends in PROs over the 6-month enrollment period were observed in both groups. Participants reported improvements in quality of life and worsening of financial toxicity. Interestingly, slight improvements in symptom severity over time were observed in both groups while symptom interference worsened. Potential reasons for failure to detect a treatment effect for DHC may include ineffectiveness of DHC on the selected outcomes, the intervention not being strong enough as currently delivered to detect a treatment effect, varying uptake of DHC in the intervention group, heterogeneity of the sample, or the study being underpowered due to COVID restrictions affecting enrollment.

Table 1. Demographic and clinical characteristics of the study population (n = 254)

Table 1. Demographic and clinical characteristics of the study population (n = 254)

Characteristic	Control (n = 127)	Intervention (n = 127)	p-value
	Mean (SD)	Mean (SD)	
Age at diagnosis			
Mean (SD)	48.17 (9.74)	48.60 (10.59)	0.737
	N (%)	N (%)	
Employment			0.165
Employed	95 (76.0)	85 (70.3)	
Race			>0.999
White or Caucasian	94 (74.0)	94 (74.0)	
Black or African American	20 (15.8)	21 (16.5)	
Asian	6 (4.7)	6 (4.7)	
Other	6 (4.7)	6 (4.7)	
American Indian or Alaska Native	1 (0.8)	0 (0.0)	
Ethnicity			>0.999
Hispanic or Latino	25 (19.7)	25 (19.7)	
Prior Breast Cancer Treatment			
Surgery	126 (99.2)	120 (94.5)	0.066
Radiation	106 (83.5)	109 (85.8)	0.602
Chemotherapy	124 (97.6)	126 (99.2)	0.622
Hormone therapy	37 (29.1)	49 (38.6)	0.112
Immunotherapy	4 (3.2)	3 (2.4)	>0.999

Table 2. Trends in Patient Reported Outcomes and Healthcare Utilization

Table 2. Trends in Patient Reported Outcomes and Healthcare Utilization

Measure	Cohort	Baseline		Month 3		Month 6	
		Mean (SD)		Mean (SD)		Mean (SD)	
PROMIS Physical	Control	36.59 (7.52)		37.93 (5.74)		36.46 (8.19)	
	Intervention	36.92 (6.76)		37.47 (6.29)		35.08 (5.64)	
PROMIS Mental	Control	36.97 (10.15)		34.63 (9.27)		35.26 (9.74)	
	Intervention	36.31 (11.14)		37.32 (10.16)		36.11 (11.06)	
MDASI Severity	Control	2.69 (1.81)		2.10 (1.57)		1.78 (1.39)	
	Intervention	2.51 (1.91)		1.86 (1.28)		1.75 (1.31)	
MDASI Interference	Control	1.67 (1.37)		1.85 (1.44)		1.87 (1.47)	
	Intervention	1.54 (1.46)		1.74 (1.33)		2.07 (1.60)	
FACT-G	Control	75.13 (17.38)		78.71 (16.24)		79.80 (16.74)	
	Intervention	76.42 (16.99)		80.03 (14.49)		81.03 (15.70)	
COST	Control	23.75 (11.21)		26.10 (10.61)		27.26 (9.87)	
	Intervention	24.82 (11.10)		28.16 (10.54)		28.15 (11.16)	
Healthcare Utilization (n)		Baseline	Mo. 1	Mo. 2	Mo. 3	Mo. 4	Mo 6
ER Visit	Control	17	14	21	7	7	5
	Intervention	8	12	10	5	3	3
Hospitalization	Control	4	5	6	3	5	2
	Intervention	4	5	3	1	4	2

COST, Comprehensive Score for financial Toxicity (lower score represents worse financial toxicity); ER, Emergency Room; FACT-G, Functional Assessment of Cancer Therapy-General (Higher scores represent better quality of life); MDASI, M.D. Anderson Symptom Inventory (Higher score represents more of the concept of measure); PROMIS, Patient Reported Outcomes Measurement Information System (Higher scores represent better health).

Disclosure(s):

Meagan Whisenant, PhD, APRN: No financial relationships to disclose

Loretta A. Williams, PhD, APRN: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Terminated, December 31, 2021), Bayer Pharmaceuticals (Terminated, December 31, 2021), Eli Lilly, (Terminated, December 31, 2021), Genentech-Roche (Terminated, December 31, 2021), Merck & Co., Inc. (Terminated, December 31, 2021), Pack Health (Terminated, December 31, 2021)

PS02-09

Nurse-led individualized follow-up versus regular physician-led visits after early breast cancer (MyHealth) - a randomized, controlled trial

Presenting Author(s) and Co-Author(s):

- L. Saltbæk. Zealand University Hospital, Ballerup, Hovedstaden, Denmark
- P. Bidstrup. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- R. Karlsen. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- B. Høeg. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- T. Horsboel. National Institute of Public Health, University of Southern Denmark, Copenhagen, Hovedstaden, Denmark
- F. Belmonte. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- E. Andersen. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- V. Zoffmann. University of Copenhagen, Copenhagen, Hovedstaden, Denmark
- A. Friberg. Danish Cancer Society Research Center, Copenhagen, Hovedstaden, Denmark
- M. Svendsen. Zealand University Hospital, Roskilde, Sjælland, Denmark
- H. Christensen. Zealand University Hospital, Roskilde, Sjælland, Denmark
- V. Glavicic. Zealand University Hospital, Naestved, Sjælland, Denmark
- D. Nielsen. Copenhagen University Hospital, Herlev and Gentofte, Herlev, Hovedstaden, Denmark
- S. Dalton. Survivorship and Inequality in Cancer, Danish Cancer Society Research Center, Copenhagen, Denmark
- C. Johansen. Copenhagen University Hospital, Rigshospitalet, Copenhagen, Hovedstaden, Denmark

Background:

Follow-up after breast cancer with regular specialist-led visits has failed to prove superiority over other strategies in terms of recurrence detection and survival, but it is still a cornerstone in breast cancer follow-up in many healthcare systems. Follow-up provided by the general practitioner or a specialist nurse has been reported more cost-effective and non-inferior in terms of patient-reported health-related quality of life (HRQoL) and in meeting the needs of breast cancer survivors. However, no follow-up strategies have demonstrated indisputable superiority over other strategies.

Methods:

In this randomized controlled trial (MyHealth), patients who recently completed surgery, and chemo-/radiotherapy if indicated, for stage I–II breast cancer were randomly assigned to intervention or control follow-up at Zealand University Hospital, Denmark. The nurse-led intervention comprised three to five individual self-management sessions during the first six months, and regular reporting of symptoms with nurse navigation to relevant healthcare services during three years of follow-up. The control comprised outpatient visits with oncologist every six months for three years. The primary outcome was breast cancer-specific HRQoL measured by the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) summary score of the Functional Assessment of Cancer Therapy-Breast (FACT-B) two years after randomization. Secondary outcomes were fear of recurrence, anxiety, depression, and healthcare utilization.

Results:

From January 2017 to January 2019, 503 patients were randomly assigned to intervention (n=251) or control (n=252) follow-up. At two years, patients in the intervention group reported a significantly higher HRQoL (mean 75.69 (SD 12.27)) than patients in the control group (mean 71.26 (SD 14.08)), a mean difference of 5.05 (95% CI; 3.30–6.79), which is considered clinically relevant. The intervention group also reported significantly less fear of recurrence, anxiety, and depression as shown in Table 1. Furthermore, patients in the intervention group had fewer physician consultations but more nurse contacts, and an unchanged diagnostic imaging pattern as shown in Table 2. The effect on all outcomes was stable through three years of follow up.

Conclusions:

The MyHealth study suggests a new strategy for follow-up after early breast cancer providing significant improvements in HRQoL, fear of recurrence, anxiety, and depression without inflicting extra expenses to the healthcare system.

(Funded by the Danish Cancer Society, Region Zealand and Copenhagen University Hospital; Clinicaltrials.gov number; NCT02949167.)

Table 1: Outcome findings by study group at baseline, 6, 12, 24, and 36 months

	Time point	Control n = 252	Intervention n = 251	Estimate for difference	95% CI	p-value	Overall p-value	Cohen's d
Quality of life	0	67.26 (13.99)	66.37 (14.40)					
	6	69.95 (13.62)	73.06 (13.37)	4.37	(2.67; 6.08)	< 0.001	< 0.001	0.31
	12	70.59 (14.37)	74.44 (13.13)	4.71	(3.00; 6.42)	< 0.001		0.34
	24	71.26 (14.08)	75.69 (12.27)	5.05	(3.30; 6.79)	< 0.001		0.36
	36	72.60 (13.54)	76.65 (12.90)	4.91	(3.13; 6.70)	< 0.001		0.35
Fear of recurrence	0	13.74 (9.21)	14.56 (10.13)					
	6	13.11 (9.38)	9.76 (8.13)	-4.07	(-5.39; -2.76)	< 0.001	< 0.001	0.44
	12	12.13 (9.20)	9.61 (8.52)	-3.10	(-4.42; -1.78)	< 0.001		0.34
	24	11.10 (9.00)	8.57 (7.99)	-3.19	(-4.54; -1.83)	< 0.001		0.35
	36	11.21 (8.52)	9.17 (8.00)	-2.81	(-4.19; -1.44)	< 0.001		0.31
Anxiety	0	3.69 (4.03)	4.21 (4.40)					
	6	3.81 (4.09)	3.16 (3.86)	0.74	(0.62; 0.88)	< 0.001	< 0.001	0.17
	12	3.64 (3.80)	2.94 (3.74)	0.72	(0.60; 0.86)	< 0.001		0.18
	24	4.02 (4.58)	2.86 (3.30)	0.66	(0.55; 0.78)	< 0.001		0.24
	36	3.27 (3.70)	2.48 (3.08)	0.68	(0.56; 0.82)	< 0.001		0.18
Depression	0	5.78 (4.71)	6.12 (5.01)					
	6	4.92 (4.51)	4.43 (4.35)	0.84	(0.74; 0.96)	0.011	< 0.001	0.13
	12	5.15 (4.47)	4.11 (4.20)	0.75	(0.66; 0.86)	< 0.001		0.22
	24	5.15 (4.90)	3.78 (3.60)	0.70	(0.61; 0.81)	< 0.001		0.27
	36	4.51 (3.84)	3.99 (3.99)	0.83	(0.72; 0.96)	0.011		0.14

Data are mean (SD) unless otherwise stated. The effect estimates are based on the mixed model assuming no difference between groups at baseline. The QoL and fear of recurrence variables are continuous, and the estimates describe the mean difference in score between patients in the two groups. For anxiety and depression, data were zero-inflated. These estimates describe the exponential coefficients of anxiety and depression scores in the

intervention group compared to the control group. Cohen's d is a measure of effect size, and interpreted as small for Cohen's d = 0.2, medium for Cohen's d = 0.5, and large for Cohen's d = 0.8

Table 2: Number of contacts and diagnostic imaging examinations during the first three years of follow-up by study group

	Control n = 252		Intervention n = 251		p-value
	n	Mean (SD)	n	Mean (SD)	
Outpatient visit with physician	1326	5.26 (2.32)	370	1.47 (1.81)	< 0.001
Telephone contact with physician	294 ¹	1.17 (1.12)	252	1.00 (1.34)	0.140
Outpatient visit with nurse	12	0.05 (0.23)	101	0.40 (0.65)	< 0.001
Telephone contact with nurse	125	0.50 (1.14)	904	3.60 (2.71)	< 0.001
Mammography	522	2.07 (0.95)	500	1.99 (1.09)	0.384
CT scan	212	0.84 (1.55)	165	0.66 (1.06)	0.122
MR scan	118	0.47 (0.89)	133	0.53 (0.87)	0.431
Bone scintigraphy	43	0.17 (0.43)	49	0.20 (0.42)	0.514
PET CT scan	13	0.05 (0.22)	12	0.05 (0.25)	0.857
All diagnostic imaging	908	3.60 (2.50)	859	3.42 (2.07)	0.377

Data are numbers and mean (SD) per patient during the first three years of follow-up.

1 Most telephone consultations were scheduled as outpatient visits according to the protocol, but changed to telephone consultations due to the COVID-19 pandemic

Disclosure(s):

Lena Saltbæk, LSAL: No financial relationships to disclose

PS03-01

Single cell analysis of paired lymph nodes and primary tumors in breast cancer patients

Presenting Author(s) and Co-Author(s):

M. Fjørtoft. Institute for Cancer Research, Oslo University Hospital, Oslo, Oslo, Norway

I. Rye. Institute for Cancer Research, Oslo University Hospital, United States

K. Huse. Institute for Cancer Research, Oslo University Hospital, United States

J. Myklebust. Institute for Cancer Research, Oslo University Hospital, United States

H. Russnes. Institute for Cancer Research, Oslo University Hospital, United States

M. Riis. Division of Clinical Medicine, Oslo University Hospital, United States

O. Lingjærde. Institute for Informatics, University of Oslo, United States

□. Garred. Oslo University Hospital, Oslo, Norway

K. Lande. Institute for Cancer Research, Oslo University Hospital, United States

I. Bergheim. Institute for Cancer Research, Oslo University Hospital, United States

E. Schlichting. Oslo University Hospital, Oslo, Norway

A sentinel lymph node (SN) is the primary node draining the tumor and is assumed to be affected early in the metastatic process. The sentinel node holds a key position in the immune response against tumor in breast, and represents a unique connection between the tumor and the host immune response. We hypothesize that the immune profile in the primary tumor and the paired lymph node (LN) is different during tumor progression.

3.7 million single cells from paired primary tumor and lymph nodes from 33 breast cancer patients (Oslo2 cohort) was analyzed by single cell mass cytometry (CyTOF) with a 47 antibody immune panel and characterized by a semi-automatic gating approach (FlowSOM).

Tumor cells were found in 11 LN. When analyzing the leucocytes from LN we identified a significant difference in immune cell type skewing towards higher abundance of memory CD4 and CD8 T cells expressing an exhausted phenotype in LN with metastasis. In addition, a higher abundance of activated Tregs and significantly lower abundance of resting Tregs was found in the metastatic LNs compared to the sentinel lymph nodes. The change in immune composition and exhaustion was correlated to the metastatic tumor burden. The skewing towards an exhausted immune profile was also found in larger primary tumors compared to smaller primary tumors.

We further analyzed tumor cells from 8 patients with paired primary tumor and LN. No differences were identified in the primary tumor when stratified by LN status, but LNs with smaller metastasis expressed lower levels of epithelial markers essential in the Epithelial-to-Mesenchymal Transition such as E-cadherin, Pan Cytokeratin and EpCAM – this in contrast to the LN with manifested metastasis in the axilla which expressed higher levels of epithelial markers and lower levels of mesenchymal markers such as Vimentin and CD44.

We identified a skewing in the immune profile from a naive phenotype towards a memory and exhausted phenotype in CD8 and CD4 T cell population in LN with manifested metastasis, as well as in larger primary tumors. We also identified that tumor cells in smaller metastatic tumors resembled a “mesenchymal like” phenotype compared to in the larger manifested tumors.

These results suggest that the immune suppression is correlated with the tumor burden.

Disclosure(s):

Marit Otterlei Fjørtoft: No financial relationships to disclose

Poster Spotlight Session 3: Insights from Single Cell, Spatial, and Artificial Intelligence Approaches

Presenting Author(s) and Co-Author(s):

G. Broeckx. Department of Pathology (PA²), Network of Antwerp Hospitals, Antwerpen, Belgium, Antwerpen, Antwerpen, Belgium

Disclosure(s):

Glenn Broeckx, Bsc, MD: No financial relationships to disclose

PS03-02

Single-cell metabolic profiling uncovers new precision immunotherapy strategy in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

Y. Xu. Fudan University Shanghai Cancer Center, United States

Y. Xiao. Fudan University Shanghai Cancer Center, United States

H. Wang. Fudan University Shanghai Cancer Center, United States

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China (People's Republic)

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Background:

Immunotherapy has emerged as a novel cornerstone in the treatment of triple-negative breast cancer (TNBC), while its benefits have been observed in only a limited subset of patients. The intricate metabolic interplay between cancer cells and microenvironmental cells remodels the tumor microenvironment and exerts a significant influence on the responses to immunotherapy. However, there is still a lack of clarity regarding the strategies to target this metabolic crosstalk in order to predict efficacy and enhance sensitivity for immunotherapy.

Methods:

We conducted single-cell RNA sequencing (scRNA-seq) analysis on a cohort of 27 patients with TNBC receiving either immunotherapy combination regimen or chemotherapy alone. Building upon this foundation, we embarked on a comprehensive investigation of the single-cell metabolic landscape from three distinct perspectives: metabolic genes, metabolic pathways, and metabolic flux, represented by the flux balance analysis (FBA) algorithm Compass. Furthermore, we identified crucial cell subgroups that exhibited a strong correlation with immunotherapy efficacy and elucidated their metabolic characteristics to postulate potential metabolic crosstalk. Then, we employed the in vitro, in vivo, and patient-derived models to unravel the underlying mechanisms of metabolic crosstalk and proposed the translational strategies.

Results:

Utilizing newly-developed single-cell FBA method, we illustrated that different cell types have distinct metabolic features. Specifically, tumor cells and macrophages had more active metabolic reprogramming and higher metabolic heterogeneity. Furthermore, we illustrated that a subset of tumor cells having active antioxidant metabolism (featured by the upregulation of GSTP1) and macrophage subset depending on glutamine metabolism (characterized by CCL3⁺) were negatively and positively predictive of immunotherapy responses, respectively. Mechanistically, GSTP1-mediated excessive consumption of glutamine by tumor cells competitively restrained the intake of glutamine into CCL3⁺ macrophages to promote their ferroptosis and reduce their infiltration. Clinically, we demonstrated that targeting the GSTP1, which is specifically expressed in tumor cells, remodeled immune-metabolic microenvironment and enhanced immunotherapy efficacy. Furthermore, we established the utility of plasma CCL3 abundance, GSTP1 protein abundance, and CCL3 protein abundance, as robust predictors of response to immunotherapy, in several independent immunotherapy cohorts.

Conclusion:

Our study presented a comprehensive and multidimensional analysis of the single-cell metabolic landscape. Identifying the crucial metabolic crosstalk remodeling the immune microenvironment, our promising finding highlights the potential significance of modulating cell-cell metabolic interactions in sensitizing TNBC to immunotherapy, providing valuable insights for future therapeutic interventions.

Disclosure(s):

Yi-Zhou Jiang, MD: No financial relationships to disclose

PS03-03

The spatially resolved single-cell atlas of the tumor immune architecture revealed the central role of IFN-alpha and plasmacytoid dendritic cells in triple-negative breast cancer in the Mayo Clinic cohort and FinXX trial

Presenting Author(s) and Co-Author(s):

S. Chumsri. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

Y. Liu. Mayo Clinic, United States

Y. Ma. Mayo Clinic, United States

J. Carter. University of Alberta, Edmonton, Alberta, Canada

M. Gregory. NanoString Technologies, United States

S. Church. NanoString Technologies, United States

J. Reeves. NanoString Technologies, United States

H. Brauer. NanoString Technologies, United States

S. Warren. NanoString Technologies, United States

H. Joensuu. Helsinki University Hospital and University of Helsinki, United States

E. Perez. Mayo, United States

R. Leon-Ferre. Mayo Clinic, Rochester, Minnesota, United States

D. Hillman. Mayo Clinic, Rochester, Minnesota, United States

J. Boughey. Division of Breast and Melanoma Surgical Oncology, Department of Surgery, Mayo Clinic, Rochester, Minnesota, United States

J. Ingle. Mayo Clinic, Rochester, Minnesota, United States

K. Kalari. Mayo Clinic, Rochester, Minnesota, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

K. Knutson. Mayo Clinic, United States

E. Thompson. Mayo Clinic, United States

Background:

Multiple studies have confirmed the central role of preexisting immune response measured by stromal tumor-infiltrating lymphocytes (sTILs) in triple-negative breast cancer (TNBC). Emerging studies showed that not only the number of TILs but also the location of TILs is important. There are 3 distinct immune architectures described based on the amount and locations of TILs, namely immune enriched (IN), immune excluded (IE), and immune desert (ID). Here we evaluated outcomes and characteristics associated with each immune landscape.

Methods:

NanoString Digital Spatial Profiling (DSP) and CosMx, a spatial multi-omics single-cell imaging platform, were performed in 75 samples from the Mayo Clinic (MC) TNBC cohort (Leon-Ferre BCRT 2018). NanoString IO360 was performed in 114 samples from the FinXX trial (NCT00114816). Firstly, tumors with sTIL quantified by H&E \leq 30% were classified as ID. The rest of the tumors with high sTIL $>$ 30% were categorized according to the intratumoral CD8 protein expression by DSP, with IE having intratumoral CD8 in the lower median and IN having intratumoral CD8 in the upper median. Chi-square test, gene set enrichment, Cox regression,

and Kaplan-Meier analysis were used. Differential expression listed as log 2-fold change (FC) was estimated from the linear mixed model with significance defined as two-sided $p < 0.05$.

Results:

ID is associated with low Ki67 $< 5\%$ (23.3% vs. 9.6% ID, $p 0.02$) as well as apocrine (11/13, 84.6%) and metaplastic histology (10/12, 83%). In both univariate and multivariate analysis, patients with IN had significantly improved recurrence-free survival (RFS) compared to those with ID (HR 0.37, 95%CI 0.18-0.74, $p 0.005$). Despite having high sTILs, IE had poor outcomes similar to ID (HR 0.84, 95%CI 0.36-1.98). Strikingly, we identified that IE patients had significantly lower plasmacytoid dendritic cells (pDCs) compared to IN (mean 0 vs. 0.26 /100 tumor cells, 95%CI 0.08-0.43, $p 0.01$). Using Gene Set Enrichment Analysis to evaluate differential hallmarks between IN and IE, we identified IFN α and IFN γ (FDR < 0.001) responses as significantly enriched in IN group, consistent with the function of pDCs, which are a subset of dendritic cells specialized in secreting high levels of type I interferon. To validate this finding, we further evaluated the 11 leading edge gene IFN α signature in the FinXX trial. A high IFN α signature score was associated with significantly improved outcomes in the FinXX trial (HR 0.21, 95%CI 0.09-0.51, $p < 0.001$). Similar findings were observed using Kaplan-Meier analysis in the FinXX trial with significantly improved RFS ($p 0.0006$) and overall survival ($p 0.0001$) in patients with high IFN α signature scores. Furthermore, we evaluated the differential gene expression unique to IN tumors in the Mayo cohort. Expressions of MHC class I and class II in tumor cells, including HLA-A, HLA-B, HLA-C, HLA-DRA, HLA-DRB1, HLA-DPA1, and HLA-E, were associated with IN and significantly improved outcomes ($p < 0.05$) compared to ID and IE.

Conclusions:

Highlighting the importance of spatial context, we identified that patients with IE tumors had poor outcomes despite having high TILs. Moreover, using an in-depth analysis with spatially defined context, we identified the central role of pDC and the significance of IFN α in TNBC.

Support:

Breast Cancer Research Foundation, Mayo Clinic Breast Cancer SPORE (P50CA116201-17)

W81XWH-15-1-0292, P50CA015083, R35CA253187

Disclosure(s):

Saranya Chumsri, MD: No financial relationships to disclose

Fergus J. Couch, PhD: No financial relationships to disclose

Matthew P. Goetz, MD: Advisory Committee/Board Member: ARC Therapeutics (Ongoing), Bioltheranostics (Ongoing), Blueprint Medicines (Ongoing), Novartis (Ongoing), RNA Diagnostics (Ongoing), Seattle Genetics (Ongoing), Sermonix Pharmaceuticals (Ongoing); CME Activity: Clinical Education Alliance (Terminated), Medscape (Terminated), MJH Life Sciences (Terminated), Research to Practice (Terminated); Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing), Engage Health Media (Ongoing), Lilly (Ongoing); Grant funding to institution: AstraZeneca (Ongoing), ATOSSA (Ongoing), Lilly (Ongoing), LOXO (Ongoing), Pfizer (Ongoing), Sermonix Pharmaceuticals (Ongoing); Moderator: Curio Science (Terminated); Panel Discussant: Total Health Conferencing (Terminated)

PS03-04

Tumor immune microenvironment modulates resistance to estrogen suppression in ER+ breast cancer

Presenting Author(s) and Co-Author(s):

F. Napolitano. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

Y. Wang. Division of Gastroenterology, Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

D. Sudhan. UT Southwestern medical center, United States

P. Gonzalez-Ericsson. Vanderbilt University Medical Center, United States

L. Formisano. Department of Clinical Medicine and Surgery, University of Naples "Federico II", United States

L. Guo. UT Southwestern Medical Center, United States

M. Chica-Parrado. University of Texas Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, United States

C. Lin. University of Texas Southwestern Simmons Comprehensive Cancer Center, United States

K. Lee. Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, USA; Department of Life Sciences, College of Natural Science, Hanyang University, Seoul, Republic of South Korea., United States

H. Ma. Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon, United States

N. Evans. Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; Division of Bioinformatics & Computational Biology, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, Oregon, United States

A. Servetto. Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, USA; Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy., United States

S. Mendiratta. UT Southwestern Simmons Comprehensive Cancer Center, United States

S. Barnes. Lyda Hill Department of Bioinformatics, University of Texas Southwestern Medical Center, Dallas, Texas, United States

Y. Fang. University of Texas Southwestern Medical Center, United States

L. Xu. UT Southwestern, United States

J. Balko. Vanderbilt University Medical Center, Nashville, Tennessee, United States

G. Mills. Knight Cancer Institute, Oregon Health & Science University, United States

M. Labrie. Department of Immunology and Cell Biology, Université de Sherbrooke, Sherbrooke, QC, Canada; Department of Obstetrics and Gynecology, Université de Sherbrooke, Sherbrooke, Quebec, Canada

A. Hanker. UT Southwestern Medical Center, Dallas, Texas, United States

C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

Despite major advances in the treatment of estrogen receptor positive (ER+) breast cancer (BC), advanced disease continues to be the main cause of death from this disease. The role of the tumor immune microenvironment (TIME) in the progression of ER+ BC and its response to treatment is not completely understood. The aim of this study was to elucidate the role the TIME in the response of ER+ tumors to estrogen deprivation (ED).

We collected samples from 215 postmenopausal patients with stage I-III ER+ BC, treated with letrozole for 2-4 weeks, to induce ED. We used AQUA on pre-treatment biopsies and on-treatment surgical biopsies to assess ER, PR, HER2, and Ki67. Then, we categorized the patients' response to ED based on the Ki67 score in on-treatment samples: ED-sensitive (ED-S) if natural log (ln) of the Ki67 score ≤ 1.0 or $\leq 2.7\%$ Ki67+ cells vs. ED-resistant (ED-R) if $\ln \geq 2.0$ or $\geq 7.4\%$ Ki67+ cells.

Firstly, we assessed TIME composition by investigating stromal tumor-infiltrating lymphocytes (sTILs) in H&E-stained FFPE of on-treatment tumor sections. ED-R tumors exhibited a significantly higher stromal TILs score ($p=0.0001$) relative to ED-S tumors. We next prepared tissue microarrays from 227 (on-treatment) surgical sections and subjected them to cyclic immunofluorescence (CycIF) with 38 antibodies to examine their intra-tumoral immune cell infiltration. From each tumor core, we segmented single cells and labeled them as immune, cancer, or stromal cells based on expression of a set of markers. Briefly, cells that stained strongly for CD45 (leukocyte marker), and/or CD4 (T lymphocyte marker), or CD68 (macrophage marker) were labeled immune cells. CD45/CD4/CD68-negative cells were categorized as tumor if E-cadherin and/or cytokeratin-positive, or stromal cells if -negative.

Next, we assessed cell specific spatial enrichment by quantifying the expression of immune markers in the area immediately adjacent to each tumor cell. Immune-suppressive T-reg (FOXP3+) cells were enriched in the ED-S tumors ($p=0.0004$), as well as PD1+ (exhausted) T cells ($p=0.0004$), and CD68+ cells ($p < 0.0001$) compared to ED-R tumors. ED-R tumors exhibited higher CD20+ B cells ($p < 0.0001$), higher CD8+ T cells ($p=0.0329$), in addition to higher CD45+ cells ($p < 0.0001$), compared to ED-S tumors. RNA-sequencing of the same surgical samples showed a higher T cells cytolytic score in ED-R relative to ED-S ($p=0.0058$), suggesting enhanced CD8+ T cells activity, in addition to their higher infiltration. We are currently analyzing letrozole-induced changes in TIME composition using Geomix digital spatial profiler in paired pre- and on-treatment biopsies from ED-R and ED-S tumors and will be presented at the meeting.

Consistent with the CycIF findings, GSEA of hallmark gene signatures from bulk RNA-sequencing of treated tumors revealed that immune-related gene sets, such as "IFN α response", "IFN γ response", and "allograft rejection" were upregulated in ED-R vs. ED-S cancers. ED-R tumors showed enrichment of CXCL9, CXCL10, and CXCL11 chemokines and their receptor, CXCR3. Publicly available datasets of patients with ER+ breast cancers showed that higher expression CXCL9 (HR 1.36; $p=0.016$), CXCL10 (HR 1.71; $p < 0.0001$), and CXCL11 (HR 1.5; $p=0.0016$) are predictive of shorter relapse-free survival on antiestrogen therapy. We are currently investigating whether these chemokines play a causal role in resistance to ED, and if this is phenocopied by co-cultures of ER+ BC cells and CD8+ T-cells.

Conclusions

ED-resistant tumors are enriched with stromal TILs and exhibit higher immune cell intra-tumoral infiltration and CD8+T cells cytolytic activity compared to ER+ tumors sensitive to estrogen suppression. In contrast, ED-S tumors showed a more immunosuppressed milieu. The role of CXCL9, CXCL10 and CXCL11 in inducing resistance to ED warrants further investigation.

Disclosure(s):

Fabiana Napolitano, MD: No financial relationships to disclose

Justin Balko, PharmD, PhD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus)) (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Genentech-Roche (Ongoing), Incyte (Ongoing)

Ariella Hanker, PhD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Eli Lilly (Ongoing)

PS03-06

Clinical implementation of artificial-intelligence-assisted detection of breast cancer metastases in sentinel lymph nodes: saving costs and time (the CONFIDENT-B trial)

Presenting Author(s) and Co-Author(s):

C. van Dooijeweert. University Medical Centre Utrecht, Utrecht, Utrecht, Netherlands

R. Flach. University Medical Centre Utrecht, Utrecht, Netherlands

N. ter Hoeve. University Medical Centre Utrecht, Utrecht, Netherlands

C. Vreuls. University Medical Centre Utrecht, Utrecht, Netherlands

R. Goldschmeding. University Medical Centre Utrecht, Utrecht, Netherlands

J. Freund. University Medical Centre Utrecht, Utrecht, Netherlands

P. Pham. University Medical Centre Utrecht, Utrecht, Netherlands

T. Nguyen. University Medical Centre Utrecht, Utrecht, Netherlands

E. Van der Wall. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

G. Frederix. University Medical Centre Utrecht, Utrecht, Netherlands

N. Stathonikos. University Medical Centre Utrecht, Utrecht, Netherlands

P. Van Diest. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

Background

Metastases in sentinel lymph nodes (SN) of breast cancer (BC) patients are strongly associated with a worse survival and consequently guide treatment. If metastases are absent upon pathologist' assessment of the regular hematoxylin and eosin (HE)-slide, additional immunohistochemistry (IHC)-stains are performed to ensure that no metastases are missed. However, these stains come at high additional costs, which may exceed specimen reimbursement. Fortunately, digital pathology is becoming more common, thereby creating an avenue of opportunities for artificial intelligence (AI) assistance. Although the number of studies on (promising) AI-algorithms increases exponentially, studies on actual clinical implementation are lacking. In this single-center prospective trial, we investigated to which extent an artificial intelligence (AI)-assisted clinical workflow for the detection of SN-metastases reduces IHC-use, while maintaining current diagnostic safety standards.

Methods

We enrolled 190 SN-specimens of 182 patients with invasive or in situ BC from September 2022 to May 2023. SN-specimens were allocated bi-weekly to either the control-arm (n=90) or the intervention-arm (n=100). In the control-arm, SN-specimens were digitally assessed according to the current clinical workflow, while pathologists in the intervention-arm assessed the SN-specimen with the output the 'Metastasis-Detection-App' (Visiopharm©) available. In both groups, IHC was performed in all morphologically negative cases. Main outcome was the relative risk (RR) of IHC-use per detected case of SN-metastases. Case-mix adjustment was performed by log-binomial regression.

Results

Overall, 59 SN-specimens contained metastases (31.1%). AI-assistance resulted in a significantly lower risk of IHC-use per detected case of SN-metastases (adjusted RR: 0.680, 95% CI: 0.347-0.878). Besides preventing IHC-use, thereby reducing costs, AI-assisted pathologists also spent significantly less time on their assessment of the SN-specimen (3m:41s vs. 6m:04s, $p = 0.028$). Furthermore, the sensitivity of AI-assisted pathologists was up to 30%

higher. The AI-assisted pathologists missed two cases of micro-metastases in the intervention arm, one of which was in retrospect highlighted by the algorithm, while in the other case the tumor cells were located in a heavily cauterized area of the HE-slide and therefore only visible on the (serial) IHC-slides. In the control arm, the algorithm in retrospect picked up all micro- and macro-metastases and nearly half of the isolated tumor cells (ITC). In addition, all participating pathologists stated that AI was easy to use, that they felt confident using AI, and that besides saving them time, AI made their work more enjoyable.

Cost reductions on IHC by AI-assistance depend on laboratory policy (i.e. when and on how many levels IHC is performed), but, at a cost of €25,- per IHC-stain, range from €1.500 to €3.500 per 100 SN's in a scenario where IHC is performed in all morphologically negative cases. In a scenario where IHC is only performed in patients in whom finding ITC has clinical consequences (i.e. patients who received neoadjuvant treatment), cost savings on IHC range from €7.500-€12.500 per 100 SNs, depending on laboratory policy.

Conclusion

AI-implementation for the detection of SN-metastases in BC-patients leads to a significant reduction of IHC-use and subsequent costs, while saving pathologists time and making their work more enjoyable. Importantly, AI-implementation during this trial was safe and patients were not at risk of an inferior diagnosis. By doing this trial alone, an estimated €3,000 on IHC-use was saved. Such tangible cost savings are crucial to build a viable business case for AI implementation in diagnostic pathology.

Disclosure(s):

Carmen van Doijeweert: No financial relationships to disclose

PS03-07

Morphometric signature identifies ductal carcinoma in situ of the breast with low risk of progression to invasive breast cancer

Presenting Author(s) and Co-Author(s):

M. Sobral-Leite. Netherlands Cancer Institute, Amsterdam, Noord-Holland, Netherlands

S. Castillo. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Vonk. Netherlands Cancer Institute, Amsterdam, Netherlands

X. Melillo. Netherlands Cancer Institute, Amsterdam, Netherlands

N. Lam. Netherlands Cancer Institute, Amsterdam, Netherlands

B. de Bruijn. Netherlands Cancer Institute, Amsterdam, Netherlands

Y. Hagos. The Institute of Cancer Research, London, United Kingdom

J. Sanders. Netherlands Cancer Institute, Amsterdam, Netherlands

M. Almekinders. Netherlands Cancer Institute, Amsterdam, Netherlands

L. Visser. Netherlands Cancer Institute, Amsterdam, Netherlands

E. Groen. Netherlands Cancer Institute, Amsterdam, Netherlands

C. Van der Borden. Netherlands Cancer Institute, Amsterdam, Netherlands

P. Kristel. Netherlands Cancer Institute, Amsterdam, Netherlands

E. Caner. University Hospital Basel, Basel, Switzerland

L. Azarang. Netherlands Cancer Institute, Amsterdam, Netherlands

Y. Yuan. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

R. Menezes. Netherlands Cancer Institute, Amsterdam, Netherlands

E. Lips. Netherlands Cancer Institute, Amsterdam, Netherlands

J. Wesseling. Netherlands Cancer Institute, Amsterdam, Netherlands

G. PRECISION Consortium. Netherlands Cancer Institute, Amsterdam, Netherlands

Background.

Ductal carcinoma in situ (DCIS) is a frequently found precursor of invasive breast cancer (IBC). However, the majority of DCIS will never progress to IBC. As we cannot distinguish yet which DCIS will remain indolent ('harmless') from those that might progress in the future to IBC, almost all women with DCIS are intensively treated by surgery, often followed by radiotherapy. This brings an urgent clinical need to learn distinguishing harmless from potentially progressive DCIS to save many women with indolent DCIS the burden of unnecessary overtreatment.

Aim.

We aimed to investigate if the geometry and spatial configuration of DCIS ducts in Hematoxylin-Eosin (H&E) stained tissue sections are related to the risk of progression of DCIS to ipsilateral IBC (iIBC).

Methods.

We obtained data from a population-based cohort of women diagnosed with primary DCIS between 1989 and 2004 in the Netherlands, treated with breast conserving surgery (BCS) only and a median follow-up time of 12 years. A nested case-control study (n=689) was designed in

which patients diagnosed with iIBC recurrences during follow-up were considered as “cases” (n= 226) and those with no subsequent iIBC as “controls” (n=463). The DCIS and stroma regions were digitally annotated on H&E-stained whole slide images (WSIs) by a pathologist as ground truth for the deep learning neural network of HALO AI module (IndicaLabs). We developed a computational pipeline to automatically detect and measure stroma areas, DCIS ducts, and the nucleus of their cells. We validated the accuracy of DCIS detection in H&Es WSIs from an external study, in which DCIS regions were digitally annotated by an independent pathologist (Translational Breast Cancer Research Consortium, TBCRC). We classified cases and controls according to morphological measurements using logistic ridge regression with double-loop cross-validation, followed by hierarchical clustering. The risk of subsequent iIBC after primary DCIS diagnosis was evaluated by multivariate Cox proportional hazards models.

Results.

The accuracy of DCIS detection performed by the computational pipeline was compared with pathologist annotations in 20 slides from the TBCRC study. Results showed a satisfactory DCIS overlap area agreement of 0.76 (0.68 – 0.83). We applied the DCIS computational pipeline on the case-control series. We obtained 15 morphological measurements for each DCIS duct, such as duct area, cell density, distance between ducts, average nucleus area, etc. We calculated 8 distribution parameters from each measurement in each WSI, including median and range. After leaving out redundant variables, 55 unique morphometric variables were obtained, representing the heterogeneity of DCIS ducts per WSI. The classifier revealed a median area-under the curve (AUC) of 0.66 (0.55-0.77) to predict 5-years free of iIBC, 0.59 (0.50-0.67) to predict 10-years and 0.60 (0.52-0.68) to predict 15-years. The 30 variables with the highest association with outcome were used to build four morphometric signatures. Signature number 1, which is characterized by lesions with small-sized ducts, a lower number of cells and a lower DCIS/stroma area ratio, showed a significant lower risk of developing iIBC compared to the other three signatures in a multivariate Cox regression model including grade, ER, COX-2 and HER2 expression: HR = 0.56 (0.28-0.78 95%CI).

Conclusion.

We developed a computational pipeline able to detect and measure DCIS ducts in H&E WSIs with high accuracy and reproducibility. DCIS lesions presenting the morphometric signature of small-sized DCIS ducts have a very low chance to progress to invasive breast cancer. After successful validation, our morphometric method will serve as a robust and easy to implement biomarker for de-escalation strategies in DCIS, and as such, could limit unnecessary overtreatment in the near future.

Disclosure(s):

Marcelo Sobral-Leite, PharmD PhD: No financial relationships to disclose

PS03-08

Spatial biomechanics determines fate in breast cancer

Presenting Author(s) and Co-Author(s):

S. Nizzero. Houston Methodist Research Institute, Houston, Texas, United States

M. Pelaez Soni. Houston Methodist Research Institute/Rice University, United States

G. Zaugg. Artidis, United States

M. Gachechiladze. Artidis, United States

Y. Xu. Houston Methodist Research Institute, United States

L. Zhang. Houston Methodist Research Institute, United States

J. Zheng. Houston Methodist Research Institute, United States

B. Menegaz. Baylor College of Medicine, United States

L. Jordan. University of Dundee/NHS Tayside, United States

C. Purdie. University of Dundee/NHS Tayside, United States

P. Quinlan. University of Nottingham, United Kingdom

C. Nagi. Baylor College of Medicine, United States

K. Sepulveda. Baylor College of Medicine, Texas, United States

P. Oertle. Artidis, United States

T. Appenzeller. Artidis, United States

M. Loparic. Artidis, United States

Z. Wang. Houston Methodist Research Institute, United States

S. Chen. Houston Methodist Research Institute, United States

V. Cristini. Houston Methodist Research Institute, United States

M. Plodinec. Artidis, United States

A. Thompson. Baylor College of Medicine, Houston, Texas, United States

Background:

With the recent advancements of spatial omics, it has become increasingly recognized that spatial analysis of tumor architecture is key to decipher the heterogeneous intratumoral relationships between different tumor components and provide better understanding of cancer therapy resistance, as well as help to identify potential targets for personalized therapy. The challenge of the discovery and implementation of such biomarkers still lies in the technological and methodological difficulties, and their translation into clinical practice. In parallel a major advancement in cancer research has been the recognition of the importance of cancer biomechanical properties in cancer progression, metastasis, and therapy response.

Methods:

We developed a new computational platform to identify biomechanical drivers of cancer outcome from spatial omics data. We used it to identify recurring spatial patterns of these markers within the tumor microenvironment, and define the spatial scale of heterogeneity of such patterns. Our dataset consists in 700 primary breast cancer baseline samples analyzed with two 30-marker imaging mass cytometry panels to identify cancer, immune, and stromal cells and structures and their biomechanical states. Our patient cohort includes 20+ years of follow up, with up to 6 samples per patient from 64 patients alive 12 years post diagnosis, and

49 patients lost to breast cancer deaths. Patients were treated with surgery, radiation, chemotherapy, endocrine therapy, or combinations of these post-surgery. Based on this approach, we derived a new three-parameter quantitative metric of preferential spatial co-localization between different cells or structures, and we use this metric to stratify patients into responders and non-responders with the aid of single and multivariate survival analysis. Finally, we include a correlation with Atomic Force Microscopy to identify the mechanical signature of these driving patterns in breast cancer.

Results:

Our work enabled the identification of tumor-immune-stromal spatial patterns that drive breast cancer outcome and their spatial scale. Among our results, we were able to further define spatial regions of hypoxia-driven EMT. We found these regions to be usually on the scale of 50 mm radius, and enriched in presence of unspecified immune cells. They are also more frequent in ER+ areas, with high NaKATPase activity. Our analysis also shed light on the controversy on the role of fibroblasts. We have found that the presence of a strong, spatially structured stroma, in fibroblast-rich regions is a strong predictor of positive outcome. Similarly, in our analysis collagen cross-linking emerges as a positive control factor in Vimentin-rich microenvironments, offering new interpretation to the role of the ECM structure. Importantly, our first principle approach allows for the identification of driving structures beyond heterogeneity, and thus enables easy extension to additional datasets. Finally, when correlating these patterns with Atomic force microscopy measurements, we can clearly see that patterns predictive of poor survival present a clear heterogeneous stiffness signature, as opposed to a very homogenous good survival pattern signature.

Conclusion:

These results confirm the importance of spatial distribution of biomechanical drivers in cancer, offering new avenues of physics-based therapeutic targets. Our results also offer a solid base to inform machine learning algorithms on how to significantly parametrize spatial patterns in breast cancer for clinical significance. Furthermore, we demonstrate for the first time the use of Atomic Force Microscopy as a single biomarker for these patterns in breast cancer with a direct correlation based on pathology matching.

Disclosure(s):

Sara Nizzero, PhD: Consulting Fees (e.g., advisory boards): Artidis (Ongoing); Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Artidis (Ongoing)

Alastair M. Thompson, MD: Spouse employed by Eli Lilly: Eli Lilly, (Ongoing)

PS03-09

Age-related normal breast tissue features differ in women with germline BRCA1/2 mutations

Presenting Author(s) and Co-Author(s):

A. Grigoriadis. King's College London, Comprehensive Cancer Centre, Faculty of Life Sciences and Medicine, London; School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom

M. Parreno-Centeno. King's College London, United States

S. Chen. King's College London, United States

G. Verghese. King's College London, United States

E. Lips. NCI, United States

C. Gillett. King's Health Partners Cancer Biobank, King's College London, United States

L. Jones. Barts Cancer Institute, United States

S. Pinder. School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom

Ageing, a breast cancer risk factor, can be reflected in histologically normal breast tissue (NBT). However, the relationship between age-related histological features and cancer risk is not fully understood. We propose that biological and microscopic features can be identified in seemingly histologically NBT in gBRCA1/2m carriers that are indicative of the earliest tissue changes of breast cancer, potentially as a result of accelerated tissue ageing.

To study NBT, we have put in place a unique and scalable repository, named OASIS, storing currently >2,000 digitised whole slide images (WSI) of H&E-stained NBT from individuals with long clinical follow-up. These tissues are from individuals with a spectrum of risk for developing breast cancer and derived from reduction surgery from non-gBRCA1/2m carriers, risk reducing mastectomies, and from contralateral and peri-tumoural NBT from gBRCA1/2m carriers and women with breast cancer.

Across 6 NBT resources, 70 selected WSIs were manually annotated for epithelial cells, fibrous stroma and adipocytes, resembling the "ground truth". Extensive comparisons of different tile sizes, tile overlapping ratios, stain normalisation techniques and deep learning (DL) feature extractors were conducted to implement a Tissue-Classifer, which achieved 95% accuracy in 3-fold cross-validation. Based on the MobileNet architecture, a DL-framework achieved a sensitivity of 81.2% and specificity of 81.8% (84.7% AUC) in predicting Tissue-Age based on discernible histological patterns in healthy women. In gBRCA1/2m carriers, we discovered features of accelerated tissue ageing (e.g. degree of lobule involution), indicating that the biological NBT age differs from their chronological age.

Our DL-based framework robustly captured histological patterns to predict tissue components and age. The global organisation of these patterns showed variations in WSIs of women with different risks of developing breast cancers, which may provide new insights into premalignant alterations in NBT.

Disclosure(s):

Anita Grigoriadis, PhD: No financial relationships to disclose

PS04-01

Clinical impact of timing of systemic therapy in patients with early triple negative breast cancer

Presenting Author(s) and Co-Author(s):

M. Hatzipanagiotou. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Bayern, Germany

M. Pigerl. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

M. Gerken. Bavarian Cancer Registry, Regional Centre Regensburg, Bavarian Health and Food Safety Authority, United States

S. Räßle. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

V. Zeltner. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

M. Hetterich. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

E. Inwald. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

M. Klinkhammer-Schalke. Tumor Center Regensburg - Centre for Quality Management and Health Services Research, University of Regensburg, United States

O. Ortmann. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

S. Seitz. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Regensburg, Bayern, Germany

Introduction TNBC is known for its aggressive nature, with early recurrence and limited treatment options beyond chemotherapy and recently immunotherapy. We aim to clarify, whether timing of systemic therapy has an impact on survival in patients with early TNBC. **Methods** Data from a large population-based regional cancer registry covering over 2.2 million people was used for evaluation, including women with diagnoses of TNBC between 2010 and 2018. Patients were categorized into subgroups according to the interval from TNBC pathologic diagnosis to the date of first administration of NACT (TTNC) or according to the interval from primary surgery to the date of first administration of adjuvant chemotherapy (TTAC). Univariable analyses of survival rates were conducted using the Kaplan-Meier method, the log-rank test was used for group comparisons. IBM SPSS Statistic 25 was used to perform statistical analysis, with hazard ratios, p-values, and 95% confidence intervals calculated for each model. All tests were two-sided, and significance was set at $p < .05$. **Results** We identified 37 382 patients with malignant neoplasms of the mammary gland. The final study cohort included 732 patients with early TNBC, of whom 43.6% were treated with NACT and 40.3% with adjuvant chemotherapy. Timing of NACT 270 patients with TNBC treated with NACT had a valid TTNC. Median follow up was 3.5 years. Patients with TTNC ≤ 14 , ≤ 42 , >42 , and >56 days had estimated mean OS of 8.4, 6.9, 4.6, and 3.3 years, respectively. Patients with a TTNC ≤ 14 days were more likely to survive than patients with a TTNC ≥ 56 days ($p = 0.054$). Significance was barely not reached in the group of NACT. Timing of adjuvant chemotherapy 245 patients with TNBC treated with adjuvant chemotherapy had a valid TTAC. Treatment given within 22-

28 days led to the best outcome with a mean OS of 10.2 years, while later treatment (29-35, 36-42 days, or >6 weeks) had significant reduced mean OS of 8.3, 7.8, and 6.9 years. Patients who received therapy within 22-28 days had significantly better survival than those who received therapy between 29-35 days ($p=0.043$) or after more than 43 days ($p=0.033$).

Conclusion Although significance was barely not reached in the subgroup of patients treated with NACT, the results in this large population-based study indicate that there are critical time intervals for initiation of systemic therapy in patients with early TNBC, with reduced OS if NACT is applied later than 42 days after diagnosis or if adjuvant chemotherapy is applied later than 42 days after surgery. We recommend not to exceed the 6-week interval until the initiation of systemic therapy in patients with early TNBC.

PS04-02

BRCA testing and PARP inhibitor utilization in real-world HER2-negative metastatic breast cancer

Presenting Author(s) and Co-Author(s):

S. Yadav. Mayo Clinic, Rochester, Minnesota, United States

S. Hillman. AstraZeneca, Cambridge, United Kingdom

L. Luo. AstraZeneca, Gaithersburg, Maryland, United States

W. Li. AstraZeneca, Gaithersburg, Maryland, United States

J. Earla. Merck & Co., Inc., Rahway, New Jersey, United States

X. Xu. AstraZeneca, United States

Background: PARP inhibitors (PARPi) have demonstrated progression-free survival benefits vs. chemotherapy in patients (pts) with metastatic breast cancer (mBC) and germline BRCA mutations (gBRCAm). NCCN guidelines recommend that all pts with mBC are offered gBRCAm testing to aid in systemic treatment decisions with PARPi. Understanding real-world gBRCAm testing patterns and PARPi use would be beneficial for improving clinical outcomes of pts with gBRCAm mBC. Methods: This retrospective cohort study identified pts ≥ 18 years old with HER2-negative mBC, diagnosed from 2014 to 2022 (US Flatiron Electronic Health Record database). gBRCAm testing patterns in mBC over time were examined by BC subtype (hormone receptor-positive [HR+] or triple-negative breast cancer [TNBC]) and disease stage at diagnosis [de novo or recurrent]. Timing of gBRCAm testing and subsequent initiation of first-line or later PARPi in pts with gBRCAm HR+ and TNBC mBC was assessed in pts diagnosed after 2018 when PARPi were approved in mBC. Prevalence of gBRCAm was calculated overall and by mBC subtype. Demographic and clinical characteristics were described by gBRCAm testing and PARPi initiation (yes/no). Real-world overall survival (OS) by PARPi use since mBC diagnosis was estimated using the Kaplan-Meier method and a log-rank test. Results: Of 15,006 total pts, 4654 (31.0%) had a gBRCAm test. Compared with pts who were not tested, gBRCAm-tested pts were younger at initial mBC diagnosis (median age: 53.5 vs. 62.0 years), had a shorter median disease-free interval before mBC diagnosis (821 vs. 959 days), and were less likely to have de novo mBC (28.0% vs. 31.2%). gBRCAm testing prevalence was 6.1% in the HR+ group (n=11,945) and 8.9% in the TNBC group (n=2430). gBRCAm testing rates mostly increased from 2014 to 2022 and were lowest in HR+ tumor subtypes; $< 2/3$ of all pts had a gBRCAm test from 2020 onwards (Table). Most pts with recurrent mBC (HR+: 68.3%; TNBC: 76.1%) were gBRCAm tested before diagnosis, whereas pts with de novo mBC were tested at a later timepoint (> 60 days after mBC diagnosis – HR+: 48.3%; TNBC: 38.4%). Of all pts with gBRCAm diagnosed from 2018 onwards (n=187), 44.4% initiated PARPi. A higher proportion of pts with gBRCAm in the TNBC group initiated PARPi (52.9%) than in the HR+ group (42.4%). Pts with gBRCAm in the TNBC group received PARPi earlier than pts with gBRCAm in the HR+ group (mean days from mBC diagnosis to first PARPi use: 173 and 411 days, respectively). Fewer pts with de novo mBC (35.7%) initiated PARPi than pts with recurrent mBC (50.8%). With a median follow-up of 15.3 months, pts with gBRCAm initiated on PARPi had numerically longer median OS (32.3 months [95% CI: 24.2–47.4]) than PARPi non-initiators (21.4 months [95% CI: 18.4–43.5]). OS results should be regarded with caution due to the small sample size (n=187). Conclusions: Despite NCCN guideline gBRCAm-testing recommendations, $< 2/3$ of pts with HER2-negative mBC in our study were gBRCAm tested from 2020 onwards. gBRCAm testing was lower in pts with HR+ disease and was performed at a later timepoint for pts with de novo disease. Wider and timelier implementation of gBRCAm

testing to identify pts that could benefit from PARPi is warranted. Fewer pts with gBRCAm who had HR+ tumors or de novo disease received PARPi than pts with TNBC. Our data suggest that pts who initiated PARPi had numerically longer OS than PARPi non-initiators; further research into OS trends and PARPi use in gBRCAm mBC would be of interest. Editorial acknowledgment: Medical writing assistance was provided by Leigh-Ann Booth, Ph.D. from BOLDSCIENCE Inc., funded by AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, US Legal entity responsible for the study: AstraZeneca. Funding: This study was supported by AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, US, who are codeveloping olaparib.

Table. gBRCAm testing rates over time in pts with H

		Year									
		2014	2015	2016	2017	2018*	2019	2020	2021	2022†	
Pts with HER2- negative mBC that received a gBRCAm test, %	HR-positive, recurrent	18.3	22.6	22.6	29.7	31.8	34.3	37.6	42.1	43.5	
	TNBC, recurrent	30.1	35.0	40.5	38.8	52.4	52.0	58.5	55.7	62.3	
	HR-positive, de novo	19.2	18.7	20.2	25.0	24.0	34.4	32.4	32.9	29.9	
	TNBC, de novo	22.2	30.7	28.1	35.3	39.1	55.2	59.2	51.9	56.4	

ER2-negative mBC

HER2-negative mBC is defined as IHC 0, or 1-positive, or IHC2-positive/ISH-negative.

*Olaparib approved in mBC; †Olaparib approved in eBC. eBC, early breast cancer; gBRCAm, germline breast cancer gene mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; pt, patient; TNBC, triple-negative breast cancer.

PS04-03

Survival benefit of regional nodal irradiation in clinically node-positive breast cancer following neoadjuvant chemotherapy and breast-conserving surgery

Presenting Author(s) and Co-Author(s):

M. Vasigh. Department of surgical Oncology, Fox Chase Cancer Center, Baltimore, Maryland, United States

R. Bleicher. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Williams. Department of surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Aggon. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

M. Pronovost. Temple University, Philadelphia, Pennsylvania, United States

A. Porpiglia. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

M. Pierotti. Department of surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

C. Cruz Pico. Department of surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

Introduction: In recent years, there has been increasing use of neoadjuvant chemotherapy (NAC) and pathologic complete response (pCR) rates for certain breast cancer phenotypes (40-70%). Although encouraging, this has resulted in uncertainties in traditional axillary management. Meanwhile, clinically node-positive (cN+) patients who have a low burden of disease downstaged to node-negative (ypN0) after NAC and get breast-conserving surgery (BCS) may avoid an axillary lymph node dissection (cALND) but still have regional nodal irradiation (RNI) recommended regardless of axillary surgery. Those who remain node-positive (ypN+) undergo cALND and RNI with an increased risk of lymphedema. In this study, we evaluated the survival benefit of RNI in cN+ patients after NAC and BCS. **Methods:** We reviewed (cN+) stage I-III non-inflammatory female breast cancer patients who underwent NAC followed by BCS between 2010 and 2020 in the National Cancer Database (NCDB). Patients having a history of another malignancy who received hormone therapy or radiotherapy before surgery or whose pathologic nodal status (ypN) was unknown were excluded. Overall survival (OS) from surgery was compared between those who did and did not receive RNI. Patient and tumor characteristics were compared across subgroups using chi-square and Wilcoxon rank sum tests. Weighted Kaplan-Meier curves and log-rank tests were used to assess the effect of RNI on OS. As a sensitivity analysis, analyses were stratified based on ypN status. Finally, multivariable logistic regression was used to determine predictors of receiving RNI. **Results:** The 8,250 cN+ patients had a mean age of 54.6±11.1 years. In total, 69.1% of patients were White, 23.9% were Black, and 10.2% were Hispanic. The mean number of removed and positive nodes were 10.0 ±7.8 and 2.3±3.8. The most common histology and phenotype were invasive ductal carcinoma (IDC) in 94.3% and hormone-positive (HR+) in 41.0%. Breast and nodal pCR rates were 25.9% and 34.7%, with nodal pCR achieved in 20.7%, 46.0%, and 44.4% of HR+, HER2+, and triple-negative tumors. RNI was performed in 52.1% of the patients (45.3% of the ypN0 and 55.9% of the ypN+). The mean number of nodes removed was 10.4±7.8 in the RNI+ and 9.6±7.7 in the RNI- groups (P< 0.01). The mean number of positive nodes was 2.6±4.0 in the RNI+ and 1.9±3.6 in the RNI- groups (P< 0.01). On multivariable analysis, the predictors of RNI administration included the number of positive nodes (p< 0.01), cN stage (p< 0.01), cT3 (p< 0.01), and tumor phenotype (p< 0.01). Grade I tumors (p=0.04) and Medicare beneficiaries (p=0.01) were less likely to get RNI. The survival rates were 79.9% and

81.9% in the RNI+ and RNI- groups, with a median follow-up of 62.1±31.4 and 62.8±32.2 in the RNI+ and RNI- groups. In the entire cohort, ypN0 patients had improved OS when compared with ypN+ patients ($p < 0.001$), but in adjusted analyses, there was no difference in OS between those who did and did not receive RNI ($p=0.6$). There was also no difference in OS comparing those who did and did not receive RNI in the ypN0 ($p=0.96$) or ypN+ ($p=0.76$) groups.

Conclusion: For breast cancer patients having a modest nodal burden of disease and BCS after NAC, traditional prognostic factors such as stage and nodal status, as well as phenotype, grade, and the presence or absence of pCR, impact overall survival. Although some such factors appear to bias practitioners into giving RNI for patients undergoing NAC and BCS, RNI after NAC and BCS does not improve OS, regardless of pCR status, even at a mean follow-up time of 5.5 years. Further studies evaluating the impact on local control and longer-term outcomes should be pursued to enable the creation of specific guidelines surrounding indications for RNI based on the initial burden of disease and the final response from NAC administration.

PS04-04

Adverse effects (AEs) reported via Patient Reported Outcome Measures (PROMs): A longitudinal analysis of the IMPORT HIGH breast radiotherapy trial (CRUK/06/003)

Presenting Author(s) and Co-Author(s):

S. Ng. Clinical Trials and Statistics Unit, Institute of Cancer Research, London, England, United Kingdom

I. Bhattacharya. Cambridge University Hospitals NHS Foundation Trust, United States

J. Haviland. Queen Mary University of London, United Kingdom

C. Griffin. Clinical Trials and Statistics Unit, Institute of Cancer Research, London, England, United Kingdom

M. Sydenham. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

A. Kirby. The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, United States

P. Hopwood. Clinical Trials and Statistics Unit, Institute of Cancer Research, London, England, United States

C. Kirwan. The University of Manchester, United States

C. Coles. University of Cambridge, United Kingdom

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

Background IMPORT HIGH is a multicentre phase III randomised controlled trial showing efficacy and safety of appropriately-dosed simultaneous integrated boost (SIB) in terms of local control, patient and clinician reported AEs among women with early breast cancer (BC)[1]. The PROMs sub-study collected baseline demographics and quality of life over 5 years. This exploratory analysis details the patient experience over time. Methods Women with higher-than-average risk of local relapse (≥ 18 years, breast conserving surgery, T1-3, pN0-pN3a, M0 invasive BC) were eligible. Randomisation (1:1:1) was between 40Gy whole breast and 16Gy sequential boost radiotherapy (control) and, 36Gy whole breast, 40Gy partial breast with either 48Gy SIB (test group 1), or 53Gy SIB (test group 2) radiotherapy. AEs from EORTC QLQ-BR23[2]; Body Image Scale (BIS)[3]; and protocol-specific (PS) items used in previous breast radiotherapy trials[4] were reported by patients at baseline (pre-randomisation), 6 months, and years 1, 3, 5. 24 AEs[4] were included in the analysis, dichotomised as none/mild versus moderate/marked. Anxiety and depression were measured over 5 years using Hospital Anxiety and Depression Scale. Surgical deficit was scored from baseline photographs. Multivariable generalized estimating equation models were fitted for each AE. Potential baseline predictors included those used previously[4] plus ethnicity, smoking, deprivation, employment, cardiovascular disease history, post-operative infection, haematoma, post-surgery complication. Backwards selection and Quasi-likelihood criterion were used for model selection. Results Between 2009-2013, 1338 patients were offered the PROMs sub-study and 1078 (81%) participated. Median age was 48.8 years (IQR 44.0-54.9). 17% reported 'Borderline' or 14% 'Case' anxiety at baseline. 11% reported 'Borderline' or 7% 'Case' depression at baseline. 747/1015 (74%), 686/986 (70%), 604/916 (66%), 532/845 (63%), 461/709 (65%) of participants reported at least 1 moderate/marked AE at baseline, 6 months, 1, 3 and 5 years. Number of moderate/marked AEs reported per person reduced over time after year 1 ($p < 0.005$). BIS reported moderate/marked AEs (except dissatisfaction with scar) decreased, whereas

individual items from BR23 and PS items showed mixed patterns of reporting (increased, decreased, stayed the same) over time (Table 1). From multivariable analysis, 'Borderline' or 'Case' depression or anxiety (time-varying) was associated with increased reports for almost all AEs. Chemotherapy and younger age were associated with increased reports of moderate/marked AEs for items in BIS, and large surgical deficit predicted more breast symptoms. Conclusion Change of overall breast appearance was the most reported moderate/marked AE that persisted over time. Although patients reported fewer moderate/marked AEs over time, trends in individual moderate/marked AEs showed mixed patterns. This study identified factors associated with increased risks of patient-reported moderate/marked AEs. Early identification of patients more likely to report AEs could facilitate implementation of targeted support. References 1. Coles et al, The Lancet 2023 2. Sprangers et al, J Clin Oncol 1996 3. Hopwood et al, Eur J Cancer 2001 4. Bhattacharya et al, J Clin

Oncol 2019 Table 1

Prevalence of Moderate/Marked Adverse Effects	Baseline (%)	6 months (%)	1 year (%)	3 years (%)	5 years (%)	Cochran-Armitage test for trend (p value)*
BR23 (shoulder, breast and arm) (during the past week)						
Did you have any pain in your arm or shoulder?	188(18.6)	186(18.9)	165(18.0)	142(16.8)	127(17.9)	0.83
Body image scale (during the past week)						
Have you felt less physically attractive as a result of your disease or treatment?	432(42.7)	303(30.7)	191(20.9)	157(18.6)	130(18.3)	<0.0001
Protocol specific items (any changes to your breast that may have resulted from any of your breast cancer treatments)						
Has the overall appearance of your breast changed, compared with the other side?	261(25.8)	306(31.0)	291(31.8)	233(27.6)	242(34.1)	0.009
*Cochran-Armitage test for trend performed for those items where patients reported ≥ 10% moderate/marked AEs overall.						

Trend over time for most commonly reported AE from each questionnaire

PS04-06

Breast cancer recurrence among women with pre-diagnostic major depression and co-existing substance abuse disorder: A retrospective study in the United States Veterans Health Administration Cohort

Presenting Author(s) and Co-Author(s):

M. Aboumrad. Johns Hopkins Bloomberg School of Public Health, MD and White River Junction VA Medical Center, Baltimore, Maryland, United States

K. Visvanathan. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, MD and Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States

Background: Our prior study observed a 34% higher risk of breast cancer (BC) recurrence among women with major depressive disorder (MDD) at the time of their BC diagnosis compared to women without MDD after adjusting for sociodemographic, clinical, and prognostic factors. Given the high prevalence of substance abuse disorders among individuals with MDD and the positive association between alcohol use and mortality among BC survivors, we were interested to examine whether the risk of BC recurrence was compounded for women with both conditions. **Objective:** To investigate whether pre-diagnostic substance abuse disorders modify the association between MDD and BC recurrence. **Methods:** We established a retrospective cohort of women (age ≥ 18 years) with incident, early-stage BC diagnosed from 2010 through 2019 using the VHA's electronic medical record database. A two-year window was used to identify women with MDD and co-existing substance abuse disorders prior to their BC diagnosis. We examined potential interactions between MDD and alcohol abuse and MDD and other substance abuse using multivariable proportional hazards regression, accounting for competing risk of death. Our outcome of interest was BC recurrence. The reference group for all analyses was women with BC alone. The models were adjusted for patient characteristics including age, race, ethnicity, marital status, rurality of primary residence, priority group rating (proxy for socioeconomic status), any homelessness or economic problems, comorbidity burden, body mass index, smoking status, receipt of a screening mammography, year of BC diagnosis, cancer stage, cancer subtype, and cancer treatment. Subgroup analyses were conducted by cancer subtype. **Results:** Our cohort comprised 6,045 women with BC, of whom 1,754 (29%) had a pre-diagnostic MDD diagnosis and 1,509 (25%) had a substance abuse disorder. Among women with MDD, 386 (22%) abused alcohol and 336 (19%) abused other substances. The median length of follow-up from BC diagnosis was 4.5 years (IQR=4.8 years). The average age at BC diagnosis was 57 years (SD=11 years) overall, 56 years (SD=10 years) among women with MDD, and 57 years (SD=9 years) among women with substance abuse disorders. On multivariable analysis, MDD (HR=1.33; 95% CI: 1.14, 1.53), alcohol abuse disorder (HR=1.37; 95% CI: 1.12, 1.68), and other substance abuse disorders (HR=1.33; 95% CI: 1.13, 1.56) were independent risk factors for BC recurrence. Further, there was a statistically significant interaction between pre-diagnostic MDD and alcohol abuse disorder (p -interaction=0.003). Women with BC who had both pre-diagnostic MDD and alcohol abuse disorder were at a 65% (HR=1.65; 95% CI: 1.29, 2.11) higher risk of BC recurrence compared to women with BC alone. A statistically significant interaction was also observed between pre-diagnostic MDD and other substance abuse disorders (p -interaction < 0.001). Women with BC who had both pre-diagnostic MDD and other substance abuse disorders were at a 90% (HR=1.90; 95% CI: 1.50, 2.42) higher risk of BC recurrence compared to women with BC alone. In subgroup analyses, the interaction between MDD and alcohol abuse disorders (p -interaction=0.001) and MDD and other substance abuse disorders (p -interaction < 0.001) was limited to women with estrogen receptor positive cancer but not estrogen receptor negative cancer. **Conclusion:** Women with incident BC who have prior diagnoses of both MDD and

substance abuse disorder are at higher risk of recurrence than women with either exposure independently. Further research is needed to examine the etiology of our findings and to evaluate whether this newly defined risk group would benefit from closer monitoring and more tailored treatment options.

PS04-07

Associations between Virtual Care Access and Psychological and Mental Health Conditions among Adults with Breast Cancer in the US: A Population-Based Analysis

Presenting Author(s) and Co-Author(s):

J. Freeman. Department of Public Health Sciences, University of Chicago, Chicago, Illinois, United States

T. Akhiwu. Department of Medicine, MedStar Union Memorial Hospital, Baltimore, Maryland, United States

Y. Lee. Rutgers, The State University of New Jersey, New Brunswick, New Jersey, United States

X. Li. Milken Institute School of Public Health, The George Washington University, Washington, District of Columbia, United States

Background: Adults with breast cancer (AwBC) often experience psychological and mental health challenges and face many barriers to accessing mental health care and services. Telemedicine can help facilitate access to these care and services and AwBC may benefit uniquely from virtual care. However, little is known about the relationships between virtual care access (VCA) and psychological and mental health conditions in AwBC nationally. **Methods:** We obtained a population-based sample from the 2021 National Health Interview Survey that used stratified clustering sampling to interview US adults. This study was limited to adults who ever had breast cancer. VCA was defined as having had a virtual (i.e., phone or video) medical visit with a health provider in the past 12 months and was categorized as “yes/no.” Serious psychological distress, measured using the 6-item Kessler scale, was dichotomized based on a cutoff score of 13. Having an anxiety disorder or depression was self-reported as “yes/no.” Weighted proportions and 95% confidence intervals (CI) were tabulated and compared using Rao-Scott chi-square tests. Multivariable logistic regression models were fit to calculate adjusted odds ratios (AOR) and 95% CIs. All statistical analyses accounted for complex sample design and survey weights. **Results:** The unweighted sample size was 698, representing a weighted sample of 4,379,870 AwBC in the US. The mean age was 67.7 years; 77.6% were White and 9.6% were Black; 53.8% and 38.9% were privately insured and on Medicaid/Medicare, respectively. Of the total, 20.9% (95% CI: 17.3-24.6%) had depression, 17.4% (95% CI: 14.0-20.9%) had an anxiety disorder, and 3.2% (95% CI: 1.7-4.7%) experienced serious psychological distress. Overall, 50.3% (95% CI: 46.1-54.4%) had a virtual visit. White AwBC reported a higher proportion of VCA than Black AwBC (50.6% vs. 38.6%). AwBC on Medicaid/Medicare reported a lower proportion of VCA than those privately insured (47.8% vs. 51.8%). AwBC who experienced serious psychological distress had a higher percentage of VCA than those who did not (78.5% [95% CI: 60.8-96.2%] vs. 48.5% [95% CI: 44.2-52.8%], $p=.007$). Compared with AwBC who did not have depression, those who did had a higher percentage of VCA (63.9% [95% CI: 54.6-73.2%] vs. 46.6% [42.0-51.3%], $p=.002$). Similarly, AwBC with an anxiety disorder reported a higher percentage of VCA than those without (60.4% [95% CI: 50.3-70.6%] vs. 48.1% [43.6-52.6%], $p=.032$). Furthermore, AwBC who frequently felt anxious or depressed were more likely than those who felt less frequently to use telemedicine. In the adjusted regression models, AwBC experiencing serious psychological distress had significantly greater odds of VCA than those not experiencing (AOR=3.79, 95% CI: 1.05-13.7). AwBC with depression had significantly greater odds of VCA than those without (AOR=2.02, 95% CI: 1.25-3.28). Although AwBC with an anxiety disorder also had greater odds of VCA than those without (AOR=1.45, 95% CI: 0.89-2.38), the association was not statistically significant. **Conclusions:** In this nationally representative sample of US AwBC, more than one in

6 had an anxiety disorder or depression and VCA was prevalent in the past 12 months. AwBC with serious psychological distress, anxiety, or depression were more likely than those without to use telemedicine, indicating a greater need for virtual care among AwBC. Our findings also suggest that to help AwBC improve their psychological and mental health conditions and address their unmet needs, breast cancer support programs would need to ensure equitable access to virtual care and services in this patient population.

PS04-08

Sociodemographic Risk Factors and Prediction of Aromatase Inhibitor Non-Adherence in Women with Breast Cancer Enrolled in SWOG S1105

Presenting Author(s) and Co-Author(s):

D. Hershman. Columbia University, New York, New York, United States

A. Moseley. Fred Hutchinson Cancer Research Institute, United States

K. Arnold. SWOG Statistics and Data Management Center, Seattle, Washington, United States

J. Gralow. ASCO, United States

A. Neugut. Herbert Irving Comprehensive Cancer Center, Vagelos College of Physicians and Surgeons, Columbia University, United States

S. Ramsey. Fred Hutchinson Cancer Research Institute, United States

N. Henry. University of Michigan Medical School, United States

J. Unger. Fred Hutchinson Cancer Center, United States

Background: Non-adherence to aromatase inhibitors (AIs) for breast cancer is common and increases risk of recurrence. Few prospective studies have systematically evaluated non-adherence and non-clinical factors associated with it. We analyzed baseline sociodemographic characteristics and financial factors associated with non-adherence to create a baseline composite risk-score for AI non-adherence. **Methods:** Patients enrolled in S1105 were required to have been on an AI for ≥ 30 days at enrollment. Patients were assessed for non-adherence of AIs every 3 months for 36 months, with non-adherence defined as urine AI metabolite assay results satisfying any of the following: < 10 ng/mL, undetectable, specimen submitted outside of the ± 21 -day follow-up appointment window, or no submitted specimen. Factors included race, Hispanic ethnicity, age, education, income, health insurance type, and prescription cost. We also included socioeconomic deprivation and rural or urban residence using trial participants' residential zip codes linked to the Area Deprivation Index (ADI) and Rural Urban Continuum codes (RUCC) respectively. For numeric factors and categorical factors with more than two levels, we used cutpoint analysis to determine the highest risk range by optimizing the Chi-squared statistic. For each resulting binary factor, we performed a logistic regression, adjusting for the study stratification factors and stratifying by treatment arm. Factors associated with adherence at the $\alpha=0.10$ level were combined into a composite risk score, with study participants given one point for each baseline adverse risk factor. Secondarily, we examined a composite risk score including all factors, regardless of statistical significance. **Results:** In total, 724 patients were registered from 40 institutions between May 2012 and September 2013. The median age was 60.9 years, and 64.5% were on AI < 12 months prior to registration. Only 8% had out of pocket (OOP) cost $> \$30$. Observed adherence at 36 months was 35.9%. Patients living in metro areas with populations $\geq 250,000$ ($\text{RUCC} \leq 3$) were more likely to be non-adherent (37.5% vs 28.3%, $\text{OR}=1.50$, $p=.08$); as were those who were younger, those without a college education, and those with limited ($\leq \$5$) OOP cost. ADI, race and ethnicity were not associated with non-adherence. The composite risk score was strongly associated with 36-month adherence. For each 1 unit increase in risk level, the risk of non-adherence increased 47% ($\text{OR}=1.47$, $p < .001$); the risk increased 64% for those with > 2 vs. ≤ 2 risk factors ($\text{OR}=1.64$, $p=.002$). Results using all factors regardless of statistical significance were consistent. **Conclusions:** A composite model comprised of sociodemographic risk factors can identify patients on AI's at much greater risk of long-term AI non-adherence. In addition to mitigating side effects, targeted interventions to improve adherence should focus on structural barriers among those at highest risk.

Non-adherence (+/- 6 months) = factor + AI duration + AI type, stratified by arm

Non-adherence (+/- 6 months) = factor + AI duration + AI type, stratified by arm			
Baseline factor	Adverse vs. Non-Adverse Risk Category (% non-adherent)	OR (95% CI)	P
Univariate Models			
Age	≤ 65 (38.6%) vs >65 (28.7%)	1.48 (1.03-2.13)	.03
Race	Not Black (36.2%) vs Black (32.6%)	1.09 (0.57-2.07)	.79
Ethnicity	Hispanic (46.7%) vs Not Hispanic (35.5%)	1.59 (0.76-3.34)	.22
Education	<High School (39.5%) vs College/graduate school (32.6%)	1.35 (0.98-1.86)	.07
Income	≤ 90,000 (37.4%) vs >90,000 (31.5%)	1.30 (0.89-1.90)	.17
Insurance	Other or no insurance (37.1%) vs Private insurance (34.1%)	1.17 (0.85-1.60)	.34
Out of pocket cost	≤ \$5 (40.9%) vs >\$5 (32.3%)	1.45 (1.03-2.03)	.03
RUCC code	≤ 3 (37.5%) vs >3 (28.3%)	1.50 (0.96-2.34)	.08
ADI national rank	>20 (36.8%) vs ≤ 20 (29.9%)	1.35 (0.80-2.26)	.26
Composite Risk Models			
Statistically significant factors only	Each 1 unit increase	1.47 (1.23-1.75)	<.001
	>2 (42.8%) vs ≤ 2 (30.8%) factors	1.64 (1.20-2.25)	.002
All factors	Each 1 unit increase	1.31 (1.16-1.48)	<.001
	>5 (44.5%) vs ≤ 5 (28.6%) factors	1.97 (1.44-2.70)	<.001

PS04-09

Patient-Reported Benefit of Resources Designed to Assist with the Financial Toxicity of Breast Cancer

Presenting Author(s) and Co-Author(s):

F. Chino. Memorial Sloan Kettering Cancer Center, New York, New York, United States

S. Meske. Breastcancer.org, United States

M. Giaddui. Lankenau Institute for Medical Research, United States

D. Manasseh. Maimonides Medical Center, United States

B. Thom. UNC Lineberger Comprehensive Cancer Center, United States

M. Weiss. Breastcancer.org, United States

Background: A breast cancer (BC) diagnosis can cause financial stress, which may worsen disease outcomes and create financial instability. Tailored interventions are urgently needed, but the patient perspective on the utility of financial resource options is limited. Methods: From 6-7/2022, Breastcancer.org community members consented to an online survey in English or Spanish. Eligibility included: US resident, age \geq 18, and BC diagnosis within 10 years. Survey assessed burden of out-of-pocket expenses and perceived benefit of available (1 “Not at all” to 5 “Very much”) and potential (ranked choice) resources. Results: 1,437 participated. Mean age and time since diagnosis was 46 and 2 years, respectively; 75% were in active treatment for non-metastatic (89%) or metastatic (11%) disease. Patients were 60% White, 27% Hispanic, 8% Black, and 4% other race; 94% were women. 47% had either “significant” or “catastrophic” financial burden due to BC, with higher burdens in those with metastatic disease (61% vs 45%, $p < 0.001$). Direct assistance programs (e.g., reduced cost medications, grants, transportation) were rated the most helpful to respondents (Table). A grant list, a provider question checklist, and access to professional advice were most often ranked as 1st choice for potential resources. There were significant differences by race/ethnicity and disease status. Conclusions: Almost one-half of surveyed patients had significant financial burden due to BC. Patient-centered solutions to lessen financial burdens and optimize patient outcomes should consider direct assistance and patient education to improve knowledge, communication, and self-advocacy.

How helpful were/are each of these resources in helping you cope with the financial burdens of BC?	Overall Mean	Disease Status		Race/Ethnicity			
		Non-metastatic	Metastatic	White	Black	Hispanic	Other

Patient assistance programs offered by pharma or medical test companies	2.9 (n=1,107)	2.9 (n=975)	3.1* (n=132)	2.9* (n=618)	2.6 (n=94)	3.1* (n=357)	2.6 (n=388)
Nonprofits that provide grants to help cover expenses of people with cancer	2.8 (n=1,113)	2.8 (n=991)	2.7 (n=122)	2.8 (n=611)	2.6 (n=100)	3.1* (n=358)	2.4 (n=44)
Financial assistance department at the cancer center or hospital	2.8 (n=1,176)	2.8 (n=1,046)	2.7 (n=130)	2.7* (n=669)	2.7 (n=103)	3.1* (n=362)	2.2 (n=42)
Coupons and savings cards to reduce the cost of prescription drugs	2.8 (n=1,140)	2.8 (n=1,008)	2.7 (n=132)	2.7 (n=648)	2.5 (n=92)	3.0* (n=358)	2.5 (n=42)
Programs that provide free or low-cost transportation to medical appointments	2.7 (n=1,042)	2.8* (n=934)	2.4 (n=108)	2.6 (n=556)	2.5 (n=93)	3.0* (n=356)	2.3 (n=37)
Clinical trials	2.7 (n=1,032)	2.7* (n=928)	2.5 (n=104)	2.6* (n=557)	2.3 (n=84)	3.0* (n=357)	2.1 (n=34)
Professional medical billing advocates	2.7 (n=1,105)	2.7* (n=994)	2.3 (n=111)	2.5* (n=612)	2.4 (n=94)	3.0* (n=358)	2.1 (n=41)

Social worker or case manager	2.7 (n=1,146)	2.7 (n=1,027)	2.6 (n=119)	2.6* (n=644)	2.3 (n=99)	2.9* (n=360)	2.4 (n=43)
Nonprofits that provide advice and education about financial issues	2.7 (n=1,100)	2.7 (n=983)	2.5 (n=117)	2.6* (n=607)	2.3 (n=96)	3.0* (n=359)	2.0 (n=38)
Financial navigator	2.6 (n=1,087)	2.6 (n=976)	2.5 (n=111)	2.5 (n=598)	2.5 (n=94)	2.9* (n=356)	2.1 (n=39)
Which of the following programs and resources would have been (or would be) most useful to you in navigating the financial burdens of BC?	Total	Non-metastatic (n=1,282)	Metastatic (n=155)	White (n=686)	Black (n=121)	Hispanic (n=384)	Other (n=64)
A list of financial grants people diagnosed with BC can apply for	18%	18%	19%	19%*	24%*	14%	25%*
A checklist of questions to ask your healthcare team to help you minimize the financial	15%	16%	12%	16%	17%	15%	9%

burdens of BC							
Access to free or reduced-price professionals to help with medical billing, financial, benefits, and/or legal issues	13%	13%	8%	11%	8%	15%*	20%*

* p< 0.001

PS04-01

Clinical impact of timing of systemic therapy in patients with early triple negative breast cancer

Presenting Author(s) and Co-Author(s):

M. Hatzipanagiotou. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Bayern, Germany

M. Pigerl. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

M. Gerken. Bavarian Cancer Registry, Regional Centre Regensburg, Bavarian Health and Food Safety Authority, United States

S. Räßle. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

V. Zeltner. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

M. Hetterich. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

E. Inwald. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

M. Klinkhammer-Schalke. Tumor Center Regensburg - Centre for Quality Management and Health Services Research, University of Regensburg, United States

O. Ortmann. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Germany

S. Seitz. Department of Gynecology and Obstetrics, University Medical Centre Regensburg, Regensburg, Bayern, Germany

Introduction

TNBC is known for its aggressive nature, with early recurrence and limited treatment options beyond chemotherapy and recently immunotherapy. We aim to clarify, whether timing of systemic therapy has an impact on survival in patients with early TNBC.

Methods

Data from a large population-based regional cancer registry covering over 2.2 million people was used for evaluation, including women with diagnoses of TNBC between 2010 and 2018. Patients were categorized into subgroups according to the interval from TNBC pathologic diagnosis to the date of first administration of NACT (TTNC) or according to the interval from primary surgery to the date of first administration of adjuvant chemotherapy (TTAC). Univariable analyses of survival rates were conducted using the Kaplan-Meier method, the log-rank test was used for group comparisons. IBM SPSS Statistic 25 was used to perform statistical analysis, with hazard ratios, p-values, and 95% confidence intervals calculated for each model. All tests were two-sided, and significance was set at $p < .05$.

Results

We identified 37 382 patients with malignant neoplasms of the mammary gland. The final study cohort included 732 patients with early TNBC, of whom 43.6% were treated with NACT and 40.3% with adjuvant chemotherapy.

Timing of NACT

270 patients with TNBC treated with NACT had a valid TTNC. Median follow up was 3.5 years. Patients with TTNC ≤ 14 , ≤ 42 , >42 , and >56 days had estimated mean OS of 8.4, 6.9, 4.6, and 3.3 years, respectively. Patients with a TTNC ≤ 14 days were more likely to survive than patients with a TTNC ≥ 56 days ($p=0.054$). Significance was barely not reached in the group of NACT.

Timing of adjuvant chemotherapy

245 patients with TNBC treated with adjuvant chemotherapy had a valid TTAC. Treatment given within 22-28 days led to the best outcome with a mean OS of 10.2 years, while later treatment (29-35, 36-42 days, or >6 weeks) had significant reduced mean OS of 8.3, 7.8, and 6.9 years. Patients who received therapy within 22-28 days had significantly better survival than those who received therapy between 29-35 days ($p=0.043$) or after more than 43 days ($p=0.033$).

Conclusion

Although significance was barely not reached in the subgroup of patients treated with NACT, the results in this large population-based study indicate that there are critical time intervals for initiation of systemic therapy in patients with early TNBC, with reduced OS if NACT is applied later than 42 days after diagnosis or if adjuvant chemotherapy is applied later than 42 days after surgery. We recommend not to exceed the 6-week interval until the initiation of systemic therapy in patients with early TNBC.

Disclosure(s):

Stephan Seitz: Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing), Gilead (Ongoing), GSK (Ongoing), Lilly (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Roche (Ongoing)

Poster Spotlight Session 4: Gaps in the Timing, Treatment Selection, and Supportive Services for Cancer Care

Presenting Author(s) and Co-Author(s):

M. West. University of Wisconsin, Madison, Madison, Wisconsin, United States

Disclosure(s):

Malinda T. West, MD, MS: No financial relationships to disclose

PS04-02

BRCA testing and PARP inhibitor utilization in real-world HER2-negative metastatic breast cancer

Presenting Author(s) and Co-Author(s):

S. Yadav. Mayo Clinic, Rochester, Minnesota, United States

S. Hillman. AstraZeneca, Cambridge, United Kingdom

L. Luo. AstraZeneca, Gaithersburg, Maryland, United States

W. Li. AstraZeneca, Gaithersburg, Maryland, United States

J. Earla. Merck & Co., Inc., Rahway, New Jersey, United States

X. Xu. AstraZeneca, United States

Background:

PARP inhibitors (PARPi) have demonstrated progression-free survival benefits vs. chemotherapy in patients (pts) with metastatic breast cancer (mBC) and germline BRCA mutations (gBRCAm). NCCN guidelines recommend that all pts with mBC are offered gBRCAm testing to aid in systemic treatment decisions with PARPi. Understanding real-world gBRCAm testing patterns and PARPi use would be beneficial for improving clinical outcomes of pts with gBRCAm mBC.

Methods:

This retrospective cohort study identified pts ≥ 18 years old with HER2-negative mBC, diagnosed from 2014 to 2022 (US Flatiron Electronic Health Record database). gBRCAm testing patterns in mBC over time were examined by BC subtype (hormone receptor-positive [HR+] or triple-negative breast cancer [TNBC]) and disease stage at diagnosis [de novo or recurrent]). Timing of gBRCAm testing and subsequent initiation of first-line or later PARPi in pts with gBRCAm HR+ and TNBC mBC was assessed in pts diagnosed after 2018 when PARPi were approved in mBC. Prevalence of gBRCAm was calculated overall and by mBC subtype. Demographic and clinical characteristics were described by gBRCAm testing and PARPi initiation (yes/no). Real-world overall survival (OS) by PARPi use since mBC diagnosis was estimated using the Kaplan-Meier method and a log-rank test.

Results:

Of 15,006 total pts, 4654 (31.0%) had a gBRCAm test. Compared with pts who were not tested, gBRCAm-tested pts were younger at initial mBC diagnosis (median age: 53.5 vs. 62.0 years), had a shorter median disease-free interval before mBC diagnosis (821 vs. 959 days), and were less likely to have de novo mBC (28.0% vs. 31.2%). gBRCAm testing prevalence was 6.1% in the HR+ group (n=11,945) and 8.9% in the TNBC group (n=2430). gBRCAm testing rates mostly increased from 2014 to 2022 and were lowest in HR+ tumor subtypes; $< 2/3$ of all pts had a gBRCAm test from 2020 onwards (Table). Most pts with recurrent mBC (HR+: 68.3%; TNBC: 76.1%) were gBRCAm tested before diagnosis, whereas pts with de novo mBC were tested at a later timepoint (> 60 days after mBC diagnosis – HR+: 48.3%; TNBC: 38.4%). Of all pts with gBRCAm diagnosed from 2018 onwards (n=187), 44.4% initiated PARPi. A higher proportion of pts with gBRCAm in the TNBC group initiated PARPi (52.9%) than in the HR+ group (42.4%). Pts with gBRCAm in the TNBC group received PARPi earlier than pts with gBRCAm in the HR+ group (mean days from mBC diagnosis to first PARPi use: 173 and 411 days, respectively). Fewer pts with de novo mBC (35.7%) initiated PARPi than pts with recurrent mBC (50.8%). With a median follow-up of 15.3 months, pts with gBRCAm initiated on

PARPi had numerically longer median OS (32.3 months [95% CI: 24.2–47.4]) than PARPi non-initiators (21.4 months [95% CI:18.4–43.5]). OS results should be regarded with caution due to the small sample size (n=187).

Conclusions:

Despite NCCN guideline gBRCAm-testing recommendations, < 2/3 of pts with HER2-negative mBC in our study were gBRCAm tested from 2020 onwards. gBRCAm testing was lower in pts with HR+ disease and was performed at a later timepoint for pts with de novo disease. Wider and timelier implementation of gBRCAm testing to identify pts that could benefit from PARPi is warranted. Fewer pts with gBRCAm who had HR+ tumors or de novo disease received PARPi than pts with TNBC. Our data suggest that pts who initiated PARPi had numerically longer OS than PARPi non-initiators; further research into OS trends and PARPi use in gBRCAm mBC would be of interest.

Editorial acknowledgment:

Medical writing assistance was provided by Leigh-Ann Booth, Ph.D. from BOLDSCIENCE Inc., funded by AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, US

Legal entity responsible for the study: AstraZeneca.

Funding:

This study was supported by AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, US, who are codeveloping olaparib.

Table. gBRCAm testing rates over time in pts with HER2-negative mBC

		Year									
		2014	2015	2016	2017	2018*	2019	2020	2021	2022†	
Pts with HER2-negative mBC that received a gBRCAm test, %	HR-positive, recurrent	16.3	22.6	22.6	29.7	31.8	34.3	37.6	42.1	43.5	
	TNBC, recurrent	30.1	35.0	40.5	38.8	52.4	52.0	58.5	55.7	62.3	
	HR-positive, de novo	19.2	18.7	20.2	25.0	24.0	34.4	32.4	32.9	29.9	
	TNBC, de novo	22.2	30.7	28.1	35.3	39.1	55.2	59.2	51.9	56.4	

HER2-negative mBC is defined as IHC 0, or 1-positive, or IHC2-positive/ISH-negative.
*Olaparib approved in mBC; †Olaparib approved in eBC. eBC, early breast cancer; gBRCAm, germline breast cancer gene mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; pt, patient; TNBC, triple-negative breast cancer.

Disclosure(s):

Siddhartha Yadav, MD: Advisory Board (no personal compensation): AstraZeneca (Terminated); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZenca (Ongoing), REPARE Therapeutics (Ongoing)

PS04-03

Survival benefit of regional nodal irradiation in clinically node-positive breast cancer following neoadjuvant chemotherapy and breast-conserving surgery

Presenting Author(s) and Co-Author(s):

M. Vasigh. Department of surgical Oncology, Fox Chase Cancer Center, Baltimore, Maryland, United States

R. Bleicher. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Williams. Department of surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Aggon. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

M. Pronovost. Temple University, Philadelphia, Pennsylvania, United States

A. Porpiglia. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

M. Pierotti. Department of surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

C. Cruz Pico. Department of surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

Introduction:

In recent years, there has been increasing use of neoadjuvant chemotherapy (NAC) and pathologic complete response (pCR) rates for certain breast cancer phenotypes (40-70%). Although encouraging, this has resulted in uncertainties in traditional axillary management. Meanwhile, clinically node-positive (cN+) patients who have a low burden of disease downstaged to node-negative (ypN0) after NAC and get breast-conserving surgery (BCS) may avoid an axillary lymph node dissection (cALND) but still have regional nodal irradiation (RNI) recommended regardless of axillary surgery. Those who remain node-positive (ypN+) undergo cALND and RNI with an increased risk of lymphedema. In this study, we evaluated the survival benefit of RNI in cN+ patients after NAC and BCS.

Methods:

We reviewed (cN+) stage I-III non-inflammatory female breast cancer patients who underwent NAC followed by BCS between 2010 and 2020 in the National Cancer Database (NCDB). Patients having a history of another malignancy who received hormone therapy or radiotherapy before surgery or whose pathologic nodal status (ypN) was unknown were excluded. Overall survival (OS) from surgery was compared between those who did and did not receive RNI. Patient and tumor characteristics were compared across subgroups using chi-square and Wilcoxon rank sum tests. Weighted Kaplan-Meier curves and log-rank tests were used to assess the effect of RNI on OS. As a sensitivity analysis, analyses were stratified based on ypN status. Finally, multivariable logistic regression was used to determine predictors of receiving RNI.

Results:

The 8,250 cN+ patients had a mean age of 54.6±11.1 years. In total, 69.1% of patients were White, 23.9% were Black, and 10.2% were Hispanic. The mean number of removed and positive nodes were 10.0 ±7.8 and 2.3±3.8. The most common histology and phenotype were invasive ductal carcinoma (IDC) in 94.3% and hormone-positive (HR+) in 41.0%. Breast and nodal pCR rates were 25.9% and 34.7%, with nodal pCR achieved in 20.7%, 46.0%, and 44.4% of HR+, HER2+, and triple-negative tumors. RNI was performed in 52.1% of the patients

(45.3% of the ypN0 and 55.9% of the ypN+). The mean number of nodes removed was 10.4 ± 7.8 in the RNI+ and 9.6 ± 7.7 in the RNI- groups ($P < 0.01$). The mean number of positive nodes was 2.6 ± 4.0 in the RNI+ and 1.9 ± 3.6 in the RNI- groups ($P < 0.01$). On multivariable analysis, the predictors of RNI administration included the number of positive nodes ($p < 0.01$), cN stage ($p < 0.01$), cT3 ($p < 0.01$), and tumor phenotype ($p < 0.01$). Grade I tumors ($p=0.04$) and Medicare beneficiaries ($p=0.01$) were less likely to get RNI. The survival rates were 79.9% and 81.9% in the RNI+ and RNI- groups, with a median follow-up of 62.1 ± 31.4 and 62.8 ± 32.2 in the RNI+ and RNI- groups. In the entire cohort, ypN0 patients had improved OS when compared with ypN+ patients ($p < 0.001$), but in adjusted analyses, there was no difference in OS between those who did and did not receive RNI ($p=0.6$). There was also no difference in OS comparing those who did and did not receive RNI in the ypN0 ($p=0.96$) or ypN+ ($p=0.76$) groups.

Conclusion:

For breast cancer patients having a modest nodal burden of disease and BCS after NAC, traditional prognostic factors such as stage and nodal status, as well as phenotype, grade, and the presence or absence of pCR, impact overall survival. Although some such factors appear to bias practitioners into giving RNI for patients undergoing NAC and BCS, RNI after NAC and BCS does not improve OS, regardless of pCR status, even at a mean follow-up time of 5.5 years. Further studies evaluating the impact on local control and longer-term outcomes should be pursued to enable the creation of specific guidelines surrounding indications for RNI based on the initial burden of disease and the final response from NAC administration.

Disclosure(s):

Mahtab Vasigh, MD: No financial relationships to disclose

Richard J. Bleicher, MD: Consulting Fees (e.g., advisory boards): Elucent Medical (Ongoing)

PS04-04

Adverse effects (AEs) reported via Patient Reported Outcome Measures (PROMs): A longitudinal analysis of the IMPORT HIGH breast radiotherapy trial (CRUK/06/003)

Presenting Author(s) and Co-Author(s):

S. Ng. Clinical Trials and Statistics Unit, Institute of Cancer Research, London, England, United Kingdom

I. Bhattacharya. Cambridge University Hospitals NHS Foundation Trust, United States

J. Haviland. Queen Mary University of London, United Kingdom

C. Griffin. Clinical Trials and Statistics Unit, Institute of Cancer Research, London, England, United Kingdom

M. Sydenham. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

A. Kirby. The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, United States

P. Hopwood. Clinical Trials and Statistics Unit, Institute of Cancer Research, London, England, United States

C. Kirwan. The University of Manchester, United States

C. Coles. University of Cambridge, United Kingdom

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

Background

IMPORT HIGH is a multicentre phase III randomised controlled trial showing efficacy and safety of appropriately-dosed simultaneous integrated boost (SIB) in terms of local control, patient and clinician reported AEs among women with early breast cancer (BC)[1]. The PROMs sub-study collected baseline demographics and quality of life over 5 years. This exploratory analysis details the patient experience over time.

Methods

Women with higher-than-average risk of local relapse (≥ 18 years, breast conserving surgery, T1-3, pN0-pN3a, M0 invasive BC) were eligible. Randomisation (1:1:1) was between 40Gy whole breast and 16Gy sequential boost radiotherapy (control) and, 36Gy whole breast, 40Gy partial breast with either 48Gy SIB (test group 1), or 53Gy SIB (test group 2) radiotherapy.

AEs from EORTC QLQ-BR23[2]; Body Image Scale (BIS)[3]; and protocol-specific (PS) items used in previous breast radiotherapy trials[4] were reported by patients at baseline (pre-randomisation), 6 months, and years 1, 3, 5. 24 AEs[4] were included in the analysis, dichotomised as none/mild versus moderate/marked. Anxiety and depression were measured over 5 years using Hospital Anxiety and Depression Scale. Surgical deficit was scored from baseline photographs.

Multivariable generalized estimating equation models were fitted for each AE. Potential baseline predictors included those used previously[4] plus ethnicity, smoking, deprivation, employment, cardiovascular disease history, post-operative infection, haematoma, post-surgery complication. Backwards selection and Quasi-likelihood criterion were used for model selection.

Results

Between 2009-2013, 1338 patients were offered the PROMs sub-study and 1078 (81%) participated. Median age was 48.8 years (IQR 44.0-54.9). 17% reported 'Borderline' or 14% 'Case' anxiety at baseline. 11% reported 'Borderline' or 7% 'Case' depression at baseline.

747/1015 (74%), 686/986 (70%), 604/916 (66%), 532/845 (63%), 461/709 (65%) of participants reported at least 1 moderate/marked AE at baseline, 6 months, 1, 3 and 5 years. Number of moderate/marked AEs reported per person reduced over time after year 1 ($p < 0.005$). BIS reported moderate/marked AEs (except dissatisfaction with scar) decreased, whereas individual items from BR23 and PS items showed mixed patterns of reporting (increased, decreased, stayed the same) over time (Table 1).

From multivariable analysis, 'Borderline' or 'Case' depression or anxiety (time-varying) was associated with increased reports for almost all AEs. Chemotherapy and younger age were associated with increased reports of moderate/marked AEs for items in BIS, and large surgical deficit predicted more breast symptoms.

Conclusion

Change of overall breast appearance was the most reported moderate/marked AE that persisted over time. Although patients reported fewer moderate/marked AEs over time, trends in individual moderate/marked AEs showed mixed patterns. This study identified factors associated with increased risks of patient-reported moderate/marked AEs. Early identification of patients more likely to report AEs could facilitate implementation of targeted support.

References

1. Coles et al, The Lancet 2023
2. Sprangers et al, J Clin Oncol 1996
3. Hopwood et al, Eur J Cancer 2001
4. Bhattacharya et al, J Clin Oncol 2019

Table 1

Prevalence of Moderate/Marked Adverse Effects	Baseline (%)	6 months (%)	1 year (%)	3 years (%)	5 years (%)	Cochran-Armitage test for trend (p value)*
BR23 (shoulder, breast and arm) (during the past week)						
Did you have any pain in your arm or shoulder?	188(18.6)	186(18.9)	165(18.0)	142(16.8)	127(17.9)	0.83
Body image scale (during the past week)						
Have you felt less physically attractive as a result of your disease or treatment?	432(42.7)	303(30.7)	191(20.9)	157(18.6)	130(18.3)	<0.0001
Protocol specific items (any changes to your breast that may have resulted from any of your breast cancer treatments)						
Has the overall appearance of your breast changed, compared with the other side?	261(25.8)	306(31.0)	291(31.8)	233(27.6)	242(34.1)	0.009

*Cochran-Armitage test for trend performed for those items where patients reported $\geq 10\%$ moderate/marked AEs overall.

Trend over time for most commonly reported AE from each questionnaire

Disclosure(s):

Sze Yi Ng, MMath: No financial relationships to disclose

PS04-06

Breast cancer recurrence among women with pre-diagnostic major depression and co-existing substance abuse disorder: A retrospective study in the United States Veterans Health Administration Cohort

Presenting Author(s) and Co-Author(s):

M. Aboumrad. Johns Hopkins Bloomberg School of Public Health, MD and White River Junction VA Medical Center, Baltimore, Maryland, United States

K. Visvanathan. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, MD and Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States

Background:

Our prior study observed a 34% higher risk of breast cancer (BC) recurrence among women with major depressive disorder (MDD) at the time of their BC diagnosis compared to women without MDD after adjusting for sociodemographic, clinical, and prognostic factors. Given the high prevalence of substance abuse disorders among individuals with MDD and the positive association between alcohol use and mortality among BC survivors, we were interested to examine whether the risk of BC recurrence was compounded for women with both conditions.

Objective:

To investigate whether pre-diagnostic substance abuse disorders modify the association between MDD and BC recurrence.

Methods:

We established a retrospective cohort of women (age ≥ 18 years) with incident, early-stage BC diagnosed from 2010 through 2019 using the VHA's electronic medical record database. A two-year window was used to identify women with MDD and co-existing substance abuse disorders prior to their BC diagnosis. We examined potential interactions between MDD and alcohol abuse and MDD and other substance abuse using multivariable proportional hazards regression, accounting for competing risk of death. Our outcome of interest was BC recurrence. The reference group for all analyses was women with BC alone. The models were adjusted for patient characteristics including age, race, ethnicity, marital status, rurality of primary residence, priority group rating (proxy for socioeconomic status), any homelessness or economic problems, comorbidity burden, body mass index, smoking status, receipt of a screening mammography, year of BC diagnosis, cancer stage, cancer subtype, and cancer treatment. Subgroup analyses were conducted by cancer subtype.

Results:

Our cohort comprised 6,045 women with BC, of whom 1,754 (29%) had a pre-diagnostic MDD diagnosis and 1,509 (25%) had a substance abuse disorder. Among women with MDD, 386 (22%) abused alcohol and 336 (19%) abused other substances. The median length of follow-up from BC diagnosis was 4.5 years (IQR=4.8 years). The average age at BC diagnosis was 57 years (SD=11 years) overall, 56 years (SD=10 years) among women with MDD, and 57 years (SD=9 years) among women with substance abuse disorders. On multivariable analysis, MDD (HR=1.33; 95% CI: 1.14, 1.53), alcohol abuse disorder (HR=1.37; 95% CI: 1.12, 1.68), and other substance abuse disorders (HR=1.33; 95% CI: 1.13, 1.56) were independent risk factors for BC recurrence. Further, there was a statistically significant interaction between pre-diagnostic MDD and alcohol abuse disorder (p -interaction=0.003). Women with BC who had

both pre-diagnostic MDD and alcohol abuse disorder were at a 65% (HR=1.65; 95% CI: 1.29, 2.11) higher risk of BC recurrence compared to women with BC alone. A statistically significant interaction was also observed between pre-diagnostic MDD and other substance abuse disorders (p-interaction < 0.001). Women with BC who had both pre-diagnostic MDD and other substance abuse disorders were at a 90% (HR=1.90; 95% CI: 1.50, 2.42) higher risk of BC recurrence compared to women with BC alone. In subgroup analyses, the interaction between MDD and alcohol abuse disorders (p-interaction=0.001) and MDD and other substance abuse disorders (p-interaction < 0.001) was limited to women with estrogen receptor positive cancer but not estrogen receptor negative cancer.

Conclusion:

Women with incident BC who have prior diagnoses of both MDD and substance abuse disorder are at higher risk of recurrence than women with either exposure independently. Further research is needed to examine the etiology of our findings and to evaluate whether this newly defined risk group would benefit from closer monitoring and more tailored treatment options.

Disclosure(s):

Maya Aboumrad, MPH: No financial relationships to disclose

PS04-07

Associations between Virtual Care Access and Psychological and Mental Health Conditions among Adults with Breast Cancer in the US: A Population-Based Analysis

Presenting Author(s) and Co-Author(s):

J. Freeman. Department of Public Health Sciences, University of Chicago, Chicago, Illinois, United States

T. Akhiwu. Department of Medicine, MedStar Union Memorial Hospital, Baltimore, Maryland, United States

Y. Lee. Rutgers, The State University of New Jersey, New Brunswick, New Jersey, United States

X. Li. Milken Institute School of Public Health, The George Washington University, Washington, District of Columbia, United States

Background:

Adults with breast cancer (AwBC) often experience psychological and mental health challenges and face many barriers to accessing mental health care and services. Telemedicine can help facilitate access to these care and services and AwBC may benefit uniquely from virtual care. However, little is known about the relationships between virtual care access (VCA) and psychological and mental health conditions in AwBC nationally.

Methods:

We obtained a population-based sample from the 2021 National Health Interview Survey that used stratified clustering sampling to interview US adults. This study was limited to adults who ever had breast cancer. VCA was defined as having had a virtual (i.e., phone or video) medical visit with a health provider in the past 12 months and was categorized as “yes/no.” Serious psychological distress, measured using the 6-item Kessler scale, was dichotomized based on a cutoff score of 13. Having an anxiety disorder or depression was self-reported as “yes/no.” Weighted proportions and 95% confidence intervals (CI) were tabulated and compared using Rao-Scott chi-square tests. Multivariable logistic regression models were fit to calculate adjusted odds ratios (AOR) and 95% CIs. All statistical analyses accounted for complex sample design and survey weights.

Results:

The unweighted sample size was 698, representing a weighted sample of 4,379,870 AwBC in the US. The mean age was 67.7 years; 77.6% were White and 9.6% were Black; 53.8% and 38.9% were privately insured and on Medicaid/Medicare, respectively. Of the total, 20.9% (95% CI: 17.3-24.6%) had depression, 17.4% (95% CI: 14.0-20.9%) had an anxiety disorder, and 3.2% (95% CI: 1.7-4.7%) experienced serious psychological distress. Overall, 50.3% (95% CI: 46.1-54.4%) had a virtual visit. White AwBC reported a higher proportion of VCA than Black AwBC (50.6% vs. 38.6%). AwBC on Medicaid/Medicare reported a lower proportion of VCA than those privately insured (47.8% vs. 51.8%). AwBC who experienced serious psychological distress had a higher percentage of VCA than those who did not (78.5% [95% CI: 60.8-96.2%] vs. 48.5% [95% CI: 44.2-52.8%], $p=.007$). Compared with AwBC who did not have depression, those who did had a higher percentage of VCA (63.9% [95% CI: 54.6-73.2%] vs. 46.6% [42.0-51.3%], $p=.002$). Similarly, AwBC with an anxiety disorder reported a higher percentage of VCA than those without (60.4% [95% CI: 50.3-70.6%] vs. 48.1% [43.6-52.6%], $p=.032$). Furthermore, AwBC who frequently felt anxious or depressed were more likely than those who felt less frequently to use telemedicine. In the adjusted regression models, AwBC experiencing serious

psychological distress had significantly greater odds of VCA than those not experiencing (AOR=3.79, 95% CI: 1.05-13.7). AwBC with depression had significantly greater odds of VCA than those without (AOR=2.02, 95% CI: 1.25-3.28). Although AwBC with an anxiety disorder also had greater odds of VCA than those without (AOR=1.45, 95% CI: 0.89-2.38), the association was not statistically significant.

Conclusions:

In this nationally representative sample of US AwBC, more than one in 6 had an anxiety disorder or depression and VCA was prevalent in the past 12 months. AwBC with serious psychological distress, anxiety, or depression were more likely than those without to use telemedicine, indicating a greater need for virtual care among AwBC. Our findings also suggest that to help AwBC improve their psychological and mental health conditions and address their unmet needs, breast cancer support programs would need to ensure equitable access to virtual care and services in this patient population.

Disclosure(s):

Jincong Q. Freeman, MPH, MS: No financial relationships to disclose

PS04-08

Sociodemographic Risk Factors and Prediction of Aromatase Inhibitor Non-Adherence in Women with Breast Cancer Enrolled in SWOG S1105

Presenting Author(s) and Co-Author(s):

D. Hershman. Columbia University, New York, New York, United States

A. Moseley. Fred Hutchinson Cancer Research Institute, United States

K. Arnold. SWOG Statistics and Data Management Center, Seattle, Washington, United States

J. Gralow. ASCO, United States

A. Neugut. Herbert Irving Comprehensive Cancer Center, Vagelos College of Physicians and Surgeons, Columbia University, United States

S. Ramsey. Fred Hutchinson Cancer Research Institute, United States

N. Henry. University of Michigan Medical School, United States

J. Unger. Fred Hutchinson Cancer Center, United States

Background:

Non-adherence to aromatase inhibitors (AIs) for breast cancer is common and increases risk of recurrence. Few prospective studies have systematically evaluated non-adherence and non-clinical factors associated with it. We analyzed baseline sociodemographic characteristics and financial factors associated with non-adherence to create a baseline composite risk-score for AI non-adherence.

Methods:

Patients enrolled in S1105 were required to have been on an AI for ≥ 30 days at enrollment. Patients were assessed for non-adherence of AIs every 3 months for 36 months, with non-adherence defined as urine AI metabolite assay results satisfying any of the following: < 10 ng/mL, undetectable, specimen submitted outside of the ± 21 -day follow-up appointment window, or no submitted specimen. Factors included race, Hispanic ethnicity, age, education, income, health insurance type, and prescription cost. We also included socioeconomic deprivation and rural or urban residence using trial participants' residential zip codes linked to the Area Deprivation Index (ADI) and Rural Urban Continuum codes (RUCC) respectively. For numeric factors and categorical factors with more than two levels, we used cutpoint analysis to determine the highest risk range by optimizing the Chi-squared statistic. For each resulting binary factor, we performed a logistic regression, adjusting for the study stratification factors and stratifying by treatment arm. Factors associated with adherence at the $\alpha=0.10$ level were combined into a composite risk score, with study participants given one point for each baseline adverse risk factor. Secondarily, we examined a composite risk score including all factors, regardless of statistical significance.

Results:

In total, 724 patients were registered from 40 institutions between May 2012 and September 2013. The median age was 60.9 years, and 64.5% were on AI < 12 months prior to registration. Only 8% had out of pocket (OOP) cost $> \$30$. Observed adherence at 36 months was 35.9%. Patients living in metro areas with populations $\geq 250,000$ (RUCC ≤ 3) were more likely to be non-adherent (37.5% vs 28.3%, OR=1.50, $p=.08$); as were those who were younger, those without a college education, and those with limited ($\leq \$5$) OOP cost. ADI, race and ethnicity were not associated with non-adherence. The composite risk score was strongly associated with 36-month adherence. For each 1 unit increase in risk level, the risk of non-adherence

increased 47% (OR=1.47, p< .001); the risk increased 64% for those with >2 vs. ≤2 risk factors (OR=1.64, p=.002). Results using all factors regardless of statistical significance were consistent.

Conclusions:

A composite model comprised of sociodemographic risk factors can identify patients on AI's at much greater risk of long-term AI non-adherence. In addition to mitigating side effects, targeted interventions to improve adherence should focus on structural barriers among those at highest risk.

Non-adherence (+/- 6 months) = factor + AI duration + AI type, stratified by arm

Non-adherence (+/- 6 months) = factor + AI duration + AI type, stratified by arm			
Baseline factor	Adverse vs. Non-Adverse Risk Category (% non-adherent)	OR (95% CI)	P
Univariate Models			
Age	≤ 65 (38.6%) vs >65 (28.7%)	1.48 (1.03-2.13)	.03
Race	Not Black (36.2%) vs Black (32.6%)	1.09 (0.57-2.07)	.79
Ethnicity	Hispanic (46.7%) vs Not Hispanic (35.5%)	1.59 (0.76-3.34)	.22
Education	≤High School (39.5%) vs College/graduate school (32.6%)	1.35 (0.98-1.86)	.07
Income	≤ 90,000 (37.4%) vs >90,000 (31.5%)	1.30 (0.89-1.90)	.17
Insurance	Other or no insurance (37.1%) vs Private insurance (34.1%)	1.17 (0.85-1.60)	.34
Out of pocket cost	≤ \$5 (40.9%) vs >\$5 (32.3%)	1.45 (1.03-2.03)	.03
RUCC code	≤ 3 (37.5%) vs >3 (28.3%)	1.50 (0.96-2.34)	.08
ADI national rank	>20 (36.8%) vs ≤ 20 (29.9%)	1.35 (0.80-2.26)	.26
Composite Risk Models			
Statistically significant factors only	Each 1 unit increase	1.47 (1.23-1.75)	<.001
	>2 (42.8%) vs ≤ 2 (30.8%) factors	1.64 (1.20-2.25)	.002
All factors	Each 1 unit increase	1.31 (1.16-1.48)	<.001
	>5 (44.5%) vs ≤ 5 (28.6%) factors	1.97 (1.44-2.70)	<.001

Disclosure(s):

Dawn Hershman, MD, MS, FASCO: No financial relationships to disclose

PS04-09

Patient-Reported Benefit of Resources Designed to Assist with the Financial Toxicity of Breast Cancer

Presenting Author(s) and Co-Author(s):

F. Chino. Memorial Sloan Kettering Cancer Center, New York, New York, United States

S. Meske. Breastcancer.org, United States

M. Giaddui. Lankenau Institute for Medical Research, United States

D. Manasseh. Maimonides Medical Center, United States

B. Thom. UNC Lineberger Comprehensive Cancer Center, United States

M. Weiss. Breastcancer.org, United States

Background:

A breast cancer (BC) diagnosis can cause financial stress, which may worsen disease outcomes and create financial instability. Tailored interventions are urgently needed, but the patient perspective on the utility of financial resource options is limited.

Methods:

From 6-7/2022, Breastcancer.org community members consented to an online survey in English or Spanish. Eligibility included: US resident, age ³ 18, and BC diagnosis within 10 years. Survey assessed burden of out-of-pocket expenses and perceived benefit of available (1 “Not at all” to 5 “Very much”) and potential (ranked choice) resources.

Results:

1,437 participated. Mean age and time since diagnosis was 46 and 2 years, respectively; 75% were in active treatment for non-metastatic (89%) or metastatic (11%) disease. Patients were 60% White, 27% Hispanic, 8% Black, and 4% other race; 94% were women. 47% had either “significant” or “catastrophic” financial burden due to BC, with higher burdens in those with metastatic disease (61% vs 45%, $p < 0.001$).

Direct assistance programs (e.g., reduced cost medications, grants, transportation) were rated the most helpful to respondents (Table). A grant list, a provider question checklist, and access to professional advice were most often ranked as 1st choice for potential resources. There were significant differences by race/ethnicity and disease status.

Conclusions:

Almost one-half of surveyed patients had significant financial burden due to BC. Patient-centered solutions to lessen financial burdens and optimize patient outcomes should consider direct assistance and patient education to improve knowledge, communication, and self-advocacy.

How helpful were/are each of these resources in helping	Overall Mean	Disease Status	Race/Ethnicity
---	--------------	----------------	----------------

you cope with the financial burdens of BC?							
		Non-metastatic	Metastatic	White	Black	Hispanic	Other
Patient assistance programs offered by pharma or medical test companies	2.9 (n=1,107)	2.9 (n=975)	3.1* (n=132)	2.9* (n=618)	2.6 (n=94)	3.1* (n=357)	2.6 (n=38)
Nonprofits that provide grants to help cover expenses of people with cancer	2.8 (n=1,113)	2.8 (n=991)	2.7 (n=122)	2.8 (n=611)	2.6 (n=100)	3.1* (n=358)	2.4 (n=44)
Financial assistance department at the cancer center or hospital	2.8 (n=1,176)	2.8 (n=1,046)	2.7 (n=130)	2.7* (n=669)	2.7 (n=103)	3.1* (n=362)	2.2 (n=42)
Coupons and savings cards to reduce the cost of prescription drugs	2.8 (n=1,140)	2.8 (n=1,008)	2.7 (n=132)	2.7 (n=648)	2.5 (n=92)	3.0* (n=358)	2.5 (n=42)
Programs that provide free or low-cost transportation to medical appointments	2.7 (n=1,042)	2.8* (n=934)	2.4 (n=108)	2.6 (n=556)	2.5 (n=93)	3.0* (n=356)	2.3 (n=37)

Clinical trials	2.7 (n=1,032)	2.7* (n=928)	2.5 (n=104)	2.6* (n=557)	2.3 (n=84)	3.0* (n=357)	2.1 (n=34)
Professional medical billing advocates	2.7 (n=1,105)	2.7* (n=994)	2.3 (n=111)	2.5* (n=612)	2.4 (n=94)	3.0* (n=358)	2.1 (n=41)
Social worker or case manager	2.7 (n=1,146)	2.7 (n=1,027)	2.6 (n=119)	2.6* (n=644)	2.3 (n=99)	2.9* (n=360)	2.4 (n=43)
Nonprofits that provide advice and education about financial issues	2.7 (n=1,100)	2.7 (n=983)	2.5 (n=117)	2.6* (n=607)	2.3 (n=96)	3.0* (n=359)	2.0 (n=38)
Financial navigator	2.6 (n=1,087)	2.6 (n=976)	2.5 (n=111)	2.5 (n=598)	2.5 (n=94)	2.9* (n=356)	2.1 (n=39)
Which of the following programs and resources would have been (or would be) most useful to you in navigating the financial burdens of BC?	Total	Non-metastatic (n=1,282)	Metastatic (n=155)	White (n=686)	Black (n=121)	Hispanic (n=384)	Other (n=64)
A list of financial grants people diagnosed with BC can apply for	18%	18%	19%	19%*	24%*	14%	25%*
A checklist of	15%	16%	12%	16%	17%	15%	9%

questions to ask your healthcare team to help you minimize the financial burdens of BC							
Access to free or reduced-price professionals to help with medical billing, financial, benefits, and/or legal issues	13%	13%	8%	11%	8%	15%*	20%*

* p< 0.001

Disclosure(s):

Fumiko Chino, MD: No financial relationships to disclose

PS05-01

Accuracy and safety of fibroblast activation protein inhibitor (FAPI) PET/CT in diagnosis of axillary lymph node metastasis in early breast cancer patients: a prospective cohort study (PFB-01&02 study)

Presenting Author(s) and Co-Author(s):

B. Pan. Peking Union Medical College Hospital, United States

Z. Hao. Peking Union Medical College Hospital, United States

C. Ren. Peking Union Medical College Hospital, United States

L. Zhang. Peking Union Medical College Hospital, United States

Y. Zhou. Peking Union Medical College Hospital, United States

Q. Sun. Peking Union Medical College Hospital, United States

L. Huo. Peking Union Medical College Hospital, United States

Background Axillary lymph node (ALN) is the most common metastatic site of breast cancer (BC) and the status of ALN determines the staging, treatment and prognosis for BC patients. Traditional imaging techniques, including ultrasound (US), mammography, MRI, and ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) were still unsatisfactory to evaluate the status of ALN non-invasively. Fibroblast activation protein (FAP) is highly expressed in cancer-associated fibroblasts and FAP inhibitor (FAPI) PET has been found quite promising in BC. Well-designed prospective large cohort study concerning the diagnostic performance and safety profile of FAPI PET/CT in detection of ALN metastasis of BC is still lacking. Furthermore, FAPI could be radio-labeled with different radio-nuclides including ^{68}Ga and ^{18}F , and there is yet no data concerning the ^{18}F -labeled FAPI in BC. In this study, we investigated the accuracy of FAPI (both ^{68}Ga -FAPI-04 and Al^{18}F -FAPI-04) PET/CT in newly diagnosed BC patients for assessing ALN metastasis. We also compared the diagnostic performance of FAPI PET/CT with that of ^{18}F -FDG PET/CT and US. Methods This prospective study was approved by the Peking Union Medical College Hospital Ethics Committee and was registered online at NIH ClinicalTrials.gov (NCT05574907, NCT05574920). The inclusion criteria were as follows: (1) age 18-80 years old; (2) newly diagnosed BC confirmed by biopsy or with BI-RADS category 4C or 5 lesions by US. The exclusion criteria were as follows: (1) pregnancy or lactation; (2) patients unwilling to undergo PET/CT scans. All patients received biopsy or surgery on breast lesion and ALN. Patients received FAPI and ^{18}F -FDG PET/CT after enrollment. The safety profile of FAPI PET was monitored after injection using the Common Terminology Criteria for Adverse Events. Two experienced nuclear medicine physicians, who were blinded to the pathological diagnosis and other imaging results, assessed the PET/CT images. It was defined as visually positive if the radioactive uptake of the ALN was higher than that of the adjacent normal tissue. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each diagnostic test. The McNemar test was applied to compare the differences of sensitivity and specificity between FAPI PET/CT, ^{18}F -FDG PET/CT, and US. All statistical tests were performed two-sided, and $P < 0.05$ was considered statistically significant. Results In total, 113 patients (27-79 years old, median age 66) were enrolled. 53 patients underwent ^{68}Ga -FAPI-04 PET/CT, and the other 60 patients underwent Al^{18}F -FAPI-04 PET/CT. All patients underwent ^{18}F -FDG PET/CT and US. A total of 53/113 (46.9%) patients were finally diagnosed with ALN metastasis. The sensitivity, specificity, accuracy, PPV, and NPV were 90.6%, 90.0%, 90.3%, 88.9%, and 91.5% for FAPI

PET/CT, 84.9%, 73.3%, 78.8%, 73.8%, and 84.6% for 18F-FDG PET/CT, 83.0%, 76.7%, 79.6%, 75.9%, and 83.6% for US, respectively (Table 1). The specificity of FAPI PET/CT was significantly higher than that of ¹⁸F-FDG PET/CT (P < 0.05) and US (P < 0.05). The sensitivity of FAPI PET/CT was higher than that of ¹⁸F-FDG PET/CT (P= 0.45) and US (P= 0.29). There was no significant difference of sensitivity and specificity between ¹⁸F-FDG PET/CT and US (P > 0.05). The sensitivity, specificity, accuracy, PPV, and NPV were 92.0%, 92.9%, 92.5%, 92.0%, and 92.9% for ⁶⁸Ga-FAPI-04 PET/CT, and 89.3%, 87.5%, 88.3%, 86.2%, and 90.3% for AI¹⁸F-FAPI-04 PET/CT, respectively (Table 2).

The ⁶⁸Ga-FAPI-04 PET/CT and AI¹⁸F-FAPI-04 PET/CT procedures were well tolerated in all patients. The only adverse event was injection pain in 12/53 (22.6%) patients injected with ⁶⁸Ga-FAPI-04, and 7/69 (10.1%) patients injected with AI¹⁸F-FAPI-04, which might relate to the ethanol in the imaging agent. Conclusion The FAPI PET/CT outperformed ¹⁸F-FDG PET/CT and US in the diagnosis of ALN metastasis among early breast cancer patients. The ⁶⁸Ga-FAPI-04 and AI¹⁸F-FAPI-04 PET/CT have similar diagnostic performance. The FAPI PET/CT procedures were well tolerated in all patients.

Table 1 Diagnostic performance of FAPI PET/CT, 18F-FDG PET/CT, and ultrasound in the diagnosis of ALN metastasis

	Sensitivity	Specificity	Accuracy	PPV	NPV
FAPI PET/CT	90.6%	90.0%	90.3%	88.9%	91.5%
¹⁸ F-FDG PET/CT	84.9%	73.3%	78.8%	73.8%	84.6%
Ultrasound	83.0%	76.7%	79.6%	75.9%	83.6%

Table 2 Diagnostic performance of ⁶⁸Ga-FAPI-04 and AI¹⁸F-FAPI-04 PET/CT in diagnosis of ALN metastasis

	Sensitivity	Specificity	Accuracy	PPV	NPV
^{68}Ga -FAPI-04	92.0%	92.9%	92.5%	92.0%	92.9%
Al^{18}F -FAPI-04	89.3%	87.5%	88.3%	86.2%	90.3%

PS05-02

PET Imaging of PARP Expression as a Biomarker of Response to Chemotherapy in Breast Cancer: A Nonrandomized Clinical Trial

Presenting Author(s) and Co-Author(s):

S. Gitto. University of Pennsylvania, Philadelphia, Pennsylvania, United States

A. Young. University of Pennsylvania, United States

I. Bleiweiss. University of Pennsylvania, United States

A. Clark. University of Pennsylvania, United States

A. Pantel. University of Pennsylvania, United States

Introduction: Poly-(adenosine diphosphate-ribose) polymerase (PARP) proteins are involved in double-stranded break repair, mediated through homologous recombination (HR) and non-homologous end joining (NHEJ). The majority of PARP activity in this context is attributed to PARP-1 (85-90%). PARP-1 binding to damaged DNA, catalytic activity, and subsequent release to allow access for other DNA repair proteins are necessary for efficient DNA repair. The critical function of PARP-1 in these processes makes this protein a unique potential biomarker of DNA repair capability. [¹⁸F]FluorThanatrace ([¹⁸F]FTT) is an ¹⁸F-labeled PARP inhibitor analog that binds to the same site as approved PARPi drugs. We hypothesized that the biologically relevant form of PARP in untreated breast cancer might provide an indication of functional tumor DNA repair capabilities and therefore predict chemotherapy response. Thus, this study aimed to determine whether a non-invasive quantitative measure of in vivo PARP expression correlated with response to chemotherapy in breast cancer. **Methods:** A single-arm prospective trial enriched for subjects with triple negative breast cancer (TNBC) was conducted at the University of Pennsylvania from May 2017 to March 2022 (NCT03083288 and NCT03846167). Inclusion criteria were primary breast cancer with tumor diameter of at least 1 cm on conventional imaging and willingness to undergo an [¹⁸F]FTT-PET scan prior to neoadjuvant chemotherapy. Participants provided written informed consent. [¹⁸F]FTT uptake in breast cancer was measured pre-therapy and tested for association with pathologic complete response (pCR). Subjects were scanned on an Ingenuity TF PET/CT (Philips Healthcare) following injection of [¹⁸F]FTT using a 20-minute static acquisition. Peak 1 cm³ average uptake (SUV_{peak}) were recorded from a spherical region-of-interest (ROI) covering the primary malignancy, guided by CT and prior imaging studies. All SUVs were partial volume corrected and normalized using muscle (NM). A Mann-Whitney test was used to determine if [¹⁸F]FTT uptake differed by pCR. Receiver operating characteristic (ROC) curves were constructed to test the performance of [¹⁸F]FTT uptake in predicting pCR. Statistical analyses utilized STATA v15.1 with significance based on a two-sided alpha level of ≤0.05. **Participants:** Twenty-six women with stage I-III breast cancer met inclusion criteria with age range of 29-74 years and self-reported race as Asian (1, 4%), Black (9, 37%) or White (16, 60%). One subject had bilateral tumors (ER+ stage IIA and HER2+ stage I) that were evaluated separately (27 total tumors). Breast tumors were pathologically confirmed and included 6 (22%) ER+/HER2-, 5 (19%) HER2+, and 16 (59%) TNBC. Germline sequencing was available for 21 participants. **Results:** Mean tumor diameter ranged from 15 to 91 mm (median 30 mm). A considerable range of [¹⁸F]FTT uptake was seen across subjects (SUV_{peak}/NM 0.66-6.5). [¹⁸F]FTT uptake was independent of subtype (ER+, HER2+, TN) (P=0.35), stage (P=0.39), and between mutations in genes associated with homologous recombination deficiency (i.e., BRCA1/2, PALB2) and wild-type (P=0.73). In the TNBC cohort, pre-treatment [¹⁸F]FTT uptake was higher

in subjects who went on to have a pCR (n=16, P=0.05), while a trend toward higher uptake was seen when including all tumor types (n=27, P=0.11). ROC analysis of the value of [¹⁸F]FTT uptake for predicting pCR revealed an AUC of 0.79 and showed that a threshold SUV ratio < 2.47 predicted pCR in TNBC patients with a 100% specificity and 64% sensitivity. Conclusions: These early clinical results suggest a relationship between [¹⁸F]FTT uptake, a measure of PARP expression, and chemotherapy sensitivity in TNBC, warranting future studies to elucidate underlying mechanistic processes and potential clinical implications.

PS05-03

MagSense® HER2, a Molecularly Targeted Magnetic Resonance Imaging Agent for the Detection of Axillary Nodal Metastasis in Subjects with Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Breast Cancer

Presenting Author(s) and Co-Author(s):

j. Fox. Department of Surgery, School of Clinical Sciences at Monash Health, Monash University, Victoria, Australia

S. Velaiutham. Breast Center, Lake Macquarie Private Hospital, New South Wales, Australia

N. Yang. Austin Health, United States

E. Iau. Austin Health, United States

K. Murugappan. Royal Brisbane Hospital, Queensland, Australia

B. Kumar. Monash Health, United States

A. Laslowski. Monash Medical Center, Victoria, Australia

K. Govindarajan. Imagion Biosystems Inc., United States

S. Reich. Imagion Biosystems Inc., United States

S. Thomas. Imagion Biosystems Inc., United States

N. Neha. Imagion Biosystems Ltd, United States

M. Zhang. Imagion Biosystems Ltd, United States

I. Bright. Imagion Biosystems Inc, San Diego, California, United States

Background Precise nodal staging is critical in guiding systemic and regional treatments including surgery in the management of breast cancer. Regional nodal assessment includes axillary imaging (mostly by ultrasound) and lymph node sampling. Since imaging findings suggestive of nodal metastasis are based on size and morphologic changes and not specific to tumor type, pathologic confirmation through either biopsy or removal of sentinel lymph node (SLN) remains the gold standard. Imagion is developing the MagSense® HER2 Imaging Agent (MSH2IA), an anti-human epidermal growth factor receptor 2 (HER2) conjugated with iron oxide nanoparticles, for the detection of nodal metastasis in HER2+ breast cancer patients. MSH2IA is currently being investigated in a first-in-human phase 1 study (ACTRN12621000126819) in HER2+ breast cancer patients who are diagnosed to have suspicious nodes by conventional imaging. **Methods** The key objectives of the phase 1 study are safety and tolerability of MSH2IA and confirmation that MSH2IA drains to the axillary lymph nodes. The study also explores MSH2IA's ability to detect metastatic nodes when used with magnetic resonance imaging (MRI), with tumor status assessed by standard tissue histopathology. All eligible subjects receive a 22.5 mg (iron equivalent) subareolar or peritumoral injection of MSH2IA. MRI of the axilla are obtained before and 24 to 72 hours after MSH2IA injection. Core biopsy or dissection of a node suspicious by ultrasound is obtained for histopathology assessments. After completing the first cohort of 6 subjects, the protocol was amended to include the insertion of an MRI compatible clip in a node suspicious by ultrasound to localize the suspicious node for core biopsy and postdose MRI scan. Review of MRI scans and histopathology are performed in respective central laboratories. **Results** Thirteen participants with HER2+ breast cancer have completed the study. MSH2IA appears safe and well tolerated. The imaging agent, as administered, is detectable by MRI and pathology, confirming that MSH2IA drains to the lymph nodes via the chosen route of administration. In postdose MRI scans, study central radiologists reported distinct and differentiable MRI appearance in morphologically normal and suspicious

nodes. The presence of a distinct postdose MR image appearance was confirmed by a group of independent radiologists in a separate blinded review. While normal nodes appeared with homogeneous hypointensity, morphologically suspicious nodes showed partial irregular darkening and/or speckled heterogeneous hypointensity. In evaluable subjects, histopathology of the core biopsies obtained from the clipped nodes confirmed the presence of HER2+ nodal metastasis, providing preliminary evidence for node-level concordance between MRI vs pathology observations. Safety, imaging, and pathology results from all available subjects will be presented. This phase 1 study in Australia will be closing enrollment by July 31, 2023. A phase 2 study in the United States and elsewhere is being planned with the objectives of optimizing dose, schedule, and imaging parameters for best diagnostic performance for clinical utility. Conclusion Available data from the ongoing phase 1 study show that MSH2IA appears safe and drains to the axillary lymph nodes. MSH2IA displays a distinct and differentiable MRI appearance in nodes morphologically highly suspicious for tumor, which is confirmed to be HER2+ metastasis by histopathology by node level concordance. This data provides preliminary proof of principle for the mechanism of molecularly targeted MR imaging and suggests that MSH2IA has the potential to provide tumor-specific MR imaging not currently available in conventional axillary imaging.

PS05-04

[⁸⁹Zr]Trastuzumab-PET/MRI to Characterize HER2+ Breast Cancer: A Quantitative Approach on Tumor Heterogeneity

Presenting Author(s) and Co-Author(s):

A. Mansur. University of Alabama at Birmingham, Birmingham, Alabama, United States

M. Nikpanah. University of Alabama at Birmingham, Birmingham, Alabama, United States

J. McConathy. University of Alabama at Birmingham, Birmingham, Alabama, United States

E. Stringer-Reasor. University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, Alabama, United States

G. Rocque. University of Alabama at Birmingham, Birmingham, Alabama, United States

A. Elkhanany. University of Alabama at Birmingham, Birmingham, Alabama, United States

K. Khoury. O'Neal Comprehensive Cancer Center at the University of Alabama, Birmingham, Alabama, United States

N. Jahan. University of Alabama at Birmingham, Birmingham, Alabama, United States

S. Lapi. University of Alabama at Birmingham, Birmingham, Alabama, United States

A. Sorace. University of Alabama at Birmingham, Birmingham, Alabama, United States

Introduction: Molecular imaging of human epidermal receptor 2 (HER2) aims to overcome limitations of traditional HER2 assessment through biopsy, including invasiveness and inability to detect intra and inter-tumoral spatial heterogeneity. Prior human studies suggest that [⁸⁹Zr]Trastuzumab-positron emission tomography (PET) imaging can effectively differentiate HER2 lesions (Dehdashti et al, Breast Cancer Res. Treat. 2018). Commonly, CT complements PET for anatomical reference, however, integrating MRI enables the sensitivity of soft-tissue contrast required for anatomic and morphological breast imaging and can provide for quantitative multiparametric characterization. Diffusion weighted-MRI (DW-MRI) contributes to tumor characterization by assessing intratumoral cellularity via the apparent diffusion coefficient (ADC), and can be combined with molecular expression from HER2-PET. We present preliminary results in 13 patients with HER2 PET/MRI to define tumor and normal tissue imaging metrics. **Methods:** A phase II clinical trial assessing the feasibility of [⁸⁹Zr]trastuzumab-PET with simultaneous quantitative DW-MRI to enhance understanding of tumor heterogeneity in patients with HER2-positive metastatic breast cancer. 13 patients (ages 40-70; mean 60) with HER2-positive breast cancer based on prior biopsy underwent whole-body [⁸⁹Zr]trastuzumab-PET/MR imaging (5 ± 1 days post-injection of radiopharmaceutical) during the course of HER2-directed therapy. Normal organ and tumor regions of interest (ROI) were identified on concurrently acquired whole-body T₁-weighted MRI for ADC (cellularity) and standardized uptake value (SUV, PET uptake) mean quantification. Tumor presence was confirmed via bone scintigraphy, FDG-PET/CT, or contrast-enhanced MRI. Non-parametric T-tests compared lesions to normal organs. Lesions greater than 30 mm in diameter underwent multiparametric intratumoral habitat analysis. Using the median HER2 values, tumors were evaluated for heterogeneity of high and low HER2 expression in conjunction with ADC. Long-term treatment response evaluation is ongoing. **Results:** Mean [⁸⁹Zr]trastuzumab uptake, SUV, and ADC values for normal tissue were summarized in Table 1. All tumors demonstrated higher overall uptake of [⁸⁹Zr]trastuzumab (bone: p=0.019, brain: p=0.014, breast: p=0.069, juxtapulmonary: p=0.026) and increased ADC_{mean} values (bone: p=0.002, brain: p=0.5, breast: p=0.03, juxtapulmonary: p=0.037), in comparison to matched normal organs. Notably, one of

five patients with a breast lesion, who completely responded to HER2 targeted therapy, exhibited the highest breast lesion SUV_{mean} . Brain and lymph node lesions demonstrated intratumoral heterogeneity of HER2 expression. Conclusion: Our study demonstrates the potential value of quantitative MRI along with molecular imaging to characterize metastatic HER2+ breast cancer and evaluate intratumoral heterogeneity. We underscore the importance of standardizing processing techniques and contribute to this effort by summarizing [^{89}Zr]trastuzumab uptake and cellularity values of normal physiological uptake. Higher SUV_{mean} and ADC_{mean} values observed in lesions, compared to normal tissue, highlight their potential roles in intratumoral classification. While studies have shown the utility of [^{89}Zr]trastuzumab-PET/CT, our findings demonstrate that integrated DW-MRI can aid in tumor classification. Table 1: Physiological ^{89}Zr -Trastuzumab Uptake (SUV_{mean}) and Apparent Diffusion Coefficient (ADC_{mean}) in Healthy Tissues

Organ/Region	SUV_{mean}	ADC_{mean}	Number of Patients
Brain	0.30 ± 0.08	1.13 ± 0.11	10
Frontal Lobe	0.14 ± 0.06	0.94 ± 0.09	10
Lateral Ventricle	0.12 ± 0.06	2.80 ± 0.31	10
Bone	0.66 ± 0.15	0.33 ± 0.15	10
Breast	0.34 ± 0.12	0.91 ± 0.23	7
Breast Fat	0.31 ± 0.07	0.86 ± 0.21	7
Fibroglandular Tissue	0.66 ± 0.34	1.53 ± 0.26	7
Cardiac Blood Pool	4.40 ± 1.34	0.63 ± 0.51	13
Liver	5.07 ± 1.09	1.27 ± 0.14	11
Lung	1.06 ± 0.33	0.24 ± 0.32	11
Kidney	4.55 ± 1.09	1.95 ± 0.15	13
Muscle	0.46 ± 0.12	1.52 ± 0.20	13

PS05-06

Outcomes of Surveillance using Contrast Enhanced Mammography in Women with a Personal History of Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Matheson. Department of Surgery, Royal Melbourne Hospital and the University of Melbourne, Parkville, Victoria, Australia

C. Nickson. Daffodil Centre, The University of Sydney, a joint venture with Cancer Council New South Wales. Melbourne School of Population and Global Health, The University of Melbourne, Australia

K. Elder. Royal Melbourne Hospital, Melbourne, VIC, Australia

A. Park. Royal Melbourne Hospital, Melbourne, VIC, Australia

A. Rose. RMH, United States

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

Background Women with a personal history of breast cancer (PHBC) have a high rate of subsequent breast malignancy. Annual mammography with selective ultrasound has been the standard method of surveillance after breast cancer for many years, aiming for early detection, treatment and improved survival. In surveillance populations, interval cancers, which can account for ~30% of subsequent breast cancers, are more likely to be larger, hormone receptor negative and lymph node positive than cancers detected by surveillance (Lee et al, Radiology 2021). Interval cancer rates of 3.6 per 1000 mammographic screens have been reported previously in women with PHBC (Houssami et al, JAMA 2011). For women with PHBC a more sensitive surveillance approach may be justified, noting mammography has lower program sensitivity in PHBC surveillance than in screening. Magnetic resonance imaging (MRI) is used selectively but with resource and access limitations. Contrast enhanced mammography (CEM) offers a more sensitive modality than conventional mammography with specificity comparable to MRI, but its utility for surveillance is uncertain. **Methods** Retrospective study of 1,190 women with PHBC who commenced annual CEM surveillance in an Australian hospital setting between June 2016 and December 2022 (Elder et al, Breast Cancer Res Treat 2023) combining outcomes of initial CEM and any subsequent surveillance imaging over that period, including incident surveillance-detected cancers and interval cancers (cancers diagnosed in the year following a negative surveillance episode), recalls for assessment, the contribution of contrast to recall, and pathology and treatment details for cancer diagnoses. Outcomes were reported using descriptive statistics and hazards modelling. **Results** There were 3,784 episodes for analysis: 1,190 first CEM surveillance episodes, and 2,594 subsequent surveillance episodes of which >90% were contrast based imaging. 79% of women had at least three annual rounds of surveillance imaging. 186 cases from the total 3784 surveillance episodes were recalled for assessment (recall rate 4.9%). 72 (39%) recalled cases identified malignant lesions (true positives (TP)), with 50 invasive cancers and 22 cases of DCIS. 114 (61%) recalled cases were false positives (FP). 51% of cases were only recalled due to contrast and 35% of these were TP. Invasive cancers were predominantly stage 1 (64%) or stage 2 (32%) and most were grade 2 (44%) or grade 3 (47%). The median invasive cancer size was 16mm (IQR 9-25mm). 62% of invasive cancers were hormone receptor positive HER2 negative, and 24% were triple negative. The median DCIS size was 19mm (IQR 10-26mm) with only a single low grade case. 40% of invasive cancers and 59% of DCIS were recalled due to contrast. Comparison of tumour features indicates similarities between contrast-directed recalls and other diagnoses; conclusive findings would require a larger sample. Five interval cancers were identified, of

which three were asymptomatic and detected on surveillance imaging scheduled early for other reasons. Thus, the rate of symptomatic interval cancers was 0.8 per 1000 screens (program sensitivity 96.0%). Surveillance-detected cancer rates differed significantly by index cancer subtype ($\chi^2=11.9$, $p=0.0026$), with highest rates for women with triple negative index cancers. Incidence cancer rates were higher among the 6.9% of women with moderate or marked BPE at first CEM surveillance episode ($\chi^2=8.8$, $p=0.032$), but did not differ significantly by age group ($\chi^2=5.2$, $p=0.39$) nor breast density ($\chi^2=4.7$, $p=0.19$). Conclusions Routine use of CEM in annual surveillance of women with PHBC led to 1.85-fold increase in the detection of clinically significant malignant lesions, with lower interval cancer rates than previous published series of women with PHBC. CEM appears to increase the sensitivity of surveillance programs for women with PHBC, improving on imaging without contrast.

PS05-07

Early prediction of response to Neoadjuvant Immunotherapy in Triple Negative Breast Cancer (TNBC) with DCE-MRI

Presenting Author(s) and Co-Author(s):

G. Rauch. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Guirguis. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Patel. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

R. Candelaria. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

R. Mohamed. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Moseley. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

H. Le-Petross. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Leung. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

G. Whitman. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Lane. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Scoggins. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

F. Perez. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Sun. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Pashapoor. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Z. Xu. MD Anderson Cancer Center, Texas, United States

J. White. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

P. Wei. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

B. Reed. UT MD Anderson Cancer Center, United States

J. Son. University of Texas MD Anderson Cancer Center, United States

K. Hwang. University of Texas MD Anderson Cancer Center, United States

B. Panthi. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Korkut. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

L. Huo. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Clayborn. MD Anderson Cancer Center, Houston, Texas, United States

J. Litton. UT MD Anderson Cancer Center, Houston, Texas, United States

V. Valero. Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Bellaire, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

C. Yam. Breast Medical Oncology Department, The University of Texas MD Anderson Cancer Center, United States

W. Yang. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Ma. University of Texas MD Anderson Cancer Center, United States

B. Adrada. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Purpose: Neoadjuvant immunotherapy (NIT) in combination with neoadjuvant chemotherapy (NCT) was recently approved for treatment of TNBC patients with increased rates of pathologic complete response (pCR) compared to NCT alone. The aim of this study was to evaluate if dynamic contrast-enhanced (DCE)-MRI performed after 2 and/or 4 cycles of NIT + NCT, can predict which patients will achieve pCR, potentially triaging them to continuation of NIT+NCT or, when appropriate, to de-escalation trials. Alternatively, identified chemoresistant tumors who are unlikely to achieve pCR may be directed to other treatment strategies, including novel targeted trials, and avoid the unnecessary toxicity of NIT. **Methods and Materials:** Preliminary analysis included 64 patients from prospective IRB-approved study (NCT02276443) with stage I-III TNBC who underwent DCE-MRI at baseline (BL), after 2 cycles (C2), and 4 cycles (C4) of NIT combined with standard of care NCT (Paclitaxel +/- carboplatin). Tumor volumes were calculated using 3 axis measurements of the index lesion at the DCE MRI and percent tumor volume reduction (TVR) between BL, C2, and C4 was calculated. pCR was assessed at surgery after completion of neoadjuvant treatment. Correlation between pCR and TVR was evaluated using ROC analysis. **Results:** 59% (38/64) of TNBC patients achieved pCR after NIT+NCT. DCE-MRI after 2 cycles of NIT+NCT was able to predict pCR with an AUC of 0.71 (95% CI: 0.57-0.84). TVR >90% at C2 predicted pCR with PPV 86%, and TVR < 35% predicted chemoresistance with NPV 100%. Following 4 cycles of treatment DCE-MRI was able to predict pCR with an AUC of 0.81 (95% CI: 0.69-0.92). TVR >95% at C4 was predictive of chemosensitivity with PPV 82%, while TVR < 75% was predictive of chemoresistance with NPV 100%. **Conclusions:** DCE-MRI volumetric changes early during NIT + NCT were able to predict pCR status of TNBC patients as either excellent responders or nonresponders, triaging them to SOC neoadjuvant therapy with option for de-escalation trials, or targeted therapies, respectively. These preliminary results will be validated in the larger cohort after completion of the ongoing prospective clinical trial.

PS05-08

Restriction Spectrum Imaging MRI for automated evaluation of response to neoadjuvant therapy in breast cancer

Presenting Author(s) and Co-Author(s):

M. Andreassen. Section of Oncology, Vestre Viken Hospital Trust, Drammen, Norway, Drammen, Not Applicable, Norway

S. Loubrie. Department of Radiology, University of California, San Diego, La Jolla, California, United States

M. Tong. Department of Radiology, University of California, San Diego, La Jolla, California, United States

L. Fang. Department of Radiology, University of California, San Diego, La Jolla, California, United States

T. Seibert. Department of Radiation Medicine and Applied Sciences, University of California, San Diego, La Jolla, California, United States

A. Wallace. University of California San Diego, San Diego, California, United States

S. Zare. School of Medicine, University of California, San Diego, La Jolla, California, United States

H. Ojeda-Fournier. Department of Radiology, University of California, San Diego, La Jolla, California, United States

J. Kuperman. Department of Radiology, University of California, San Diego, La Jolla, California, United States

M. Hahn. Department of Radiology, University of California, San Diego, La Jolla, California, United States

N. Jerome. Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

T. Bathen. Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

A. Rodríguez-Soto. Department of Radiology, University of California, San Diego, La Jolla, California, United States

A. Dale. Department of Radiology, University of California, San Diego, La Jolla, California, United States

R. Rakow-Penner. Department of Radiology, University of California, San Diego, La Jolla, California, United States

Introduction: Dynamic contrast-enhanced MRI (DCE) is currently used to evaluate neoadjuvant therapy response of breast cancer (1). However, DCE requires expert radiologist readers to assess the change in longest tumor dimension during therapy, as well as administration of Gadolinium contrast agents. One MRI modality that does not require contrast agents is diffusion-weighted MRI (DWI), a method that detects the microscopic diffusion of water molecules. However, the commonly used DWI method apparent diffusion coefficient (ADC) is not fully optimised in the breast (2). The purpose of the current study was to evaluate the recent DWI method Restriction Spectrum Imaging (RSI) (2) to automatically monitor breast tumor size during neoadjuvant therapy. Methods: Twenty-seven women underwent 3T MRI at four time points during therapy at University of California San Diego; 17 received all four scans (see Table 1 for patient details). Inclusion criteria included biopsy-proven unilateral invasive breast

cancer ≥ 2.5 cm (defined on clinical examination/imaging) with indication for neoadjuvant therapy. The therapy used was primarily paclitaxel (+/-experimental agent) followed by anthracycline. The MRI protocol included Gadolinium DCE and DWI (b-values 0, 500, 1500, 4000 s/mm²); TE/TR = 82/9000 ms. ADC was calculated using b-values < 1000 s/mm² while signal from all available b-values were fitted to the previously-developed three-component RSI model (2). The tumor size by RSI was assessed against manual DCE tumor size and mean ADC values. Prediction of therapy response during therapy and residual tumor post-therapy were assessed using non-pathological complete response (non-pCR) as endpoint. pCR was defined as ypT0/is or ypN0. Results: Ten patients experienced pCR. Prediction of non-pCR by ROC AUC at the early-therapy time point was 0.65 for RSI, 0.64 for DCE and 0.45 for ADC (Table 2). Prediction of post-therapy residual tumor is given in Table 3. Discussion: The novel RSI cancer tissue classifier predicted response to neoadjuvant therapy after only 19 days. RSI could also identify 71% of cases with residual tumor at surgery with 90% specificity post-therapy. RSI performance was similar to performance by standard MRI by manual tumor measurement on DCE. In contrast to standard-of-care MRI by using DCE and ADC that requires manual user input, the RSI classifier is automatic. This suggests that RSI may aid to cost-efficiently evaluate neoadjuvant therapy of breast cancer, with the aim to help guide clinical decision-making and enable tailored therapy regimens. References: 1. Reig B et al: Breast MRI for Evaluation of Response to Neoadjuvant Therapy. Radiographics, 2021 2. Andreassen MMS et al: Discrimination of breast cancer from healthy breast tissue using a three-component diffusion-weighted MRI model. Clin Cancer Res, 2021 Table 1

No. Patients	27
Median patient age, years (range)	47 (20-66)
Lesion type mass (mass vs. NME)	
Mass	24
Mass + NME	3
Histologic type	
NST	24
Metaplastic carcinoma	2
Mixed IDC/ILC	1
MBR score	
1	1
2	11
3	15
ER status	
Positive	15
Negative	12
PR status	
Positive	13
Negative	14
HER2 status	
Positive	3
Negative	23
Not analyzed	1
pCR status	
pCR	10
non-pCR	17
Median time from therapy start to MRI scan, days (range)	
Early-therapy	19 (15-26)
Mid-therapy	81 (48-94)
Post-therapy	147 (98-190)

Patient cohort details.

Table 2

		Δ DCE	Δ RSI	Δ ADC (\uparrow = response)
Early-Tx (3 weeks)	ROC AUC (95%CI)	0.64 (0.36-0.91)	0.65 (0.38-0.92)	0.45 (0.16-0.75)
Mid-Tx (12 weeks)	ROC AUC (95%CI)	0.71 (0.45-0.96)	0.60 (0.32-0.88)	0.35 (0.06-0.64)
Post-Tx	ROC AUC (95%CI)	0.80 (0.59-1.00)	0.76 (0.52-0.99)	0.36 (0.07-0.65)

Receiver operating characteristics (ROC) area under the curve (AUC) for performance of Δ DCE, Δ RSI and Δ ADC for predicting non-pCR at each time point. There were no significant differences between modalities at any timepoint ($p > 0.025$) as assessed by DeLong's test.

pCR = pathological complete response, Tx = therapy, Δ DCE = change in size from pre-therapy time point for manual dynamic contrast-enhanced MRI, Δ RSI = change in size from pre-therapy time point for automatic Restriction Spectrum Imaging classifier, Δ ADC = change in mean value from pre-therapy time point for apparent diffusion coefficient.

Table 3

	DCE	RSI	ADC
Threshold value	1.3 cm	0.75 cm	$0.5 \times 10^{-3} \text{ mm}^2/\text{s}$
Specificity threshold	0.90	0.90	1.00
Sens ₉₀ (95% CI) Post-Tx	0.65 (0.38-0.86)	0.71 (0.44-0.90)	0.00 (0.00-0.20)*
Acc ₉₀ (95% CI) Post-Tx	0.74 (0.54-0.89)	0.78 (0.58-0.91)	0.37 (0.19-0.58)*
ROC AUC	0.79	0.80	0.52

Sensitivity and accuracy given specificity $\geq 90\%$ and receiver operating characteristics (ROC) area under the curve (AUC) for predicting non-pCR for manual dynamic contrast-enhanced MRI (DCE), Restriction Spectrum Imaging (RSI) classifier and the mean apparent diffusion coefficient (ADC) after all neoadjuvant therapy prior to surgical intervention (post-Tx time point). There was no significant difference for comparison between DCE and RSI ($p = 0.56$) as assessed by McNemar's test, but they were significant for DCE vs. ADC ($p < 0.001$) and RSI vs. ADC ($p < 0.001$). *Specificity $\geq 90\%$ is achieved by a threshold where all cases are classified as pCR (specificity = 100%). For reference, sensitivity was 0.18 and accuracy 0.41 when using a specificity $\geq 80\%$. pCR = pathological complete response, Sens90 = sensitivity given specificity $\geq 90\%$, Acc90 = accuracy given specificity $\geq 90\%$, Tx = therapy.

PS05-09

A single-arm Phase II clinical study of fulvestrant combined with chemotherapy in the neoadjuvant treatment of HR+/HER2- locally advanced breast cancer

Presenting Author(s) and Co-Author(s):

X. Zeng. Chongqing University Cancer Hospital, Chongqing, Chongqing, China (People's Republic)

Q. Shao. Chongqing University Cancer Hospital, United States

J. Wu. Chongqing University Cancer Hospital, United States

N. Zhang. Chongqing University Cancer Hospital, United States

Background: HR+/HER2- breast cancer has been found to be less sensitive to neoadjuvant chemotherapy (NCT), leading to an objective response rate (ORR) of approximately 65%. Endocrine therapy combined with chemotherapy may help improve the ORR in these patients. The objective of this Phase II study was to evaluate the efficacy and safety of adding fulvestrant to NCT in patients with HR+/HER2- locally advanced breast cancer(LABC). Additionally, the study aimed to investigate the association of ¹⁸F-FES PET/CT and metabolites with efficacy. Methods: In this single-arm Phase II study, eligible patients were females with histologically confirmed HR+/HER2- LABC (Stage IIB-IIIC). Patients received fulvestrant (500 mg, on days 0, 14, 28, then every 28 days thereafter, every 4 weeks for six cycles) plus AC-T regimen, followed by surgery. Premenopausal women were administered a concomitant GnRH analogue. Patients underwent ¹⁸F-FES PET/CT before the initiation of fulvestrant, and plasma samples were collected for LC-MS analysis at baseline. The primary endpoint was ORR. Secondary endpoints included pathological complete response (tpCR) and safety. Results: From December 2020 to September 2022, 36 patients were enrolled. The median age was 53 years (range 35-67). 78% were ECOG PS of 1, 69% were postmenopausal, 92% were nodal involved, and 83% were in stage III. After neoadjuvant therapy, the ORR was 86.1%. All patients completed the surgery, with a tpCR rate of 8.3% (3/36). 80.6% (29/36) patients were classified as Miller-Payne (MP) grade ≥ 3 . Grade ≥ 3 treatment-emergent adverse events (TEAEs) occurred in 22% (8/36) of the participants. The most common TEAEs were neutropenia (13.9%) and leukopenia (8.3%). The expression of ER, PR, and Ki-67 in postoperative pathology significantly decreased compared to baseline ($p < 0.05$). Additionally, the change in ER expression was significantly correlated with the regression volume of primary breast tumors ($R = 0.56$, $p = 0.0044$). The decrease in ER value in patients with MP ≥ 4 was significantly larger than in patients with MP ≤ 3 ($p = 0.0054$). Among the 36 patients, 24 completed the ¹⁸F-FES PET/CT scan before initiating fulvestrant. The average SUVmax in primary breast lesions was 4.17 (range 1.00-12.80). The SUVmax of breast lesions was significantly correlated with clinical efficacy ($p = 0.0018$) and with changes in ER expression before and after treatment ($R = 0.68$, $p = 0.00023$). Meanwhile, the SUVmax of patients with MP ≥ 4 grade was significantly higher than that of patients with MP ≤ 3 grade ($p = 0.018$). A total of 25 plasma samples were available for metabolic analysis. Among these samples, 13 differential metabolites were identified between patients with MP ≥ 4 grade and MP ≤ 3 grade, which were markedly enriched in 19 metabolic pathways. Conclusions: The addition of fulvestrant to NCT showed manageable toxicity and promising antitumor activity for patients with HR+/HER2- LABC. ¹⁸F-FES PET/CT might serve as a tool to predict the effectiveness of neoadjuvant combination therapy. Altered metabolites or metabolic pathways might be associated with the response to this combined treatment approach.

Keywords: breast cancer, HR+/HER2-, fulvestrant, neoadjuvant treatment, ¹⁸F-FES PET/CT

PS05-01

Accuracy and safety of fibroblast activation protein inhibitor (FAPI) PET/CT in diagnosis of axillary lymph node metastasis in early breast cancer patients: a prospective cohort study (PFB-01&02 study)

Presenting Author(s) and Co-Author(s):

B. Pan. Peking Union Medical College Hospital, United States

Z. Hao. Peking Union Medical College Hospital, United States

C. Ren. Peking Union Medical College Hospital, United States

L. Zhang. Peking Union Medical College Hospital, United States

Y. Zhou. Peking Union Medical College Hospital, United States

Q. Sun. Peking Union Medical College Hospital, United States

L. Huo. Peking Union Medical College Hospital, United States

Background

Axillary lymph node (ALN) is the most common metastatic site of breast cancer (BC) and the status of ALN determines the staging, treatment and prognosis for BC patients. Traditional imaging techniques, including ultrasound (US), mammography, MRI, and ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) were still unsatisfactory to evaluate the status of ALN non-invasively.

Fibroblast activation protein (FAP) is highly expressed in cancer-associated fibroblasts and FAP inhibitor (FAPI) PET has been found quite promising in BC. Well-designed prospective large cohort study concerning the diagnostic performance and safety profile of FAPI PET/CT in detection of ALN metastasis of BC is still lacking. Furthermore, FAPI could be radio-labeled with different radio-nuclides including ^{68}Ga and ^{18}F , and there is yet no data concerning the ^{18}F -labeled FAPI in BC. In this study, we investigated the accuracy of FAPI (both ^{68}Ga -FAPI-04 and ^{18}F -FAPI-04) PET/CT in newly diagnosed BC patients for assessing ALN metastasis. We also compared the diagnostic performance of FAPI PET/CT with that of ^{18}F -FDG PET/CT and US.

Methods

This prospective study was approved by the Peking Union Medical College Hospital Ethics Committee and was registered online at NIH ClinicalTrials.gov (NCT05574907, NCT05574920). The inclusion criteria were as follows: (1) age 18-80 years old; (2) newly diagnosed BC confirmed by biopsy or with BI-RADS category 4C or 5 lesions by US. The exclusion criteria were as follows: (1) pregnancy or lactation; (2) patients unwilling to undergo PET/CT scans. All patients received biopsy or surgery on breast lesion and ALN. Patients received FAPI and ^{18}F -FDG PET/CT after enrollment. The safety profile of FAPI PET was monitored after injection using the Common Terminology Criteria for Adverse Events. Two experienced nuclear medicine physicians, who were blinded to the pathological diagnosis and other imaging results, assessed the PET/CT images. It was defined as visually positive if the radioactive uptake of the ALN was higher than that of the adjacent normal tissue. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each diagnostic test. The McNemar test was applied to compare the differences of sensitivity and specificity between FAPI PET/CT, ^{18}F -FDG PET/CT, and US. All statistical tests were

performed two-sided, and $P < 0.05$ was considered statistically significant.

Results

In total, 113 patients (27-79 years old, median age 66) were enrolled. 53 patients underwent ^{68}Ga -FAPI-04 PET/CT, and the other 60 patients underwent Al^{18}F -FAPI-04 PET/CT. All patients underwent ^{18}F -FDG PET/CT and US. A total of 53/113 (46.9%) patients were finally diagnosed with ALN metastasis.

The sensitivity, specificity, accuracy, PPV, and NPV were 90.6%, 90.0%, 90.3%, 88.9%, and 91.5% for FAPI PET/CT, 84.9%, 73.3%, 78.8%, 73.8%, and 84.6% for ^{18}F -FDG PET/CT, 83.0%, 76.7%, 79.6%, 75.9%, and 83.6% for US, respectively (Table 1). The specificity of FAPI PET/CT was significantly higher than that of ^{18}F -FDG PET/CT ($P < 0.05$) and US ($P < 0.05$). The sensitivity of FAPI PET/CT was higher than that of ^{18}F -FDG PET/CT ($P = 0.45$) and US ($P = 0.29$). There was no significant difference of sensitivity and specificity between ^{18}F -FDG PET/CT and US ($P > 0.05$).

The sensitivity, specificity, accuracy, PPV, and NPV were 92.0%, 92.9%, 92.5%, 92.0%, and 92.9% for ^{68}Ga -FAPI-04 PET/CT, and 89.3%, 87.5%, 88.3%, 86.2%, and 90.3% for Al^{18}F -FAPI-04 PET/CT, respectively (Table 2).

The ^{68}Ga -FAPI-04 PET/CT and Al^{18}F -FAPI-04 PET/CT procedures were well tolerated in all patients. The only adverse event was injection pain in 12/53 (22.6%) patients injected with ^{68}Ga -FAPI-04, and 7/69 (10.1%) patients injected with Al^{18}F -FAPI-04, which might relate to the ethanol in the imaging agent.

Conclusion

The FAPI PET/CT outperformed ^{18}F -FDG PET/CT and US in the diagnosis of ALN metastasis among early breast cancer patients. The ^{68}Ga -FAPI-04 and Al^{18}F -FAPI-04 PET/CT have similar diagnostic performance. The FAPI PET/CT procedures were well tolerated in all patients.

Table 1 Diagnostic performance of FAPI PET/CT, ^{18}F -FDG PET/CT, and ultrasound in the diagnosis of ALN metastasis

	Sensitivity	Specificity	Accuracy	PPV	NPV
FAPI PET/CT	90.6%	90.0%	90.3%	88.9%	91.5%
¹⁸ F-FDG PET/CT	84.9%	73.3%	78.8%	73.8%	84.6%
Ultrasound	83.0%	76.7%	79.6%	75.9%	83.6%

Table 2 Diagnostic performance of ⁶⁸Ga-FAPI-04 and Al¹⁸F-FAPI-04 PET/CT in diagnosis of ALN metastasis

	Sensitivity	Specificity	Accuracy	PPV	NPV
⁶⁸ Ga-FAPI-04	92.0%	92.9%	92.5%	92.0%	92.9%
Al ¹⁸ F-FAPI-04	89.3%	87.5%	88.3%	86.2%	90.3%

Disclosure(s):
Zhixin Hao, n/a: No financial relationships to disclose

Poster Spotlight Session 5: Shining a New Light on Breast Cancer: Novel Molecular and Functional Imaging Approaches to Detect and Characterize Breast Cancer

Presenting Author(s) and Co-Author(s):

D. Mankoff. University of Pennsylvania, Philadelphia, PA, United States

Disclosure(s):

David Mankoff, MD, PhD: Advisory Committee/Board Member: ImaginAb (Ongoing), Reflexion Medical (Ongoing), Trevarx (Ongoing); Consulting Fees (e.g., advisory boards): GE Healthcare (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): ImaginAb (Ongoing), Reflexion Medical (Ongoing), Trevarx (Ongoing); wife is CEO: Trevarx (Ongoing)

PS05-02

PET Imaging of PARP Expression as a Biomarker of Response to Chemotherapy in Breast Cancer: A Nonrandomized Clinical Trial

Presenting Author(s) and Co-Author(s):

S. Gitto. University of Pennsylvania, Philadelphia, Pennsylvania, United States

A. Young. University of Pennsylvania, United States

I. Bleiweiss. University of Pennsylvania, United States

A. Clark. University of Pennsylvania, United States

A. Pantel. University of Pennsylvania, United States

Introduction:

Poly-(adenosine diphosphate-ribose) polymerase (PARP) proteins are involved in double-stranded break repair, mediated through homologous recombination (HR) and non-homologous end joining (NHEJ). The majority of PARP activity in this context is attributed to PARP-1 (85-90%). PARP-1 binding to damaged DNA, catalytic activity, and subsequent release to allow access for other DNA repair proteins are necessary for efficient DNA repair. The critical function of PARP-1 in these processes makes this protein a unique potential biomarker of DNA repair capability.

[¹⁸F]FluorThanatrace ([¹⁸F]FTT) is an ¹⁸F-labeled PARP inhibitor analog that binds to the same site as approved PARPi drugs. We hypothesized that the biologically relevant form of PARP in untreated breast cancer might provide an indication of functional tumor DNA repair capabilities and therefore predict chemotherapy response. Thus, this study aimed to determine whether a non-invasive quantitative measure of in vivo PARP expression correlated with response to chemotherapy in breast cancer.

Methods:

A single-arm prospective trial enriched for subjects with triple negative breast cancer (TNBC) was conducted at the University of Pennsylvania from May 2017 to March 2022 (NCT03083288 and NCT03846167). Inclusion criteria were primary breast cancer with tumor diameter of at least 1 cm on conventional imaging and willingness to undergo an [¹⁸F]FTT-PET scan prior to neoadjuvant chemotherapy. Participants provided written informed consent.

[¹⁸F]FTT uptake in breast cancer was measured pre-therapy and tested for association with pathologic complete response (pCR). Subjects were scanned on an Ingenuity TF PET/CT (Philips Healthcare) following injection of [¹⁸F]FTT using a 20-minute static acquisition. Peak 1 cm³ average uptake (SUV_{peak}) were recorded from a spherical region-of-interest (ROI) covering the primary malignancy, guided by CT and prior imaging studies. All SUVs were partial volume corrected and normalized using muscle (NM). A Mann-Whitney test was used to determine if [¹⁸F]FTT uptake differed by pCR. Receiver operating characteristic (ROC) curves were constructed to test the performance of [¹⁸F]FTT uptake in predicting pCR. Statistical analyses utilized STATA v15.1 with significance based on a two-sided alpha level of ≤0.05.

Participants:

Twenty-six women with stage I-III breast cancer met inclusion criteria with age range of 29-74 years and self-reported race as Asian (1, 4%), Black (9, 37%) or White (16, 60%). One subject had bilateral tumors (ER+ stage IIA and HER2+ stage I) that were evaluated separately (27

total tumors). Breast tumors were pathologically confirmed and included 6 (22%) ER+/HER2-, 5 (19%) HER2+, and 16 (59%) TNBC. Germline sequencing was available for 21 participants.

Results:

Mean tumor diameter ranged from 15 to 91 mm (median 30 mm). A considerable range of [¹⁸F]FTT uptake was seen across subjects (SUV_{peak}/NM 0.66-6.5). [¹⁸F]FTT uptake was independent of subtype (ER+, HER2+, TN) (P=0.35), stage (P=0.39), and between mutations in genes associated with homologous recombination deficiency (i.e., BRCA1/2, PALB2) and wild-type (P=0.73).

In the TNBC cohort, pre-treatment [¹⁸F]FTT uptake was higher in subjects who went on to have a pCR (n=16, P=0.05), while a trend toward higher uptake was seen when including all tumor types (n=27, P=0.11). ROC analysis of the value of [¹⁸F]FTT uptake for predicting pCR revealed an AUC of 0.79 and showed that a threshold SUV ratio < 2.47 predicted pCR in TNBC patients with a 100% specificity and 64% sensitivity.

Conclusions:

These early clinical results suggest a relationship between [¹⁸F]FTT uptake, a measure of PARP expression, and chemotherapy sensitivity in TNBC, warranting future studies to elucidate underlying mechanistic processes and potential clinical implications.

Disclosure(s):

Sarah B. Gitto, PhD: No financial relationships to disclose

PS05-03

MagSense® HER2, a Molecularly Targeted Magnetic Resonance Imaging Agent for the Detection of Axillary Nodal Metastasis in Subjects with Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Breast Cancer

Presenting Author(s) and Co-Author(s):

j. Fox. Department of Surgery, School of Clinical Sciences at Monash Health, Monash University, Victoria, Australia

S. Velaiutham. Breast Center, Lake Macquarie Private Hospital, New South Wales, Australia

N. Yang. Austin Health, United States

E. Iau. Austin Health, United States

K. Murugappan. Royal Brisbane Hospital, Queensland, Australia

B. Kumar. Monash Health, United States

A. Laslowski. Monash Medical Center, Victoria, Australia

K. Govindarajan. Imagination Biosystems Inc., United States

S. Reich. Imagination Biosystems Inc., United States

S. Thomas. Imagination Biosystems Inc., United States

N. Neha. Imagination Biosystems Ltd, United States

M. Zhang. Imagination Biosystems Ltd, United States

I. Bright. Imagination Biosystems Inc, San Diego, California, United States

Background

Precise nodal staging is critical in guiding systemic and regional treatments including surgery in the management of breast cancer. Regional nodal assessment includes axillary imaging (mostly by ultrasound) and lymph node sampling. Since imaging findings suggestive of nodal metastasis are based on size and morphologic changes and not specific to tumor type, pathologic confirmation through either biopsy or removal of sentinel lymph node (SLN) remains the gold standard. Imagination is developing the MagSense® HER2 Imaging Agent (MSH2IA), an anti-human epidermal growth factor receptor 2 (HER2) conjugated with iron oxide nanoparticles, for the detection of nodal metastasis in HER2+ breast cancer patients. MSH2IA is currently being investigated in a first-in-human phase 1 study (ACTRN12621000126819) in HER2+ breast cancer patients who are diagnosed to have suspicious nodes by conventional imaging.

Methods

The key objectives of the phase 1 study are safety and tolerability of MSH2IA and confirmation that MSH2IA drains to the axillary lymph nodes. The study also explores MSH2IA's ability to detect metastatic nodes when used with magnetic resonance imaging (MRI), with tumor status assessed by standard tissue histopathology. All eligible subjects receive a 22.5 mg (iron equivalent) subareolar or peritumoral injection of MSH2IA. MRI of the axilla are obtained before and 24 to 72 hours after MSH2IA injection. Core biopsy or dissection of a node suspicious by ultrasound is obtained for histopathology assessments. After completing the first cohort of 6 subjects, the protocol was amended to include the insertion of an MRI compatible clip in a node suspicious by ultrasound to localize the suspicious node for core biopsy and postdose MRI scan. Review of MRI scans and histopathology are performed in respective central laboratories.

Results

Thirteen participants with HER2+ breast cancer have completed the study. MSH2IA appears safe and well tolerated. The imaging agent, as administered, is detectable by MRI and pathology, confirming that MSH2IA drains to the lymph nodes via the chosen route of administration. In postdose MRI scans, study central radiologists reported distinct and differentiable MRI appearance in morphologically normal and suspicious nodes. The presence of a distinct postdose MR image appearance was confirmed by a group of independent radiologists in a separate blinded review. While normal nodes appeared with homogeneous hypointensity, morphologically suspicious nodes showed partial irregular darkening and/or speckled heterogeneous hypointensity. In evaluable subjects, histopathology of the core biopsies obtained from the clipped nodes confirmed the presence of HER2+ nodal metastasis, providing preliminary evidence for node-level concordance between MRI vs pathology observations. Safety, imaging, and pathology results from all available subjects will be presented. This phase 1 study in Australia will be closing enrollment by July 31, 2023. A phase 2 study in the United States and elsewhere is being planned with the objectives of optimizing dose, schedule, and imaging parameters for best diagnostic performance for clinical utility.

Conclusion

Available data from the ongoing phase 1 study show that MSH2IA appears safe and drains to the axillary lymph nodes. MSH2IA displays a distinct and differentiable MRI appearance in nodes morphologically highly suspicious for tumor, which is confirmed to be HER2+ metastasis by histopathology by node level concordance. This data provides preliminary proof of principle for the mechanism of molecularly targeted MR imaging and suggests that MSH2IA has the potential to provide tumor-specific MR imaging not currently available in conventional axillary imaging.

Disclosure(s):

Isaac Bright, MD: No financial relationships to disclose

PS05-04

[⁸⁹Zr]Trastuzumab-PET/MRI to Characterize HER2+ Breast Cancer: A Quantitative Approach on Tumor Heterogeneity

Presenting Author(s) and Co-Author(s):

A. Mansur. University of Alabama at Birmingham, Birmingham, Alabama, United States

M. Nikpanah. University of Alabama at Birmingham, Birmingham, Alabama, United States

J. McConathy. University of Alabama at Birmingham, Birmingham, Alabama, United States

E. Stringer-Reasor. University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, Alabama, United States

G. Rocque. University of Alabama at Birmingham, Birmingham, Alabama, United States

A. Elkhanany. University of Alabama at Birmingham, Birmingham, Alabama, United States

K. Khoury. O'Neal Comprehensive Cancer Center at the University of Alabama, Birmingham, Alabama, United States

N. Jahan. University of Alabama at Birmingham, Birmingham, Alabama, United States

S. Lapi. University of Alabama at Birmingham, Birmingham, Alabama, United States

A. Sorace. University of Alabama at Birmingham, Birmingham, Alabama, United States

Introduction:

Molecular imaging of human epidermal receptor 2 (HER2) aims to overcome limitations of traditional HER2 assessment through biopsy, including invasiveness and inability to detect intra and inter-tumoral spatial heterogeneity. Prior human studies suggest that [⁸⁹Zr]Trastuzumab-positron emission tomography (PET) imaging can effectively differentiate HER2 lesions (Dehdashti et al, Breast Cancer Res. Treat. 2018). Commonly, CT complements PET for anatomical reference, however, integrating MRI enables the sensitivity of soft-tissue contrast required for anatomic and morphological breast imaging and can provide for quantitative multiparametric characterization. Diffusion weighted-MRI (DW-MRI) contributes to tumor characterization by assessing intratumoral cellularity via the apparent diffusion coefficient (ADC), and can be combined with molecular expression from HER2-PET. We present preliminary results in 13 patients with HER2 PET/MRI to define tumor and normal tissue imaging metrics.

Methods:

A phase II clinical trial assessing the feasibility of [⁸⁹Zr]trastuzumab-PET with simultaneous quantitative DW-MRI to enhance understanding of tumor heterogeneity in patients with HER2-positive metastatic breast cancer. 13 patients (ages 40-70; mean 60) with HER2-positive breast cancer based on prior biopsy underwent whole-body [⁸⁹Zr]trastuzumab-PET/MR imaging (5 ± 1 days post-injection of radiopharmaceutical) during the course of HER2-directed therapy. Normal organ and tumor regions of interest (ROI) were identified on concurrently acquired whole-body T₁-weighted MRI for ADC (cellularity) and standardized uptake value (SUV, PET uptake) mean quantification. Tumor presence was confirmed via bone scintigraphy, FDG-PET/CT, or contrast-enhanced MRI. Non-parametric T-tests compared lesions to normal organs. Lesions greater than 30 mm in diameter underwent multiparametric intratumoral habitat analysis. Using the median HER2 values, tumors were evaluated for heterogeneity of high and low HER2 expression in conjunction with ADC. Long-term treatment response evaluation is ongoing.

Results:

Mean [⁸⁹Zr]trastuzumab uptake, SUV, and ADC values for normal tissue were summarized in Table 1. All tumors demonstrated higher overall uptake of [⁸⁹Zr]trastuzumab (bone: p=0.019, brain: p=0.014, breast: p=0.069, juxtapulmonary: p=0.026) and increased ADC_{mean} values (bone: p=0.002, brain: p=0.5, breast: p=0.03, juxtapulmonary: p=0.037), in comparison to matched normal organs. Notably, one of five patients with a breast lesion, who completely responded to HER2 targeted therapy, exhibited the highest breast lesion SUV_{mean}. Brain and lymph node lesions demonstrated intratumoral heterogeneity of HER2 expression.

Conclusion:

Our study demonstrates the potential value of quantitative MRI along with molecular imaging to characterize metastatic HER2+ breast cancer and evaluate intratumoral heterogeneity. We underscore the importance of standardizing processing techniques and contribute to this effort by summarizing [⁸⁹Zr]trastuzumab uptake and cellularity values of normal physiological uptake. Higher SUV_{mean} and ADC_{mean} values observed in lesions, compared to normal tissue, highlight their potential roles in intratumoral classification. While studies have shown the utility of [⁸⁹Zr]trastuzumab-PET/CT, our findings demonstrate that integrated DW-MRI can aid in tumor classification.

Table 1: Physiological ⁸⁹Zr-Trastuzumab Uptake (SUV_{mean}) and Apparent Diffusion Coefficient (ADC_{mean}) in Healthy Tissues

Organ/Region	SUV _{mean}	ADC _{mean}	Number of Patients
Brain	0.30 ± 0.08	1.13 ± 0.11	10
Frontal Lobe	0.14 ± 0.06	0.94 ± 0.09	10
Lateral Ventricle	0.12 ± 0.06	2.80 ± 0.31	10
Bone	0.66 ± 0.15	0.33 ± 0.15	10
Breast	0.34 ± 0.12	0.91 ± 0.23	7
Breast Fat	0.31 ± 0.07	0.86 ± 0.21	7
Fibroglandular Tissue	0.66 ± 0.34	1.53 ± 0.26	7
Cardiac Blood Pool	4.40 ± 1.34	0.63 ± 0.51	13
Liver	5.07 ± 1.09	1.27 ± 0.14	11
Lung	1.06 ± 0.33	0.24 ± 0.32	11
Kidney	4.55 ± 1.09	1.95 ± 0.15	13
Muscle	0.46 ± 0.12	1.52 ± 0.20	13

Disclosure(s):

Ameer Mansur: No financial relationships to disclose

PS05-06

Outcomes of Surveillance using Contrast Enhanced Mammography in Women with a Personal History of Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Matheson. Department of Surgery, Royal Melbourne Hospital and the University of Melbourne, Parkville, Victoria, Australia

C. Nickson. Daffodil Centre, The University of Sydney, a joint venture with Cancer Council New South Wales. Melbourne School of Population and Global Health, The University of Melbourne, Australia

K. Elder. Royal Melbourne Hospital, Melbourne, VIC, Australia

A. Park. Royal Melbourne Hospital, Melbourne, VIC, Australia

A. Rose. RMH, United States

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

Background

Women with a personal history of breast cancer (PHBC) have a high rate of subsequent breast malignancy. Annual mammography with selective ultrasound has been the standard method of surveillance after breast cancer for many years, aiming for early detection, treatment and improved survival. In surveillance populations, interval cancers, which can account for ~30% of subsequent breast cancers, are more likely to be larger, hormone receptor negative and lymph node positive than cancers detected by surveillance (Lee et al, Radiology 2021). Interval cancer rates of 3.6 per 1000 mammographic screens have been reported previously in women with PHBC (Houssami et al, JAMA 2011).

For women with PHBC a more sensitive surveillance approach may be justified, noting mammography has lower program sensitivity in PHBC surveillance than in screening. Magnetic resonance imaging (MRI) is used selectively but with resource and access limitations. Contrast enhanced mammography (CEM) offers a more sensitive modality than conventional mammography with specificity comparable to MRI, but its utility for surveillance is uncertain.

Methods

Retrospective study of 1,190 women with PHBC who commenced annual CEM surveillance in an Australian hospital setting between June 2016 and December 2022 (Elder et al, Breast Cancer Res Treat 2023) combining outcomes of initial CEM and any subsequent surveillance imaging over that period, including incident surveillance-detected cancers and interval cancers (cancers diagnosed in the year following a negative surveillance episode), recalls for assessment, the contribution of contrast to recall, and pathology and treatment details for cancer diagnoses. Outcomes were reported using descriptive statistics and hazards modelling.

Results

There were 3,784 episodes for analysis: 1,190 first CEM surveillance episodes, and 2,594 subsequent surveillance episodes of which >90% were contrast based imaging. 79% of women had at least three annual rounds of surveillance imaging.

186 cases from the total 3784 surveillance episodes were recalled for assessment (recall rate 4.9%). 72 (39%) recalled cases identified malignant lesions (true positives (TP)), with 50 invasive cancers and 22 cases of DCIS. 114 (61%) recalled cases were false positives (FP).

51% of cases were only recalled due to contrast and 35% of these were TP.

Invasive cancers were predominantly stage 1 (64%) or stage 2 (32%) and most were grade 2 (44%) or grade 3 (47%). The median invasive cancer size was 16mm (IQR 9-25mm). 62% of invasive cancers were hormone receptor positive HER2 negative, and 24% were triple negative. The median DCIS size was 19mm (IQR 10-26mm) with only a single low grade case. 40% of invasive cancers and 59% of DCIS were recalled due to contrast. Comparison of tumour features indicates similarities between contrast-directed recalls and other diagnoses; conclusive findings would require a larger sample.

Five interval cancers were identified, of which three were asymptomatic and detected on surveillance imaging scheduled early for other reasons. Thus, the rate of symptomatic interval cancers was 0.8 per 1000 screens (program sensitivity 96.0%).

Surveillance-detected cancer rates differed significantly by index cancer subtype ($\chi^2=11.9$, $p=0.0026$), with highest rates for women with triple negative index cancers. Incidence cancer rates were higher among the 6.9% of women with moderate or marked BPE at first CEM surveillance episode ($\chi^2=8.8$, $p=0.032$), but did not differ significantly by age group ($\chi^2=5.2$, $p=0.39$) nor breast density ($\chi^2=4.7$, $p=0.19$).

Conclusions

Routine use of CEM in annual surveillance of women with PHBC led to 1.85-fold increase in the detection of clinically significant malignant lesions, with lower interval cancer rates than previous published series of women with PHBC. CEM appears to increase the sensitivity of surveillance programs for women with PHBC, improving on imaging without contrast.

Disclosure(s):

Julia Matheson, MBChB DPhil FRACS: No financial relationships to disclose

Bruce Mann, MBBS, PhD, FRACS: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Prelude corporation (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Prelude corporation (Ongoing)

PS05-07

Early prediction of response to Neoadjuvant Immunotherapy in Triple Negative Breast Cancer (TNBC) with DCE-MRI

Presenting Author(s) and Co-Author(s):

G. Rauch. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Guirguis. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Patel. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

R. Candelaria. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

R. Mohamed. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Moseley. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

H. Le-Petross. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Leung. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

G. Whitman. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Lane. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Scoggins. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

F. Perez. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Sun. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Pashapoor. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Z. Xu. MD Anderson Cancer Center, Texas, United States

J. White. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

P. Wei. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

B. Reed. UT MD Anderson Cancer Center, United States

J. Son. University of Texas MD Anderson Cancer Center, United States

K. Hwang. University of Texas MD Anderson Cancer Center, United States

B. Panthi. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Korkut. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

L. Huo. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Clayborn. MD Anderson Cancer Center, Houston, Texas, United States

J. Litton. UT MD Anderson Cancer Center, Houston, Texas, United States

V. Valero. Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Bellaire, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

C. Yam. Breast Medical Oncology Department, The University of Texas MD Anderson Cancer Center, United States

W. Yang. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Ma. University of Texas MD Anderson Cancer Center, United States

B. Adrada. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Purpose:

Neoadjuvant immunotherapy (NIT) in combination with neoadjuvant chemotherapy (NCT) was recently approved for treatment of TNBC patients with increased rates of pathologic complete response (pCR) compared to NCT alone. The aim of this study was to evaluate if dynamic contrast-enhanced (DCE)-MRI performed after 2 and/or 4 cycles of NIT + NCT, can predict which patients will achieve pCR, potentially triaging them to continuation of NIT+NCT or, when appropriate, to de-escalation trials. Alternatively, identified chemoresistant tumors who are unlikely to achieve pCR may be directed to other treatment strategies, including novel targeted trials, and avoid the unnecessary toxicity of NIT.

Methods and Materials:

Preliminary analysis included 64 patients from prospective IRB-approved study (NCT02276443) with stage I-III TNBC who underwent DCE-MRI at baseline (BL), after 2 cycles (C2), and 4 cycles (C4) of NIT combined with standard of care NCT (Paclitaxel +/- carboplatin). Tumor volumes were calculated using 3 axis measurements of the index lesion at the DCE MRI and percent tumor volume reduction (TVR) between BL, C2, and C4 was calculated. pCR was assessed at surgery after completion of neoadjuvant treatment. Correlation between pCR and TVR was evaluated using ROC analysis.

Results:

59% (38/64) of TNBC patients achieved pCR after NIT+NCT. DCE-MRI after 2 cycles of NIT+NCT was able to predict pCR with an AUC of 0.71 (95% CI: 0.57-0.84). TVR >90% at C2 predicted pCR with PPV 86%, and TVR < 35% predicted chemoresistance with NPV 100%. Following 4 cycles of treatment DCE-MRI was able to predict pCR with an AUC of 0.81 (95% CI: 0.69-0.92). TVR >95% at C4 was predictive of chemosensitivity with PPV 82%, while TVR < 75% was predictive of chemoresistance with NPV 100%.

Conclusions:

DCE-MRI volumetric changes early during NIT + NCT were able to predict pCR status of TNBC patients as either excellent responders or nonresponders, triaging them to SOC neoadjuvant therapy with option for de-escalation trials, or targeted therapies, respectively. These preliminary results will be validated in the larger cohort after completion of the ongoing prospective clinical trial.

Disclosure(s):

Gaiane M. Rauch, MD PhD: No financial relationships to disclose

Vicente Valero, MD, FACP: Advisory Committee/Board Member: Astra Zeneca (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Novartis (Ongoing), Roche Pharma (Ongoing)

PS05-08

Restriction Spectrum Imaging MRI for automated evaluation of response to neoadjuvant therapy in breast cancer

Presenting Author(s) and Co-Author(s):

M. Andreassen. Section of Oncology, Vestre Viken Hospital Trust, Drammen, Norway, Drammen, Not Applicable, Norway

S. Loubrie. Department of Radiology, University of California, San Diego, La Jolla, California, United States

M. Tong. Department of Radiology, University of California, San Diego, La Jolla, California, United States

L. Fang. Department of Radiology, University of California, San Diego, La Jolla, California, United States

T. Seibert. Department of Radiation Medicine and Applied Sciences, University of California, San Diego, La Jolla, California, United States

A. Wallace. University of California San Diego, San Diego, California, United States

S. Zare. School of Medicine, University of California, San Diego, La Jolla, California, United States

H. Ojeda-Fournier. Department of Radiology, University of California, San Diego, La Jolla, California, United States

J. Kuperman. Department of Radiology, University of California, San Diego, La Jolla, California, United States

M. Hahn. Department of Radiology, University of California, San Diego, La Jolla, California, United States

N. Jerome. Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

T. Bathen. Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

A. Rodríguez-Soto. Department of Radiology, University of California, San Diego, La Jolla, California, United States

A. Dale. Department of Radiology, University of California, San Diego, La Jolla, California, United States

R. Rakow-Penner. Department of Radiology, University of California, San Diego, La Jolla, California, United States

Introduction:

Dynamic contrast-enhanced MRI (DCE) is currently used to evaluate neoadjuvant therapy response of breast cancer (1). However, DCE requires expert radiologist readers to assess the change in longest tumor dimension during therapy, as well as administration of Gadolinium contrast agents. One MRI modality that does not require contrast agents is diffusion-weighted MRI (DWI), a method that detects the microscopic diffusion of water molecules. However, the commonly used DWI method apparent diffusion coefficient (ADC) is not fully optimised in the breast (2). The purpose of the current study was to evaluate the recent DWI method Restriction Spectrum Imaging (RSI) (2) to automatically monitor breast tumor size during neoadjuvant therapy.

Methods:

Twenty-seven women underwent 3T MRI at four time points during therapy at University of California San Diego; 17 received all four scans (see Table 1 for patient details). Inclusion criteria included biopsy-proven unilateral invasive breast cancer ≥ 2.5 cm (defined on clinical examination/imaging) with indication for neoadjuvant therapy. The therapy used was primarily paclitaxel (+/-experimental agent) followed by anthracycline.

The MRI protocol included Gadolinium DCE and DWI (b-values 0, 500, 1500, 4000 s/mm²); TE/TR = 82/9000 ms. ADC was calculated using b-values < 1000 s/mm² while signal from all available b-values were fitted to the previously-developed three-component RSI model (2). The tumor size by RSI was assessed against manual DCE tumor size and mean ADC values. Prediction of therapy response during therapy and residual tumor post-therapy were assessed using non-pathological complete response (non-pCR) as endpoint. pCR was defined as ypT0/is or ypN0.

Results:

Ten patients experienced pCR. Prediction of non-pCR by ROC AUC at the early-therapy time point was 0.65 for RSI, 0.64 for DCE and 0.45 for ADC (Table 2). Prediction of post-therapy residual tumor is given in Table 3.

Discussion:

The novel RSI cancer tissue classifier predicted response to neoadjuvant therapy after only 19 days. RSI could also identify 71% of cases with residual tumor at surgery with 90% specificity post-therapy. RSI performance was similar to performance by standard MRI by manual tumor measurement on DCE. In contrast to standard-of-care MRI by using DCE and ADC that requires manual user input, the RSI classifier is automatic. This suggests that RSI may aid to cost-efficiently evaluate neoadjuvant therapy of breast cancer, with the aim to help guide clinical decision-making and enable tailored therapy regimens.

References:

1. Reig B et al: Breast MRI for Evaluation of Response to Neoadjuvant Therapy. Radiographics, 2021
2. Andreassen MMS et al: Discrimination of breast cancer from healthy breast tissue using a three-component diffusion-weighted MRI model. Clin Cancer Res, 2021

Table 1

No. Patients	27
Median patient age, years (range)	47 (30-68)
Lesion type (mass vs. NME)	
Mass	24
Mass + NME	3
Histologic type	
HER2	24
Mucopolysaccharin carcinoma	2
Mixed (DCIS/LC)	1
MRI score	
1	1
2	11
3	15
ER status	
Positive	19
Negative	8
PR status	
Positive	13
Negative	14
HER2 status	
Positive	5
Negative	22
Not analyzed	1
pCR status	
pCR	10
non-pCR	17
Median time from therapy start to MRI exam, days (range)	
Early therapy	19 (10-26)
Mid-therapy	81 (48-94)
Post-therapy	147 (96-190)

Patient cohort details.

Table 2

		Δ DCE	Δ RSI	Δ ADC (\uparrow = response)
Early-Tx (3 weeks)	ROC AUC (95%CI)	0.64 (0.36-0.91)	0.65 (0.38-0.92)	0.45 (0.16-0.75)
Mid-Tx (12 weeks)	ROC AUC (95%CI)	0.71 (0.45-0.96)	0.60 (0.32-0.88)	0.35 (0.06-0.64)
Post-Tx	ROC AUC (95%CI)	0.80 (0.59-1.00)	0.76 (0.52-0.99)	0.36 (0.07-0.65)

Receiver operating characteristics (ROC) area under the curve (AUC) for performance of Δ DCE, Δ RSI and Δ ADC for predicting non-pCR at each time point. There were no significant differences between modalities at any timepoint ($p > 0.025$) as assessed by DeLong's test.

pCR = pathological complete response, Tx = therapy, Δ DCE = change in size from pre-therapy time point for manual dynamic contrast-enhanced MRI, Δ RSI = change in size from pre-therapy time point for automatic Restriction Spectrum Imaging classifier, Δ ADC = change in mean value from pre-therapy time point for apparent diffusion coefficient.

Table 3

	DCE	RSI	ADC
Threshold value	1.3 cm	0.75 cm	0.5×10^{-3} mm ² /s
Specificity threshold	0.90	0.90	1.00
Sens ₉₀ (95% CI) Post-Tx	0.65 (0.38-0.86)	0.71 (0.44-0.90)	0.00 (0.00-0.20)*
Acc ₉₀ (95% CI) Post-Tx	0.74 (0.54-0.89)	0.78 (0.58-0.91)	0.37 (0.19-0.58)*
ROC AUC	0.79	0.80	0.52

Sensitivity and accuracy given specificity $\geq 90\%$ and receiver operating characteristics (ROC) area under the curve (AUC) for predicting non-pCR for manual dynamic contrast-enhanced MRI (DCE), Restriction Spectrum Imaging (RSI) classifier and the mean apparent diffusion coefficient (ADC) after all neoadjuvant therapy prior to surgical intervention (post-Tx time point). There was no significant difference for comparison between DCE and RSI ($p = 0.56$) as assessed by McNamar's test, but they were significant for DCE vs. ADC ($p < 0.001$) and RSI vs. ADC ($p < 0.001$).

*Specificity $\geq 90\%$ is achieved by a threshold where all cases are classified as pCR (specificity = 100%). For reference, sensitivity was 0.18 and accuracy 0.41 when using a specificity $\geq 80\%$.

pCR = pathological complete response, Sens₉₀ = sensitivity given specificity $\geq 90\%$, Acc₉₀ = accuracy given specificity $\geq 90\%$, Tx = therapy.

Disclosure(s):

Maren Andreassen, MD PhD: No financial relationships to disclose

PS05-09

A single-arm Phase II clinical study of fulvestrant combined with chemotherapy in the neoadjuvant treatment of HR+/HER2- locally advanced breast cancer

Presenting Author(s) and Co-Author(s):

X. Zeng. Chongqing University Cancer Hospital, Chongqing, Chongqing, China (People's Republic)

Q. Shao. Chongqing University Cancer Hospital, United States

J. Wu. Chongqing University Cancer Hospital, United States

N. Zhang. Chongqing University Cancer Hospital, United States

Background:

HR+/HER2- breast cancer has been found to be less sensitive to neoadjuvant chemotherapy (NCT), leading to an objective response rate (ORR) of approximately 65%. Endocrine therapy combined with chemotherapy may help improve the ORR in these patients. The objective of this Phase II study was to evaluate the efficacy and safety of adding fulvestrant to NCT in patients with HR+/HER2- locally advanced breast cancer(LABC). Additionally, the study aimed to investigate the association of ¹⁸F-FES PET/CT and metabolites with efficacy.

Methods:

In this single-arm Phase II study, eligible patients were females with histologically confirmed HR+/HER2- LABC (Stage IIB-IIIC). Patients received fulvestrant (500 mg, on days 0, 14, 28, then every 28 days thereafter, every 4 weeks for six cycles) plus AC-T regimen, followed by surgery. Premenopausal women were administered a concomitant GnRH analogue.

Patients underwent ¹⁸F-FES PET/CT before the initiation of fulvestrant, and plasma samples were collected for LC-MS analysis at baseline. The primary endpoint was ORR. Secondary endpoints included pathological complete response (tpCR) and safety.

Results:

From December 2020 to September 2022, 36 patients were enrolled. The median age was 53 years (range 35-67). 78% were ECOG PS of 1, 69% were postmenopausal, 92% were nodal involved, and 83% were in stage III. After neoadjuvant therapy, the ORR was 86.1%. All patients completed the surgery, with a tpCR rate of 8.3% (3/36). 80.6% (29/36) patients were classified as Miller-Payne (MP) grade ≥ 3 . Grade ≥ 3 treatment-emergent adverse events (TEAEs) occurred in 22% (8/36) of the participants. The most common TEAEs were neutropenia (13.9%) and leukopenia (8.3%). The expression of ER, PR, and Ki-67 in postoperative pathology significantly decreased compared to baseline ($p < 0.05$). Additionally, the change in ER expression was significantly correlated with the regression volume of primary breast tumors ($R = 0.56$, $p = 0.0044$). The decrease in ER value in patients with MP ≥ 4 was significantly larger than in patients with MP ≤ 3 ($p = 0.0054$). Among the 36 patients, 24 completed the ¹⁸F-FES PET/CT scan before initiating fulvestrant. The average SUVmax in primary breast lesions was 4.17 (range 1.00-12.80). The SUVmax of breast lesions was significantly correlated with clinical efficacy ($p = 0.0018$) and with changes in ER expression before and after treatment ($R = 0.68$, $p = 0.00023$). Meanwhile, the SUVmax of patients with MP ≥ 4 grade was significantly higher than that of patients with MP ≤ 3 grade ($p = 0.018$). A total of 25 plasma samples were available for metabolic analysis. Among these samples, 13 differential metabolites were identified between patients with MP ≥ 4 grade and MP ≤ 3 grade, which were markedly enriched in 19 metabolic pathways.

Conclusions: The addition of fulvestrant to NCT showed manageable toxicity and promising antitumor activity for patients with HR+/HER2- LABC. ^{18}F -FES PET/CT might serve as a tool to predict the effectiveness of neoadjuvant combination therapy. Altered metabolites or metabolic pathways might be associated with the response to this combined treatment approach.

Keywords: breast cancer, HR+/HER2-, fulvestrant, neoadjuvant treatment, ^{18}F -FES PET/CT

Disclosure(s):

Xiaohua Zeng, MD, PhD: No financial relationships to disclose

PS06-01**Results from a pilot study exploring ctDNA detection using a tumor-informed assay in the monarchE trial of adjuvant abemaciclib with endocrine therapy in HR+, HER2-, node-positive, high-risk early breast cancer**

Presenting Author(s) and Co-Author(s):

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

S. Johnston. The Royal Marsden Hospital, London, United Kingdom

C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States

H. Sasano. Department of Pathology, Tohoku University Hospital, Sendai, Japan.

V. Rodrik-Outmezguine. Eli Lilly and Company, Indianapolis, Indiana, United States

A. Sireci. Eli Lilly and Company, Indianapolis, Indiana, United States

C. Sandoval Rubenstein. Eli Lilly and Company, Indianapolis, Indiana, United States

H. Won. Eli Lilly and Company, Indianapolis, Indiana, United States

D. Liu. Eli Lilly and Company, Indianapolis, Indiana, United States

L. M. Litchfield. Eli Lilly and Company, Indianapolis, Indiana, United States

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background

Two years of adjuvant abemaciclib + endocrine therapy (ET) resulted in significant and clinically meaningful improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) in patients (pts) with HR+, HER2-, node-positive, high-risk early breast cancer (EBC) in the monarchE trial (NCT03155997). The benefit of abemaciclib was sustained beyond completion of treatment and deepened in magnitude at 4 years for IDFS and DRFS. This pilot study investigated the technical feasibility of ctDNA detection beginning prior to study treatment, as well as rates of persistence and clearance in a subset of EBC pts from monarchE using the clinically validated Signatera™ ctDNA assay.

Methods

Samples were analyzed from a selected subset of pts (n=178; 84 from abemaciclib+ET arm; 94 ET alone) who had blood collected both before initiating protocol directed therapy, Visit 1 (V1; randomization + ≤ 3 days) and near completion of the 2-year treatment period, Visit 27 (V27; 24 months +/- 5 days from V1). This cohort of pts was enriched for overall IDFS events compared to the total monarchE study population, however pts with relapses occurring prior to V27 were excluded. Primary tumors from selected pts were subjected to whole exome sequencing (WES). Selected samples included those from pts with a range of tumor mutation burden. Cell-

free DNA was extracted from 356 plasma samples. A Signatera ctDNA assay was developed for each pt based on up to 16 variants detected by WES from each baseline tumor sample.

Results

The IDFS event rate for the selected subset (n=178) was 39.3% (abemaciclib+ET 34.5% [29/84] and ET alone 43.6% [41/94]). Ten pts (5.6%) were initially ctDNA+ and 42 pts (23.6%) were persistently (7 pts, 3.9%) or became (35 pts, 19.7%) ctDNA+ at V27. Notably, 70% of pts who were initially ctDNA+ and 100% of pts who were either persistently ctDNA+ or became ctDNA+ experienced recurrence (see Table 1). In contrast, none of the 3 pts that cleared ctDNA+ developed recurrence. In pts persistently ctDNA negative (neg), 28 (21.1%) experienced recurrence. Overall, 10% (7/70) of pts with IDFS events were initially ctDNA+ and 50% (35/70) had detectable ctDNA at V27.

Conclusions

Detection of ctDNA soon after completing neoadjuvant chemotherapy was infrequent, but also associated with a high-risk of recurrence. ctDNA positivity was common at the end of the 2-year treatment period and was highly prognostic with all pts subsequently developing disease recurrence. Importantly, ~30% of pts with early ctDNA detection ultimately dropped below detection limits during the 2-year treatment period and none developed recurrence. Although some pts remained persistently ctDNA neg during this study and experienced recurrence, the delay in recurrence may indicate longitudinal benefit from remaining ctDNA neg. Future planned analysis of an expanded cohort reflective of the intent to treat population including additional timepoints within the 2-year treatment period will further define how ctDNA dynamics may identify pts at high-risk of recurrence.

Table 1. Summary of Subset Positivity Rates.

	N (%)	ctDNA Positivity at baseline (%)	ctDNA positivity at 24 months (%)	IDFS event (%)	Median time from ctDNA detection at baseline to recurrence in months (range)	Median time from ctDNA detection at 24 months to recurrence in months (range)
Pilot Subset	178	10 (5.6)	42 (23.6)	70 (39.3)	NA	NA
With recurrence	70 (39.3)	7 (10.0)	42 (60.0)	70 (100.0)	NA	NA
Without recurrence	108 (60.7)	3 (2.8)	0 (0.0)	0 (0.0)	NA	NA
ctDNA+ at baseline	10 (5.6)	10 (100.0)	7 (70.0)	7 (70.0)	27 (25-43)	3 (1-19)
Remained ctDNA+	7 (3.9)	7 (100.0)	7 (100.0)	7 (100.0)	27 (25-43)	3 (1-19)
Cleared at 24 months	3 (1.7)	3 (100.0)	NA	0 (0.0)	NA	NA
Became ctDNA+ at 24 months	35 (19.7)	NA	35 (100.0)	35 (100.0)	NA	5 (0-25)
Persistently ctDNA-	133 (74.7)	NA	NA	28 (21.1)	NA	NA

*95% of patients had prior chemotherapy treatment and subset excludes patients who recurred before 24 months; positivity rates may vary

NA = Not Applicable

+ positive; - negative; NA, not applicable.

PS06-02

Circulating tumor DNA (ctDNA) monitoring of estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) high risk breast cancer during adjuvant endocrine therapy

Presenting Author(s) and Co-Author(s):

L. pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

E. Kalashnikova. Natera, San Carlos, California, United States

E. Hobbs. Division of Hematology & Medical Oncology, Knight Cancer Institute, Oregon Health & Science University, United States

U. Brown-Glaberman. University of New Mexico Cancer Center, Albuquerque, New Mexico, United States

M. Mita. Cedars-Sinai, United States

P. Klein. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

F. Yan. Swedish Medical Center, Washington, United States

S. Ehsani. University of Arizona Cancer Center, Arizona, United States

W. Razaq. Oklahoma university of health Sciences, Oklahoma City, Oklahoma, United States

A. Stopeck. Stony Brook Cancer Center, United States

M. Bhave. Emory University School of Medicine, Atlanta, Georgia, United States

M. Loch. LSUHSC, New Orleans, United States

S. Sardesai. The Ohio State University Comprehensive Cancer Center, United States

E. Roussos Torres. University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, United States

M. Burkard. DEPARTMENT OF MEDICINE University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States

F. Okubanjo. Criterium, United States

E. Gauthier. Pfizer Inc, San Francisco, California, United States

A. Rodriguez. Natera, United States

M. Liu. Natera, United States

P. Kabos. University of Colorado Denver, Aurora, Colorado, United States

Background: ctDNA monitoring during adjuvant endocrine therapy provides an opportunity to detect molecular relapse before clinically apparent recurrence. The rate and dynamics of ctDNA positivity and the frequency of asymptomatic but imaging detectable metastatic disease at the time of ctDNA detection remain unknown in high-risk ER+/HER2- breast cancers. We present results of ctDNA positivity rates in 508 and imaging results in ctDNA+ patients from a prospective, multicenter, randomized ctDNA surveillance and intervention trial, DARE (NCT04567420). Patients and methods: Patients receiving adjuvant endocrine therapy for > 6 months but < 7 years, with either (i) risk of recurrence > 15% calculated by PREDICT, RSPC, or CTS5, or (ii) > 4 positive axillary lymph nodes, or (iii) primary tumor > 5 cm, or (iv) 1-3 positive nodes with grade 3 histology, or > 3 cm tumor, or Oncotype Dx RS > 26, MammaPrint high risk, EndoPredict > 4, Prosigna score > 60 were eligible for ctDNA surveillance with the Signatera™ assay (Natera Inc.) every 4-6 months during routine follow up visits. ctDNA+ patients underwent systemic staging with imaging and randomized to continuation of adjuvant

therapy versus switching to fulvestrant plus palbociclib if there was no evidence of distant metastatic disease. The primary objectives are to assess the incidence of ctDNA positivity in the surveillance phase and to assess if palbociclib plus fulvestrant improves relapse-free survival in 100 randomized patients. This is an updated, protocol-driven interim report to determine if screening eligibility criteria needs to be revised to keep randomization rate > 15% of the screened population. Results: The trial is open at 15 sites and enrolled 508 patients between May 2021 and June 2023; 882 plasma ctDNA tests were performed successfully in 364 patients (72%). The most common reason for failure to generate a personalized ctDNA assay was insufficient tissue submitted, 78% of failed tests were due to preanalytical failure, the technical failure rate was 22%. Thirty patients, 8.2% of those with results available, had >1 positive ctDNA result, the overall positivity rate across all assays was 3.4% (n=30/882). Patient characteristics are shown in the table (not all patients have complete data), 47% of ctDNA+ cases had >4 + lymph nodes. ctDNA positivity rate in the first test was 3.8%, and anytime ctDNA detection rate among those with serial testing was 7.2%. Among ctDNA+ patients, the first ctDNA draw was positive in 23 of 30 cases (77%) with 36.5 months median time (range 6-102 months) from surgery to testing. Using 12 months interval brackets from surgery to 1st ctDNA positivity, annual detection rates were 2.3% (1/44), 8.5% (7/82), 10.8% (9/83), 7.5% (4/53), 13.2% (5/38), and 6.2% (4/64), at 1st, 2nd, 3rd, 4th and > 5th year post-surgery, respectively, due to small sample sizes, 95% confidence broadly overlap. Five ctDNA+ patients (16.7%) had asymptomatic, imaging-detectable metastatic disease, 22 ctDNA+ patients were randomized, the goal is to accrue a total of 100 patients. Conclusions: ctDNA surveillance of ER+/HER2- breast cancers during adjuvant endocrine therapy indicate 8.3% detection rate at patient level and 3.4% at assay level. Serial screening increases detection rates as 23% of positive ctDNA tests occurred after an initial negative result. 83% of ctDNA+ patients had true molecular relapse without imaging detectable metastatic disease. Eligibility for screening on the trial is now restricted to patients with >4 + lymph nodes, randomization is open for any patients who are ctDNA+ including routine commercial screening. Table of patient characteristics

	with ctDNA result (n=364)	ctDNA+ (n=30)
Age < 50	29%	23%
Age >50	71%	77%
PR +	78%	73%
PR -	7%	17%
HER2 IHC negative	79%	77%
Grade 1	8%	7%
Grade 2	53%	50%
Grade 3	29%	37%
T 1	19%	17%
T2	43%	43%
T3	27%	27%
T4	2%	7%

0 +nodes	12%	12%
1 +node	24%	10%
2 +nodes	15%	13%
3 +nodes	8%	13%
>4 +nodes	0	47%

PS06-03

Differences in ctDNA genomic profiles and outcomes of Black and White patients with metastatic breast cancer: results from a large multicenter consortium

Presenting Author(s) and Co-Author(s):

- E. Podany. Washington University in St. Louis, St. Louis, Missouri, United States
L. Foffano. Department of Medicine, University of Udine, United States
L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy
A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States
K. Clifton. Washington University in St Louis School of Medicine, United States
W. Hensing. St. Luke's Cancer Institute, United States
R. Morecroft. Washington University in St. Louis, United States
M. Velimirovic. Cleveland Clinic, United States
A. Shah. Northwestern University - Feinberg School of Medicine, United States
C. REDUZZI. Weill Cornell Medicine, United States
L. Munoz Arcos. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, New York, United States
C. Dai. MGH Cancer Center, United States
J. Keenan. Cancer Center, Massachusetts General Hospital, United States
E. Denault. Massachusetts General Hospital, United States
F. Ademuyiwa. Washington University in St Louis School of Medicine, United States
F. Puglisi. National Cancer Institute, Centro di Riferimento Oncologico (CRO), IRCCS, United States
C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States
A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States
M. Cristofanilli. Weill Cornell Medicine, United States
A. Davis. Washington University in St Louis School of Medicine, United States

Background: Black breast cancer patients have a well-documented survival disparity when compared to White patients. It is imperative to explore the reasons for this disparity from both a socioeconomic and biological perspective. Prior studies evaluating somatic genetic differences have primarily focused on tumor tissue analysis, which could be limited by inter- and intra-tumor heterogeneity. Circulating tumor DNA (ctDNA) testing allows for non-invasive detection of these heterogenous somatic mutations in the peripheral blood. We hypothesized that there could be differences in cancer-specific genetic profiles across Black and White patients with metastatic breast cancer (MBC), and that these differences may impact treatment response and clinical outcomes. Methods: This retrospective cohort study included a total of 1327 patients with MBC who were treated at Washington University in St. Louis (N=474 patients), Massachusetts General Hospital (N=412), and Northwestern University (N=441). All patients underwent ctDNA profiling using the commercially available Guardant360 assay. Race information was patient-reported, and ancestry data were not available. Descriptive analysis of clinical variables and

pathway variants was performed. Univariate and multivariate analyses were done to evaluate single gene mutations and genetic pathways in both the entire cohort and the hormone-receptor positive (HR+), HER2-negative population (HR+/HER2-). The potential prognostic impact of these somatic mutations was assessed through multivariate analysis in both White and Black patient populations. Results: The cohort of 1327 patients included 1057 White patients (79.6%) and 140 Black patients (10.5%). The remaining patients (9.9%) were not included in the analysis due to low numbers. Black patients had significantly higher rates of GATA3 single nucleotide variants (snv) (OR 2.13, 95% CI 1.07-4.25, P=0.03), PTPN11 snv (OR 7.90, CI 1.10-56.56, P=0.04), and CCND2 copy number variants (cnv) (OR 3.78, CI 1.51-9.45, P=0.004). These alterations were also significantly more common in Black patients in the HR+/HER2- population (N = 812) for GATA3 snv (OR 2.28, CI 1.09-4.76, P=0.028), PTPN11 snv (OR 16.60, CI 1.49-184.93, p=0.022), and CCND2 cnv (OR 4.17, CI 1.02-16.97, P=0.046). Multivariate analysis confirmed that GATA3 snv (OR 2.23, CI 1.12-4.45, P=0.023) and CCND2 cnv (OR 3.97, CI 1.59-9.94, P=0.003) were significantly more common in Black patients in both the full cohort and HR+/HER2- subset. Mutations in the PI3K pathway were more prevalent in White patients, but this difference was not statistically significant in univariate or multivariate analysis. Overall survival (OS) from time of ctDNA collection was significantly worse in Black patients compared to White patients when corrected for lines of therapy and sites of metastasis (median 22 vs. 29 months, log-rank test, P=0.03). Among HR+/HER2- patients specifically, worse prognosis in White patients was associated with TP53 snv (HR 1.55, CI 1.19-2.01, P=0.001), NF1 snv (HR 1.99, CI 1.11-3.56, P=0.021), MYC cnv (HR 1.76, CI 1.09-2.87, P=0.02), PIK3CA cnv pathway (HR 1.69, CI 1.07-2.66, P=0.024), and MYC cnv pathway (HR 1.85, CI 1.15-2.97, P=0.011). No significant gene mutation or pathway association was found in Black patients. Prognostic differences in the cohort based on clinical, pathological, and treatment history were also explored and will be presented. Discussion: To our knowledge, this is the largest clinical genomic dataset examining ctDNA differences across Black and White patients. Our findings revealed that Black patients had higher frequencies of GATA3 snv and CCND2 cnv. The shorter OS observed in Black patients in our study aligns with previous studies and is likely multifactorial, especially given the early separation of the survival curves. Future research should focus on both socioeconomic and genetic factors to explain this disparity.

PS06-04

The prognostic and predictive impact of circulating tumour DNA (ctDNA) dynamics in patients with metastatic Triple Negative Breast Cancer (TNBC) on olaparib based therapy: Results from Cohort E of the PlasmaMATCH trial

Presenting Author(s) and Co-Author(s):

I. Browne. The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, England, United Kingdom

J. Pascual. The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, United States

R. Cutts. The Institute of Cancer Research, United Kingdom

B. Kingston. The Institute of Cancer Research, London, United Kingdom

S. Hrebien. The Institute of Cancer Research, United Kingdom

L. Kilburn. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

A. Pearson. The Institute of Cancer Research, London, United Kingdom.

L. Moretti. Clinical Trials & Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

A. Wardley. Outreach Research & Innovation Group Ltd, Manchester, England, United Kingdom

I. Macpherson. University of Glasgow - Institute of Cancer Sciences, United Kingdom

R. Baird. CRUK Cambridge Centre, University of Cambridge, United Kingdom

R. Roylance. University College London Hospital, London, United Kingdom

I. Faull. Guardant Health, Inc., Redwood City, California, United States

K. Banks. Guardant Health, Inc., Redwood City, California, United States

I. Garcia-Murillas. The Institute of Cancer Research, United States

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

A. Ring. The Royal Marsden NHS Foundation Trust, Breast Unit - Department of Medicine, The Royal Marsden NHS Foundation Trust, London, UK/ Breast Cancer Research Division – The Institute of Cancer Research, London, England, United Kingdom

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background: Early changes in ctDNA levels, ctDNA dynamics, may help identify which patients are responding to therapy earlier than imaging. Few studies have assessed ctDNA dynamics during PARP inhibitor therapy. Here we report paired baseline and early on treatment ctDNA analysis from cohort E of plasmaMATCH, that recruited patients with TNBC to treatment with olaparib (PARP inhibitor) plus ceralasertib (ATR inhibitor). Methods: The plasmaMATCH trial assessed the ability of ctDNA testing to allocate patients to mutation matched treatment cohorts (A-D). Patients with TNBC, and without mutations matching cohorts B-D, were enrolled on cohort E. Samples were collected for ctDNA analysis pre-treatment at cycle 1-day1 (C1D1) and cycle 2-day 1 (C2D1). A minimum of 14 days of treatment in the first cycle was required for inclusion in this analysis. Samples were sequenced using error-corrected gene targeted panels (Guardant360, or GuardantOMNI, Guardant Health). Circulating DNA ratio (CDR) was

calculated as the ratio of C2D1 ctDNA level to C1D1, pre-specified using the weighted mean of variant allele fractions (AF) of clonal mutations at C1D1, excluding variants with AF < 0.3%, and variants in genes frequently mutated in clonal haematopoiesis (GNAS, JAK2, IDH1, IDH2 and ATM). The optimal cut-point for predicting progression free survival (PFS) was assessed as the cut-point with the highest Harrell's C-index. Results: Of the 75 patients that were enrolled into cohort E, 53 patients had samples sent for paired C1D1-C2D1 ctDNA sequencing, 2 failed sequencing, and all 51 (68%) patients had detectable ctDNA at C1D1. The ctDNA analysis set was representative of the overall enrolled population. The optimal ctDNA dynamics C-index cut-point for predicting PFS was 0 (undetectable ctDNA at C2D1). Median PFS with ctDNA CDR >0 (detectable ctDNA at C2D1) was 4.3 months (95% CI 2.4-5.8), and with undetectable ctDNA was 12 months (95% CI 8-NA) (HR 4.02, 95% CI 1.22-13.23, p=0.01). Splitting patients by median CDR was not predictive (HR=0.98; 95%CI: 0.52-1.82, p=0.94). Confirmed objective response rate was 85.7% (42.1-99.6) in patients with undetectable ctDNA at C2D1, and with detectable ctDNA was 11.4% (3.8-24.6) (OR 4.02, 95% CI 1.22-13.23, p=0.01). Of the 7 patients with undetectable ctDNA at C2D1, one had a BRCA2 germline mutation, and all other patients were wildtype for BRCA1/2 mutations in tumour and germline. All patients with undetectable ctDNA and BRCA1/2 wildtype had a confirmed response. In cohorts A-D (mutation targeted therapies, in predominantly ER positive cancer), the optimal ctDNA dynamics C-index CDR cut-point was 0.165 (HR 3.44, 95%CI: 2.06-5.75, p< 0.001), with median CDR cut-point also highly predictive (HR=2.14, 95%CI: 1.36-3.36, p=0.001). Undetectable ctDNA was also strongly predictive (HR=4.41; 95%CI: 1.97-9.87, p< 0.001) in cohort A-D. In cohort E, a significant association was found between baseline ctDNA and PFS, with an optimal C-index cutpoint of 6.81% (HR=3.02, 95% CI: 1.39-6.56, p=0.001). Median PFS for baseline ctDNA ≤ 6.81% was 10.2 months (95% CI 3.7-17.2), and for baseline ctDNA >6.81% was 4.4 months (95% CI 2.2-5.5). Conclusions: 'Clearance' of ctDNA to become undetectable at C2D1 identified sporadic TNBC patients who benefited from olaparib and ceralasertib. Although 'clearance' of ctDNA was associated with good outcome on olaparib plus ceralasertib, median CDR was not predictive of treatment benefit. This contrasts the results of ctDNA dynamic assessment of cohort A-D, where median CDR was highly predictive of treatment benefit. ctDNA dynamic assessment may differ between mutation targeted therapies (cohorts A-D) that induce cell-cycle arrest, and PARP inhibitors (cohort E) that inhibit DNA repair mechanisms. Implementing ctDNA dynamics into clinical trials and care may require distinct analysis for different therapies.

PS06-06

Analysis of ctDNA for the detection of minimal residual disease (MRD) using a tissue-free, multiomic assay in patients with early-stage breast cancer

Presenting Author(s) and Co-Author(s):

W. Janni. Department Gynecology and Obstetrics, University of Ulm, Ulm, Baden-Wuerttemberg, Germany

T. Friedl. Department of Obstetrics and Gynecology, University Hospital Ulm, Germany

B. Rack. Department of Obstetrics and Gynecology, University Hospital Ulm, Germany

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

H. Tesch. Onkologie Bethanien Frankfurt am Main, Germany

R. Lorenz. Gemeinschaftspraxis Braunschweig, Germany

G. Heinrich. Department of Gynecologic Oncology, Schwerpunktpraxis für Gynäkologische Onkologie, Fürstenwalde, Germany

J. Blohmer. Charité - Universitätsmedizin Berlin, Germany

T. Fehm. University Hospital Düsseldorf, Düsseldorf, Germany

V. Müller. Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

M. Beckmann. Department of Gynecology and Obstetrics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany

M. Ruebner. Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich-Alexander-University Erlangen-Nürnberg, Germany

N. Harbeck. University of Munich, Munich, Bayern, Germany

K. Pantel. Department of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

D. Dustin. Guardant Health, Inc., Palo Alto, California, United States

M. Cai. Guardant Health, Inc., Palo Alto, California, United States

Background: The detection of ctDNA in patients with early-stage breast cancer after completion of adjuvant therapy is associated with a high risk of recurrence. Current clinical guidelines do not recommend routine screening for metastatic disease unless there are clinical signs and symptoms in patients who completed adjuvant therapy. However, ctDNA may serve as an early biomarker of recurrence which may allow effective identification of patients with asymptomatic distant metastases or molecular relapse only, who could benefit from early treatment intervention. Herein, we utilized a tissue-free, multiomic assay for the sensitive and specific detection of MRD in patients with early-stage breast cancer. **Methods:** Plasma samples were collected from patients with stage I-III breast cancer who were enrolled in the SUCCESS-A phase 3 clinical trial (NCT02181101) between 2006 and 2007. All patients received adjuvant chemotherapy +/- endocrine therapy and/or anti-HER2 therapy. Samples were collected approximately two years after completion of adjuvant chemotherapy, and plasma samples

selected for analysis were from patients without evidence of disease recurrence prior to sample collection. Presence of MRD was assessed using Guardant Reveal powered by Infinity, which evaluates the epigenomic signals associated with cancer versus normal DNA for the detection of ctDNA. Samples with the presence of ctDNA are characterized for somatic alterations with common sources of interference such as clonal hematopoiesis excluded. An analytically validated bioinformatics pipeline was used for the detection of breast cancer ctDNA. Samples were analyzed blinded to the clinical data. Median survival times were estimated using the Kaplan-Meier method and hazard ratios were calculated based on univariable cox regression models. Results: A total of 311 plasma samples from 311 patients were evaluable. ctDNA was detected in 34% (13/38) of patients who subsequently developed distant recurrence and in none (0/7) of the patients who had local or contralateral breast cancer recurrence. ctDNA was detected in 60% (9/15) of samples that were collected within one year before recurrence. In the ctDNA detected samples from patients who had disease recurrence, the median time from sample collection to recurrence was 7.9 months (range, 1.4-28.6 months). ctDNA was detected in 6 patients who did not have a documented disease recurrence, resulting in a specificity of 97.7% (260/266). In the overall cohort, ctDNA detection was prognostic for recurrence-free survival (RFS; HR 11.0, 95% CI 2.28-53.6; $p < 0.0001$), distant recurrence-free survival (D-RFS; HR 13.7, 95% CI 2.52-74.9; $p < 0.0001$), and overall survival (OS; HR 17.4, 95% CI 1.33-227; $p < 0.0001$). Conclusion: Detection of ctDNA after adjuvant chemotherapy was highly prognostic and demonstrated high specificity in an early-stage breast cancer cohort. Larger, prospective studies are needed to confirm the prognostic value of ctDNA in the post-treatment setting and assess the clinical utility of MRD detection in this population.

PS06-07

Liquid biopsy determination of HER2 status in breast cancer: results from a novel epigenomic platform

Presenting Author(s) and Co-Author(s):

H. Parsons. Dana Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

S. Baca. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. D'Ippolito. Precede Biosciences, United States

H. Jeong. Precede Biosciences, United States

K. Smith. Dana-Farber Cancer Institute, United States

P. Tarantino. Breast Oncology Program, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

M. Hughes. Dana Farber Cancer Institute, United States

K. Sendrick. Dana-Farber Cancer Institute, United States

C. Painter. Precede biosciences, United States

J. Seo. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

E. Grant. Dana-Farber Cancer Institute, United States

J. Guess. Precede Biosciences, United States

M. Davidsohn. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

G. Lakshminarayanan. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Strauss. Dana-Farber Cancer Institute, United States

H. Savignano. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Canniff. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

B. Fortunato. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

M. Eaton. Precede Biosciences, United States

T. Choueiri. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

M. Freedman. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

Background: Tumor HER2 status remains a critical predictive biomarker for patients with breast cancer given the availability of highly effective anti-HER2 therapies. However, determination of HER2 status relies on a complex, tissue-dependent algorithm optimized for extremes of the

phenotype – HER2+ vs HER2- status. Given the challenges in reliably obtaining informative tissue biopsies as disease progresses, the new therapeutic relevance of HER2-low breast cancer (IHC 1+ and FISH-negative IHC 2+), and the undependability of biomarkers in this range, better approaches are needed. Epigenomic signatures detectable in cell-free tumor DNA (cfDNA) may provide a minimally invasive, reliable determination of HER2 status. Here, we present a multimodal epigenomic liquid biopsy platform that could offer a minimally invasive alternative to tissue-based determination of transcriptionally regulated targets such as HER2. Methods: We identified patients with metastatic breast cancer (n=20) that were HER2-positive with IHC 3+ (n=6) or HER2-negative with IHC 0 (n=14) based on ASCO/CAP guidelines who underwent research biopsies at the Dana-Farber Cancer Institute from 2012-2023. Study participants had undergone concurrent blood sampling collected in Streck Tubes, processed as plasma, and stored at -80°C. We applied a novel, multimodal epigenomic assay to profile tumor-derived gene regulatory programs from 1mL plasma. This genome-wide approach analyzed histone modifications associated with active gene promoters and enhancers, and DNA methylation. Classifier feature selection was derived from epigenomically profiled breast cancer cell lines. Final classifier performance was cross validated using a standard Leave one Out (LoO) scheme. Results: Our cross-validated classifier yielded an area under the ROC curve (AUC) of 0.91 in the 20 samples tested. When including only samples with detectable ctDNA as assessed by low pass whole genome sequencing (ichorCNA algorithm) (N=13), our classifier had an AUC of 0.98. Using regularized regression approach, we identified 33 loci with the highest predictive value; 8 loci were within the ERBB2 amplicon on chromosome 17, while the remaining 25 loci were in other genomic regions. We will present results from this and an expanded cohort, including participants with HER2 IHC 1+ and 2+ disease. Conclusions: We present a novel, minimally invasive HER2 classifier leveraging epigenomic information from cell-free tumor DNA from 1 mL plasma. If this approach remains robust in accurately classifying additional HER2 states, it could address the limitations of current tissue-based testing. Integration of this epigenomic platform in prospective interventional studies could support the development of novel and improved predictive classifiers for response to HER2-directed therapy.

PS06-08

Longitudinal Neoadjuvant and Post-operative Evaluation of Circulating Tumor DNA in Early Breast Cancer using a Tumor-Informed Assay: Updated Analysis of the TRACER Cohort

Presenting Author(s) and Co-Author(s):

M. Elliott. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

J. Fuentes Antras. UHN - University Health Network - Princess Margaret Cancer Centre, United States

P. Echelard. University Health Network, United States

A. Dou. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

Z. Veitch. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

P. Bedard. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

E. Amir. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

M. Nadler. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

N. Meti. Saint Mary's Hospital, McGill University, Montreal, Quebec, Canada

N. Gregorio. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

E. Shah. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

C. Yu. Cancer Genomics Program, United States

N. Campbell. Inivata Inc., United States

C. Pipinikas. NeoGenomics, United States

K. Howarth. Bradfield Centre, Cambridge Science Park, United States

L. Siu. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

H. Berman. University Health Network, Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

D. Cescon. Princess Margaret Cancer Centre/UHN, Toronto, Ontario, Canada

Background: ctDNA is detectable in early breast cancer (EBC) using sensitive assays and treatment-related changes in ctDNA are associated with clinical response. RaDaR® (NeoGenomics), a tumor-informed assay, has been shown to detect circulating tumor DNA (ctDNA) prior to clinical recurrence. We retrospectively quantified ctDNA using RaDaR in serial samples from a large cohort of patients with EBC receiving standard neoadjuvant therapy (NAT). Methods: Unselected patients with EBC were enrolled prior to NAT in the TRACER cohort from 2015 onwards. Plasma samples were collected at baseline, during treatment, perioperatively, and in follow-up. For patients with available tissue for assay generation, RaDaR was performed on all available plasma timepoints. Clinical and pathologic characteristics (assessed on core biopsy), treatment, and outcomes were recorded. Results: Of 128 patients evaluated, 9 (7.0%) were excluded from this analysis due to panel quality control metrics, leaving 119 patients (41 ER+, 32 TNBC, 46 HER2+) with 681 individual timepoints (median=6, range: 1-12). 103/119 patients (86%) received neoadjuvant anthracycline- and taxane-based chemotherapy. Median followup from diagnosis was 3.8 years (range: 0.6-6.3 years) and 16 recurrences have occurred (9 ER+, 6 TN, 1 HER2+). 114 patients had a baseline plasma sample collected prior to NAT, in which the detection rate was 77% (70% ER+, 90% TNBC, 76% HER2+), with a median estimated variant allele frequency (eVAF) of 0.0823% (range: 2.90E-5 - 7.5%). All patients with clinical recurrence had ctDNA detected at baseline. Baseline

detection was associated with tumor grade ($p=0.050$) but not size ($p=0.65$) or clinical nodal status ($p=0.36$). There were non-significant associations between eVAF and grade ($p=0.097$) and eVAF and tumor size ($p=0.086$). Persistent ctDNA detection midway through neoadjuvant therapy (pre-cycle 5) was associated with an increased risk of recurrence in patients with ER+ (HR: 10.27, 95%CI: 1.61-65.4; $p=0.014$) and TNBC (HR: 20.17, 95%CI: 1.97-206.4; $p=0.011$). Residual cancer burden (RCB) status further stratified the risk of recurrence; those with RCB-2/3 disease and ctDNA detected pre-cycle 5 were at the highest risk. Few patients had detectable ctDNA in pre- or initial post-operative specimens, all of which had residual disease (non-pCR). 9/16 patients with clinical recurrence had evaluable post-operative and follow-up samples for lead time calculation; ctDNA was detected prior to recurrence in 7/9 (78 %), with a median lead time of 152 days (range: 13-699 days). Of the 2 patients without a positive test, one had an ipsilateral local recurrence (grade 2, 1.8 mm), the other had a negative, but borderline, test 72 days prior to recurrence (solitary 8 mm lung nodule on PET). Follow up is ongoing for two patients with ctDNA detected but no recurrence at data cutoff (time since last positive test: 0.60 and 1.78 years). Any ctDNA detection postoperatively or in follow-up was strongly associated with disease recurrence (HR: 37.35, 95%CI: 2.7-520.7; $p< 0.0001$). Conclusion: RaDaR detects ctDNA in most patients prior to the initiation of NAT for EBC. Changes in ctDNA levels during treatment and its presence are associated with clinical outcomes. Prospective evaluation and integration of RaDaR testing into clinical trials are warranted. Further analysis of ctDNA detection, clinical outcomes, and genomic data will be presented at the meeting.

PS06-09

Fragmentomic analysis of a circulating tumor DNA targeted cancer gene panel discriminates ER status in metastatic breast cancer liquid biopsies.

Presenting Author(s) and Co-Author(s):

K. Helzer. University of Wisconsin, Madison, Madison, Wisconsin, United States
J. Sperger. University of Wisconsin, Madison, Madison, Wisconsin, United States
Y. Shi. University of Wisconsin, Madison, Madison, Wisconsin, United States
V. Carreno. University of Wisconsin, Madison, Madison, Wisconsin, United States
H. Krause. University of Wisconsin, Madison, Madison, Wisconsin, United States
K. Kaufmann. University of Wisconsin, Madison, Madison, Wisconsin, United States
L. Mora-Rodriguez. University of Wisconsin, Madison, Madison, Wisconsin, United States
M. Bootsma. University of Wisconsin, Madison, Madison, Wisconsin, United States
M. Burkard. DEPARTMENT OF MEDICINE University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States
R. O'Regan. University of Rochester Medical Center, Rochester, New York, United States
K. Wisinski. University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, United States
J. Lang. University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, United States
S. Zhao. University of Wisconsin, Madison, Madison, Wisconsin, United States
M. West. University of Wisconsin, Madison, Madison, Wisconsin, United States
M. Sharifi. University of Wisconsin, Madison, Madison, Wisconsin, United States

Background: Circulating tumor DNA (ctDNA) isolated from the peripheral blood of patients with cancer is now routinely used in the clinic to detect tumor somatic mutations, with multiple ctDNA-targeted sequencing panels commercially available for Food and Drug Administration (FDA)-approved biomarker indications to guide targeted therapy options. More recently, it has been appreciated that ctDNA fragmentation patterns are influenced by the chromatin structure of the cell of origin, with greater diversity in fragment size in areas with open chromatin and less diversity in fragment size in areas with closed chromatin. In consequence, multiple studies have found that ctDNA fragmentation patterns can be used to accurately infer epigenomic and transcriptomic phenotypes from their tumor cells of origin. However, these analyses have previously relied on whole-genome sequencing (WGS), and it is not feasible to identify FDA-approved biomarker indications in a cost-effective manner with WGS. Methods: Peripheral blood was collected from a cohort of 90 patients with metastatic HER2-negative breast cancer (ER-positive n=71, ER-negative n=19). Cell-free DNA was extracted from plasma and sequenced using a custom 822 gene pan-cancer targeted sequencing panel (IDT). Shannon entropy of first coding exon fragment sizes (E1SE) was used to quantify fragmentation patterns. Higher diversity of fragment sizes, leading to a higher E1SE, are expected in ctDNA derived from areas of the genome with more open chromatin. A machine learning model utilizing the E1SE metric across all genes in the targeted panel was developed to distinguish between ER-positive and ER-negative disease. Results: Training cross-validated accuracy of the machine learning model was 87.8% with AUC of 0.91 to distinguish between ER-positive and ER-negative disease, despite a median ctDNA fraction of only 0.02. E1SE metrics for ESR1 and CCND1 were significantly higher in ER-positive than ER-negative samples, while E1SE metrics for EGFR, c-Kit and members of the MAP kinase family were significantly higher in ER-negative

than ER-positive samples, consistent with anticipated differences in gene expression between ER-positive and ER-negative triple negative breast cancers. In contrast, HER2 E1SE was similar between groups, as expected in this clinically HER2-negative cohort. Conclusions: We have shown for the first time that sequencing from standard targeted ctDNA panels can be utilized to infer phenotypic information through analysis of ctDNA fragmentation patterns in patients with metastatic breast cancer. This expands the depth of potential biologic data that can be extracted from targeted ctDNA sequencing panels in addition to DNA mutation status in a cost-effective manner. In the future, this approach can be exploited to expand ctDNA-based biomarker development beyond DNA mutation status.

PS06-01

Results from a pilot study exploring ctDNA detection using a tumor-informed assay in the monarchE trial of adjuvant abemaciclib with endocrine therapy in HR+, HER2-, node-positive, high-risk early breast cancer

Presenting Author(s) and Co-Author(s):

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

S. Johnston. The Royal Marsden Hospital, London, United Kingdom

C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States

H. Sasano. Department of Pathology, Tohoku University Hospital, Sendai, Japan.

V. Rodrik-Outmezguine. Eli Lilly and Company, Indianapolis, Indiana, United States

A. Sireci. Eli Lilly and Company, Indianapolis, Indiana, United States

C. Sandoval Rubenstein. Eli Lilly and Company, Indianapolis, Indiana, United States

H. Won. Eli Lilly and Company, Indianapolis, Indiana, United States

D. Liu. Eli Lilly and Company, Indianapolis, Indiana, United States

L. M. Litchfield. Eli Lilly and Company, Indianapolis, Indiana, United States

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background

Two years of adjuvant abemaciclib + endocrine therapy (ET) resulted in significant and clinically meaningful improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) in patients (pts) with HR+, HER2-, node-positive, high-risk early breast cancer (EBC) in the monarchE trial (NCT03155997). The benefit of abemaciclib was sustained beyond completion of treatment and deepened in magnitude at 4 years for IDFS and DRFS. This pilot study investigated the technical feasibility of ctDNA detection beginning prior to study treatment, as well as rates of persistence and clearance in a subset of EBC pts from monarchE using the clinically validated Signatera™ ctDNA assay.

Methods

Samples were analyzed from a selected subset of pts (n=178; 84 from abemaciclib+ET arm; 94 ET alone) who had blood collected both before initiating protocol directed therapy, Visit 1 (V1; randomization + ≤ 3 days) and near completion of the 2-year treatment period, Visit 27 (V27; 24 months +/- 5 days from V1). This cohort of pts was enriched for overall IDFS events compared to the total monarchE study population, however pts with relapses occurring prior to V27 were excluded. Primary tumors from selected pts were subjected to whole exome sequencing (WES). Selected samples included those from pts with a range of tumor mutation burden. Cell-

free DNA was extracted from 356 plasma samples. A Signatera ctDNA assay was developed for each pt based on up to 16 variants detected by WES from each baseline tumor sample.

Results

The IDFS event rate for the selected subset (n=178) was 39.3% (abemaciclib+ET 34.5% [29/84] and ET alone 43.6% [41/94]). Ten pts (5.6%) were initially ctDNA+ and 42 pts (23.6%) were persistently (7 pts, 3.9%) or became (35 pts, 19.7%) ctDNA+ at V27. Notably, 70% of pts who were initially ctDNA+ and 100% of pts who were either persistently ctDNA+ or became ctDNA+ experienced recurrence (see Table 1). In contrast, none of the 3 pts that cleared ctDNA+ developed recurrence. In pts persistently ctDNA negative (neg), 28 (21.1%) experienced recurrence, but had the longest median IDFS (41.7 months). Overall, 10% (7/70) of pts with IDFS events were initially ctDNA+ and 50% (35/70) had detectable ctDNA at V27.

Conclusions

Detection of ctDNA soon after completing neoadjuvant chemotherapy was infrequent, but also associated with a high-risk of recurrence. ctDNA positivity was common at the end of the 2-year treatment period and was highly prognostic with all pts subsequently developing disease recurrence. Importantly, ~30% of pts with early ctDNA detection ultimately dropped below detection limits during the 2-year treatment period and none developed recurrence. Although some pts remained persistently ctDNA neg during this study and experienced recurrence, the delay in recurrence may indicate longitudinal benefit from remaining ctDNA neg. Future planned analysis of an expanded cohort reflective of the intent to treat population including additional timepoints within the 2-year treatment period will further define how ctDNA dynamics may identify pts at high-risk of recurrence.

Table 1. Summary of ctDNA positivity

	N (%)	Prior chemotherapy (%)	IDFS event (%)	Median IDFS Months (95% CI)	Median recurrence from ctDNA+ detection (months)
All pts	178 (100)	169 (94.9)	70 (39.3)	39.7 (24.4-54.8)	NA
Initially ctDNA+ (V1 +)	10 (5.6)	9 (90.0)	7 (70)	35.1 (25.0-49.0)	26.7
Persistently ctDNA+ (V1 +, V27 +)	7 (3.9)	6 (85.7)	7 (100)	26.7 (24.9-40.8)	26.7
Cleared ctDNA+ (V1 +, V27 -)	3 (1.7)	3 (100)	0	38.0 (36.9-52.6)	NA
Became ctDNA+ (V1 -, V27 +)	35 (19.7)	32 (91.4)	35 (100)	29.3 (23.7-45.4)	5.3
Persistently ctDNA neg (V1 -, V27 -)	133 (74.7)	128 (96.2)	28 (21.1)	41.7 (26.4-54.8)	NA

+ positive; - negative; NA, not applicable.

Disclosure(s):

Sherene Loi, MD, PhD: Advisory Committee/Board Member: Bristol-Myers Squibb Company (Ongoing), MSD Co., Ltd. (Ongoing); Consulting Fees (e.g., advisory boards): Aduro Biotech (Ongoing), Amunix (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst)

(Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), MSD Co., Ltd. (Ongoing), Nektar Therapeutics (Ongoing), Novartis International AG (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics (Ongoing); Uncompensated consultant: Aduro Biotech (Ongoing), Amunix (Ongoing), Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing)

Stephanie L. Graff, MD: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Terminated, April 1, 2023)

Matthew P. Goetz, MD: Advisory Committee/Board Member: ARC Therapeutics (Ongoing), Bioltheranostics (Ongoing), Blueprint Medicines (Ongoing), Novartis (Ongoing), RNA Diagnostics (Ongoing), Seattle Genetics (Ongoing), Sermonix Pharmaceuticals (Ongoing); CME Activity: Clinical Education Alliance (Terminated), Medscape (Terminated), MJH Life Sciences (Terminated), Research to Practice (Terminated); Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing), Engage Health Media (Ongoing), Lilly (Ongoing); Grant funding to institution: AstraZeneca (Ongoing), ATOSSA (Ongoing), Lilly (Ongoing), LOXO (Ongoing), Pfizer (Ongoing), Sermonix Pharmaceuticals (Ongoing); Moderator: Curio Science (Terminated); Panel Discussant: Total Health Conferencing (Terminated)

Christine Desmedt, PhD, Prof.: No financial relationships to disclose

Jorge Reis-Filho, MD, PhD: No relevant disclosure to display

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Guardant Health (Ongoing), Invitae (Ongoing), Natera (Ongoing), Personalis (Ongoing)

Poster Spotlight Session 6: Prognostic and Predictive Uses of Cell Free DNA

Presenting Author(s) and Co-Author(s):

M. Cheang. The Institute of Cancer Research, London, England, United Kingdom

Disclosure(s):

Maggie Chon U Cheang, PhD: Royalty: Veracyte (Ongoing)

PS06-02

Circulating tumor DNA (ctDNA) monitoring of estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) high risk breast cancer during adjuvant endocrine therapy

Presenting Author(s) and Co-Author(s):

L. pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

E. Kalashnikova. Natera, San Carlos, California, United States

E. Hobbs. Division of Hematology & Medical Oncology, Knight Cancer Institute, Oregon Health & Science University, United States

U. Brown-Glaberman. University of New Mexico Cancer Center, Albuquerque, New Mexico, United States

M. Mita. Cedars-Sinai, United States

P. Klein. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

F. Yan. Swedish Medical Center, Washington, United States

S. Ehsani. University of Arizona Cancer Center, Arizona, United States

W. Razaq. Oklahoma university of health Sciences, Oklahoma City, Oklahoma, United States

A. Stopeck. Stony Brook Cancer Center, United States

M. Bhave. Emory University School of Medicine, Atlanta, Georgia, United States

M. Loch. LSUHSC, New Orleans, United States

S. Sardesai. The Ohio State University Comprehensive Cancer Center, United States

E. Roussos Torres. University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, United States

M. Burkard. DEPARTMENT OF MEDICINE University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States

F. Okubanjo. Criterium, United States

E. Gauthier. Pfizer Inc, San Francisco, California, United States

A. Rodriguez. Natera, United States

M. Liu. Natera, United States

P. Kabos. University of Colorado Denver, Aurora, Colorado, United States

Background:

ctDNA monitoring during adjuvant endocrine therapy provides an opportunity to detect molecular relapse before clinically apparent recurrence. The rate and dynamics of ctDNA positivity and the frequency of asymptomatic but imaging detectable metastatic disease at the time of ctDNA detection remain unknown in high-risk ER+/HER2- breast cancers. We present results of ctDNA positivity rates in 508 and imaging results in ctDNA+ patients from a prospective, multicenter, randomized ctDNA surveillance and intervention trial, DARE (NCT04567420).

Patients and methods:

Patients receiving adjuvant endocrine therapy for > 6 months but < 7 years, with either (i) risk of recurrence > 15% calculated by PREDICT, RSPC, or CTS5, or (ii) > 4 positive axillary lymph nodes, or (iii) primary tumor > 5 cm, or (iv) 1-3 positive nodes with grade 3 histology, or > 3 cm

tumor, or Oncotype Dx RS > 26, MammaPrint high risk, EndoPredict > 4, Prosigna score > 60 were eligible for ctDNA surveillance with the Signatera™ assay (Natera Inc.) every 4-6 months during routine follow up visits. ctDNA+ patients underwent systemic staging with imaging and randomized to continuation of adjuvant therapy versus switching to fulvestrant plus palbociclib if there was no evidence of distant metastatic disease. The primary objectives are to assess the incidence of ctDNA positivity in the surveillance phase and to assess if palbociclib plus fulvestrant improves relapse-free survival in 100 randomized patients. This is an updated, protocol-driven interim report to determine if screening eligibility criteria needs to be revised to keep randomization rate > 15% of the screened population.

Results:

The trial is open at 15 sites and enrolled 508 patients between May 2021 and June 2023; 882 plasma ctDNA tests were performed successfully in 364 patients (72%). The most common reason for failure to generate a personalized ctDNA assay was insufficient tissue submitted, 78% of failed tests were due to preanalytical failure, the technical failure rate was 22%. Thirty patients, 8.2% of those with results available, had >1 positive ctDNA result, the overall positivity rate across all assays was 3.4% (n=30/882). Patient characteristics are shown in the table (not all patients have complete data), 47% of ctDNA+ cases had >4 + lymph nodes. ctDNA positivity rate in the first test was 3.8%, and anytime ctDNA detection rate among those with serial testing was 7.2%. Among ctDNA+ patients, the first ctDNA draw was positive in 23 of 30 cases (77%) with 36.5 months median time (range 6-102 months) from surgery to testing. Using 12 months interval brackets from surgery to 1st ctDNA positivity, annual detection rates were 2,3% (1/44), 8.5% (7/82), 10.8% (9/83), 7.5% (4/53), 13,2% (5/38), and 6.2% (4/64), at 1st, 2nd, 3rd, 4th and > 5th year post-surgery, respectively, due to small sample sizes, 95% confidence broadly overlap. Five ctDNA+ patients (16.7%) had asymptomatic, imaging-detectable metastatic disease, 22 ctDNA+ patients were randomized, the goal is to accrue a total of 100 patients.

Conclusions:

ctDNA surveillance of ER+/HER2- breast cancers during adjuvant endocrine therapy indicate 8.3% detection rate at patient level and 3.4% at assay level. Serial screening increases detection rates as 23% of positive ctDNA tests occurred after an initial negative result. 83% of ctDNA+ patients had true molecular relapse without imaging detectable metastatic disease. Eligibility for screening on the trial is now restricted to patients with >4 + lymph nodes, randomization is open for any patients who are ctDNA+ including routine commercial screening.

Table of patient characteristics

	with ctDNA result (n=364)	ctDNA+ (n=30)
Age < 50	29%	23%
Age >50	71%	77%
PR +	78%	73%
PR -	7%	17%
HER2 IHC negative	79%	77%
Grade 1	8%	7%

Grade 2	53%	50%
Grade 3	29%	37%
T 1	19%	17%
T2	43%	43%
T3	27%	27%
T4	2%	7%
0 +nodes	12%	12%
1 +node	24%	10%
2 +nodes	15%	13%
3 +nodes	8%	13%
>4 +nodes	0	47%

Disclosure(s):

Lajos puztai, MD, DPhil: Consulting Fees (e.g., advisory boards): Natera Inc (Ongoing)

Evanthia T. Roussos Torres, MD, PhD: Consulting Fees (e.g., advisory boards): Synaptical Inc (Ongoing)

PS06-04

The prognostic and predictive impact of circulating tumour DNA (ctDNA) dynamics in patients with metastatic Triple Negative Breast Cancer (TNBC) on olaparib based therapy: Results from Cohort E of the PlasmaMATCH trial

Presenting Author(s) and Co-Author(s):

I. Browne. The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, England, United Kingdom

J. Pascual. The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, United States

R. Cutts. The Institute of Cancer Research, United Kingdom

B. Kingston. The Institute of Cancer Research, London, United Kingdom

S. Hrebien. The Institute of Cancer Research, United Kingdom

L. Kilburn. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

A. Pearson. The Institute of Cancer Research, London, United Kingdom.

L. Moretti. Clinical Trials & Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

A. Wardley. Outreach Research & Innovation Group Ltd, Manchester, England, United Kingdom

I. Macpherson. University of Glasgow - Institute of Cancer Sciences, United Kingdom

R. Baird. CRUK Cambridge Centre, University of Cambridge, United Kingdom

R. Roylance. University College London Hospital, London, United Kingdom

I. Faull. Guardant Health, Inc., Redwood City, California, United States

K. Banks. Guardant Health, Inc., Redwood City, California, United States

I. Garcia-Murillas. The Institute of Cancer Research, United States

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

A. Ring. The Royal Marsden NHS Foundation Trust, Breast Unit - Department of Medicine, The Royal Marsden NHS Foundation Trust, London, UK/ Breast Cancer Research Division – The Institute of Cancer Research, London, England, United Kingdom

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background:

Early changes in ctDNA levels, ctDNA dynamics, may help identify which patients are responding to therapy earlier than imaging. Few studies have assessed ctDNA dynamics during PARP inhibitor therapy. Here we report paired baseline and early on treatment ctDNA analysis from cohort E of plasmaMATCH, that recruited patients with TNBC to treatment with olaparib (PARP inhibitor) plus ceralasertib (ATR inhibitor).

Methods:

The plasmaMATCH trial assessed the ability of ctDNA testing to allocate patients to mutation matched treatment cohorts (A-D). Patients with TNBC, and without mutations matching cohorts B-D, were enrolled on cohort E. Samples were collected for ctDNA analysis pre-treatment at

cycle 1-day1 (C1D1) and cycle 2-day 1 (C2D1). A minimum of 14 days of treatment in the first cycle was required for inclusion in this analysis. Samples were sequenced using error-corrected gene targeted panels (Guardant360, or GuardantOMNI, Guardant Health). Circulating DNA ratio (CDR) was calculated as the ratio of C2D1 ctDNA level to C1D1, pre-specified using the weighted mean of variant allele fractions (AF) of clonal mutations at C1D1, excluding variants with AF < 0.3%, and variants in genes frequently mutated in clonal haematopoiesis (GNAS, JAK2, IDH1, IDH2 and ATM). The optimal cut-point for predicting progression free survival (PFS) was assessed as the cut-point with the highest Harrell's C-index.

Results:

Of the 75 patients that were enrolled into cohort E, 53 patients had samples sent for paired C1D1-C2D1 ctDNA sequencing, 2 failed sequencing, and all 51 (68%) patients had detectable ctDNA at C1D1. The ctDNA analysis set was representative of the overall enrolled population. The optimal ctDNA dynamics C-index cut-point for predicting PFS was 0 (undetectable ctDNA at C2D1). Median PFS with ctDNA CDR >0 (detectable ctDNA at C2D1) was 4.3 months (95% CI 2.4-5.8), and with undetectable ctDNA was 12 months (95% CI 8-NA) (HR 4.02, 95% CI 1.22-13.23, p=0.01). Splitting patients by median CDR was not predictive (HR=0.98; 95%CI: 0.52-1.82, p=0.94). Confirmed objective response rate was 85.7% (42.1-99.6) in patients with undetectable ctDNA at C2D1, and with detectable ctDNA was 11.4% (3.8-24.6) (OR 4.02, 95% CI 1.22-13.23, p=0.01). Of the 7 patients with undetectable ctDNA at C2D1, one had a BRCA2 germline mutation, and all other patients were wildtype for BRCA1/2 mutations in tumour and germline. All patients with undetectable ctDNA and BRCA1/2 wildtype had a confirmed response. In cohorts A-D (mutation targeted therapies, in predominantly ER positive cancer), the optimal ctDNA dynamics C-index CDR cut-point was 0.165 (HR 3.44, 95%CI: 2.06-5.75, p< 0.001), with median CDR cut-point also highly predictive (HR=2.14, 95%CI:1.36-3.36, p=0.001). Undetectable ctDNA was also strongly predictive (HR=4.41; 95%CI: 1.97-9.87, p< 0.001) in cohort A-D. In cohort E, a significant association was found between baseline ctDNA and PFS, with an optimal C-index cutpoint of 6.81% (HR=3.02, 95% CI: 1.39-6.56, p=0.001). Median PFS for baseline ctDNA ≤ 6.81% was 10.2 months (95% CI 3.7-17.2), and for baseline ctDNA >6.81% was 4.4 months (95% CI 2.2-5.5).

Conclusions:

'Clearance' of ctDNA to become undetectable at C2D1 identified sporadic TNBC patients who benefited from olaparib and ceralasertib. Although 'clearance' of ctDNA was associated with good outcome on olaparib plus ceralasertib, median CDR was not predictive of treatment benefit. This contrasts the results of ctDNA dynamic assessment of cohort A-D, where median CDR was highly predictive of treatment benefit. ctDNA dynamic assessment may differ between mutation targeted therapies (cohorts A-D) that induce cell-cycle arrest, and PARP inhibitors (cohort E) that inhibit DNA repair mechanisms. Implementing ctDNA dynamics into clinical trials and care may require distinct analysis for different therapies.

Disclosure(s):

Iseult M. Browne, MD: No financial relationships to disclose

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Guardant Health (Ongoing), Invitae (Ongoing), Natera (Ongoing), Personalis (Ongoing)

PS06-08

Longitudinal Neoadjuvant and Post-operative Evaluation of Circulating Tumor DNA in Early Breast Cancer using a Tumor-Informed Assay: Updated Analysis of the TRACER Cohort

Presenting Author(s) and Co-Author(s):

M. Elliott. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

J. Fuentes Antras. UHN - University Health Network - Princess Margaret Cancer Centre, United States

P. Echelard. University Health Network, United States

A. Dou. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

Z. Veitch. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

P. Bedard. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

E. Amir. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

M. Nadler. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

N. Meti. Saint Mary's Hospital, McGill University, Montreal, Quebec, Canada

N. Gregorio. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

E. Shah. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

C. Yu. Cancer Genomics Program, United States

N. Campbell. Inivata Inc., United States

C. Pipinikas. NeoGenomics, United States

K. Howarth. Bradfield Centre, Cambridge Science Park, United States

L. Siu. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

H. Berman. University Health Network, Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

D. Cescon. Princess Margaret Cancer Centre/UHN, Toronto, Ontario, Canada

Background:

ctDNA is detectable in early breast cancer (EBC) using sensitive assays and treatment-related changes in ctDNA are associated with clinical response. RaDaR® (NeoGenomics), a tumor-informed assay, has been shown to detect circulating tumor DNA (ctDNA) prior to clinical recurrence. We retrospectively quantified ctDNA using RaDaR in serial samples from a large cohort of patients with EBC receiving standard neoadjuvant therapy (NAT).

Methods:

Unselected patients with EBC were enrolled prior to NAT in the TRACER cohort from 2015 onwards. Plasma samples were collected at baseline, during treatment, perioperatively, and in follow-up. For patients with available tissue for assay generation, RaDaR was performed on all available plasma timepoints. Clinical and pathologic characteristics (assessed on core biopsy), treatment, and outcomes were recorded.

Results:

Of 128 patients evaluated, 9 (7.0%) were excluded from this analysis due to panel quality control metrics, leaving 119 patients (41 ER+, 32 TNBC, 46 HER2+) with 681 individual timepoints (median=6, range: 1-12). 103/119 patients (86%) received neoadjuvant

anthracycline- and taxane-based chemotherapy. Median followup from diagnosis was 3.8 years (range: 0.6-6.3 years) and 16 recurrences have occurred (9 ER+, 6 TN, 1 HER2+). 114 patients had a baseline plasma sample collected prior to NAT, in which the detection rate was 77% (70% ER+, 90% TNBC, 76% HER2+), with a median estimated variant allele frequency (eVAF) of 0.0823% (range: 2.90E-5 - 7.5%). All patients with clinical recurrence had ctDNA detected at baseline. Baseline detection was associated with tumor grade ($p=0.050$) but not size ($p=0.65$) or clinical nodal status ($p=0.36$). There were non-significant associations between eVAF and grade ($p=0.097$) and eVAF and tumor size ($p=0.086$). Persistent ctDNA detection midway through neoadjuvant therapy (pre-cycle 5) was associated with an increased risk of recurrence in patients with ER+ (HR: 10.27, 95%CI: 1.61-65.4; $p=0.014$) and TNBC (HR: 20.17, 95%CI: 1.97-206.4; $p=0.011$). Residual cancer burden (RCB) status further stratified the risk of recurrence; those with RCB-2/3 disease and ctDNA detected pre-cycle 5 were at the highest risk. Few patients had detectable ctDNA in pre- or initial post-operative specimens, all of which had residual disease (non-pCR). 9/16 patients with clinical recurrence had evaluable post-operative and follow-up samples for lead time calculation; ctDNA was detected prior to recurrence in 7/9 (78%), with a median lead time of 152 days (range: 13-699 days). Of the 2 patients without a positive test, one had an ipsilateral local recurrence (grade 2, 1.8 mm), the other had a negative, but borderline, test 72 days prior to recurrence (solitary 8 mm lung nodule on PET). Follow up is ongoing for two patients with ctDNA detected but no recurrence at data cutoff (time since last positive test: 0.60 and 1.78 years). Any ctDNA detection postoperatively or in follow-up was strongly associated with disease recurrence (HR: 37.35, 95%CI: 2.7-520.7; $p < 0.0001$).

Conclusion:

RaDaR detects ctDNA in most patients prior to the initiation of NAT for EBC. Changes in ctDNA levels during treatment and its presence are associated with clinical outcomes. Prospective evaluation and integration of RaDaR testing into clinical trials are warranted. Further analysis of ctDNA detection, clinical outcomes, and genomic data will be presented at the meeting.

Disclosure(s):

Mitchell J. Elliott, MD: No financial relationships to disclose

Philippe Bedard, MD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Amgen (Ongoing), AstraZeneca inc. (Ongoing), Bicara Therapeutics, Inc (Ongoing), Bristol Meyer Squibb (Ongoing), Eli Lilly (Ongoing), GlaxoSmithKline (Ongoing), Medicenna (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Roche/Genentech (Ongoing), Sanofi (Ongoing), Seagen Inc (Ongoing), Takeda Pharmaceuticals, Ltd. (Ongoing), Zymeworks Inc. (Ongoing)

David W. Cescon, MD, PhD: Advisory Committee/Board Member: Inivata/NeoGenomics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co. Ltd. (Ongoing), Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), GlaxoSmithKline (Ongoing), Inflex Ltd (Ongoing), Lilly (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer, Inc. (Ongoing), SAGA Diagnostics (Ongoing); Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Gilead Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing), GlaxoSmithKline (Ongoing), Guardant Health Inc. (Ongoing), Inivata/NeoGenomics (Ongoing), Knight Therapeutics (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), ProteinQure (Ongoing), Roche (Ongoing)

PS06-03

Differences in ctDNA genomic profiles and outcomes of Black and White patients with metastatic breast cancer: results from a large multicenter consortium

Presenting Author(s) and Co-Author(s):

- E. Podany. Washington University in St. Louis, St. Louis, Missouri, United States
L. Foffano. Department of Medicine, University of Udine, United States
L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy
A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States
K. Clifton. Washington University in St Louis School of Medicine, United States
W. Hensing. St. Luke's Cancer Institute, United States
R. Morecroft. Washington University in St. Louis, United States
M. Velimirovic. Cleveland Clinic, United States
A. Shah. Northwestern University - Feinberg School of Medicine, United States
C. REDUZZI. Weill Cornell Medicine, United States
L. Munoz Arcos. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, New York, United States
C. Dai. MGH Cancer Center, United States
J. Keenan. Cancer Center, Massachusetts General Hospital, United States
E. Denault. Massachusetts General Hospital, United States
F. Ademuyiwa. Washington University in St Louis School of Medicine, United States
F. Puglisi. National Cancer Institute, Centro di Riferimento Oncologico (CRO), IRCCS, United States
C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States
A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States
M. Cristofanilli. Weill Cornell Medicine, United States
A. Davis. Washington University in St Louis School of Medicine, United States

Background:

Black breast cancer patients have a well-documented survival disparity when compared to White patients. It is imperative to explore the reasons for this disparity from both a socioeconomic and biological perspective. Prior studies evaluating somatic genetic differences have primarily focused on tumor tissue analysis, which could be limited by inter- and intra-tumor heterogeneity. Circulating tumor DNA (ctDNA) testing allows for non-invasive detection of these heterogenous somatic mutations in the peripheral blood. We hypothesized that there could be differences in cancer-specific genetic profiles across Black and White patients with metastatic breast cancer (MBC), and that these differences may impact treatment response and clinical outcomes.

Methods:

This retrospective cohort study included a total of 1327 patients with MBC who were treated at

Washington University in St. Louis (N=474 patients), Massachusetts General Hospital (N=412), and Northwestern University (N=441). All patients underwent ctDNA profiling using the commercially available Guardant360 assay. Race information was patient-reported, and ancestry data were not available. Descriptive analysis of clinical variables and pathway variants was performed. Univariate and multivariate analyses were done to evaluate single gene mutations and genetic pathways in both the entire cohort and the hormone-receptor positive (HR+), HER2-negative population (HR+/HER2-). The potential prognostic impact of these somatic mutations was assessed through multivariate analysis in both White and Black patient populations.

Results:

The cohort of 1327 patients included 1057 White patients (79.6%) and 140 Black patients (10.5%). The remaining patients (9.9%) were not included in the analysis due to low numbers. Black patients had significantly higher rates of GATA3 single nucleotide variants (snv) (OR 2.13, 95% CI 1.07-4.25, P=0.03), PTPN11 snv (OR 7.90, CI 1.10-56.56, P=0.04), and CCND2 copy number variants (cnv) (OR 3.78, CI 1.51-9.45, P=0.004). These alterations were also significantly more common in Black patients in the HR+/HER2- population (N = 812) for GATA3 snv (OR 2.28, CI 1.09-4.76, P=0.028), PTPN11 snv (OR 16.60, CI 1.49-184.93, p=0.022), and CCND2 cnv (OR 4.17, CI 1.02-16.97, P=0.046). Multivariate analysis confirmed that GATA3 snv (OR 2.23, CI 1.12-4.45, P=0.023) and CCND2 cnv (OR 3.97, CI 1.59-9.94, P=0.003) were significantly more common in Black patients in both the full cohort and HR+/HER2- subset. Mutations in the PI3K pathway were more prevalent in White patients, but this difference was not statistically significant in univariate or multivariate analysis. Overall survival (OS) from time of ctDNA collection was significantly worse in Black patients compared to White patients when corrected for lines of therapy and sites of metastasis (median 22 vs. 29 months, log-rank test, P=0.03). Among HR+/HER2- patients specifically, worse prognosis in White patients was associated with TP53 snv (HR 1.55, CI 1.19-2.01, P=0.001), NF1 snv (HR 1.99, CI 1.11-3.56, P=0.021), MYC cnv (HR 1.76, CI 1.09-2.87, P=0.02), PIK3CA cnv pathway (HR 1.69, CI 1.07-2.66, P=0.024), and MYC cnv pathway (HR 1.85, CI 1.15-2.97, P=0.011). No significant gene mutation or pathway association was found in Black patients. Prognostic differences in the cohort based on clinical, pathological, and treatment history were also explored and will be presented.

Discussion:

To our knowledge, this is the largest clinical genomic dataset examining ctDNA differences across Black and White patients. Our findings revealed that Black patients had higher frequencies of GATA3 snv and CCND2 cnv. The shorter OS observed in Black patients in our study aligns with previous studies and is likely multifactorial, especially given the early separation of the survival curves. Future research should focus on both socioeconomic and genetic factors to explain this disparity.

Disclosure(s):

Emily L. Podany, MD: No financial relationships to disclose

Cynthia Ma, MD, PhD: Advisory Committee/Board Member: Puma Biotechnology, Inc (Ongoing); Authorship/Article Publication: Wolters Kluwer/UpToDate (Ongoing); Consulting Fees (e.g., advisory boards): Agendia (Ongoing), AstraZeneca (Ongoing), Athenex (Ongoing), Bayer Healthcare (Ongoing), Biovica (Ongoing), Eisai (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), Inivata (Ongoing), Jacobio (Ongoing), Natera (Ongoing), Novartis (Ongoing), Olaris (Ongoing), OncoSignal (Ongoing), Pfizer (Ongoing), Phillips Electronics (Ongoing), Puma Biotechnology, Inc (Ongoing), Sanofi (Ongoing), Seattle Genetics (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers'

bureaus); PlusOne Heath GmbH (Ongoing); Filled out Surveys for Tempus regarding these tests. Did not impact clinical or research activity.: Tempus (Ongoing); Royalty: Wolters Kluwer/UpToDate (Ongoing)

Aditya Bardia, MD, MPH: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Menarini/Stemline (Ongoing)

PS06-06

Analysis of ctDNA for the detection of minimal residual disease (MRD) using a tissue-free, multiomic assay in patients with early-stage breast cancer

Presenting Author(s) and Co-Author(s):

W. Janni. Department Gynecology and Obstetrics, University of Ulm, Ulm, Baden-Wuerttemberg, Germany

T. Friedl. Department of Obstetrics and Gynecology, University Hospital Ulm, Germany

B. Rack. Department of Obstetrics and Gynecology, University Hospital Ulm, Germany

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

H. Tesch. Onkologie Bethanien Frankfurt am Main, Germany

R. Lorenz. Gemeinschaftspraxis Braunschweig, Germany

G. Heinrich. Department of Gynecologic Oncology, Schwerpunktpraxis für Gynäkologische Onkologie, Fürstenwalde, Germany

J. Blohmer. Charité - Universitätsmedizin Berlin, Germany

T. Fehm. University Hospital Düsseldorf, Düsseldorf, Germany

V. Müller. Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

M. Beckmann. Department of Gynecology and Obstetrics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany

M. Ruebner. Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich-Alexander-University Erlangen-Nürnberg, Germany

N. Harbeck. University of Munich, Munich, Bayern, Germany

K. Pantel. Department of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

D. Dustin. Guardant Health, Inc., Palo Alto, California, United States

M. Cai. Guardant Health, Inc., Palo Alto, California, United States

Background:

The detection of ctDNA in patients with early-stage breast cancer after completion of adjuvant therapy is associated with a high risk of recurrence. Current clinical guidelines do not recommend routine screening for metastatic disease unless there are clinical signs and symptoms in patients who completed adjuvant therapy. However, ctDNA may serve as an early biomarker of recurrence which may allow effective identification of patients with asymptomatic distant metastases or molecular relapse only, who could benefit from early treatment intervention. Herein, we utilized a tissue-free, multiomic assay for the sensitive and specific detection of MRD in patients with early-stage breast cancer.

Methods:

Plasma samples were collected from patients with stage I-III breast cancer who were enrolled

in the SUCCESS-A phase 3 clinical trial (NCT02181101) between 2006 and 2007. All patients received adjuvant chemotherapy +/- endocrine therapy and/or anti-HER2 therapy. Samples were collected approximately two years after completion of adjuvant chemotherapy, and plasma samples selected for analysis were from patients without evidence of disease recurrence prior to sample collection. Presence of MRD was assessed using Guardant Reveal powered by Infinity, which evaluates the epigenomic signals associated with cancer versus normal DNA for the detection of ctDNA. Samples with the presence of ctDNA are characterized for somatic alterations with common sources of interference such as clonal hematopoiesis excluded. An analytically validated bioinformatics pipeline was used for the detection of breast cancer ctDNA. Samples were analyzed blinded to the clinical data. Median survival times were estimated using the Kaplan-Meier method and hazard ratios were calculated based on univariable cox regression models.

Results:

A total of 311 plasma samples from 311 patients were evaluable. ctDNA was detected in 34% (13/38) of patients who subsequently developed distant recurrence and in none (0/7) of the patients who had local or contralateral breast cancer recurrence. ctDNA was detected in 60% (9/15) of samples that were collected within one year before recurrence. In the ctDNA detected samples from patients who had disease recurrence, the median time from sample collection to recurrence was 7.9 months (range, 1.4-28.6 months). ctDNA was detected in 6 patients who did not have a documented disease recurrence, resulting in a specificity of 97.7% (260/266). In the overall cohort, ctDNA detection was prognostic for recurrence-free survival (RFS; HR 11.0, 95% CI 2.28-53.6; $p < 0.0001$), distant recurrence-free survival (D-RFS; HR 13.7, 95% CI 2.52-74.9; $p < 0.0001$), and overall survival (OS; HR 17.4, 95% CI 1.33-227; $p < 0.0001$).

Conclusion:

Detection of ctDNA after adjuvant chemotherapy was highly prognostic and demonstrated high specificity in an early-stage breast cancer cohort. Larger, prospective studies are needed to confirm the prognostic value of ctDNA in the post-treatment setting and assess the clinical utility of MRD detection in this population.

Disclosure(s):

Wolfgang Janni, MD: Advisory Committee/Board Member: Guardant Health Inc. (Ongoing)
Nadia Harbeck, MD, PhD: Advisory Committee/Board Member: Roche (Ongoing); Consulting Fees (e.g., advisory boards): Gilead (Ongoing), Sandoz (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Amgen (Ongoing), Astra Zeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Roche (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): West German Study Group (WSG) (Ongoing)

PS06-07

Liquid biopsy determination of HER2 status in breast cancer: results from a novel epigenomic platform

Presenting Author(s) and Co-Author(s):

H. Parsons. Dana Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

S. Baca. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. D'Ippolito. Precede Biosciences, United States

H. Jeong. Precede Biosciences, United States

K. Smith. Dana-Farber Cancer Institute, United States

P. Tarantino. Breast Oncology Program, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

M. Hughes. Dana Farber Cancer Institute, United States

K. Sendrick. Dana-Farber Cancer Institute, United States

C. Painter. Precede biosciences, United States

J. Seo. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

E. Grant. Dana-Farber Cancer Institute, United States

J. Guess. Precede Biosciences, United States

M. Davidsohn. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

G. Lakshminarayanan. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Strauss. Dana-Farber Cancer Institute, United States

H. Savignano. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Canniff. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

B. Fortunato. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

M. Eaton. Precede Biosciences, United States

T. Choueiri. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

M. Freedman. Department of Medical Oncology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

Background:

Tumor HER2 status remains a critical predictive biomarker for patients with breast cancer given the availability of highly effective anti-HER2 therapies. However, determination of HER2 status

relies on a complex, tissue-dependent algorithm optimized for extremes of the phenotype – HER2+ vs HER2- status. Given the challenges in reliably obtaining informative tissue biopsies as disease progresses, the new therapeutic relevance of HER2-low breast cancer (IHC 1+ and FISH-negative IHC 2+), and the undependability of biomarkers in this range, better approaches are needed. Epigenomic signatures detectable in cell-free tumor DNA (cfDNA) may provide a minimally invasive, reliable determination of HER2 status. Here, we present a multimodal epigenomic liquid biopsy platform that could offer a minimally invasive alternative to tissue-based determination of transcriptionally regulated targets such as HER2.

Methods:

We identified patients with metastatic breast cancer (n=20) that were HER2-positive with IHC 3+ (n=6) or HER2-negative with IHC 0 (n=14) based on ASCO/CAP guidelines who underwent research biopsies at the Dana-Farber Cancer Institute from 2012-2023. Study participants had undergone concurrent blood sampling collected in Streck Tubes, processed as plasma, and stored at -80°C. We applied a novel, multimodal epigenomic assay to profile tumor-derived gene regulatory programs from 1mL plasma. This genome-wide approach analyzed histone modifications associated with active gene promoters and enhancers, and DNA methylation. Classifier feature selection was derived from epigenomically profiled breast cancer cell lines. Final classifier performance was cross validated using a standard Leave one Out (LoO) scheme.

Results:

Our cross-validated classifier yielded an area under the ROC curve (AUC) of 0.91 in the 20 samples tested. When including only samples with detectable ctDNA as assessed by low pass whole genome sequencing (ichorCNA algorithm) (N=13), our classifier had an AUC of 0.98. Using regularized regression approach, we identified 33 loci with the highest predictive value; 8 loci were within the ERBB2 amplicon on chromosome 17, while the remaining 25 loci were in other genomic regions. We will present results from this and an expanded cohort, including participants with HER2 IHC 1+ and 2+ disease.

Conclusions:

We present a novel, minimally invasive HER2 classifier leveraging epigenomic information from cell-free tumor DNA from 1 mL plasma. If this approach remains robust in accurately classifying additional HER2 states, it could address the limitations of current tissue-based testing. Integration of this epigenomic platform in prospective interventional studies could support the development of novel and improved predictive classifiers for response to HER2-directed therapy.

Disclosure(s):

Heather A. Parsons, MD, MPH: Advisory Committee/Board Member: AstraZenca (Terminated, December 9, 2022), Caris (Terminated, December 9, 2022); Consulting Fees (e.g., advisory boards): Daiichi-Sankyo (Terminated, June 3, 2023)

Paolo Tarantino, MD: Advisory Committee/Board Member: AstraZeneca PLC (Terminated, October 24, 2023), Daiichi-Sankyo (Terminated, October 24, 2023), Loxo@Lilly | Eli Lilly and Company (Terminated, October 24, 2023); Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Terminated, October 24, 2023), Daiichi-Sankyo (Terminated, October 24, 2023), F. Hoffman La Roche Ltd (Terminated, October 24, 2023), Genentech (Terminated, October 24, 2023), Gilead Science (Terminated, October 24, 2023), Loxo@Lilly | Eli Lilly and Company (Terminated, October 24, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing)

Toni K. Choueiri, MD: The institution (Dana-Farber Cancer Institute) may have received additional independent funding of drug companies or/and royalties potentially involve: Michael Brigham, Pan Mass Challenge, Hinda and Arthur Marcus Fund and Loker Pinard Funds for Kidney Cancer Research at DFCI (Ongoing)

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

Nancy U. Lin, MD: Consulting Fees (e.g., advisory boards): Affinia Therapeutics (Ongoing), Aleta Biopharma (Ongoing), AstraZeneca (Ongoing), Blueprint Medicine (Ongoing), Daiichi-Sankyo (Ongoing), Genetech / Roche (Ongoing), Janssen (Ongoing), Menarini/Stemline (Ongoing), Olema Pharmaceuticals (Ongoing), Prelude Therapeutics (Ongoing), Reverie Labs (Ongoing), SeaGen (Ongoing), Voyager Therapeutics (Ongoing); Independent Contractor: Artera (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Genetech / Roche (Ongoing), Menarini/Stemline (Ongoing), Merck (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing), SeaGen (Ongoing), Zion Pharmaceuticals (Ongoing)

PS06-09

Fragmentomic analysis of a circulating tumor DNA targeted cancer gene panel discriminates ER status in metastatic breast cancer liquid biopsies.

Presenting Author(s) and Co-Author(s):

K. Helzer. University of Wisconsin, Madison, Madison, Wisconsin, United States
J. Sperger. University of Wisconsin, Madison, Madison, Wisconsin, United States
Y. Shi. University of Wisconsin, Madison, Madison, Wisconsin, United States
V. Carreno. University of Wisconsin, Madison, Madison, Wisconsin, United States
H. Krause. University of Wisconsin, Madison, Madison, Wisconsin, United States
K. Kaufmann. University of Wisconsin, Madison, Madison, Wisconsin, United States
L. Mora-Rodriguez. University of Wisconsin, Madison, Madison, Wisconsin, United States
M. Bootsma. University of Wisconsin, Madison, Madison, Wisconsin, United States
M. Burkard. DEPARTMENT OF MEDICINE University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States
R. O'Regan. University of Rochester Medical Center, Rochester, New York, United States
K. Wisinski. University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, United States
J. Lang. University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, United States
S. Zhao. University of Wisconsin, Madison, Madison, Wisconsin, United States
M. West. University of Wisconsin, Madison, Madison, Wisconsin, United States
M. Sharifi. University of Wisconsin, Madison, Madison, Wisconsin, United States

Background:

Circulating tumor DNA (ctDNA) isolated from the peripheral blood of patients with cancer is now routinely used in the clinic to detect tumor somatic mutations, with multiple ctDNA-targeted sequencing panels commercially available for Food and Drug Administration (FDA)-approved biomarker indications to guide targeted therapy options. More recently, it has been appreciated that ctDNA fragmentation patterns are influenced by the chromatin structure of the cell of origin, with greater diversity in fragment size in areas with open chromatin and less diversity in fragment size in areas with closed chromatin. In consequence, multiple studies have found that ctDNA fragmentation patterns can be used to accurately infer epigenomic and transcriptomic phenotypes from their tumor cells of origin. However, these analyses have previously relied on whole-genome sequencing (WGS), and it is not feasible to identify FDA-approved biomarker indications in a cost-effective manner with WGS.

Methods:

Peripheral blood was collected from a cohort of 90 patients with metastatic HER2-negative breast cancer (ER-positive n=71, ER-negative n=19). Cell-free DNA was extracted from plasma and sequenced using a custom 822 gene pan-cancer targeted sequencing panel (IDT). Shannon entropy of first coding exon fragment sizes (E1SE) was used to quantify fragmentation patterns. Higher diversity of fragment sizes, leading to a higher E1SE, are expected in ctDNA derived from areas of the genome with more open chromatin. A machine learning model utilizing the E1SE metric across all genes in the targeted panel was developed to distinguish between ER-positive and ER-negative disease.

Results:

Training cross-validated accuracy of the machine learning model was 87.8% with AUC of 0.91 to distinguish between ER-positive and ER-negative disease, despite a median ctDNA fraction of only 0.02. E1SE metrics for ESR1 and CCND1 were significantly higher in ER-positive than ER-negative samples, while E1SE metrics for EGFR, c-Kit and members of the MAP kinase family were significantly higher in ER-negative than ER-positive samples, consistent with anticipated differences in gene expression between ER-positive and ER-negative triple negative breast cancers. In contrast, HER2 E1SE was similar between groups, as expected in this clinically HER2-negative cohort.

Conclusions:

We have shown for the first time that sequencing from standard targeted ctDNA panels can be utilized to infer phenotypic information through analysis of ctDNA fragmentation patterns in patients with metastatic breast cancer. This expands the depth of potential biologic data that can be extracted from targeted ctDNA sequencing panels in addition to DNA mutation status in a cost-effective manner. In the future, this approach can be exploited to expand ctDNA-based biomarker development beyond DNA mutation status.

Disclosure(s):

Ruth O'Regan, MD: Advisory Committee/Board Member: Pfizer, Inc. (Ongoing)

Malinda T. West, MD, MS: No financial relationships to disclose

Marina N. Sharifi, MD, PhD: No financial relationships to disclose

GS01-01

Biomarker Results in High-risk Estrogen Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative Primary Breast Cancer Following Neoadjuvant Chemotherapy ± Nivolumab: an Exploratory Analysis of CheckMate 7FL

Presenting Author(s) and Co-Author(s):

- S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy
R. Salgado. GZA-ZNA-Hospitals, Antwerp, Belgium; Peter Mac Callum Cancer Centre, Temse, Belgium
R. Díaz. Consultorio de Oncólogo Médico, Oaxaca, Mexico
S. Delaloge. Institut Gustave Roussy, Villejuif, Ile-de-France, France
C. García. Bradford Hill Investigación Clínica, Santiago, Región Metropolitana, Chile
M. Kok. Netherlands Cancer Institute, Amsterdam, Noord-Holland, Netherlands
C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain
N. Harbeck. University of Munich, Munich, Bayern, Germany
E. Mittendorf. Dana Farber Cancer Institute, Boston, Massachusetts, United States
D. Yardley. Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, United States
L. Pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States
A. Zaizar. CENEIT Oncológicos, Mexico City, Mexico
A. Ungureanu. Radiotherapy Center CLUJ S.R.L., Florești, Romania
F. Ades. Bristol Myers Squibb, Princeton, NJ, United States
R. Chandra. Bristol Myers Squibb, Princeton, NJ, United States
R. Nathani. Bristol Myers Squibb, Princeton, NJ, United States
M. Pacius. Bristol Myers Squibb, Princeton, NJ, United States
T. Spires. Bristol Myers Squibb, Princeton, NJ, United States
J. Wu. Bristol Myers Squibb, United States
H. McArthur. UT Southwestern, Dallas, Texas, United States

Background:

CheckMate 7FL (CM 7FL; NCT04109066) is a prospective, phase 3, randomized, multicenter, double-blind trial investigating nivolumab (NIVO) in combination with neoadjuvant chemotherapy (NACT) and adjuvant endocrine therapy (ET) in patients (pts) with high-risk, estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) primary breast cancer (BC).

The primary endpoint (pathological complete response, pCR) was met, resulting in a statistically significant improvement with added NIVO to NACT; residual cancer burden (RCB) 0–1 rate was meaningfully improved. NIVO benefit was larger in pts with PD-L1+ tumors (SP142 assay, % immune cells ≥ 1%).

This analysis focuses on additional biomarkers to explore associations with NIVO treatment effect. Methods:

The study enrolled newly diagnosed pts, stages T1c–2 N1–2 or T3–4 N0–2, grade 2 (ER 1–10%) or 3 (ER ≥ 1%). Pts were randomized 1:1 to NACT + NIVO 360 mg Q3W/NIVO 240 mg Q2W (arm A) or NACT + placebo (PBO; arm B). Clinical efficacy data included pCR (ypT0/is ypN0) and RCB 0–1 rates in the modified ITT (mITT) population and the SP142 PD-L1+ subgroup.

Baseline PD-L1 expression from core biopsies was evaluated with the Dako 28-8 assay using the combined positive score (CPS) algorithm. Various cutoffs (CPS ≥ 1, 10, and 20) were used for this exploration. Concordance between PD-L1 SP142 and 28-8 CPS was evaluated, with assays performed on different slides from the same tumor biopsy blocks.

Results of efficacy by ER and/or progesterone receptor (PR) expression, as well as Ki67 index and stromal tumor-infiltrating lymphocytes, will be presented at the meeting. Results: Overall, 830 pts were screened, 521 randomized, and 517 treated, with the primary efficacy population (mITT; n = 510) including all randomized pts but excluding 11 pts from Russian sites with insufficient follow-up. A total of 510 and 349 pts (68.4% of mITT population) were evaluated by PD-L1 SP142 and 28-8 CPS assays, respectively.

The prevalence of PD-L1+ by CPS was balanced in arms A and B (52% vs 50% had CPS ≥ 1; 19% vs 16% had CPS ≥ 10, and 11% vs 9% had CPS ≥ 20, respectively).

NIVO effect was larger in pts with tumors with increasing PD-L1 expression, with a Δ pCR rate (unweighted rate difference between arms A and B) of 16.6% in CPS ≥ 1 (40.4% vs 23.8% in arms A/B; 95% CI, 2.8 to 29.4), 32.4% in CPS ≥ 10 (65.7% vs 33.3% in arms A/B; 95% CI, 7.3 to 52.3), and 52.3% in CPS ≥ 20 (78.9% vs 26.7% in arms A/B; 95% CI, 18.6 to 72.4). In comparison, the Δ pCR rate was 10.7% in the mITT population (24.5% vs 13.8% in arms A/B; 95% CI, 3.9 to 17.4) and 5.7% in pts with CPS < 1 (14.0% vs 8.2% in arms A/B; 95% CI, -4.0 to 15.5; refer to the Table for additional details).

Unweighted rate differences between arms A and B for RCB 0–1 (Δ RCB 0–1 rate) followed a similar trend and were observed to be 17.0% in CPS ≥ 1, 34.4% in CPS ≥ 10, and 52.3% in CPS ≥ 20. In comparison, the Δ RCB 0–1 rate was 9.4% in the mITT population and 3.3% in pts with CPS < 1 (refer to the Table for additional details).

Further biomarker data and cutoffs will be presented at the meeting. Conclusions:

Greater PD-L1 expression was associated with higher pCR and RCB 0–1 rates, suggesting that pts with PD-L1+, high-risk, ER+/HER2– primary BC can achieve substantial pCR rates with the addition of NIVO to NACT.

Table. Summary pCR and RCB 0–1 rates by PD-L1 SP142 and 28-8 CPS at various cutoffs.

PD-L1 prevalence by various cutoffs	pCR rate n/N, % (95% CI)		ΔpCR, % (95% CI) Unweighted rate difference, Arm A vs B	RCB 0-1 rate, n/N, % (95% CI)		ΔRCB, % (95% CI) Unweighted rate difference, Arm A vs B
	Arm A NIVO + NACT / NIVO + ET n = 257	Arm B PBO + NACT / ET n = 253		Arm A NIVO + NACT / NIVO + ET n = 257	Arm B PBO + NACT / ET n = 253	
Overall (mITT population)	63/257, 24.5 (19.4-30.2)	35/253, 13.8 (9.8-18.7)	10.7 (3.9-17.4)	79/257, 30.7 (25.2-36.8)	54/253, 21.3 (16.5-26.9)	9.4 (1.8-16.9)
PD-L1: SP142						
< 1% (66%)	24/169, 14.2 (9.3-20.4)	18/169, 10.7 (6.4-16.3)	3.6 (-3.6-10.7)	31/169, 18.3 (12.8-25.0)	32/169, 18.9 (13.3-25.7)	-0.6 (-8.9-7.7)
≥ 1% (34%)	39/88, 44.3 (33.7-55.3)	17/84, 20.2 (12.3-30.4)	24.1 (10.1-36.7)	48/88, 54.5 (43.6-65.2)	22/84, 26.2 (17.2-36.9)	28.4 (13.7-41.3)
PD-L1: 28-8 CPS						
< 1 (49%)	12/86, 14.0 (7.4-23.1)	7/85, 8.2 (3.4-16.2)	5.7 (4.0-15.5)	16/86, 18.6 (11.0-28.4)	13/85, 15.3 (8.4-24.7)	3.3 (-8.1-14.6)
≥ 1 (51%)	38/94, 40.4 (30.4-51.0)	20/84, 23.8 (15.2-34.3)	16.6 (2.8-29.4)	44/94, 46.8 (36.4-57.4)	25/84, 29.8 (20.3-40.7)	17.0 (2.7-30.3)
PD-L1: 28-8 CPS						
< 10 (82%)	27/145, 18.6 (12.6-25.9)	18/142, 12.7 (7.7-19.3)	5.9 (-2.5-14.4)	35/145, 24.1 (17.4-31.9)	28/142, 19.7 (13.5-27.2)	4.4 (-5.2-13.9)
≥ 10 (18%)	23/35, 65.7 (47.8-80.9)	9/27, 33.3 (16.5-54.0)	32.4 (7.3-52.3)	25/35, 71.4 (53.7-85.4)	10/27, 37.0 (19.4-57.6)	34.4 (9.4-54.1)
PD-L1: 28-8 CPS						
< 20 (90%)	35/161, 21.7 (15.6-28.9)	23/154, 14.9 (9.7-21.6)	6.8 (-1.8-15.3)	45/161, 28.0 (21.2-35.6)	34/154, 22.1 (15.8-29.5)	5.9 (-3.7-15.3)
≥ 20 (10%)	15/19, 78.9 (54.4-93.9)	4/15, 26.7 (7.8-55.1)	52.3 (18.6-72.4)	15/19, 78.9 (54.4-93.9)	4/15, 26.7 (7.8-55.1)	52.3 (18.6-72.4)

Note: CPS data with the cutoff at 5 will be presented at the meeting.

Disclosure(s):

Sherene Loi, MD, PhD: Advisory Committee/Board Member: Bristol-Myers Squibb Company (Ongoing), MSD Co., Ltd. (Ongoing); Consulting Fees (e.g., advisory boards): Aduro Biotech (Ongoing), Amunix (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), MSD Co., Ltd. (Ongoing), Nektar Therapeutics (Ongoing), Novartis International AG (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics (Ongoing); Uncompensated consultant: Aduro Biotech (Ongoing), Amunix (Ongoing), Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing)

Giuseppe Curigliano, Prof, MD, PhD: Advisory Committee/Board Member: Menarini Silicon Biosystems (Terminated); Consulting Fees (e.g., advisory boards): Astra Zeneca, Roche, Novartis, Biocad, R-Pharm, Eisai, Eli Lilly, Pfizer, MSD, BMS (Terminated), Gilead (Terminated), PFS Genomics/Exact Sciences (Terminated)

Roberto Salgado, MD, PhD: Advisory Committee/Board Member: Astra Zeneca (Terminated), BMS (Terminated), Daichii Sankyo (Terminated), Exact Sciences (Terminated); Consulting

Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Daichii Sankyo (Ongoing), Roche (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Terminated), BMS (Terminated), Merck (Terminated), Puma Biotechnology, Inc (Terminated)

Suzette Delalogue, MD, MSc: Consulting Fees (e.g., advisory boards): Elsan (Ongoing), Gilead Science (Ongoing), Novartis International AG (Ongoing), Sanofi Aventis (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): BMS (Ongoing), Gilead Science (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Sanofi Aventis (Ongoing)

Marleen Kok, MD, PhD: Adboard and research funding paid to the institute: AZ/Daiichi (Ongoing), BMS (Ongoing), Roche (Ongoing); Adboard and Speakers Fee paid to institute: MSD (Ongoing); Advisory Committee/Board Member: BMS (Ongoing), MSD (Ongoing); Consulting Fees (e.g., advisory boards): AZ/Daiichi (Ongoing), Roche (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Gilead (Ongoing), MSD (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AZ/Daiichi (Ongoing), BMS (Ongoing), Roche (Ongoing); Speakers fee paid to the institute: Gilead (Ongoing)

Nadia Harbeck, MD, PhD: Advisory Committee/Board Member: Roche (Ongoing); Consulting Fees (e.g., advisory boards): Gilead (Ongoing), Sandoz (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Amgen (Ongoing), Astra Zeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Roche (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): West German Study Group (WSG) (Ongoing)

Elizabeth A. Mittendorf, MD, PhD, MHCM: Consulting Fees (e.g., advisory boards): astra Zeneca (Terminated), BioNTech (Terminated), Merck (Terminated); Steering Committee: Roche/GNE (Ongoing); Trial Steering Committee: BMS (Ongoing)

Lajos pusztai, MD, DPhil: Consulting Fees (e.g., advisory boards): Natera Inc (Ongoing)

Heather McArthur, MD, MPH: Consulting Fees (e.g., advisory boards): Crown Bioscience (Ongoing), Daiichi Sankyo |Astrazeneca (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer (Ongoing), Seattle Genetics/Seagen (Ongoing)

General Session 1

Presenting Author(s) and Co-Author(s):

A. Kurian. Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California, United States

D. Jain. Houston Methodist Neal Cancer Center, Houston, Texas, United States

Disclosure(s):

Allison W. Kurian, MD, MSc: No financial relationships to disclose

Dharamvir Jain, MD: No financial relationships to disclose

GS01-02

Phase 3 study of neoadjuvant pembrolizumab or placebo plus chemotherapy, followed by adjuvant pembrolizumab or placebo plus endocrine therapy for early-stage high-risk ER+/HER2- breast cancer: KEYNOTE-756

Presenting Author(s) and Co-Author(s):

F. Cardoso. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

H. McArthur. UT Southwestern, Dallas, Texas, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

N. Harbeck. University of Munich, Munich, Bayern, Germany

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

D. Cescon. Princess Margaret Cancer Centre/UHN, Toronto, Ontario, Canada

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China (People's Republic)

D. Loirat. Institut Curie, Medical Oncology Department and D3i, Paris, France

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

M. Fernandez. IMAT-Oncomedica, Montería, Colombia, United States

G. Rubovszky. National Institute of Oncology, Budapest, Hungary

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

R. Hui. Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia

T. Takano. The Cancer Institute Hospital of JFCR, Koto-ku, Tokyo, Japan

F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France

H. Yasojima. Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

Z. Liu. Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China

Y. Ding. Merck & Co., Inc., Rahway, NJ, United States

L. Jia. Merck & Co., Inc., Rahway, NJ, United States

V. Karantza. Merck Sharp & Dohme LLC, Rahway, New Jersey, United States

K. Tryfonidis. Merck & Co., Inc., Rahway, New Jersey, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background: KEYNOTE-756 (NCT03725059) is a global phase 3 study of neoadjuvant pembrolizumab or placebo + chemotherapy followed by adjuvant pembrolizumab or placebo + endocrine therapy (ET) in patients with early-stage high-risk ER⁺/HER2⁻ breast cancer. Here, we report primary pCR results and residual cancer burden (RCB) outcomes. Methods: Eligible patients with T1c-2 (≥2 cm) cN1-2 or T3-4 cN0-2, centrally confirmed, grade 3, invasive ductal ER⁺/HER2⁻ breast cancer were randomized 1:1 to receive neoadjuvant pembrolizumab 200 mg Q3W or placebo, both given with paclitaxel QW for 12 weeks, then 4 cycles of doxorubicin or epirubicin + cyclophosphamide (neoadjuvant treatment). After definitive surgery (± radiation therapy), patients received pembrolizumab or placebo for 9 cycles + standard ET. Stratification factors include region (Eastern Europe, China, or Other), tumor PD-L1 status (CPS ≥1 [positive] vs CPS < 1 [negative]), nodal involvement (positive vs negative), ER positivity (≥10% vs < 10%) and anthracycline schedule (Q3W vs Q2W). Dual primary endpoints are pCR (ypT0/Tis ypN0) and EFS. Secondary endpoints include OS, pCR defined as ypT0 ypN0 and ypT0/Tis and safety. RCB was an exploratory endpoint and was assessed by a local pathologist at the time of surgery. RCB-0, -1, -2, and -3 denote increasingly larger residual disease. Results: 1278 patients were randomized to pembrolizumab + chemotherapy (n=635) or placebo + chemotherapy (n=643). At the final pCR analysis (May 25, 2023, first interim analysis data cutoff), median follow-up was 33.2 mo (range, 9.7-51.8). In the ITT population, pembrolizumab + chemotherapy showed a statistically significant improvement in pCR (ypT0/Tis ypN0) vs placebo + chemotherapy: 24.3% (95% CI, 21.0-27.8) vs 15.6% (95% CI, 12.8-18.6); estimated difference, 8.5 percentage points (95% CI, 4.2-12.8); P=0.00005; results were consistent for the secondary pCR definitions, ypT0 ypN0 (21.3% vs 12.8%) and ypT0/Tis (29.4% vs 18.2%). The benefit of pembrolizumab + chemotherapy on pCR was generally consistent in the prespecified subgroups. There were more patients with RCB-0 (24.7% vs. 15.6%) and RCB-1 (10.2% vs 8.1%) and fewer patients in the RCB-2 (40.8% vs. 45.3%) and RCB-3 categories (20.5% vs. 28.9%) in the pembrolizumab group versus the placebo group. In the neoadjuvant phase, grade ≥3 treatment-related AE rates were 52.5% with pembrolizumab + chemotherapy and 46.4% with placebo + chemotherapy, with 1 death in the pembrolizumab arm due to acute myocardial infarction. EFS results are still immature and continue to be evaluated. Conclusions: The addition of pembrolizumab to chemotherapy significantly increased the pCR rate and shifted RCB to lower residual disease categories in patients with early-stage high-risk ER⁺/HER2⁻ breast cancer. Safety was consistent with the known profiles of each regimen.

Disclosure(s):

Joyce O'Shaughnessy, MD: Consulting Fees (e.g., advisory boards): Agendia (Ongoing), Aptitude Health (Ongoing), AstraZeneca (Ongoing), Carrick Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), ELY LILLY (Ongoing), F. Hoffman La Roche Ltd (Ongoing), G1-Therapeutics (Ongoing), Genentech (Ongoing), Loxo@Lilly (Ongoing), Merck Sharp & Dohme, Lda. (Ongoing), Novartis (Ongoing), Ontada (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Samsung Bioepis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing), Synthon (Ongoing)

Heather McArthur, MD, MPH: Consulting Fees (e.g., advisory boards): Crown Bioscience (Ongoing), Daiichi Sankyo |Astrazeneca (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer (Ongoing), Seattle Genetics/Seagen (Ongoing)

Peter Schmid, MD, PhD: Consulting Fees (e.g., advisory boards): Eli Lilly & Company (Ongoing), Gilead Science (Ongoing)

Javier Cortés, MD, PhD: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), Astrazeneca (Ongoing), Bioasis (Ongoing), BioInvent Pharma (Ongoing), Boehringer Ingelheim

(Ongoing), BridgeBio (Ongoing), Clovis Oncology (Ongoing), Daiichi-Sankyo (Ongoing), Ellipses (Ongoing), Expres2ion Biotechnologies (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gemoab (Ongoing), Gilead (Ongoing), HiberCell (Ongoing), Jazz Pharmaceuticals (Ongoing), Leuko (Ongoing), Lilly (Ongoing), Menarini (Ongoing), Merck Sharp&Dhome (Ongoing), Reveal Genomics, S.L. (Ongoing), Scorpion Therapeutics (Ongoing), Seattle genetics (Ongoing), Zymeworks Inc. (Ongoing); honoraria: Lilly (Ongoing), Novartis (Ongoing); honoraria, research funding to the institution, travel and expenses: Astrazeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Europe Ltd. (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Merck Sharp&Dhome (Ongoing), Pfizer, Inc. (Ongoing); honoraria, travel and expenses: Gilead (Ongoing), Steamline Therapeutics (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1 (Ongoing), MAJ3 Capital (Ongoing), Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. (Ongoing); research funding to the institution: Ariad pharmaceuticals (Ongoing), Baxalta GMBH/Servier Affaires (Ongoing), Bayer Pharmaceuticals (Ongoing), Guardant Health Inc. (Ongoing), IQVIA Inc. (Ongoing), Piquar Therapeutics (Ongoing), Queen Mary University of London (Ongoing); stock (relative): Leuko (Ongoing)

Nadia Harbeck, MD, PhD: Advisory Committee/Board Member: Roche (Ongoing); Consulting Fees (e.g., advisory boards): Gilead (Ongoing), Sandoz (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Amgen (Ongoing), Astra Zeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Roche (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): West German Study Group (WSG) (Ongoing)

Melinda Telli, MD: Advisory Committee/Board Member: Blueprint Medicine (Terminated, July 20, 2023), Natera, Inc. (Terminated, July 20, 2023), Novartis Pharma GmbH (Terminated, July 20, 2023), Reflexion Medical (Terminated, July 20, 2023), Replicate (Terminated, July 20, 2023), Sanofi Aventis (Terminated, July 20, 2023); Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated, July 20, 2023), Daiichi-Sankyo (Terminated, July 20, 2023), G1 Therapeutics (Terminated, July 20, 2023), Gilead Science (Terminated, July 20, 2023), Guardant health (Terminated, July 20, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Arvinas (Ongoing), Astra Zeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Genentech-Roche (Ongoing), Hummingbird Biosciences (Ongoing), Merck & Co., Inc. (Ongoing), OncoSec (Ongoing), Pfizer, Inc. (Ongoing)

David W. Cescon, MD, PhD: Advisory Committee/Board Member: Inivata/NeoGenomics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co. Ltd. (Ongoing), Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), GlaxoSmithKline (Ongoing), Inflex Ltd (Ongoing), Lilly (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer, Inc. (Ongoing), SAGA Diagnostics (Ongoing); Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Gilead Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing), GlaxoSmithKline (Ongoing), Guardant Health Inc. (Ongoing), Inivata/NeoGenomics (Ongoing), Knight Therapeutics (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), ProteinQure (Ongoing), Roche (Ongoing)

Vassiliki Karantza, MD, PhD: Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Merck Sharp & Dohme (MSD) (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Merck Sharp & Dohme (MSD) (Ongoing)

Aditya Bardia, MD, MPH: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Menarini/Stemline (Ongoing)

GS01-03

Adding atezolizumab to adjuvant chemotherapy for stage II and III triple-negative breast cancer is unlikely to improve efficacy: interim analysis of the ALEXANDRA/IMpassion030 phase 3 trial.

Presenting Author(s) and Co-Author(s):

M. Ignatiadis. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Brussels Hoofdstedelijk Gewest, Belgium

A. Bailey. Frontier Science Scotland, Kincaig, Kingussie, United Kingdom

H. McArthur. UT Southwestern, Dallas, Texas, United States

S. El-Abed. Breast International Group BIG, Brussels, Belgium

E. de Azambuja. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Brussels Hoofdstedelijk Gewest, Belgium

O. Metzger. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Chui. Genentech, Inc., South San Francisco, CA, United States

M. Dieterich. F. Hoffmann-La Roche Ltd, United States

T. Perretti. F. Hoffman-La Roche, United States

G. Steger. Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria, Wien, Austria

J. Jassem. Medical University of Gdańsk, Gdańsk, Poland

S. Chin Lee. National University of Singapore, United States

M. Higgins. Cancer Trials Ireland, United States

J. Zarbá. Medical College of Tucuman, United States

M. Schmidt. Universität Mainz, Klinik und Poliklinik für Geburtshilfe und Frauengesundheit, Mainz, Germany

H. Gomez. Instituto Nacional de Enfermedades Neoplásicas, INEN, Departamento de Oncología Médica, Lima, Peru

A. Guerrero. Fundación Instituto Valenciano de Oncología (FIVO). GEICAM Spanish Breast Cancer Group., Valencia, Comunidad Valenciana, Spain

L. Moscetti. University Hospital of Modena and Reggio Emilia, Department of Oncology and Hematology, Modena, Italy

J. Chiu. Queen Mary Hospital, Hong Kong, China

C. DuFrane. Alliance Foundation Trials, United States

V. Honvault. Institut Jules Bordet, United States

R. Altarcheh. BIG Against Breast Cancer, United States

L. Molinero. Translational Medicine Oncology - Genentech, United States

A. Ellingson. Frontier Science Scotland, Kincaig, Kingussie, United Kingdom

E. Munzone. European Institute of Oncology, IRCCS, Milano, Italy

N. Efrat Ben-Baruch. Holy Family Hospital, Nazareth, Israel

E. Bajetta. Fondazione Policlinico di Monza - Presidente Gruppo I.T.M.O., United States

S. Ohno. Breast Oncology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

G. Werutsky. Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

X. Gonzalez-Farré. Instituto Oncológico Dr. Rosell, Hospital General de Catalunya, Catalonia, Spain

L. Tseng. Taipei Veterans General Hospital, United States

W. Jacot. Institut du Cancer de Montpellier, Université de Montpellier, INSERM U1194, Paris, Montpellier, Languedoc-Roussillon, France

O. Gluz. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; University Clinics Cologne, Moenchengladbach, Nordrhein-Westfalen, Germany

Z. Shao. Fudan University Shanghai Cancer Center, United States

Y. Shparyk. Danylo Halytsky Lviv National Medical University, United States

I. Sinielnikov. Volyn Regional Oncology Center, Lutsk, Ukraine

Z. Anastasia. Russian Federation, United States

A. Vasiliev. Nuz "Dkb Oao Rzd", Saint-Petersburg, Russian Federation

E. Shearer-Kang. Genentech, Inc., South San Francisco, CA, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

D. Martins-Branco. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Academic Trials Promoting Team (ATPT), Brussels, Belgium

S. Fielding. Frontier Science Scotland, Kincaig, Kingussie, United Kingdom

D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom

G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy

S. Saji. Fukushima Medical University, Fukushima, Japan

R. Gelber. Dana-Farber Cancer Institute, Boston, MA, United States

M. Piccart. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), United States

Background: Early stage triple negative breast cancer (TNBC) is associated with a high risk of distant relapse. ALEXANDRA/IMpassion030 is a global, prospective, randomized, open-label, phase 3 trial that investigated the efficacy, safety and pharmacokinetic profile of adjuvant atezolizumab plus standard anthracycline/taxane chemotherapy (arm A) versus chemotherapy alone (arm B) in early-stage TNBC. Methods: ALEXANDRA/IMpassion030 (NCT03498716) aimed to randomize (1:1) 2300 patients with operable stage II-III TNBC, confirmed by central pathology review. Patients were stratified by type of surgery (breast conserving versus mastectomy), nodal status (0 versus 1-3 versus ≥ 4 nodes), and centrally assessed PD-L1 status (IC 0 vs $\geq 1\%$). Adjuvant chemotherapy consisted of weekly paclitaxel 80 mg/m² for 12 weeks followed by dose dense anthracycline (epirubicin 90 mg/m² or doxorubicin 60 mg/m²) and cyclophosphamide 600 mg/m² for 4 doses every 2 weeks given concomitantly with atezolizumab 840 mg every 2 weeks followed by maintenance atezolizumab 1200 mg every 3 weeks until completion of 1 year of atezolizumab (Arm A) or the same chemotherapy regimen (T-EC/AC) alone (Arm B). The primary endpoint was invasive disease-free survival (iDFS); secondary endpoints included, iDFS in the PD-L1 positive and lymph node-positive subpopulations, overall survival, safety, patient functioning and health related quality of life

(HRQoL). On the 14th of November 2022, following an IDMC recommendation, the study accrual was temporarily stopped. In February 2023, the protocol was amended in order for the IDMC to perform an early interim analysis of efficacy and futility, at approximately 62% of the planned (390) iDFS events. The futility boundary was set to a Hazard Ratio (HR) > 1. Results: The IDMC recommendations of 15th March 2023 reported that the primary endpoint crossed the futility boundary, accrual to the study was permanently stopped and the experimental treatment was discontinued. Between August 2018 and November 2022, the study enrolled 2199 patients, with 1101 randomised to the atezolizumab arm (A) and 1098 to the control arm (B). At a median follow-up of 25.3 months, 239 (10.9%) iDFS events were observed in the 2199 enrolled patients; 127 versus 112 iDFS events were observed (61.3% of 390) in the A versus B arms respectively, HR 1.12, (95% confidence interval, CI, 0.87, 1.45). In the PD-L1 positive subgroup, (1567/2199 patients, 71.3%), 77 versus 73 iDFS events were observed in the A versus B arms respectively, HR 1.03, (95% CI 0.75, 1.42). Among patients with lymph node positive tumors (1066/2199 patients, 48.5%), 86 versus 66 iDFS events were observed in the A versus B arm respectively, HR 1.41, (95% CI 1.02, 1.96). Incidence of adverse events grade ≥ 3 was 58.01% versus 48.15% in the A versus B arms, including death in 1.01% (11) and 0.55% (6) of patients, respectively. Conclusions: Crossing the pre-specified futility boundary of HR > 1 provides evidence that adjuvant atezolizumab is very unlikely to improve invasive disease-free survival when added to adjuvant anthracycline and taxane based chemotherapy in patients with stage II-III triple-negative breast cancer. With longer treatment exposure in the atezolizumab arm (A), adverse events were more frequent but consistent with the atezolizumab safety profile. No new or unexpected safety issue was identified.

Disclosure(s):

Michail Ignatiadis, MD, PhD: Consulting Fees (e.g., advisory boards): Rejuvenon senescence therapeutics (Ongoing), Seattle Genetics Inc. (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Novartis Pharma GmbH (Terminated, October 31, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): F. Hoffman La Roche Ltd (Ongoing), Inivata/NeoGenomics (Ongoing), Menarini/Stemline (Ongoing), Natera, Inc. (Ongoing)

Heather McArthur, MD, MPH: Consulting Fees (e.g., advisory boards): Crown Bioscience (Ongoing), Daiichi Sankyo |Astrazeneca (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer (Ongoing), Seattle Genetics/Seagen (Ongoing)

Evandro de Azambuja, MD/PhD: Advisory Committee/Board Member: F. Hoffman La Roche Ltd (Ongoing); Consulting Fees (e.g., advisory boards): AstraZenca (Terminated), Eli Lilly and Co (Terminated), F. Hoffman La Roche Ltd (Terminated), Gilead Science (Terminated), Libs (Terminated), MSD Co., Ltd. (Terminated), Novartis Pharma GmbH (Terminated), PierreFabre (Terminated), SeaGen (Terminated), Zodiac (Terminated)

Otto Metzger, MD: Consulting Fees (e.g., advisory boards): Alliance for Clinical Trials in Oncology (Terminated, September 19, 2023), Astra Zeneca (Terminated, September 19, 2023), Merck & Co., Inc. (Terminated, September 19, 2023); Independent Contractor: Alliance for Clinical Trials in Oncology (Ongoing), Grupo Oncoclinicas (Ongoing)

Angel Guerrero, MD, PhD: Advisory Committee/Board Member: Pfizer, Inc. (Ongoing), SeaGen (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Exact Sciences (Genomic Health) (Ongoing), Menarini/Stemline (Ongoing), Novartis Pharma GmbH (Ongoing), PierreFabre (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Astra Zeneca (Ongoing), Novartis Pharma GmbH (Ongoing), Pfizer, Inc. (Ongoing), PierreFabre (Ongoing); Travel to medical congress support: Astra Zeneca (Ongoing), Novartis Pharma GmbH (Ongoing), Pfizer, Inc. (Ongoing)

Einav Nili Gal-Yam, MD, PhD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated, November 14, 2023), Eli Lilly & Company (Terminated, November 14, 2023), F. Hoffman La Roche Ltd (Terminated, November 14, 2023), MSD Co., Ltd. (Terminated, November 14, 2023), Novartis Pharmaceuticals (Terminated, November 14, 2023), Pfizer, Inc. (Terminated, November 14, 2023); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): F. Hoffman La Roche Ltd (Ongoing); Honoraria: Astra Zeneca (Terminated, November 14, 2023); Honoraria: Eli Lilly & Company (Terminated, November 14, 2023), MSD Co., Ltd. (Terminated, November 14, 2023), Novartis Pharmaceuticals (Terminated, November 14, 2023), Pfizer, Inc. (Terminated, November 14, 2023)

Oleg Gluz, MD: Consulting Fees (e.g., advisory boards): Roche, Novartis, Lilly, MSD, Gilead, ExactScience, Agendia, Seagen, DaichiSankyo, Pfizer, Astra Zeneca (Ongoing)

Eric Winer, MD: No financial relationships to disclose

GS01-05

Pembrolizumab + Olaparib vs Pembrolizumab + Chemotherapy After Induction With Pembrolizumab + Chemotherapy for Locally Recurrent Inoperable or Metastatic TNBC: Randomized Open-Label Phase 2 KEYLYNK-009 Study

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

M. Robson. Memorial Sloan Kettering Cancer Center, New York, United States

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

E. Yañez Ruiz. Oncology Unit, Department of Internal Medicine, School of Medicine, Universidad de la Frontera, Temuco, Chile

Y. Im. Samsung Medical Center, Seoul, Republic of Korea

S. Kulyk. Medical Center Verum, Kyiv, Ukraine

O. Dudnichenko. V.T.Zaitsev Institute of General and Urgent Surgery of Academy of Medical Sciences of Ukraine, Tumors of Visceral Organs and Soft Tissues, Kharkiv, Ukraine

N. Llinás-Quintero. Clinical Oncology Group, Fundación Colombiana de Cancerología-Clinica Vida, Medellín, Colombia

S. Saji. Fukushima Medical University Hospital, Fukushima, Japan

Y. Miyoshi. Dept of Surgery, Division of Breast and Endocrine Surgery, Hyogo Medical University, Nishinomiya-hama, Hyogo, Japan

N. Harbeck. University of Munich, Munich, Bayern, Germany

L. Fan. Merck & Co., Inc., Rahway, NJ, United States

J. Mejjia. Merck & Co., Inc., Rahway, New Jersey, United States

V. Karantza. Merck Sharp & Dohme LLC, Rahway, New Jersey, United States

D. Cescon. Princess Margaret Cancer Centre/UHN, Toronto, Ontario, Canada

Background: Pembrolizumab (pembro) plus chemotherapy (chemo) showed statistically significant improvements in PFS and OS vs placebo + chemo in patients (pts) with previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) whose tumors expressed PD-L1 with a combined positive score (CPS) ≥ 10 in the phase 3 KEYNOTE-355 study. Tolerable and effective maintenance regimens after induction therapy are needed to sustain clinical benefit. The PARP inhibitor olaparib is an established maintenance therapy for multiple platinum-sensitive tumor types and prior data suggest that PARP inhibitors combined with PD-1/PD-L1 inhibitors could provide an improved therapeutic effect. KEYLYNK-009 (NCT04191135) is a randomized open-label phase 2 study to evaluate the efficacy and safety of maintenance pembro + olaparib vs pembro + chemo in pts with locally recurrent inoperable or metastatic TNBC who had clinical benefit from induction with 1L pembro + platinum-based chemo. Methods: Eligible pts with measurable, locally recurrent inoperable or metastatic TNBC that had not been previously treated with chemo in the metastatic setting received induction therapy for up to 6 cycles of pembro 200 mg + chemo (carboplatin AUC 2 + gemcitabine 1000 mg/m² on days 1 and 8) every 3 wk (Q3W). Pts with complete response (CR), partial response (PR), or stable disease (SD) after 4-6 treatment cycles were randomized 1:1 to receive pembro

200 mg Q3W + olaparib 300 mg twice daily or pembro + chemo (continued induction regimen). Olaparib or chemo was continued until progression or unacceptable toxicity; pembro was continued for up to 35 cycles (including induction treatment), progression, or unacceptable toxicity. Pts were stratified by induction response (CR or PR vs SD, by RECIST v1.1), tumor PD-L1 status (CPS ≥ 1 vs CPS < 1), and tumor genomic status (tBRCAm vs tBRCAwt). Dual primary endpoints were PFS per RECIST v1.1 by BICR and OS from randomization in all pts. Secondary endpoints included PFS and OS from randomization in pts with PD-L1 CPS ≥ 10 tumors and in pts with tBRCAm, and safety. Results: Of the 460 pts who received induction therapy, 271 were randomly assigned to pembro + olaparib (n=135) or pembro + chemo (n=136). At the Dec 15, 2022 data cutoff, median follow-up was 17.2 mo. Maintenance pembro + olaparib did not significantly improve PFS or OS vs pembro + chemo after induction therapy (Table). Median PFS was longer with pembro + olaparib vs pembro + chemo in pts with tBRCAm, but not in pts with PD-L1 CPS ≥ 10 tumors; a similar trend was observed for OS (Table). In 268 treated pts, treatment-related AEs (TRAEs) occurred in 114 of 135 pts (84.4%) for pembro + olaparib and in 128 of 133 pts (96.2%) for pembro + chemo. Grade ≥ 3 TRAEs occurred in 44 pts (32.6%) for pembro + olaparib (0 deaths) and in 91 pts (68.4%) for pembro + chemo (2 [1.5%] deaths), with 12 (8.9%) vs 26 (19.5%) discontinuations for TRAEs, respectively. Conclusions: The primary endpoints of PFS and OS were not met in an unselected population of pts with advanced TNBC. However, directionally favorable improvements in PFS and OS were observed in pts with tBRCAm with pembro + olaparib vs pembro + chemo, representing a potential maintenance strategy. Further data are required to confirm this effect. No new safety signals were observed, and there were fewer TRAEs in the pembro + olaparib group vs the pembro + chemo group.

	Intention-to-Treat		PD-L1 CPS ≥ 10		tBRCAm	
	Pembro + Olaparib n = 135	Pembro + Chemo n = 136	Pembro + Olaparib n = 65	Pembro + Chemo n = 65	Pembro + Olaparib n = 29	Pembro + Chemo n = 30
PFS events, n (%)	80 (59.3)	90 (66.2)	36 (55.4)	45 (69.2)	12 (41.4)	17 (56.7)
PFS, median, mo	5.5	5.6	5.7	5.7	12.4	8.4
12-mo PFS rate, %	33.3	29.3	40.7	30.9	52.2	45.1
PFS, HR (95% CI)*	0.98 (0.72-1.33); P-value = 0.4556		0.92 (0.59-1.43)		0.70 (0.33-1.48)	
OS events, n (%)	50 (37.0)	54 (39.7)	22 (33.8)	22 (33.8)	6 (20.7)	8 (26.7)
OS, median, mo	25.1	23.4	NR	NR	NR	23.4
24-mo OS rate, %	51.5	43.1	58.0	52.6	62.8	46.9
OS, HR (95% CI)*	0.95 (0.64-1.40)		0.97 (0.53-1.76)		0.81 (0.28-2.37)	

PFS and OS were evaluated from the time of randomization. *Based on stratified Cox regression model with Efron's method of tie-handling with treatment as a covariate. NR = not reached.

Disclosure(s):

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

Nadia Harbeck, MD, PhD: Advisory Committee/Board Member: Roche (Ongoing); Consulting Fees (e.g., advisory boards): Gilead (Ongoing), Sandoz (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Amgen (Ongoing), Astra Zeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Roche (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): West German Study Group (WSG) (Ongoing)

Vassiliki Karantz, MD, PhD: Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Merck Sharp & Dohme (MSD) (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Merck Sharp & Dohme (MSD) (Ongoing)

David W. Cescon, MD, PhD: Advisory Committee/Board Member: Inivata/NeoGenomics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co. Ltd. (Ongoing), Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), GlaxoSmithKline (Ongoing), Inflex Ltd (Ongoing), Lilly (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer, Inc. (Ongoing), SAGA Diagnostics (Ongoing); Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Gilead Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing), GlaxoSmithKline (Ongoing), Guardant Health Inc. (Ongoing), Inivata/NeoGenomics (Ongoing), Knight Therapeutics (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), ProteinQure (Ongoing), Roche (Ongoing)

GS01-06

Advancing Evidence of the Associations Between Specific Benign Breast Diagnoses and Future Breast Cancer Risk

Presenting Author(s) and Co-Author(s):

O. Sattayapiwat. University of California at Davis, Davis, California, United States

K. Kerlikowske. University of California, San Francisco, United States

D. Weaver. University of Vermont, United States

A. Borowsky. UC Davis, Sacramento, CA, United States

T. Keegan. University of California at Davis, United States

B. Sprague. University of Vermont, United States

D. Miglioretti. University of California at Davis, United States

Background:

Benign breast disease (BBD) is a common breast biopsy finding encompassing a diverse spectrum of diagnoses. Breast cancer risk associated with many specific BBD diagnoses and their joint associations with breast density have not been extensively studied. We estimate the future risk of invasive breast cancer associated with specific BBD diagnoses typically categorized into the broad category of proliferative lesions without atypia (PWoA) and evaluate whether associations differ by breast density or by presence of calcifications. Methods:

We included 1,313,943 women ages 40-79 years who underwent 5,282,063 mammograms in the Breast Cancer Surveillance Consortium from 1996 to 2019 with no prior history of breast cancer. We fit a Cox proportional hazards model to estimate hazard ratios associated with each combination of PWoA BBD diagnoses, whether calcifications were present on biopsy, and breast density. We used classification trees to group combinations of PWoA diagnoses, breast density, age groups, and presence of calcifications with similar magnitudes of associations with 5-year risk of invasive breast cancer. Results:

Compared with women with a PWoA BBD diagnosis without calcifications, presence of calcifications significantly elevated risk for breast cancer (HR=1.19, 95% CI = 1.02 to 1.41, P=0.03). Considering specific PWoA diagnoses, classification trees identified groups of women with higher and lower invasive cancer risk than expected risk for all PWoA combined. Among women ages 60-79 years with heterogeneously or extremely dense breasts, the 2.6% of women with any PWoA diagnosis, except papillomatosis, were at high invasive breast cancer risk (5-year risk >2.5%) (Table 1). Among women ages 40-59 years with dense breasts, presence of calcifications with papillomas, usual ductal hyperplasia, columnar cell hyperplasia, or PWoA NOS diagnoses put these women at high risk (5-year risk >2.5%) compared to women with the same BBD diagnoses without calcifications who were at intermediate or average risk (1-2.49%) (Table 1). Among women ages 60-79 years with non-dense breasts, the 1.6% of women with papilloma, usual ductal hyperplasia, radial scar, or PWoA NOS diagnoses were at high breast cancer risk (Table 2). Among women ages 40-59 years with non-dense breasts, presence of calcifications with usual ductal hyperplasia or PwoA NOS diagnoses put these women at intermediate risk (1.67-2.49%) compared to women with these BBD diagnoses without calcifications who were at average risk (1-1.66%) (Table 2). Women 60-79 years with fatty breasts were at intermediate 5-year risk if they had papillomas, usual ductal hyperplasia, or PWoA NOS diagnoses. Women 40-59 years with fatty breasts were at low risk of breast cancer regardless of PWoA diagnosis (Table 2). Conclusion:

Specific BBD diagnoses and the presence of calcifications can change a woman's predicted 5-year breast cancer risk compared to broad BBD categories alone. This information could be

incorporated into risk prediction models to improve model accuracy.

Table 1: Percentage of Women with Dense Breasts and Invasive Cancer Rate Characterized by PWOA BBD, Calcification Status, and Density

PWOA diagnosis	Calcification	BI-RADS density ¹	% Women	5-year invasive cancer rate per 100		Risk
				Without specific PWOA diagnosis ²	With specific PWOA diagnosis ³	
60-79 years						
Papillomas (multiple, single); radial scar	With or without	c,d	0.4%	3.66	4.52	↑
Usual ductal hyperplasia	With or without	c,d	1.3%	3.66	3.92	↓
Columnar cell hyperplasia; PWOA NOS	With or without	c,d	0.9%	3.66	3.01	↓
No prior biopsy; Papillomatosis	With or without	c,d	97.5%	1.88	1.83	↓
40-59 years						
Papillomas (multiple, single); Usual Ductal Hyperplasia; Columnar cell hyperplasia; PWOA NOS	With calcifications	c,d	0.5%	2.02	2.58	↑
PWOA NOS	No calcifications	c,d	1.1%	2.02	2.08	↓
Usual ductal hyperplasia	No calcifications	c,d	0.5%	2.02	1.67	↓
No prior biopsy; Papillomatosis; Radial Scar	With or without	d	15.7%	1.45	1.43	↓
Papillomas (multiple, single); Columnar cell hyperplasia	No calcifications	c,d	0.2%	2.02	1.22	↓
No prior biopsy; Papillomatosis; Radial Scar	With or without	c	81.9%	1.13	1.12	↓

5-year risk Low (<1.0) Average (1.0-1.66) Intermediate (1.67-2.49) High (2.5-3.99) Very high (≥4.0)

^bRed arrows indicates more than 10% increase in risk, ^cgreen arrows indicates decrease

Table 2: Percentage of Women with Non-dense Breasts and Invasive Cancer Rate Characterized by PWOA BBD, Calcification Status, and Density

PWOA diagnosis	Calcification	BI-RADS density ¹	% Women	5-year invasive cancer rate per 100		Risk
				Without specific PWOA diagnosis ²	With specific PWOA diagnosis ³	
60-79 years						
Papillomas (multiple, single); radial scar	With or without	b	0.3%	3.2	3.64	↑
Usual ductal hyperplasia; PWOA NOS	With or without	b	1.3%	3.2	3.13	↓
Papillomas (multiple, single); Usual Ductal Hyperplasia; PWOA NOS	With or without	a	0.2%	2.12	2.16	↑
No prior biopsy; Papillomatosis; Columnar cell hyperplasia	With or without	b	81.1%	1.63	1.6	↓
No prior biopsy; Papillomatosis; Radial Scar	With or without	a	17.1%	1.06	1.05	↓
40-59 years						
Papillomas (multiple, single); Usual ductal hyperplasia; PWOA NOS	With calcifications	b	0.3%	1.57	1.83	↑
Usual ductal hyperplasia; PWOA NOS	No calcifications	b	1.0%	1.57	1.42	↓
No prior biopsy; Papillomatosis; Radial Scar; Columnar cell hyperplasia	With or without	b	85.9%	0.9	0.89	↓
Any BBD or no prior biopsy	With or without	a	12.6%	0.45	0.45	—

5-year risk Low (<1.0) Average (1.0-1.66) Intermediate (1.67-2.49) High (2.5-3.99) Very high (≥4.0)

^bRed arrows indicates more than 10% increase in risk, ^cgreen arrows indicates decrease

Disclosure(s):

Olivia Sattayapiwat, MPH, MS: No financial relationships to disclose

GS01-08**CDK4/6 inhibition is a potential vulnerability in NF1-depleted ER+ breast cancer**

Presenting Author(s) and Co-Author(s):

Z. Zheng. Baylor College of Medicine, United States

A. Chen. Baylor College of Medicine, United States

E. Jaehnig. Baylor College of Medicine, Houston, TX, United States

M. Anurag. Baylor College of Medicine, United States

J. Lei. Baylor College of Medicine, United States

C. Wang. Baylor College of Medicine, United States

L. Feng. Baylor College of Medicine, United States

P. Singh. Baylor College of Medicine, United States

H. Kennedy. Baylor College of Medicine, United States

J. Cao. Zhejiang University, United States

G. Yadav. Texas A&M University, United States

J. Tsai. Guardant, United States

X. Chen. Baylor College of Medicine, United States

C. Foulds. Baylor College of Medicine, United States

B. Lim. Baylor College of Medicine, Houston, Texas, United States

M. Ellis. AstraZeneca, United States

B. Zhang. Baylor College of Medicine, United States

E. Chang. Lester Sue Smith Breast Center, Baylor College of Medicine, Houston, Texas, United States

CDK4/6 control a key checkpoint by phosphorylating Rb, leading to Rb degradation and subsequent S-phase entry. CDK4/6 inhibition, together with endocrine therapy, is standard of care for advanced ER⁺ breast cancer; however, CDK4/6 inhibition typically is cytostatic. This study aims to identify breast cancer patients who may better respond to treatments targeting CDK4/6. NF1/neurofibromin is a key tumor suppressor that we have shown can represses not only RAS as a GAP but also ER as a transcriptional co-repressor. Dual activation of RAS and ER promotes endocrine therapy resistance. We computed kinase activity scores from phosphor-proteomic data in the CPTAC breast cancer cohort and found that both CDK4/6 activity scores and Rb-pS780 levels negatively correlated with NF1 protein levels. Furthermore, NF1 mutations co-occur with mutations in CDK4/6 and CCND1-3 in breast tumors. These results suggest a functional dependency between NF1 loss and activation of the CDK4/6-Rb pathway. To delineate how NF1 and CDK4 interact molecularly, we depleted NF1 in ER⁺ breast cancer cells and found an increase in Rb-pS780 and in phosphorylation in CDK4's activation loop (CDK4-pT172). Cyclin-D binding is required for CDK4 activation. CCND1 expression is under the direct control by ER, and upon NF1-depletion, Cyclin D1 expression was increased, partly due to enhanced ER recruitment to an ERE in CCND1. Cyclin-D-bound CDK4 must be phosphorylated at T172 to be fully active; however, what kinase is responsible for this is largely unknown. We have evidence that CDK4-T172 phosphorylation is RAF, but not ERK, dependent. When the NF1-depleted ER⁺ cells were seeded in the presence of fulvestrant together with either palbociclib or abemaciclib, apoptosis readily occurred. Remarkably,

fulvestrant plus palbociclib efficiently caused durable tumor regression in two ER⁺ PDX models, in which NF1 is undetectable by IHC. In contrast, no tumor regression was seen in a PDX model with detectable NF1. Finally, greater growth inhibition and apoptosis were detected in NF1-low tumors in the neoadjuvant NeoPalAna trial when palbociclib was added after anastrozole. These data support a model whereby ER and RAS signaling converge upon CDK4/6, and CDK4/6 activation is a key survival mechanism when ER signaling is attenuated by treatment in NF1-depleted ER⁺ breast cancer cells. This apparent addiction for CDK4/6 activity makes NF1-depleted ER⁺ breast tumors vulnerable to CDK4/6 inhibition, thus creating a potential therapeutic opportunity to match CDK4/6 inhibition with patients who can benefit the most.

Disclosure(s):

Eric Chang, PhD: No financial relationships to disclose

GS01-10

HER2CLIMB-02: Randomized, Double-Blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-Positive Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Hurvitz. Fred Hutchinson Cancer Center/University of Washington, Los Angeles, California, United States

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

A. Okines. The Royal Marsden NHS Foundation Trust, London, England, United Kingdom

S. Tolane. Dana-Farber Cancer Institute, Boston, MA, United States

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

X. Zhu. University of Alberta / Cross Cancer Institute, Edmonton, Alberta, Canada

D. Cameron. Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, United Kingdom

T. Bachelot. Medical Oncology, Centre Léon Bérard, Lyon, France

E. Hamilton. Sarah Cannon Research Institute / Tennessee Oncology-Nashville, Nashville, Tennessee, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

A. Wolff. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States

N. Harbeck. University of Munich, Munich, Bayern, Germany

N. Masuda. Nagoya University Graduate School of Medicine, Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

L. Vahdat. Dartmouth Health, Lebanon, NH, United States

K. Zaman. Breast Center, Lausanne University Hospital CHUV, Lausanne, Switzerland

F. Valdes-Albini. University of Miami, United States

M. Block. Nebraska Cancer Specialists, Omaha, Nebraska, United States

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

T. Tan. National Cancer Centre Singapore, Singapore

C. Gawryletz. UCHHealth, Fort Collins, Colorado, United States

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

P. Bedard. Princess Margaret Cancer Centre, Toronto, Ontario, Canada

R. Yerushalmi. Rabin Medical Center-Beilinson Campus, Petah Tikva, Israel

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

K. Tryfonidis. Merck & Co., Inc., Rahway, New Jersey, United States

M. Schmitt. Seagen Inc., Bothell, WA, United States

J. Xie. Seagen Inc., Bothell, WA, United States

V. Borges. University of Colorado Cancer Center, Colorado, United States

Disclosure(s):

Sara Hurvitz, MD, FACP: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Ambrx, Inc (Terminated), Arvinas (Terminated), Astra Zeneca (Terminated), Celcuity Inc. (Terminated), CytomX Therapeutics (Terminated), Daiichi-Sankyo (Terminated), Dantari, Inc. (Terminated), Eli Lilly (Terminated), F. Hoffman La Roche Ltd (Terminated), G1-Therapeutics (Terminated), Genentech (Terminated), Gilead (Terminated), Greenwich Lifesciences (Terminated), Novartis (Terminated), Orinove (Terminated), Orum Therapeutics (Terminated), Phoenix Molecular Designs, Ltd. (Terminated), Pieris Pharmaceuticals (Terminated), Puma Biotechnology, Inc (Terminated), Radius Health (Terminated), Sanofi (Inst) (Terminated), Seagen Inc (Terminated), Zymeworks Inc./Jazz (Terminated)

Sherene Loi, MD, PhD: Advisory Committee/Board Member: Bristol-Myers Squibb Company (Ongoing), MSD Co., Ltd. (Ongoing); Consulting Fees (e.g., advisory boards): Aduro Biotech (Ongoing), Amunix (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), MSD Co., Ltd. (Ongoing), Nektar Therapeutics (Ongoing), Novartis International AG (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics (Ongoing); Uncompensated consultant: Aduro Biotech (Ongoing), Amunix (Ongoing), Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing)

Joyce O'Shaughnessy, MD: Consulting Fees (e.g., advisory boards): Agendia (Ongoing), Aptitude Health (Ongoing), AstraZeneca (Ongoing), Carrick Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), ELY LILLY (Ongoing), F. Hoffman La Roche Ltd (Ongoing), G1-Therapeutics (Ongoing), Genentech (Ongoing), Loxo@Lilly (Ongoing), Merck Sharp & Dohme, Lda. (Ongoing), Novartis (Ongoing), Ontada (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Samsung Bioepis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing), Synthron (Ongoing)

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if

received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

Erika P. Hamilton, MD: Consulting Fees (e.g., advisory boards): Accutar Biotechnology (Ongoing), AstraZeneca Pharmaceutical (Ongoing), Daiichi Sankyo (Ongoing), Ellipses Pharma (Ongoing), Entos (Ongoing), Fosun Pharma (Ongoing), Gilead Sciences (Ongoing), Greenwich Lifesciences (Ongoing), Jazz Pharmaceuticals (Ongoing), Lilly (Ongoing), Medical Pharma Services (Ongoing), Mersana Therapeutics (Ongoing), Novartis (Ongoing), Olema (Ongoing), Orum Therapeutics (Ongoing), Pfizer (Ongoing), Roche/Genentech (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing), Theratechnologies (Ongoing), Tubulis (Ongoing), Verascity Science (Ongoing), Zantalis Pharmaceuticals (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AbbVie Inc (Ongoing), Accutar Biotechnology (Ongoing), Acerta Pharma (Ongoing), ADC Therapeutics (Ongoing), Akesobio (Ongoing), Amgen (Ongoing), Aravive (Ongoing), ArQule (Ongoing), Artios (Ongoing), Arvinas (Ongoing), AstraZeneca Pharmaceutical (Ongoing), AtlasMedx (Ongoing), BeiGene (Ongoing), Black Diamond (Ongoing), Bliss BioPharmaceuticals (Ongoing), Boehringer Ingelheim (Ongoing), Bristol-Myers Squibb Company (Ongoing), Cascadian Therapeutics (Ongoing), Clovis Oncology (Ongoing), Compugen (Ongoing), Context Therapeutics (Ongoing), Cullinan (Ongoing), Curis (Ongoing), CytomX (Ongoing), Daiichi Sankyo (Ongoing), Dana Farber Cancer Inst (Ongoing), Dantari Pharmaceuticals (Ongoing), Deciphera (Ongoing), Duality Biologics (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai (Ongoing), Ellipses Pharma (Ongoing), Elucida Oncology (Ongoing), EMD Serono (Ongoing), Fochon (Ongoing), FUJIFILM Pharmaceuticals U.S.A (Ongoing), G1 Therapeutics (Ongoing), Gilead Sciences (Ongoing), H3 Biomedicine (Ongoing), Harpoon Therapeutics (Ongoing), Hutchinson MediPharma (Ongoing), Immunogen (Ongoing), Immunomedics Inc (Ongoing), Incyte (Ongoing), Infinity Pharmaceuticals (Ongoing), Inspira Inc (Ongoing), InventisBio (Ongoing), Jacobio Pharmaceuticals Co., Ltd. (Ongoing), Karyopharm (Ongoing), K-Group Beta (Ongoing), Kind Pharmaceuticals (Ongoing), Leap Therapeutics (Ongoing), Lilly (Ongoing), Loxo Oncology (Ongoing), Lycera (Ongoing), Mabspace Biosciences (Ongoing), Macrogenics (Ongoing), MedImmune (Ongoing), Mersana Therapeutics (Ongoing), Merus (Ongoing), Millennium (Ongoing), Molecular Templates (Ongoing), Myriad Genetics Inc. (Ongoing), Novartis (Ongoing), Nucana (Ongoing), Olema (Ongoing), OncoMed (Ongoing), Onconova Therapeutics (Ongoing), Oncothyreon (Ongoing), ORIC Pharmaceuticals (Ongoing), Orinove (Ongoing), Orum Therapeutics (Ongoing), Pfizer (Ongoing), PharmaMar (Ongoing), Pieris Pharmaceuticals (Ongoing), Pionyr Immunotherapeutics (Ongoing), Plexxikon (Ongoing), Prelude Therapeutics (Ongoing), Profound Bio (Ongoing), Radius Health (Ongoing), Regeneron Pharmaceuticals Inc. (Ongoing), Relay Therapeutics (Ongoing), Repertoire Immune Medicine (Ongoing), Rgenix (Ongoing), Roche/Genentech (Ongoing), SeaGen (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Shattuck Labs (Ongoing), Silverback Therapeutics (Ongoing), StemCentRx (Ongoing), Stemline Therapeutics (Ongoing), Sutro (Ongoing), Syndax Pharmaceuticals (Ongoing), Syros (Ongoing), Taiho (Ongoing), TapImmune (Ongoing), Tesaro (Ongoing), Tolmar (Ongoing), Torque Therapeutics (Ongoing), Treadwell Therapeutics (Ongoing), Verastem (Ongoing), Zenith Epigenetics (Ongoing), Zymeworks Inc. (Ongoing)

Giuseppe Curigliano, Prof, MD, PhD: Advisory Committee/Board Member: Menarini Silicon Biosystems (Terminated); Consulting Fees (e.g., advisory boards): Astra Zeneca, Roche, Novartis, Biocad, R-Pharm, Eisai, Eli Lilly, Pfizer, MSD, BMS (Terminated), Gilead (Terminated), PFS Genomics/Exact Sciences (Terminated)

Antonio C. Wolff, MD: No financial relationships to disclose

Nadia Harbeck, MD, PhD: Advisory Committee/Board Member: Roche (Ongoing); Consulting Fees (e.g., advisory boards): Gilead (Ongoing), Sandoz (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Amgen (Ongoing), Astra Zeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Roche (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): West German Study Group (WSG) (Ongoing)

Arlene Chan, MBBS, FRACP, MMED: No financial relationships to disclose

Philippe Bedard, MD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Amgen (Ongoing), Astra Zeneca inc. (Ongoing), Bicara Therapeutics, Inc (Ongoing), Bristol Meyer Squibb (Ongoing), Eli Lilly (Ongoing), GlaxoSmithKline (Ongoing), Medicenna (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Roche/Genentech (Ongoing), Sanofi (Ongoing), Seagen Inc (Ongoing), Takeda Pharmaceuticals, Ltd. (Ongoing), Zymeworks Inc. (Ongoing)

PO1-01-01

ECOG-ACRIN EA1211: Interim FDG-PET/CT for predicting response of HER2-positive breast cancer to neoadjuvant therapy (DIRECT Trial)

Presenting Author(s) and Co-Author(s):

H. Jacene. Dana-Farber/Brigham Cancer Center, Boston, MA, Massachusetts, United States

C. Gatsonis. Dept of Biostatistics, Brown University School of Public Health, United States

R. Connolly. University College Cork, United States

B. Burnette. Saint Vincent Hospital Cancer Center Green Bay, Green Bay, WI, United States

E. Stringer-Reasor. University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, Alabama, United States

M. Hennessy. Cancer Research @ University College Cork, Cork, Ireland, Ireland

J. Romanoff. Brown University - ECOG-ACRIN Biostatistics Center, Providence, Rhode Island, United States

A. Taurone. Brown University - ECOG-ACRIN Biostatistics Center, Providence, RI, United States

C. O'Sullivan. Mayo Clinic, Rochester, MN, USA, ROCHESTER, Minnesota, United States

H. Le-Petross. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

C. Lawhn Heath. University of California, United States

V. Stearns. Johns Hopkins University, Baltimore, Maryland, United States

A. Fowler. University of Wisconsin Madison, Madison, Wisconsin, United States

S. Tang. Louisiana State University Health Sciences Center, New Orleans, LA, United States

K. Sepulveda. Baylor College of Medicine, Texas, United States

A. DeMichele. University of Pennsylvania, Philadelphia, Pennsylvania, United States

D. Mankoff. University of Pennsylvania, Philadelphia, Pennsylvania, United States

A. Wolff. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States

Background: Strategies to optimize treatment decision-making in early stage HER2-positive breast cancer are a current priority for the oncology and patient advocacy community. Recent studies suggest that early metabolic changes on FDG-PET/CT (imaging biomarker) predict response to HER2-directed therapy. The TBCRC026 trial showed that participants not obtaining a 40% reduction in SULmax by cycle 1 day 15 (C1D15) following neoadjuvant trastuzumab/pertuzumab (HP) were unlikely to obtain pCR [negative predictive value (NPV) 91%]. The ECOG-ACRIN EA1211/DIRECT trial aims to validate FDG-PET/CT as a neoadjuvant interim (niFDG-PET/CT) imaging integral biomarker in patients treated with standard HER2-directed regimens (NCT05710328). Design: EA1211/DIRECT is a multicenter, single-arm, primary imaging phase 2 study enrolling patients with stage II/III HER2-positive breast cancer. Patients undergo standard skull base-thigh FDG-PET/CT at baseline and C1D15 and receive standard of care pertuzumab-based neoadjuvant therapy followed by surgery. Eligibility: Age \geq 18 years, ECOG performance status 0-2, stage IIa-IIIc, untreated HER2-positive breast cancer with known hormone receptor status, suitable to undergo FDG-PET/CT

imaging and neoadjuvant therapy. Methods: Δ SULmaxD15 will be computed as: (D15 SULmax – baseline SULmax)/baseline SULmax. The primary objective is to estimate the NPV of niFDG-PET/CT for pCR using Δ SULmaxD15 of the primary breast cancer at a threshold of 40%, in patients treated with neoadjuvant HER2-directed therapy. NPV is defined as the probability that pCR will not be achieved by participants with Δ SULmaxD15 < 40%. Secondary endpoints include evaluating the sensitivity, specificity, and positive predictive value of Δ SULmaxD15 of the primary breast cancer at a threshold of 40% and the ability of the niFDG-PET/CT biomarker to predict 3-year event free survival (EFS). Sample Size: We expect that 50% of patients will not reach the Δ SULmax threshold of 40% and a pCR rate of 40-60%. The proposed sample size is 210 participants, adjusted to 235 to account for missing data in 10% of cases. Computation of exact, two-sided 95% confidence intervals (CI) for NPV determined the lower limit of the CI is at least 80% when the true NPV is at least 88%. The lower limit is 84% when the true NPV has the value of 91%, which was estimated in the TBCRC026 study. Current Status: EA1211/DIRECT was activated in May 2023 across the NCI National Clinical Trials Network (NCTN), and accrual is anticipated to complete in March 2025. Those interested in the clinical trial can email ea1211team@ecog-acrin.org. Conclusion: The EA1211/DIRECT trial is the first step in implementing a Response-Guided Treatment Strategy by validating the Δ SULmax threshold of 40% as the optimum cut point across standard of care HER2-directed neoadjuvant regimens. If EA1211/DIRECT meets its objectives, the results will be used to design clinical utility studies, and thus hoping to change practice.

PO1-01-02

Final analysis of neoadjuvant chemotherapy with pegylated liposomal doxorubicin/ cyclophosphamide followed by taxanes with full-course trastuzumab/pertuzumab for HER2-positive breast cancer: a single-arm, phase II study

Presenting Author(s) and Co-Author(s):

Y. Yang. Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, United States

L. Jin. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, United States

Y. li. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, United States

F. Gan. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, United States

N. Rao. Breast tumor center, Sun Yat-sen Memorial Hospital, United States

J. Zhang. Shenzhen Qianhai Shekou Free Trade Zone Hospital, United States

R. feng. Guilin Medical College Second Affiliated Hospital, United States

Z. Liu. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

Q. Liu. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Background: The optimal neoadjuvant treatment regimen for HER2-positive breast cancer remains unclear, especially regarding the use of anthracycline. We conducted a prospective phase II study to evaluate sequential neoadjuvant chemotherapy with pegylated liposomal doxorubicin (PLD)/cyclophosphamide followed by taxanes in the presence of full-course trastuzumab/pertuzumab in HER2-positive early breast cancer patients. **Methods:** In this single-arm, open-label, multicenter, phase II study, eligible patients with confirmed HER2-positive early breast cancer were recruited from four independent hospitals. Patients received four cycles of PLD (35 mg/m²) and cyclophosphamide (600 mg/m²), followed by four cycles of taxanes (docetaxel, 100 mg/m² or nab-paclitaxel, 260 mg/m²), concomitant with eight cycles of trastuzumab (8 mg/kg loading dose, then 6 mg/kg) and pertuzumab (840 mg loading dose, then 420 mg) every 3 weeks. The primary endpoint was total pathological complete response (ypT0/is ypN0, tpCR). Secondary endpoints included breast pCR (bpCR), objective response rate (ORR), disease control rate, the proportion of patients requiring breast-conserving surgery, and safety. For biomarkers analysis, tumor tissues were collected at baseline and evaluated for Topoisomerase 2 Alpha (TOP2A) expression assessed prospectively with immunohistochemistry (IHC) assay by independent pathologists. **Results:** Between May 27, 2020 and May 11, 2022, 78 eligible patients were treated and underwent surgery, of whom 42 (53.8%) patients underwent breast-conserving surgery. After neoadjuvant therapy, 47 (60.3%, 95% CI, 48.5%-71.2%) patients achieved a tpCR in the breast and axilla. The bpCR was observed in 49 (62.8%) patients. ORRs were 76.9% (95% CI, 66.0%-85.7%) and 93.6% (95% CI, 85.7%-97.9%) after 4-cycle and 8-cycle neoadjuvant therapy, respectively. All (100%) patients achieved disease control since the end of the first cycle. No correlations between clinicopathological variables and pathological response were observed. Grade 3 or worse AEs occurred in 35 (44.9%) patients. Nine (11.5%) patients experienced asymptomatic LVEF reduction ($\geq 10\%$ from baseline), but all with a minimum value of $>55\%$. No treatment-related surgical delay or death occurred. For biomarkers analysis, the status of TOP2A was not found

to be associated with pCR or 4th-cycle ORR. Conclusions: This dual HER2-blockade plus polychemotherapy as sequential neoadjuvant regimen demonstrates promising anti-tumor activity and acceptable tolerability for patients with HER2-positive breast cancer.

PO1-01-03

Pathological response according to early metabolic remission in an interim FDG-PET scan and to tumor infiltrating lymphocytes - A secondary analysis of the phase II trial ABCSG 52 / ATHENE investigating atezolizumab in early HER2+ BC

Presenting Author(s) and Co-Author(s):

G. Rinnerthaler. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

D. Egle. Breast Cancer Center Tirol, Department of Gynecology, Medical University Innsbruck, Austria, United States

R. Bartsch. Medical University of Vienna, Department of Medicine I, Division of Oncology, Vienna, Austria, Austria

C. Schmitt. Department for haematology and internal oncology, Med Campus III, Kepler University Hospital Linz, United States

A. Petzer. Internal Medicine I for Hematology with Stem Cell Transplantation, Hemostaseology and Medical Oncology, Ordensklinikum Linz Barmherzige Schwestern – Elisabethinen, Linz, Austria, United States

M. Balic. Division of Oncology, Department of Internal Medicine, Medical University Graz, Austria

E. Petru. Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria

U. Denison. Institute for Gynaecological Oncology and Senology, Karl Landsteiner Society, Hietzing Hospital, Vienna, Austria, United States

C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria

V. Bjelic-Radisic. Breast Unit, Helios University Clinic, University Witten/Herdecke, Germany

S. Gampenrieder. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

M. Knauer. Tumor and Breast Center Eastern Switzerland, St. Gallen, Switzerland, United States

K. Sotlar. Department of Pathology, Paracelsus Medical University Salzburg, Salzburg, Austria, United States

C. Brunner. Department of Gynecology and Gynecological Oncology, Medical University of Innsbruck, Austria

F. Posch. Division of Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria, United States

D. Hlauschek. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria

L. Sölkner. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria, United States

Z. Bago-Horvath. Department of Pathology, Medical University Vienna, United States

M. Filipits. Center for Cancer Research, Medical University of Vienna, Vienna, Austria

M. Gili. ABCSG, Austrian Breast & Colorectal Cancer Study Group, Vienna, Austria, United States

M. Gnant. Medical University of Vienna, Vienna, Austria

R. Greil. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

Background: ABCSG-52/ATHENE investigated a neoadjuvant chemotherapy de-escalation / immunotherapy escalation approach with trastuzumab, pertuzumab, atezolizumab and epirubicin for early-stage HER2-positive breast cancer. The pathological complete response rate (pCR; ypT0/Tis, ypN0) - the primary endpoint of the trial - was 60.3% (95% CI 47.5% - 71.9%), and was higher than the predefined threshold for positivity ($\geq 40\%$). Interestingly, higher pCR rates were observed in PD-L1 immune cell (IC) negative tumors (pCR 69.2%) as compared to PD-L1 IC positive tumors (pCR 55.2%). No new safety concerns were observed. Primary outcome data were reported at the ESMO Breast Cancer Conference 2023. Here, we present the correlation of pathological outcome according to early metabolic response in an interim fluorodeoxyglucose F18 positron emission tomography (FDG-PET) scan, and according to stromal tumor infiltrating lymphocytes (TILs) at baseline. Methods: Patients (pts) with previously untreated, histologically confirmed HER2-positive early breast cancer (EBC; clinical prognostic stage cT1c-4a-d, N0-3, M0) were randomized 1:1 to two 3-weekly cycles of a chemotherapy-free induction phase (Part 1) with trastuzumab and pertuzumab (TP) plus 1200 mg atezolizumab (TP+A), or TP alone. Subsequently, all pts received 4 cycles of TP+A in combination with epirubicin 90 mg/m² (Part 2). Randomization was stratified according to baseline TILs ($< 5\%$ vs $\geq 5\%$), hormone receptor status (positive vs. negative), and prognostic stage (\leq IIA vs. \geq IIB; AJCC v.8.0). An FDG-PET assessment was performed at baseline and after 2 cycles of study treatment. According to PERCIST, early metabolic responses were classified as metabolic complete response (mCR) and metabolic partial response (mPR) and association with outcome was tested with Fisher's exact test. TIL assessment in pretreatment biopsy specimen were performed according to the recommendations from the International TILs Working Group. Lymphocytic predominant phenotype was defined as a TIL proportion of $\geq 50\%$. Correlation of TILs and pCR was modeled with logistic regression. Results: Overall, 58 pts were randomized to TP-A (n=29) or TP (n=29) at 9 sites. In 45 patients, a protocol predefined PERCIST assessment was available. An early mCR was achieved in 14 pts (n=14/45, 31.1%): 5 pts (n=5/21, 23.8%) in the TP group and 9 pts (n=9/24, 37.5%) in the TP-A group. Pts with and without an early mCR achieved a pCR in 92.9% (n=13/14) and 54.8% (n=17/31) of cases (p=0.016), respectively. An early mCR/mPR was achieved in 37 pts (n=37/45, 82.2%). Pts with and without an early mCR/mPR achieved a Residual Cancer Burden (RCB) class 0 or I in 89.2% (n=33/37) and 50.0% (n=4/8) of cases (p=0.024), respectively. The mean stromal TIL proportion was 23.9% in the overall population, with 22.8% in TP group and 25.0% in TP-A group. A lymphocytic predominant phenotype was seen in 10.3% of pts treated in the TP group, and 17.2% of pts treated in the TP-A group. No association between TIL proportion at baseline and pCR could be detected (OR for a 10%-point increase = 1.02, 95% CI 0.78-1.34). A moderate positive correlation between numeric values of TILs and PD-L1 ICs was observed (spearman r=0.57, P< 0.0001). Exploratory correlation analyses of PD-L1 status, TIL proportion and metabolic responses in interim FDG-PET scans will be presented at the meeting. Conclusions: In ABCSG-52, chemotherapy de-escalation with intensified immunotherapy was effective and safe. Early metabolic response assessment was feasible and predicted pathologic response; therefore, incorporation of interim FDG-PET results into de-

escalation trials merits further investigation. In contrast to regimens without immune-checkpoint inhibitors, TIL proportion at baseline did not correlate with pathological outcome. Funding: Provision of IMP and financial support by Roche Austria GmbH

PO1-01-04

The optimal neoadjuvant treatment regimen for HR+/HER2+ breast cancer: a network meta-analysis

Presenting Author(s) and Co-Author(s):

H. Wang. Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan Province, People's Republic of China., United States

S. Liu. Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan Province, People's Republic of China., United States

M. Yu. Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan Province, People's Republic of China., United States

K. Mi. Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan Province, People's Republic of China., United States

E. Mou. Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan Province, People's Republic of China., United States

L. Xia. Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan Province, People's Republic of China., United States

W. Xie. Department of Medical Oncology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, China (People's Republic)

H. Tang. Shanghai Roche Pharmaceuticals Ltd., Shanghai, China, United States

Y. Feng. Shanghai Roche Pharmaceuticals Ltd., Shanghai, China, United States

X. Yu. Shanghai Roche Pharmaceuticals Ltd., Shanghai, China, United States

Background In patients with the HR+/HER2+ breast cancer (BC) subtype, it can be more challenging to achieve pathological complete response (pCR) after neoadjuvant therapy compared with the HR-/HER2+ subtype. The importance of neoadjuvant therapy and the association of pCR with long-term clinical benefits have been widely demonstrated in HER2+ BC. This network meta-analysis aimed to identify the optimal anti-HER2 regimen, the role of endocrine therapy, and the better chemotherapy choice for the neoadjuvant treatment of HR+/HER2+ BC patients. **Methods** Literature for neoadjuvant clinical trials in HR+/HER2+ breast cancer was searched in Medline, EMBASE, Cochrane Library, and Web of Science for publications released before June 2023. Single-arm trials, retrospective studies, and observational studies were excluded, as well as studies containing no neoadjuvant phase and/or no anti-HER2 drugs. A network meta-analysis with the fixed-effect model in a Bayesian framework was performed. Odds ratios (ORs) with 95% confidence intervals (CI) for pathological complete response (pCR) analysis and hazard ratios (HRs) with 95% CI for event-free survival (EFS) were calculated. A ranking of treatment patterns was performed using SUCRA. (Registered in PROSPERO: CRD42023385644 Results 2,844 records were identified by the literature search, 60 trials were included after the screening, and valid data were extracted. 19 trials and 2,883 patients were included in the primary analysis of pCR. Compared with trastuzumab + chemotherapy (CT), three treatment regimens showed

significantly higher pCR rates, T-DM1 based treatment (T-DM1, OR: 2.83, 95% CI: 1.90, 4.27; which includes T-DM1 alone, T-DM1 + pertuzumab or T-DM1 + endocrine therapy), trastuzumab + pertuzumab + CT (PH, OR: 2.57, 95% CI: 1.70, 3.94), and trastuzumab + tyrosine kinase inhibitor (TKI)+ CT (H+TKI, OR: 1.60, 95% CI: 1.22, 2.09; TKI includes lapatinib, neratinib and pyrotinib). The SUCRA ranking of pCR showed that T-DM1 was ranked first (SUCRA: 0.94), followed by PH (SUCRA: 0.85) and H+TKI (SUCRA: 0.60). PH came first in the SUCRA ranking of EFS (SUCRA: 0.74) as well as cumulative SUCRA combining pCR and EFS (SUCRA: 0.79). For chemotherapy strategies, platinum-containing regimens showed no significant increase in pCR rate compared to no platinum regimens (OR: 1.27, 95% CI: 0.95, 1.69), regimens with anthracycline also had no statistical difference from those without anthracycline (OR: 0.74, 95% CI: 0.51, 1.07). When assessing the impact of endocrine therapy, no significant difference in pCR rate was observed with or without endocrine therapy (OR: 1.18, 95% CI: 0.80, 1.73). Conclusions The PH regimen remains the best neoadjuvant treatment choice for HR+/HER2+ early BC patients considering pCR and EFS outcomes simultaneously. H+TKI did not show significant benefits, so it is not recommended to be given priority in clinical practice. The platinum-containing regimen's potential benefit compared to the non-platinum regimen is uncertain and needs more clinical investigation. The necessity of adding endocrine therapy is not proven due to limited data availability. Funding: This study was sponsored by Shanghai Roche Pharmaceuticals Ltd. Disclosure: Hao Tang, Shanghai Roche Pharmaceuticals Ltd.: Employee (Ongoing), Salary (Ongoing) Yajing Feng, Shanghai Roche Pharmaceuticals Ltd.: Employee (Ongoing), Salary (Ongoing) Xin Yu, Shanghai Roche Pharmaceuticals Ltd.: Employee (Ongoing), Salary (Ongoing)

PO1-01-05

Spatial PK/PD Model with HER2 Expression for Predicting Individual Tumor Response to T-DM1

Presenting Author(s) and Co-Author(s):

N. Hobbs. SimBioSys, Inc., Chicago, Illinois, United States

B. Feiger. SimBioSys, Inc., United States

J. Cole. SimBioSys, Inc., Chicago, Illinois, United States

T. Carrigan. SimBioSys, Inc., United States

J. Peterson. SimBioSys, Inc., Chicago, Illinois, United States

J. Pfeiffer. SimBioSys, Inc., Chicago, Illinois, United States

D. Cook. SimBioSys, Inc., Champaign, Illinois, United States

Introduction: As new antibody drug conjugates are developed, the question of which specific patients will respond to these therapies remains. This work develops a spatial PK/PD model for the antibody drug conjugate trastuzumab emtansine, T-DM1, and explores the relationship between HER2 (target) expression and other individual features of the tumor microenvironment using a computational approach. **Methods:** We developed a spatial PK/PD model for T-DM1 based upon an allometrically-scaled mouse model (Jumbe, Nelson L., et al., 2010) and the reported outcomes from the KRISTINE trial, which investigated T-DM1 plus pertuzumab in the neoadjuvant early-stage breast cancer setting (Hurvitz, Sara A., et al., 2018). The T-DM1 spatial PK/PD model was then integrated into our previously described 4D biophysical simulation model (Howard, Frederick M., et al., 2022). The biophysical model leverages baseline breast MRI and clinicopathologic features and predicts the individual response to a treatment regimen. Using digital twin tumors from our TumorBank to simulate the KRISTINE trial cohort (n=40), the PD model was parameterized to achieve the trial response rate. To orthogonally validate the spatial PK/PD model, volumetric response and pCR were predicted in an independent cohort of ISPY2 trial patients (n=44) who received T-DM1 followed by dose-dense doxorubicin and cyclophosphamide. We then assessed the added value of the target expression data by developing logistic regression models to predict which patients would achieve pCR based upon HER2 expression alone or HER2 expression combined with the final tumor volume simulated using the spatial PK/PD model. **Results:** A logistic regression model based upon HER2 expression from transcriptomic data is a strong predictor of response to T-DM1 with an odds ratio of 9.6 and an area under the ROC curve (AUC) of 0.81. The tumorHER2 model, which combines the HER2 expression with the spatial PK/PD model, improves the predictive value of the model with an odds ratio of 34.0 and an AUC of 0.88. **Conclusion:** The spatial PK/PD improves prognostic predictions compared to HER2 gene expression data alone. In leveraging the SBS biophysical simulation platform, the spatial PK/PD model captures the individual variability in tumor growth rate, tumor perfusion, and drug disposition, all of which influence the treatment efficacy. The rate of target expression will highly influence response to an ADC, but the biophysical model demonstrates that features of the spatial tumor microenvironment also influence response.

Table 1. Performance comparison between the SBS tumorHER2model and SBSHER2 Signature.

	SBS tumorHER2 model	SBS HER2 Signature
Odds ratio (95% CI)	34.0 (13.8 – 83.5)	9.6 (4.7 – 19.8)
Odds ratio p-value	9×10^{-5}	0.008
Precision	85%	76%
Recall	84%	75%
F1 score	84%	75%
Sensitivity	80%	72%
Specificity	89%	79%
Positive Predictive Value	91%	82%
Negative Predictive Value	77%	68%
AUC	0.88	0.81
Total patients	44	44

PO1-01-06

Patterns in use and tolerance of adjuvant neratinib in patients with hormone receptor (HR)-positive, HER2-positive early-stage breast cancer

Presenting Author(s) and Co-Author(s):

J. Blanter. Icahn School of Medicine at Mount Sinai, United States

E. Baldwin. Icahn School of Medicine at Mount Sinai, United States

R. Patel. Icahn School of Medicine at Mount Sinai, United States

T. Sheng. Icahn School of Medicine at Mount Sinai, United States

A. Tiersten. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New, New York, United States

Background: In the ExteNET study, 1 year of neratinib therapy was shown to derive a significant invasive disease-free survival (iDFS) benefit in HR+, HER2+, node-positive disease after trastuzumab-based adjuvant therapy. Currently, the NCCN guidelines recommend extended adjuvant neratinib following trastuzumab-based therapy for patients (pts) with high-risk HR+ HER2+ disease. Limitations to use of neratinib include significant gastrointestinal side effects which often result in pts discontinuing treatment. In this study, we aimed to identify high-risk clinical features and characteristics of pts who were offered adjuvant neratinib therapy and factors that impacted treatment completion versus discontinuation. Methods: We performed a retrospective review of all pts with early-stage HR+ HER2+ breast cancer who were prescribed neratinib from 2017-2023 at our institution. We used the electronic medical record to extract information on patient characteristics, clinical and high-risk features. High-risk was defined as any of the following: at least 4 lymph nodes positive for disease, 1-3 lymph nodes positive for disease and a grade 3 (poorly differentiated) tumor, tumor > 5 cm, or Ki67 > 20%. Length of time on treatment, treatment holds, dose reductions and up-titrations were documented. Statistical analysis was performed using two-sided T-tests and chi-square tests. Results: We identified 62 eligible pts of whom 34 (55%) completed 1 year of neratinib and 28 (45%) did not. Median age at diagnosis was 51.5 years. 49% of pts were pre-menopausal at diagnosis, 43% were post-menopausal, 5% were peri-menopausal and 3% had undocumented menopausal status at diagnosis. Clinical features of the pts are documented in Table 1. Sixty percent of patients offered neratinib were considered high-risk at diagnosis, based on definitions described above. 73% of pts received neoadjuvant treatment with pertuzumab in addition to trastuzumab. 24 pts (39%) had residual disease and 22 pts (35%) received adjuvant T-DM1. The most common reason for neratinib discontinuation was inability to tolerate side effects (54%) followed by pill burden (18%). The most common side effect experienced by pts was diarrhea despite anti-diarrheal prophylaxis (56%), followed by rash (8%). Pts who received an up-titration of neratinib were more likely to complete the full course of neratinib when compared to those who did not (76% vs. 40.5% p = 0.013). The median starting dose of those who completed neratinib treatment was 140 mg vs. 240 mg in those who did not (p = 0.016). The median length of time on neratinib for those that did not complete the 1-year treatment course was 30 days. Neither group experienced a statistically significant greater likelihood of treatment holds or dose reductions. In terms of outcomes, 10 pts had progression of disease of whom 7 did not complete neratinib treatment (p = 0.169). Interestingly, those 7 pts developed metastatic disease and 57% had central nervous system metastases. Conclusions: Pts are more likely to complete 1 year of adjuvant neratinib with dose up-titration. Dose reductions and interruptions did not affect neratinib adherence in our patient population. Seven pts in our study developed metastatic disease, all of whom did not complete adjuvant neratinib treatment. Future

prospective studies are needed to further determine the impact of adjuvant neratinib treatment on iDFS in pts who have received pertuzumab and/or T-DM1.

Table 1: Clinical Features of Patients Prescribed Neratinib

	Completed neratinib course	Did not complete neratinib course	p-value	All patients prescribed neratinib
n (%)	34	28		62
Tumor grade 3 (poorly differentiated)	22 (64.7%)	16 (57.1%)	0.893	38 (61.3%)
Mean Ki67 %	30.27	21.86	0.299	26.07
Pathologic T stage			0.392	
T1	20 (58.8%)	14 (50.0%)		34 (54.8%)
T2	9 (26.5%)	3 (12.5%)		12 (19.4%)
T3-4	2 (5.9%)	4 (14.3%)		6 (9.7%)
Pathologic N stage			0.702	
N0	16 (47.1%)	12 (50.0%)		28 (45.2%)
N1	14 (41.2%)	8 (28.6%)		22 (35.5%)
N2	3 (8.8%)	3 (12.5%)		6 (9.7%)
N3	0 (0.0%)	1 (4.2%)		1 (1.6%)
High-risk at diagnosis	20 (58.8%)	17 (60.7%)	1.000	37 (59.7%)

PO1-01-07

Cryoablation and endocrine therapy for clinical stage I/II, ER+ breast cancer in patients with omission of surgical axillary staging. A retrospective study

Presenting Author(s) and Co-Author(s):

J. Oliver Goldaracena. Hospital Universitario La Paz, Madrid, Spain
P. Zamora. Hospital Universitario La Paz, Madrid, Spain, Madrid, Spain
C. Marti. Hospital Universitario La Paz, United States
V. Córdoba Chicote. Hospital Universitario La Paz, United States
M. Roca Navarro. Hospital Universitario La Paz, United States
D. Garrido Alonso. Hospital Universitario La Paz, United States
Y. Navarro Monforte. Hospital Universitario La Paz, United States
T. Diaz de Bustamante Durban. Hospital Universitario La Paz, United States
F. García Martínez. Hospital Universitario La Paz, United States
J. Sanchez-Mendez. La Paz University Hospital/ La Paz Institute for Health Research – IdiPAZ / Universidad Autónoma - Madrid (Spain), United States
E. York Pineda. Hospital Universitario La Paz, United States
L. Yebeles Gregorio. Hospital Universitario La Paz, United States
A. Loayza. Hospital "La PAZ", Madrid, Madrid, Spain
L. Frías Aldeguer. Hospital Universitario La Paz, United States
E. Moreno Palacios. Hospital Universitario La Paz, United States
M. Melendez Gisper. Hospital Universitario La Paz, United States
J. Gomez Ramirez. Hospital Universitario La Paz, United States
L. Asensio Gómez. Hospital Universitario La Paz, United States
V. Martínez Marín. Hospital Universitario La Paz, United States
D. Hardisson Hernández. Hospital Universitario La Paz, United States
A. Berjón García. Hospital Universitario La Paz, United States

OBJECTIVE To evaluate the efficacy of combined treatment with ultrasound-guided cryoablation and endocrine therapy (ET) in hormone receptor-positive (ER+), HER2-negative (HER-) invasive breast cancer (BC) patients with clinical stage I/II who are not candidates for axillary surgery. **PATIENTS AND METHODS** Patients with ER+, HER- invasive BC in clinical stage I/II who did not undergo sentinel lymph node biopsy (SLNB) or target axillary dissection (TAD) were included. They received treatment consisting of ultrasound-guided cryoablation combined with daily letrozole 2.5 mg orally. Cryoablation was performed as the initial treatment for BC < 15mm, followed by adjuvant ET, while neoadjuvant ET was administered for 6-12 months before cryoablation for BC ≥ 15mm. Cryoablation was performed using the ICEfx Galil argon gas system (Boston Scientific, USA) and the ProSense liquid nitrogen system (IceCure Medical Ltd, Caesarea, Israel). Follow-up breast ultrasound examinations were conducted every six months. Patients with a minimum follow-up of 12 months after cryoablation were included in the study. Core needle biopsies were performed if recurrence was suspected, and rescue cryoablation was considered for confirmed relapse. The tolerance and safety of the procedures were recorded. **RESULTS** From March 2019 to July 2023, a total of 96 patients with 105 ER+, HER2- invasive BC in clinical stage I/II who did not undergo SLNB or TAD were

treated with ultrasound-guided cryoablation and ET. Among them, 58 patients (aged 58-96 years, mean 83, SD \pm 7.64) with 64 BC lesions (ranging from 5 to 60mm, mean 17, SD \pm 13.75) were followed up for a minimum of 12 months, with a mean follow-up period of 24 months (ranging from 12 to 50 months). The invasive carcinomas included 40 ductal, 16 lobular, 5 colloid, and 3 papillary cases. The ipsilateral breast tumor recurrence rate was 1,72% (1/58 patients). One patient with lobular carcinoma experienced a relapse at 17 months. Rescue cryoablation was performed, and after 25 months, she remains free of recurrence. Therefore, local control was achieved in all patients. Six patients died from causes unrelated to BC during the follow-up period. All procedures were well-tolerated with local anesthesia, and no serious complications were reported. **CONCLUSION** Ultrasound-guided cryoablation with ET constitutes an effective combined treatment for the local control of ER+, HER2- BC in patients with clinical stage I/II and omission for surgical axillary staging. Cryoablation is a very well

TABLE 1	
PATIENTS (N=58)	
Mean Age (years)	83 (58-96)
Standard Deviation, SD	7.64
Omitted surgical axillary staging (N=60)	
SLNB (*)	56 (97%)
TAD (**)	4 (3%)
Indications for Breast Cryoablation	
1) Not candidates for surgery	23 (37%)
- Elderly	20 (85%)
- Stabilized Stage IV neoplasm with concomitant E/II breast cancer (***)	3 (2%)
2) Candidates for surgery	35 (63%)
- Ipsilateral breast relapse (****)	1 (2%)
- Local extension	
Focal	52 (90%)
Multifocal	8 (4) (7%)
- Bilateral	2 (3%)
- Clinical Stage	
I	16 (78%)
II	16 (72%)
(**) Negative axillary ultrasound. (***) A metastatic lymph node at axillary level I (****) Lung cancer (n=1), Colon cancer (n=1), Melanoma (n=1), (I,II), Two lesions (****) Declined surgical options .	
TABLE 2	
ER+ HER2- INVASIVE BREAST CANCER FEATURES (n=64)	
Histology:	
Ductal	40 (62,5%)
Lobular	16 (25%)
Colloid	5 (8,3%)
Papillary	3 (4,2%)
Grade (*)	
G1	12 (18,8%)
G2	48 (75%)
G3	4 (6,2%)
Size (mm)	
Mean (range)	17 (5-60mm) SD +/- 13,75
(*) Nottingham Score	

tolerated procedure without morbidity.

PO1-01-08

The impact of drug-drug interactions between palbociclib and proton pump inhibitors on clinical outcomes of patients with hormone receptor positive, HER2-negative, early breast cancer: an exploratory analysis of the PALLAS study

Presenting Author(s) and Co-Author(s):

E. Agostinetto. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Bruxelles, Brussels Hoofdstedelijk Gewest, Belgium

G. Pfeiler. Medical University of Vienna, Austria, Vienna, Austria

D. Hlauschek. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria

E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy

E. de Azambuja. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Brussels Hoofdstedelijk Gewest, Belgium

M. Bellet- Ezquerro. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

G. Rubovszky. National Institute of Oncology, Budapest, Hungary

N. Zdenkowski. Breast Cancer Trials, Newcastle, New South Wales, Australia

Y. Novik. New York University (NYU), Perlmutter Cancer Center, New York, NY, USA, United States

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

K. Gelmon. BC Cancer Agency, Vancouver, British Columbia, Canada, United States

E. Mamounas. NSABP Foundation and Orlando Health Cancer Institute, Orlando, FL, USA, Windermere, Florida, United States

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

D. Lu. Pfizer, United States

L. Sölkner. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria, United States

C. Fesl. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria

M. Gnant. Medical University of Vienna, Vienna, Austria

A. DeMichele. University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Data suggest that concomitant intake of proton pump inhibitors (PPI) may create drug-drug interactions, potentially impacting efficacy of agents including palbociclib, which is widely used in the treatment of metastatic hormone-receptor-positive/HER2-negative (HR+/HER2-) breast cancer. In the open label, randomized, phase 3 PALLAS trial, the addition of palbociclib for two years to standard adjuvant endocrine therapy (ET) in patients with HR+/HER2- early breast cancer (EBC) did not improve invasive disease-free survival (IDFS) compared to adjuvant ET alone. We explored whether concomitant use of PPIs could have affected clinical outcomes in patients treated with palbociclib in PALLAS. Methods: This is an exploratory, unplanned analysis of the PALLAS trial (AFT-05/ABCSG-42/PrE0109/BIG-14-13, NCT02513394), which enrolled 5796 patients with stage II-III HR+/HER2- EBC. Patients were randomized to receive either 2 years of palbociclib (125 mg oral capsules once daily on days 1-

21 of a 28-day cycle) with adjuvant ET or ET alone. Primary endpoint was IDFS in the intention-to-treat population. The present exploratory analysis included patients who received at least one dose of palbociclib. Definitions of IDFS, distant relapse-free survival (DRFS) and overall survival (OS) were according to the PALLAS protocol (STEEP criteria), using first day of palbociclib intake as start date. Only PPI concomitant intake during palbociclib treatment was considered. To determine the association of concomitant PPI use with IDFS, DRFS, and OS, uni- and multivariable Cox models with time-dependent PPI (the latter adjusted for age, prior chemotherapy, progesterone receptor, grade, tumor stage, nodal stage, body mass index (BMI)) were used. Also, the association between PPI use and neutropenia was investigated in patients initiating PPI prior to randomization vs never. Odds ratios (OR) unadjusted and adjusted for age and BMI estimated with logistic regression models are reported. Results: Of 2840 patients treated with palbociclib + ET, 533 (18.8%) had concomitant PPI and palbociclib intake. Median duration of PPI intake was 10.8 months (interquartile range 2.3-22.3). Most patients received omeprazole as PPI (n=265, 49.7%). PPI intake was significantly associated with older age, post-menopausal status, use of aromatase inhibitors as ET, higher BMI, and worse ECOG status (all p< 0.001). Concomitant PPI intake was not significantly associated with survival outcomes (Table 1). Unadjusted all grade neutropenia rates were slightly lower in patients who initiated PPI prior study start vs patients never initiating (79% vs 85%, unadjusted OR 0.66, 95%CI 0.50-0.88). After adjustment for BMI and age, the difference between the groups decreased (adjusted OR = 0.77, 95%CI 0.57-1.04). Similar effect sizes were found for grade 3/4 neutropenia rates (54% vs 64%, unadjusted OR 0.66, 95%CI 0.52-0.83, adjusted OR 0.81, 95%CI 0.64-1.03). Conclusions: Our exploratory analysis did not demonstrate a statistically significant relationship between concomitant use of PPIs and palbociclib and survival outcomes of patients in the PALLAS trial. Nonetheless, careful consideration of concomitant medications and of drug-drug interactions is important when studying novel agents in the adjuvant breast cancer setting. Support: AFT, Pfizer; <https://acknowledgments.alliancefound.org>

Table 1.

	Unadjusted HR, 95%CI	P value	Adjusted HR, 95% CI	P value
IDFS	HR 1.18, 95%CI 0.91-1.54	p=0.21	HR 1.20, 95%CI 0.92-1.57	p=0.18
DRFS	HR 1.09, 95%CI 0.81-1.47	p=0.57	HR 1.10, 95%CI 0.81-1.48	p=0.55
OS	HR 1.39, 95%CI 0.96-2.03	p=0.84	HR 1.32, 95%CI 0.90-1.94	p=0.16

Association between PPI intake and survival outcomes.

PO1-01-09

Neoadjuvant endocrine therapy and avelumab with or without palbociclib in stage II/III endocrine receptor-positive breast cancer: the ImmunoADAPT trial

Presenting Author(s) and Co-Author(s):

P. Zavras. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD, United States

R. Chen. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD, United States

H. Qi. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD, United States

M. Jones. Johns Hopkins Sidney Kimmel Cancer Center, United States

A. Folmer. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD, United States

H. Chae. Sibley Memorial Hospital, Johns Hopkins; Washington DC, United States

A. Khodab. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD, United States

A. Cimino-Mathews. Johns Hopkins University School of Medicine, United States

L. Jacobs. Johns Hopkins University, Baltimore, Maryland, United States

L. Mullen. Breast Imaging Division, Department of Radiology at Johns Hopkins, Baltimore, MD, United States

C. Hiton. Allegheny Health Network; Pittsburgh, PA, United States

A. Elkhanany. Baylor College of Medicine, Houston, TX, Houston, Texas, United States

K. Khoury. O'Neal Comprehensive Cancer Center at the University of Alabama, Birmingham, Alabama, United States

M. Cristofanilli. Weill Cornell Medicine, United States

E. Jaffee. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD, United States

V. Stearns. Johns Hopkins University, Baltimore, Maryland, United States

C. Santa-Maria. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD & Sibley Memorial Hospital, Johns Hopkins, Washington, DC, Baltimore, Maryland, United States

Background: Pre-clinical and clinical data suggest that CDK4/6 inhibitors can promote an immunogenic tumor microenvironment (TME) and when combined with programmed cell death ligand 1 (PD-L1) inhibitors synergistic anti-cancer effects are observed. To understand the differential effects of CDK4/6 inhibition in the context of immunotherapy we designed a study evaluating neoadjuvant endocrine therapy (ET) with a PD-L1 inhibitor (avelumab) with or without a CDK4/6 inhibitor (palbociclib, palbo) in patients (pts) with stage II/III endocrine receptor (ER)-positive breast cancer. Methods: In this randomized phase 2 pilot study, pts with stage II/III ER+, HER2-negative breast cancer were randomized 2:1 to ET (aromatase inhibitor, AI, for post-menopausal pts; tamoxifen+/-ovarian function suppression for pre-menopausal pts) with avelumab, with or without palbo (palbo vs. control arms). Avelumab was added after a 1-month lead-in of ET +/- palbo, and all drugs were continued for additional 3-month-long cycles prior to surgery. We obtained tumor tissue and breast MRIs on C1D1, C2D1, and at the end of

treatment. Imaging assessment was done according to RECIST 1.1 criteria at each time point. The primary endpoint was clinical complete response (cCR) by MRI in the palbo arm (H0: cCR=10% vs. 40% at a two-sided alpha level of 0.1). Secondary endpoints included pathologic CR (pCR), overall response rates (ORR), percent sum diameter changes, and adverse effects (AE). We report descriptive statistics on patient characteristics, clinical response rates, and changes in the sum of the longest diameters of the target lesions (SLD). Translational correlates including imaging mass cytometry, spatial transcriptomic assessments, and other pathologic biomarkers will be reported at the meeting. Results: From 2018-2023, 33 pts were enrolled, and 30 were eligible for the primary analysis, including 20 pts on the palbo arm (1 pt with bilateral breast cancer, response to each breast cancer evaluated separately) and 10 to the control arm (1 pt with missing data). Clinical and pathologic characteristics were well balanced between arms, however, there was a higher proportion of patients with node-positive disease on the palbo arm (80% vs 60%). The study did not meet its primary endpoint as only 1 pt achieved a cCR and pCR in the palbo arm (cCR/pCR rate 4.8%) vs. no pts in the control arm. ORR was numerically higher in the palbo arm, 42.9% vs. 11.1% ($p=0.204$). After 1-month of ET+palbo, the mean SLD decreased by 11.6% compared to 9.4% in the ET-only control group ($p=0.704$). After avelumab was added to both arms, the mean SLD decreased by a further 15.2% in the palbo arm in contrast to a 6.9% increase in the control arm ($p=0.018$). Subgroup analysis in the palbo arm did not identify clinical or pathologic variables significantly associated with responses. No new safety or toxicity signals were observed. Notably, however expected, grade 3 or higher immune-related adverse events were observed including autoimmune diabetes ($n=1$), hepatitis ($n=1$), and colitis ($n=1$). Conclusions: As shown in previous studies, the addition of palbo to ET did not improve responses in the neoadjuvant setting; however, increased responses to palbo+ET were seen after PD-L1 inhibition, whereas not to ET, suggesting synergy between ET/palbo and avelumab. Translational correlative analysis will aim to decipher TME changes that augment PD-L1 inhibitor responses. Future studies in high-risk pts, where the toxicity of immunotherapy is acceptable, are warranted.

PO1-01-10

Comparison of the cost-effectiveness of multigene assays for HR+/HER2- node-negative early-stage breast cancer in the US

Presenting Author(s) and Co-Author(s):

V. Berdunov. Putnam PHMR, United States

G. Carter. Exact Sciences, United States

C. Russell. Exact Sciences, United States

S. Campbell. Exact Sciences, United States

J. Racz. Exact Sciences, United States

Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States

Background Traditional clinico-pathologic features, such as tumor grade and size, age, and menopausal status, may provide incomplete prognostic information, and have limited ability to predict chemotherapy benefit for patients with hormone-receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2)-, axillary lymph node-negative (N0) early-stage breast cancer, leading to both under- and over-treatment with adjuvant chemotherapy. Multigene expression profile tests have been used in clinical practice to complement clinico-pathologic information to optimize treatment decisions. To date, the Oncotype DX Breast Recurrence Score[®] test is the only multigene assay with the ability to predict chemotherapy benefit validated by evidence from randomized clinical trials and supported by NCCN and ASCO guidelines. Other commercially available assays in the US include MammaPrint[®], EndoPredict[®] and Prosigna ROR[®], which offer prognostic information beyond traditional clinico-pathologic features to improve treatment decisions. The relative cost-effectiveness of the four multigene assays compared to using clinico-pathologic risk alone to guide chemotherapy decisions was assessed from a societal perspective in the US. Methods A cost-effectiveness model built in Microsoft Excel estimated the cost-effectiveness of the Oncotype DX[®] test, MammaPrint, EndoPredict and Prosigna ROR compared to using clinical-pathological risk alone over a lifetime horizon. The model structure consisted of a decision-tree portion informed using published studies for the distribution of distant recurrence risk categories as defined by each test (low, intermediate, and high risk for the Oncotype DX test and Prosigna ROR, low and high risk for MammaPrint and EndoPredict). Decision impact studies and clinical expert opinion informed the proportion of patients allocated to adjuvant chemotherapy conditional on test result category. A Markov discrete health state model then simulated the future risk of distant recurrence, and long-term adverse effects of chemotherapy: acute myeloid leukemia (AML), and congestive heart failure (CHF), and aggregated the costs and outcomes of treatment decisions over a patient's lifetime. The probability of distant recurrence of breast cancer conditional on test result category was derived from the most up-to-date studies assessing the performance of tests: TAILORx for the Oncotype DX test, MINDACT for MammaPrint, and TransATAC for EndoPredict and Prosigna ROR. Costs were estimated from a US societal perspective in 2020 US dollars (including Medicare healthcare costs, lost productivity and patient out-of-pocket chemotherapy costs from literature), and outcomes were expressed in terms of life-years, quality-adjusted life-years (QALYs), and net monetary benefit (NMB). The cost-effectiveness of each multigene assay compared to using clinico-pathologic risk alone was presented using the incremental cost-effectiveness ratio (ICER). Results Using the Oncotype DX test resulted in the largest lifetime cost savings (-\$13,395) and generated the largest QALY gain (0.25) out of the four multigene assays included in the model, when

compared to using clinico-pathologic risk alone (Table 1). All four multigene assays represented a cost-effective use of resources from a societal perspective (based on the accepted willingness-to-pay threshold of \$100,000 per QALY gained), with a low net lifetime cost or net cost savings with positive QALY gain. Conclusion These results support the use of multigene assays to guide treatment decisions in node-negative HR+/HER2- early-stage breast cancer to improve treatment outcomes, and also result in substantial net cost savings from a societal perspective. The prediction of chemotherapy benefit using the Oncotype DX test resulted in substantially higher cost savings and improved breast cancer outcomes.

Tables:

Table 1. Cost-effectiveness of the multigene assays compared to clinical-pathological risk alone.

Test	Δ Cost	Δ QALYs	Δ life-years	ICER	NMB
The Oncotype DX [®] test	-\$13,395	0.25	0.29	Dominant	\$38,492
MammaPrint [®]	\$1,079	0.04	0.05	\$27,760	\$2,808
EndoPredict [®]	\$392	0.05	0.06	\$7,942	\$4,544
Prosigna ROR [®]	-\$2,410	0.07		Dominant	\$9,768

Dominant = the multigene assay is less costly and more effective compared to using clinico-pathologic risk alone

ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life-year

PO1-01-11

Development and Validation of a Breast Cancer Recurrence Model Demonstrates Accurate Identification of Patients with Favorable Long-Term Outcomes

Presenting Author(s) and Co-Author(s):

A. Dhungana. University of Chicago Pritzker School of Medicine, United States

A. Vannier. University of Chicago Pritzker School of Medicine, United States

F. Zhao. Department of Public Health Sciences, The University of Chicago, United States

J. Freeman. Department of Public Health Sciences, University of Chicago, Chicago, Illinois, United States

P. Saha. NorthShore University Health System, United States

M. Sullivan. NorthShore University Health System, United States

K. Yao. Northshore Medical Group, Evanston, Illinois, United States

E. Flores. Department of Pathology, Ingalls Memorial Hospital, United States

O. Olopade. University of Chicago Medicine, United States

D. Huo. Department of Public Health Sciences, The University of Chicago, Chicago, Illinois, United States

A. Pearson. University of Chicago Medicine, United States

F. Howard. Department of Medicine, Section of Hematology/Oncology, The University of Chicago, Chicago, Illinois, United States

Background: The Oncotype DX (ODX) test is a 21-gene expression assay widely used for the prediction of risk recurrence in early-stage breast cancer, but it may be possible to identify patients who can forgo testing using only clinicopathologic variables. In 2018, the National Cancer Database (NCDB) began reporting quantitative histologic parameters for estrogen receptor (ER), progesterone receptor (PR), and Ki-67 expression in breast cancer patients. Inclusion of these variables may improve the development of nationally applicable models to predict ODX results using clinicopathologic variables alone. **Methods:** Using a cohort of patients from the NCDB diagnosed from 2018–2020 with hormone receptor (HR)-positive, HER2-negative, Stage I-III breast cancer, we trained machine learning models to predict high-risk (26–100) ODX score. A subset comprising 80% of patients was used for model training, while the remaining data were set aside for internal validation. An external validation cohort was selected from the University of Chicago Medical Center (UCMC), including patients diagnosed from 2009–2021. Feature selection, model architecture selection, and hyperparameter tuning were performed using 10-fold cross-validation within the NCDB training set. We compared a model with quantitative ER, PR, and Ki-67; a model with only quantitative ER and PR, and a model without quantitative immunohistochemistry – to best reflect the likely data available in a variety of practice patterns. The primary endpoint was the area under the receiver operating characteristic curve (AUROC) for prediction of high-risk ODX results in the UCMC validation cohort. Models were also evaluated as rule-out tests to identify low-risk patients who did not require further ODX testing, using a high (90%) sensitivity threshold, fit in the NCDB training dataset. **Results:** We identified 53,346 patients from the NCDB cohort meeting the inclusion criteria; 7% had a high risk ODX score, with a median follow-up time of 28 months. The UCMC validation cohort included 896 patients, and was more diverse, with 30% non-Hispanic Black patients (versus 8% in NCDB), more high-risk patients (18% with high ODX), and a longer median follow-up time of 55 months. In the NCDB validation cohort, models incorporating quantitative ER/PR (AUROC 0.78, 95% CI 0.77–0.80) and quantitative ER/PR/Ki-67 (AUROC

0.81, 95% CI 0.80–0.83) both performed better than the non-quantitative model (AUROC 0.70, 95% CI 0.68–0.72). These results were preserved in the external UCMC cohort, where the ER/PR model (AUROC 0.86, 95% CI 0.80–0.92, $p = 0.032$) and the ER/PR/Ki-67 model (AUROC 0.87, 95% CI 0.81–0.93) outperformed the non-quantitative model (AUROC 0.80, 95% CI 0.73–0.87, $p = 0.009$). The high sensitivity rule-out threshold of the ER/PR model predicted that 30% of patients in the UCMC cohort would be low ODX, and the ER/PR/Ki-67 model predicted 44% as low risk – negative predictive value was over 96% for prediction of high ODX. Of the patients predicted to be low risk by the quantitative models, none had a documented high ODX score, and recurrence was $< 3\%$ at 5 years. The hazard ratio for recurrence free interval, adjusted for age and comorbidity score, of patients predicted to be high risk by this threshold was 2.96 (95% CI 1.02–8.58) for the ER/PR model and 3.84 (95% CI 1.48–9.97) for the ER/PR/Ki-67 model. Conclusions: We present externally validated and nationally applicable models that identify approximately half of HR-positive/HER2-negative breast cancer patients who are unlikely to have high ODX results using widely available quantitative clinicopathologic variables. Patients identified as low risk by these models have excellent long-term outcomes and may be able to forgo adjuvant chemotherapy without further genomic testing.

PO1-01-12

A retrospective cohort study on the effect of adding adjuvant ovarian function suppression to endocrine therapy in premenopausal women with T1-T2 tumor hormone-positive breast cancer on survival and disease recurrence.

Presenting Author(s) and Co-Author(s):

S. Alsafi. Asan Medical Center, Republic of Korea. Al Adan Hospital, Ministry of Health, Kuwait, Bayan, Hawalli, Kuwait

H. Kim. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

S. Kim.

S. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

J. Kim. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea., United States

T. Yoo. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

I. Chung. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

B. Ko. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

B. Son. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Breast cancer is the most common diagnosed cancer in women and is the leading cause of cancer death. Young women diagnosed with breast cancer are at higher rates of adverse outcomes in terms of survival and recurrence. Hormone sensitive breast cancer is the commonest subtype of breast cancer in this group. To date, the standard adjuvant treatment is endocrine therapy for both pre and post-menopausal women. Recent published studies have recommended adding ovarian function therapy to premenopausal women who are at high risk of recurrence. In this study we evaluated the impact of adding adjuvant ovarian function suppression for premenopausal women with small (T1 and T2) hormone receptor positive node negative breast cancer who did not receive any form of chemotherapy on overall survival and disease-free recurrence. Methods: We performed a retrospective study where we evaluated the electronic medical records of 4431 premenopausal women diagnosed with breast cancer in Asan Medical Center in Seoul, South Korea. All the analyzed patients were operated from the period of January 2006 till December 2019. The inclusion criteria were age of 55 and below, T1 and T2 tumors with N0 disease who received selective estrogen receptor modulators (SERM - Tamoxifen) and didn't receive neo or adjuvant chemotherapy. We compared patients who received SERM (Tam Only) only to patients who received SERM and ovarian function suppression (Tam + OFS) medications. The primary endpoint was overall survival (OS), and the secondary endpoint was mortality and disease-free survival (DFS). We used chi-square test for categorical variables and t-test for continuous variables. The p-value was set as $p < 0.05$ as statistically significant. Kaplan Meier curve and log rank test were used to analyze the data for overall survival, disease-free survival and mortality. We performed an additional subgroup analysis adjusted to age, tumor size, Ki67%, progesterone receptor, HER2 status and type of operation. Results: There was equal distribution of cases between tamoxifen only group and

tamoxifen + OFS group (2121 versus 2310 respectively). The median age in each group was 45 years of age. Tumor size of ≤ 0.5 cm was the commonest in the tamoxifen only group whereas tamoxifen + OFS group had majority of cases with tumor size of 1 - 2cm. Both groups had a Ki-67% of 10-20%. Histologic grade of 2 and nuclear grade of 2 were most commonly representative in the comparing groups. Invasive ductal carcinoma was the most common histological subtype (93-94%) and invasive lobular carcinoma accounted for 5-6% of cases. Regarding immunohistochemistry results, 91-93% of patients were progesterone receptor positive and 68-73% were HER2 negative. The majority underwent breast conserving surgery compared to mastectomy. We have also looked at the pattern of prescribing OFS treatment in the Tamoxifen + OFS group regarding the length of treatment. Nearly 80% of patients received OFS treatment for a period of 1-2 years whereas only 5.2% received < 1 year and 1.8% >2years. After adjusting to age, tumor size, Ki67%, PR receptor and HER2 status, the result was only significant for higher risk of DFS in the TAM + OFS group in Ki67< 20%. The OFS+TAM had more DFS and mortality events compared to TAM only group. However, the only significant result was the overall survival favoring tamoxifen only group with a p-value of 0.039 and HR of 1.05-7.99. Conclusion: Adding ovarian function suppression to tamoxifen in premenopausal hormone positive node negative T1-T2 tumors didn't show any benefit in terms of disease-free interval and overall survival. Further studies are advised to assess the benefit of adding ovarian function suppression to this group of patients

Table 1: baseline characteristics of

	TAM only	OFS + TAM	P value
	2121	2310	
Median age, (range)	45 (21, 55)	45 (20, 55)	
Age at diagnosis, mean±sd	43.81±5.54	44.64±4.92	<0.001
<30	36 (1.7)	15 (0.65)	<0.001
30-34	105 (4.95)	64 (2.77)	
35-39	293 (13.81)	254 (11)	
40-44	609 (28.71)	700 (30.3)	
45-49	778 (36.68)	895 (38.74)	
≥50	300 (14.14)	382 (16.54)	
Tumor Size, mean±sd	1.01±0.88	1.59±0.75	<0.001
T ≤0.5cm	820 (38.66)	35 (1.52)	<0.001
T 0.5-1cm	371 (17.49)	519 (22.49)	
T 1 - 2cm	688 (32.44)	1284 (55.58)	
T >2 - 3cm	180 (8.49)	366 (15.84)	
T >3 - 4cm	50 (2.36)	88 (3.81)	
T ≥4 - < or equal 5cm	12 (0.57)	22 (0.95)	
BMI, mean±sd	22.41±3.07	22.50±2.91	0.354
<18.5	138 (6.51)	121 (5.24)	0.323
18.5-24.9	1618 (76.28)	1799 (77.88)	
25-29.9	319 (15.04)	340 (14.72)	
≥30	46 (2.17)	50 (2.16)	
Ki67%			
<10	621 (29.28)	421 (18.23)	<0.001
10-20	948 (44.7)	959 (41.52)	
20-30	223 (10.51)	242 (10.48)	
≥30	153 (7.21)	180 (7.79)	
N/A	176 (8.3)	508 (21.99)	
Histologic grade			
G1	262 (12.36)	283 (12.25)	0.620
G2	1667 (78.63)	1799 (77.88)	
G3	191 (9.01)	228 (9.87)	
Nuclear grade			
N1	151 (7.12)	204 (8.83)	0.095
N2	1759 (82.93)	1869 (80.91)	
N3	211 (9.95)	237 (10.26)	
Histological Subtype			
Invasive ductal carcinoma	1972 (93.33)	2175 (94.16)	0.465
○ NOS	1071	1829	
○ Mucinous	134	124	
○ Tubular	76	62	
○ Papillary	7	4	
Invasive lobular carcinoma	138 (6.53)	131 (5.67)	
Others	3 (0.14)	4 (0.17)	
Progesterone Receptor			
Negative	190 (8.96)	156 (6.75)	0.006
Positive	1931 (91.04)	2154 (93.25)	
HER2 status			
HER2 - (1+) - negative	1456 (68.68)	1689 (73.12)	<0.001
HER2 equivocal (2+)	518 (24.43)	533 (23.07)	
HER2 + (3+) - positive	146 (6.89)	88 (3.81)	
Type of Operation			
Total mastectomy	614 (28.95)	460 (19.91)	<0.001
Breast conserving surgery	1507 (71.05)	1850 (80.09)	
Length of OFS treatment			
≤1 year		122 (5.28)	-
1-2 year		1844 (79.83)	
>2 year		42 (1.82)	
N/A		302 (13.07)	

Table 2: Disease Free Survival Subgroup Analysis

Subgroup	TAM only	OFS + TAM	Adjusted*	95% CI		P value	P for interaction
	(ref)		Hazard Ratio				
	event/n	event/n					
Age							
<40	49/434	53/333	1.096	0.735	1.635	0.654	0.533
≥40	86/1687	195/1977	1.271	0.976	1.657	0.075	
Age							
<35	19/141	18/79	1.295	0.669	2.506	0.444	0.656
35-39	30/293	35/254	0.893	0.540	1.478	0.660	
40-44	28/609	69/700	1.304	0.831	2.046	0.248	
≥45	58/1078	126/1277	1.045	0.754	1.449	0.790	
Tumor Size							
≤2cm	117/1876	174/1834	1.251	0.977	1.602	0.076	0.591
>2cm	18/245	74/476	1.068	0.634	1.801	0.805	
KI67%							
<20	72/1569	138/1380	1.441	1.068	1.945	0.017	0.004
≥20	32/376	43/422	0.839	0.523	1.345	0.466	
N/A	31/176	67/508	0.634	0.406	0.990	0.045	
Progesterone Receptor							
Negative	19/190	27/156	1.198	0.649	2.212	0.563	0.732
Positive	116/1931	221/2154	1.072	0.838	1.372	0.579	
HER2 status							
negative	117/1974	227/2222	1.075	0.842	1.373	0.560	0.765
positive	18/146	21/88	1.192	0.618	2.299	0.600	

*adjusted age, tumor size, KI67%(catetory), PR Receptor, HER2 status, Type of Operation

PO1-01-13

Clinical characterization, prognostic and predictive values of HER2-low in early breast cancer in the PALLAS trial

Presenting Author(s) and Co-Author(s):

G. Nader-Marta. Universite Libre de Bruxelles (U.L.B.), Hopital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Academic Trials Promoting Team (ATPT), Brussels, Belgium, United States

C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria

D. Hlauschek. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria

A. DeMichele. University of Pennsylvania, Philadelphia, Pennsylvania, United States

P. Tarantino. Breast Oncology Program, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

G. Pfeiler. Medical University of Vienna, Austria, Vienna, Austria

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

J. Balko. Vanderbilt University Medical Center, Nashville, Tennessee, United States

Z. Nowecki. Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland

M. Balic. Divison of Oncology, Department of Internal Medicine, Medical University Graz, Austria

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

P. G. Morris. Cancer Trials Ireland, Ireland; Beaumont RCSI Cancer Centre, Dublin, Ireland, United States

T. Haddad. Mayo Clinic, Rochester, Minnesota, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

Y. Liu. Pfizer Inc, San Diego, California, United States

L. Sölkner. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria, United States

C. Fesl. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria

E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

M. Gnant. Medical University of Vienna, Vienna, Austria

Background: Low levels of HER2 expression (HER2-low) have recently emerged as a therapeutic target in patients (pts) with breast cancer (BC). The aim of this study was to evaluate clinical and demographic variables associated with HER2 expression, as well as the value of HER2-low as a prognostic and predictive biomarker for palbociclib benefit in pts enrolled in the PALLAS trial. Methods: The phase III PALLAS trial investigated the addition of palbociclib to adjuvant endocrine therapy (ET) in pts with stage II-III hormone receptor-positive BC. The aims of this analysis are (1) to assess the association between the presence of low levels of HER2 expression with demographic and clinicopathological parameters, (2) to test the

prognostic value of HER2-low status on invasive disease-free survival (IDFS), distant relapse-free survival (DRFS), and overall survival (OS) and (3) to assess the value of HER2 expression as a predictive biomarker of response to palbociclib. HER2-low was defined as HER2 immunohistochemistry (IHC) 1+ or IHC 2+ with negative in situ hybridization; all pathologic evaluation was performed locally. Pts with HER2-0 and Her2-low BC were included in this analysis; those with HER2-positive BC or missing HER2 status were excluded. Association of HER2 with other baseline covariates were tested with Chi-squared tests. Prognostic and predictive power of HER2 were assessed with Cox Models. Multivariable models included age, T-stage, N-stage, grade and progesterone receptor (PR) expression. Hazard ratios (HR) and 95% Confidence intervals (CI) are reported. Results: From the original PALLAS intention-to-treat population (N = 5,753), 5304 pts (92.2%) were included in this analysis. Among these, 2,254 pts (42.5%) were classified as HER2 IHC 0 (HER2-0) and 3,050 (57.5%) as HER2-low (1,838 with IHC 1+ and 1,212 with IHC 2+). For this analysis, median follow-up was 59.8 months. Compared to HER2-0, pts with HER2-low tumors had statistically higher estrogen receptor expression levels (mean expression 89.2% vs 88.2%, p = 0.019), lower PR expression levels (65.9% vs 68.2%, p = 0.007). Importantly, HER2-low status varied significantly across 21 participating countries (range 16.7% to 75.6%; p < 0.001) and was more frequent in pts enrolled in North America (63.1%) than in Europe (53.4%) and other regions (53.4%) (p < 0.001). No differences in HER2 expression were observed according to anatomic stage, T-stage, N-stage, histological grade, age, menopausal status, primary surgery type, prior radiation, prior chemotherapy, or baseline performance status. There were no statistically significant differences in IDFS, DRFS or OS according to HER2 status in univariate or multivariable Cox models (prognostic value, HR provided in the Table). There was no significant interaction between the HER2 status and the benefit to palbociclib in IDFS, DRFS or OS (Table). Similar results were obtained when HER2-0 was compared to HER2 1+ and HER2 2+ separately. Conclusions: In this large, prospective and international cohort, no differences were observed in clinical parameters, prognosis, or differential benefit from palbociclib (predictive value) between HER2-0 and HER2-low tumors. Significant geographic variability was observed in the prevalence of HER2-low status, suggesting a high degree of variation in pathologic assessment of HER2 expression without impact on outcomes. Support: AFT, Abbvie Pfizer; Clinicaltrials.gov: NCT02513394 <https://acknowledgments.alliancefound.org>

Prognostic value of HER2 status (HER2-low vs HER2-0)				
		5-year survival	Unadjusted HR (CI)	Adjusted HR (CI)
IDFS	HER2-0	82.1%	0.92 (0.80 – 1.13)	0.93 (0.81 – 1.06)
	HER2-low	83.5%		
DRFS	HER2-0	85.5%	0.94 (0.81 – 1.10)	0.96 (0.82 – 1.12)
	HER2-low	86.5%		
OS	HER2-0	92.5%	0.94 (0.76 – 1.16)	0.96 (0.78 – 1.18)
	HER2-low	92.9%		
Predictive value of HER2 status (Palbo+ET vs ET)				
		Unadjusted HR (CI)	Interaction P-value	
IDFS	HER2-0	0.95 (0.77 – 1.17)	0.43	
	HER2-low	0.85 (0.71 – 1.02)		
DRFS	HER2-0	0.96 (0.76 – 1.21)	0.53	
	HER2-low	0.87 (0.71 – 1.06)		
OS	HER2-0	1.08 (0.79 – 1.48)	0.90	
	HER2-low	1.05 (0.80 – 1.38)		

PO1-02-01

T Cell Receptor Sequencing to Monitor Pelareorep-Induced Expansion of Tumor Infiltrating Lymphocytes

Presenting Author(s) and Co-Author(s):

R. Trauger. Oncolytics Biotech, United States

H. Loghmani. Oncolytics Biotech, Canada

M. Coffey. Oncolytics Biotech, Canada

F. Salvador. SOLTI Cancer Research Group, United States

J. Gavilá. Medical Oncology Department, Fundación Instituto Valenciano de Oncología, Valencia, Spain; SOLTI Cancer Research Group, United States

L. Manso. Hospital Universitario 12 de Octubre, Madrid, Spain

T. Pascual. SOLTI Cancer Research Group, Barcelona, Spain /Department of Medical Oncology, Hospital Clínic de Barcelona, Spain / Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

T. Heineman. Oncolytics Biotech, United States

Background: Tumor infiltrating lymphocytes (TILs) represent a major immunological tumor control mechanism that is associated with better prognosis in breast cancer. We have previously reported the effect of pelareorep (pela), an intravenously delivered, non-engineered oncolytic reovirus, on a composite measurement of TILs and tumor cellularity (CeTIL) from the AWARE-1 window-of-opportunity study in patients with early breast cancer (eBC). These results showed treatment increased in CeTIL scores especially in the atezolizumab group. To confirm and extend these findings we applied T cell receptor sequencing of matched tumor tissue and whole blood pre and post-treatment from the AWARE-1 study to further explore the effects of pela therapy on TILs. Methods: Newly diagnosed HR+/HER2- eBC patients were enrolled into two cohorts: Cohort 1: pela + letrozole (n=10); and Cohort 2: pela + letrozole + atezolizumab (n=10). Pela was administered on days 1, 2 and 8, 9, and atezolizumab was given on day 3. Tumor biopsies (FFPE samples) collected pre-treatment (~D-23) and on day ~21 when tumors were surgically removed. T cell fraction analysis and T cell receptor sequencing were performed by Adaptive Biotechnology (Seattle, Washington) Immunoseq protocol. Results: As was shown for the CeTIL scores, an increase in the tumor T cell fraction, a direct measurement of TILs, was observed at 1-month post-treatment in both cohorts with a mean percent increase of 21% for Cohort 1 and 67% for Cohort 2. Through TCR-sequencing of tumor tissue, we identified TIL clones and tracked their differential abundance in tumor tissue and blood post-treatment. The results of this analysis at Day 21 showed a mean post-treatment expansion of 10 tumor specific clones in the blood for Cohort 1, and a mean post-treatment increase of 40 tumor specific clones for Cohort 2. Conclusions: These results confirm the previously reported CeTIL results from AWARE-1 on pela-induced increases in TILs and demonstrate the expansion of these clones in both tumor and blood as a consequence of pela therapy for HR+/HER2- breast cancer.

PO1-02-02

Update of RSCLin with extended TAILORx follow-up and development and validation of a new tool for risk of late distant recurrence

Presenting Author(s) and Co-Author(s):

J. Sparano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

M. Crager. Exact Sciences Corporation, Redwood City, California, United States

R. Gray. Dana Farber Cancer Institute, Wellesley, Massachusetts, United States

G. Tang. NRG Oncology Statistics and Data Management Center Department of Biostatistics, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

J. Hoag. Exact Sciences, United States

F. Baehner. Exact Sciences, SAN FRANCISCO, California, United States

C. Geyer. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

S. Shak. Exact Sciences, United States

N. Wolmark. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

S. Stemmer. Davidoff Center, Rabin Medical Center, Tel Aviv, Israel

Background: RSCLin[®] (Sparano et al J Clin Oncol 2020, PMID 33306425) is an educational tool that estimates the 10-year risk of distant recurrence (DR) and the absolute benefit of chemotherapy in HR-positive, HER2-negative, node-negative early breast cancer. The RSCLin tool integrates the Recurrence Score[®] (RS) result with the clinical-pathological features tumor grade, tumor size and patient age using patient-specific meta-analysis (PSMA) applied to the NSABP B-14, TAILORx and NSABP B-20 studies. Approximately 3 years of additional follow-up data have accumulated in the TAILORx study since the RSCLin tool was developed, including 50% more DR events in the RS 11-25 group (375 vs. 250), and 46% more DR events in the overall population (561 vs. 384). Methods: The RSCLin tool estimates were updated to include the extended follow-up data from TAILORx. As before, the PSMA included 10,004 women with hormone-receptor positive, HER2-negative, node-negative breast cancer from the NSABP B-14 (n=577) trial receiving endocrine therapy (ET) alone and the TAILORx trial receiving ET alone (n=4854) or chemotherapy (CT) plus ET (n=4573). The baseline risk estimate used TAILORx event rates with ET alone. Since there was evidence of differing hazard ratios in years 0-5 versus 5+, models using time-varying effects were used. A patient-specific estimator of absolute CT benefit was computed by combining a PSMA estimate of the individualized relative CT effect from the TAILORx and NSABP B-20 (n=550 HER2-negative) trials with risk estimates for ET alone. Similar methods were used to develop and validate a new tool for assessing the risk of late DR (from year 5 to 10) in patients who survive DR-free for 5 years on ET alone after surgery. External validation of DR risk estimation was performed in an independent cohort of 1098 women enrolled in the Clalit Health Service registry. Results: With the updated data, the model integrating RS result with clinical-pathological features was more informative for DR risk than either RS result alone or the clinical-pathological features alone, both for 10-year DR risk and for late DR risk (likelihood ratio tests, each $p \leq .001$). The updated 10-year RSCLin risk estimates are similar to the existing RSCLin tool risk estimates with slightly lower risk estimates for very high RS results and more precise estimates for mid-range RS results. The updated chemotherapy effect estimates are slightly lower than for the existing RSCLin. The updated

RSCLin tool 10-year risk estimates were strongly associated with DR risk in the independent Clalit registry (Cox regression $p < .001$) and closely approximated the observed DR risk (Lin concordance 0.87). The new tool's late DR risk estimates beyond 5 years were strongly associated with late DR risk in the Clalit registry (Cox regression $p = .002$) and closely approximated the observed late DR risk (Lin concordance 0.92). Conclusions: The RSCLin tool 10-year DR risk estimates have been updated to incorporate extended follow-up data from the TAILORx study. A new tool for assessing late DR risk has been developed and validated that provides more prognostic information than either clinical-pathological features or genomic risk used individually.

PO1-02-03

Correlative analysis of Breast Cancer Index with CTS5 for prediction of extended endocrine benefit in the BCI Registry study

Presenting Author(s) and Co-Author(s):

N. Dempsey. Miami Cancer Institute, Baptist Health of South Florida, United States

J. Wong. Biotheranostics, A Hologic Company, San Diego, United States

N. Siuliukina. Biotheranostics, A Hologic Company, San Diego, California, United States

Y. Zhang. Biotheranostics, A Hologic Company, United States

K. Treuner. Biotheranostics, A Hologic Company, United States

R. Mahtani. Miami Cancer Institute, Plantation, Florida, United States

Background Hormone receptor-positive (HR+) breast cancer patients face a prolonged risk of late distant recurrence even after 5 years of primary adjuvant endocrine therapy and derive only a modest benefit from extended endocrine therapy (EET). The Breast Cancer Index (BCI) is a validated genomic assay that provides the risk of late (post 5 years) and overall (0-10 years) distant recurrence and predicts EET benefit in patients with HR+ disease. The predictive component of BCI, HOXB13/IL17BR ratio [BCI (H/I)], stratifies patients as Low- and High-Likelihood to benefit from EET and has been validated in the MA.17, Trans-aTTom, IDEAL, and B-42 trials. The Clinical Treatment Score post-5 years (CTS5) is a prognostic tool incorporating standard clinical risk factors such as age at diagnosis, tumor size, tumor grade, and nodal involvement to inform prognosis of late distant recurrence. A previous analysis in the IDEAL trial showed that CTS5 was not predictive of EET benefit. Here, we examine the relationship between BCI (H/I) and CTS5 in a large cohort from the BCI Registry study. Methods The BCI Registry study is an ongoing prospective study to evaluate the long-term clinical outcome, decision impact and medication adherence in HR+ early-stage breast cancer patients receiving BCI testing as part of routine clinical care. BCI (H/I)-Low and BCI (H/I)-High groups were determined using pre-specified cut-points. CTS5 scores were calculated using clinical information from the ClinCapture electronic data capture system and stratified into Low-, Intermediate-, and High-risk groups using published cut-points. Pearson's correlation coefficient (r) was used to estimate the correlation between BCI (H/I) and CTS5 as continuous variables. Descriptive statistics were used to summarize the distribution of BCI (H/I) groups across all CTS5 risk categories. Results BCI and CTS5 results were reported for 1520 patients (75.1% T1; 53.4% grade II; 80.3% N0). BCI (H/I) classified 934 patients (61.4%) as BCI (H/I)-Low and 586 patients (38.6%) as BCI (H/I)-High. BCI Prognostic classified 705 patients (46.4%) as BCI-Low risk for late distant recurrence and 815 patients (53.6%) as BCI-High risk. CTS5 classified 945 patients (62.2%) as CST5-Low, 400 patients (26.3%) as CTS5-Intermediate, and 175 patients (11.5%) as CTS5-High. When analyzed as continuous variables, BCI (H/I) showed a weak correlation with CTS5 ($r=0.18$). When stratifying CTS5 risk categories by BCI (H/I) groups, 65.2% (N=616) of CTS5-Low patients were classified as BCI (H/I)-Low, while 34.8% (N=329) of CTS5-High patients were classified as BCI (H/I)-High. In addition, 57.8% (N=231) and 42.2% (N=169) of CTS5-Intermediate patients were classified as BCI (H/I)-Low and BCI (H/I)-High, respectively. Finally, 49.7% (N=87) and 50.3% (N=88) of CTS5-High patients were classified as BCI (H/I)-Low and BCI (H/I)-High, respectively. Conclusion BCI (H/I) consistently stratified CTS5 risk categories into separate BCI (H/I)-Low and BCI (H/I)-High groups, indicating that risk prognostication does not equate to prediction of benefit from EET. These results confirm previous findings in the IDEAL study demonstrating that CTS5 is not predictive of EET benefit and further substantiate the clinical utility of BCI as the only predictive biomarker

for extended endocrine therapy benefit in patients with HR+ early-stage breast cancer.

PO1-02-04

The efficacy of endocrine therapy during the waiting period for surgery for hormone receptor-positive breast cancer

Presenting Author(s) and Co-Author(s):

Y. Maeda. Department of Surgery, Teikyo University School of Medicine, United States

S. Naruse. Department of Surgery, Teikyo University School of Medicine, United States

Y. Isono. Department of Surgery, Teikyo University School of Medicine, United States

A. Sato. Teikyo University School of Medicine, United States

A. Matsumoto. Teikyo University School of Medicine, United States

T. Ikeda. Department of Surgery, Teikyo University School of Medicine, United States

H. Jinno. Department of Surgery, Teikyo University School of Medicine, United States

Background: Although neoadjuvant endocrine therapy has been used to improve breast conservation rate, its prognostic relevance is unknown. The search for a valid prognostic factor equivalent to pCR in neoadjuvant chemotherapy is a current challenge in neoadjuvant endocrine therapy. In this study, we investigated the efficacy of short term neoadjuvant endocrine therapy utilizing the waiting period for surgery and the prognostic factor including Preoperative Endocrine Prognostic Index (PEPI) score. **Methods:** A total of 480 patients with Stage I -III hormone receptor-positive, HER2-negative breast cancer was treated with endocrine therapy during the waiting period for surgery between October 2012 and December 2021. Premenopausal and postmenopausal patients received tamoxifen (TAM) and non-steroidal aromatase inhibitor (AI), respectively. The primary endpoint was change in tumor size by ultrasound and Ki67 expression before and after short term endocrine therapy. The secondary endpoint was prognosis of patients divided by PEPI score which was calculated using tumor size, lymph node metastasis, Ki67 expression, and ER Allred score. This study was approved by the institutional review board of Teikyo University. **Results:** Median age and tumor size of the entire 480 patients was 55 years (range, 31 - 89), 1.65 cm (range, 0.4 – 7.5), respectively. The median duration of endocrine therapy was 39 days (range, 1-90). 19 (0.3 %) pts were clinically node-positive. Of the entire 480 patients, 211 and 269 patients had TAM and AI, respectively. After short term endocrine therapy, the tumor size was significantly reduced from 1.83cm to 1.62cm in AI group ($p=0.02$), although TAM did not decrease the tumor size ($p=0.89$). The Ki67 expression was significantly decreased from 16.4% to 11.3% in TAM group ($p=0.002$), and from 15.9% to 6.98% in AI group ($p < 0.001$). There were significant differences in the distribution of PEPI scores between TAM and AI group ($p < 0.05$) (Table). At the median follow-up of 1012 days, patients with PEPI score ≥ 4 showed worse disease-free survival compared with patients with PEPI score < 4 in TAM group (Figure1). Overall survival is not available because there were no deaths in TAM group. At the median observation period of 833 days, patients with PEPI score ≥ 4 showed worse disease-free survival compared with patients with PEPI score < 4 in AI group (Figure2). In terms of mortality, patients with PEPI score ≥ 4 had worse overall survival than patients with PEPI score 0 and 1-3 ($p=0.07$). **Conclusions:** These results suggested that neoadjuvant endocrine therapy during the waiting period for surgery might be effective in reducing Ki67 expression level and PEPI score might be useful in predicting the prognosis of hormone receptor positive breast cancer patients.

Table. Distribution of PEPI score

PEPI Score	TAM	AI
0	20 (9.5 %)	82 (30.5 %)
1 - 3	188 (89.1 %)	148 (55 %)
4≤	3 (1.4 %)	39 (14.5 %)

Figure1. Disease-free survival in patients treated with tamoxifen

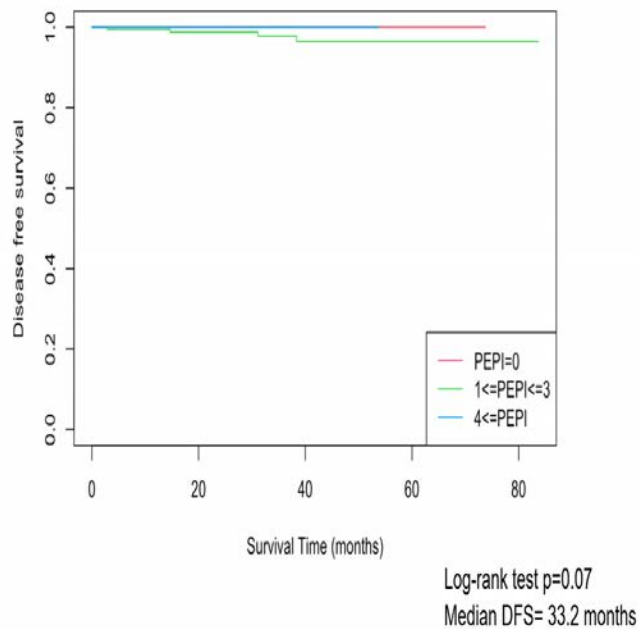
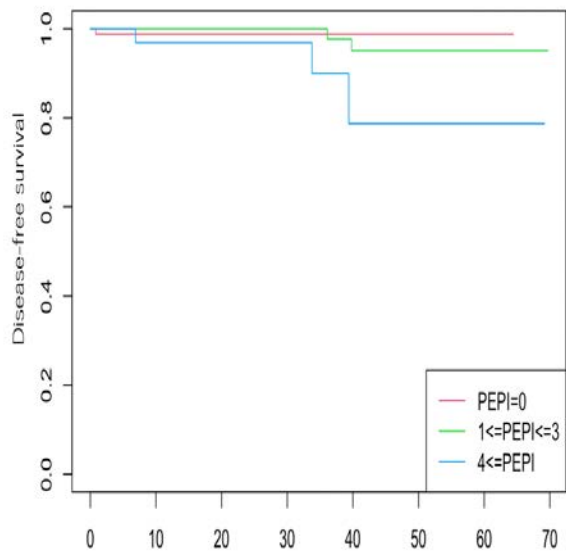


Figure2. Disease-free survival in patients treated with non-steroidal aromatase inhibitor



Survival Time (months)

Log-rank test p=0.06

Median DFS= 27.3 months

PO1-02-05

An exploratory comparison of MINDACT and TAILORx genomic risk proportions and outcomes in patients with HR+/HER2-, node-negative early-stage breast cancer, stratified by clinical risk

Presenting Author(s) and Co-Author(s):

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

J. Lopes-Cardozo. Gelre Hospital Apeldoorn, United States

F. Cardoso. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

L. Van 't Veer. The University of California, San Francisco CA, USA, United States

Introduction: Genomic tests provide physicians with critical information to evaluate the risk of distant metastasis and inform treatment plans by identifying those patients who may safely avoid chemotherapy (CT). The 70-gene signature (MammaPrint, MP) through the MINDACT trial and the 21-gene signature (Oncotype DX, ODX) through the TAILORx trial are the only tests validated with level 1A evidence that can be used for CT de-escalation decisions. Differences in trial design have made direct comparison of results difficult. We provide a comparison of MammaPrint and ODX genomic risk distributions and associated survival in patients with HR+/HER2-, node-negative (N0) early-stage breast cancer (EBC), stratified by clinical risk. **Methods:** Data from the MINDACT 2021 publication in The Lancet Oncology and landmark TAILORx 2019 publication in The New England Journal of Medicine were reviewed, in addition to publicly available data submitted to the Dutch Health Technology Assessment (HTA) authorities regarding survival data in patients with clinical High Risk in TAILORx. In MINDACT, patients were randomized based on both clinical (as per MINDACT definition) and genomic risk (clinical high/MP low, randomized to treatment according to clinical risk [i.e. CT] vs treatment according to MammaPrint risk [i.e. no CT]), while in TAILORx randomization was based on genomic risk alone. In TAILORx, enrollment for the population in the RS 11–25 group was enriched by 73% to account for the larger than expected non-adherence to randomized treatment plan based on the ODX results, as described in the original publication. This enrichment was only done for the RS 11–25 group. In this analysis, this enrollment enrichment was removed by applying the same proportional 73% corrective factor to the RS 11–25 group. Outcome data are reported for Overall Survival (OS), the only comparable endpoint used in both trials. **Results:** This explorative comparison focuses on patients with HR+/HER2- and N0 EBC in MINDACT (n=4,225) and TAILORx (n=6,686, without population enrichment). Similar proportions of patients identified as candidates for CT de-escalation (MP Low Risk or ODX RS≤25) were observed in this population of MINDACT (75%) and TAILORx (80%) when removing the RS 11–25 population enrichment in TAILORx (Table). In clinical high risk patients, the proportion with genomic low risk of distant metastasis were also comparable between MINDACT (55%) and TAILORx (63%) (Table). In the original clinical high risk but MammaPrint Low Risk population treated without CT in MINDACT the reported 8-year OS was 93.9%. In TAILORx, the comparable population of patients (ie. clinical high risk, low genomic risk, not treated with CT) had a 9-year OS of 89.2% in the RS 0–10 group and 91.6% in the RS 11–25 group (Table). **Conclusions:** Accounting for differences in trial design and population, comparable proportions of patients with genomic low risk results were observed between MP and ODX, justifying similar rates of CT de-escalation. Patients with clinical high risk tumors who are MammaPrint Low Risk had an excellent survival at 8 years. Genomic risk distributions and associated OS in HR+/HER2- N0 patients in MINDACT and TAILORx

	MammaPrint (MINDACT)	ODx (TAILORx)	
Patient Distribution, n (%)			
Overall Population	n = 4,225	n = 6,686	
Low Risk (MP Low or RS ≤ 25)	3180, 75%	5327, 80%	
		RS ≤ 10 1572, 24%	RS 11 – 25 3755, 56%
High Risk (MP High, or RS > 25)	1045, 25%	1359, 20%	
Clinical High Risk patients	n = 1,307	n = 2,096	
Low Risk (MP Low or RS ≤ 25)	715, 55%	1326, 63%	
		RS ≤ 10 345, 16%	RS 11 – 25 981, 47%
High Risk (MP High, or RS > 25)	592, 45%	770, 37%	
Reported OS in Clinical High Risk Genomic low risk patients without Chemotherapy			
Low Risk (MP Low or RS ≤ 25)	350, 93.9% at 8 years	RS ≤ 10 345, 89.2%	RS 11 – 25 842, 91.6% at 9 years

MP, MammaPrint; OS, Overall Survival; RS, Recurrence Score. Number of patients in the TAILORx RS 11 – 25 group are adjusted to remove the proportional enrichment in the trial. OS data presented per original MINDACT and TAILORx populations.

PO1-02-07

HER2 Low Non-Metastatic Breast Cancer in Qatar: A Nationwide Retrospective Cohort Study to Evaluate the Response to Neoadjuvant Chemotherapy: A Real-World Analysis

Presenting Author(s) and Co-Author(s):

A. Kardousha. National Center for Cancer Care and Research, Hamad Medical Corporation, United States

w. Shehada. National Center for Cancer Care and Research, Hamad Medical Corporation, United States

A. Basha. National Center for Cancer Care and Research, Hamad Medical Corporation, United States

S. Nasser. National Center for Cancer Care and Research, Hamad Medical Corporation, United States

M. el Mistiri. National Center for Cancer Care and Research, Hamad Medical Corporation, United States

A. Hamad. National Center for Cancer Care and Research, Hamad Medical Corporation, United States

S. Al-Bader. National Center for Cancer Care and Research, Hamad Medical Corporation, United States

S. Elazzazy. National Center for Cancer Care and Research, Hamad Medical Corporation, United States

Background:

Breast Cancer is the most diagnosed cancer type worldwide and the second leading cause of cancer-related death among women. HER2-low breast cancer is a newly defined molecular subtype of breast cancer in which tumors exhibit a minimal overexpression of HER2 or no gene amplification. To illustrate, HER2-low tumors typically have an IHC score of 1+ or a score of 2+ with negative amplification. However, emerging evidence suggests that even a minimal amplification of HER2 may significantly impact the response to therapy and prognosis. Our study aims to unveil the impact of HER2-low expression on the response to anthracycline and taxane-based neoadjuvant chemotherapy (NACT) in comparison to the HER2-negative group in non-metastatic breast cancer. The primary objective was evaluating the response to NACT comparing the favorable response (complete and partial response) in each of the two groups of HER2-low and HER2-negative patients.

Methods:

This is a retrospective cohort study. All patients' profiles with non-metastatic, HER2-Low, and HER2-negative breast cancers who received neo-adjuvant chemotherapy and underwent surgery between the 1st of January 2018 and the 30th of August 2022 were included. Patients' response was evaluated using surgical pathology reports to compare the two study groups (HER2-low and HER2-negative).

Results:

The total number of patients included was 262 patients, the majority were HER2-low 89% (233/262) vs. 11% (29/262) HER2-negative. A favorable response to NACT was shown in 71% (185/262) of all patients. The favorable response rate was similar in both groups, 70% (164/233) in the HER2-low group vs. 72% (21/29) in the HER2-negative group, OR: 1 (95% CI: 0.8-1), p-value 0.8. Similarly, the pathological complete response (pCR) rate was the same in both

study groups at 14%, OR: 0.7 (95% CI: 0.2-3), p-value: 0.6.

Interestingly, patients with hormone-positive tumors across both study groups had a higher response rate as compared to hormone-negative patients. However, statistical significance was shown in the HER2-low group only. In the HER2-low cohort, 73% of the patients (119/164) with hormone-positive tumors showed a favorable response OR: 0.8 (95% CI: 0.8- 1), p-value: 0.001. Comparatively, in the HER2-negative cohort, 52% of the patients (11/21) with hormone-positive tumors had a favorable response OR: 2 (95% CI: 1– 5), p-value: 0.05.

Conclusion:

Our results did not show any significant impact of HER2-low expression on neoadjuvant chemotherapy response. Nonetheless, a statistically significant difference in response was observed in the hormone-positive HER2-low breast cancer patients. Further studies are needed to evaluate the influence of hormonal expression on the response rate to NACT in the HER2-low patient population.

PO1-02-08

Comprehensive Molecular Profiling of Breast Cancer: A real-time PCR assay for identifying ESR1, PGR, ERBB2, MKI67 and a novel proliferative signature in core needle biopsies and resected invasive breast cancer tissues

Presenting Author(s) and Co-Author(s):

A. Gasior. APIS Assay Technologies, Manchester, England, United Kingdom

J. Gorniak. APIS Assay Technologies, United States

S. Rollinson. APIS Assay Technologies, United States

L. Gough. APIS Assay Technologies, United States

A. Wegscheider. MVZ Prof. dr medical A. Niendorf Pathologie Hamburg-West GmbH, United States

A. Niendorf. MVZ Prof. dr medical A. Niendorf Pathologie Hamburg-West GmbH, United States

Background: Accurate status determination of breast cancer (BC) biomarkers, including estrogen receptor (ER/ESR1), progesterone receptor (PR/PGR), human epidermal growth factor receptor 2 (HER2/ERBB2), and marker of proliferation Ki67 (MKI67), is crucial for guiding therapeutic decisions. However, current “gold standard” methods such as immunohistochemistry (IHC) for assessing these biomarkers in formalin-fixed paraffin-embedded (FFPE) tissues face challenges in standardization and exhibit substantial inter- and intra-laboratory variability, particularly for Ki67. To address these limitations, APIS Breast Cancer Subtyping Kit has been developed, utilizing reverse transcription quantitative real-time polymerase chain reaction (RT-qPCR) to evaluate the status of ER, PR, HER2, Ki67, and a novel proliferative signature in breast cancer core needle biopsy (CNB) and resected specimens. The APIS Breast Cancer Subtyping Kit offers enhanced accuracy, improved reproducibility, and the ability to provide results in a timely manner. Herein we report the development and validation of the APIS Breast Cancer Subtyping Kit, assessing clinical performance using retrospective and prospective sample collection. Furthermore, reproducibility and reliability across three testing sites were evaluated. By comparing the results of the kit with those obtained through standard IHC, we demonstrate the reliability and utility of the APIS Breast Cancer Subtyping Kit for precise breast cancer subtyping and guiding personalized patient management decisions. Methods: FFPE tissue sections (n=652) taken by CNB or resection underwent histological analysis in accordance with laboratory’s standard of care methods. Samples with a HER2 score of 2+ were referred to fluorescence in situ hybridization (FISH) to determine ERBB2 amplification, with the FISH result replacing the IHC result in determining the HER2 status (positive/negative) of the sample. Tumors with greater than 1% positive stained nuclei for ER/PR were scored positive. A cut-off of 20% Ki67 staining was used for positive/negative status. The performance was assessed as the agreement with IHC/ISH status and reported as OPA (overall percent agreement) with corresponding 95% confidence intervals (95% CI).

To assess the precision of the assay, a panel of RNA pools (samples) was repeatedly measured on different days across three independent laboratories. Reproducibility was evaluated using variance components analysis. Results: The APIS Breast Cancer Subtyping Kit showed high concordance (OPA) with IHC: 93.1% (95% CI: 90.9-94.8) for ER, 86.8% (95% CI: 84.0-89.2) for PR, 94.2% (95% CI: 92.2-95.8) for HER2 (IHC/FISH), 78.3% (95% CI: 75.0-81.3) for Ki67, and 80.1% (95% CI: 76.8-83.1) for proliferative signature (assessed against MKI67 IHC status). Inter-site reproducibility demonstrated excellent agreement in quantitative

measurements, with a total SD ranging from 0.00 to 0.22. Binary single-marker status (positive/negative) calling achieved 100% reproducibility for ER, PR, and HER2 for all tested samples (negative/low positive/medium positive), as well as for most Ki67 samples (87% agreement for negative samples). Conclusions: APIS Breast Cancer Subtyping Kit demonstrated a high level of concordance with standard of care IHC/FISH in assessing breast cancer biomarker status. These findings suggest that the APIS Breast Cancer Subtyping Kit provides highly precise and reproducible quantitative assessment of BC biomarkers and molecular subtypes.

Inclusion and exclusion criteria

<i>Inclusion criteria</i>	<i>Exclusion criteria</i>
<ol style="list-style-type: none"> 1. Primary unifocal or multifocal invasive breast cancer T1-T2. 2. Clinically N0. 3. Macrometastasis (>2mm) in 1-2 lymph nodes at sentinel node biopsy. 4. Oral and written consent. 5. Age ≥ 18 years. 6. Tumor-free resection margins (no tumor on ink). 7. Primary tumor ER-positive, HER2-negative. 	<ol style="list-style-type: none"> 1. Regional or distant metastases outside the ipsilateral axilla. 2. Previous RT towards the planned target area, i.e. the ipsilateral chest/lymph nodes. 3. Neoadjuvant systemic therapy. 4. Axillary lymph node dissection or other previous axillary surgery on the affected side. 5. Prior history of invasive breast cancer. 6. Pregnancy. 7. Bilateral invasive breast cancer. 8. Contraindication for radiotherapy or systemic treatment, if indicated. Hence endocrine treatment, chemotherapy and/or targeted therapy should at inclusion be planned to be given according to standard of care, taking age and comorbidity into consideration. 9. Inability to absorb or understand the contents of the informed consent form; for example, through disability, insufficient language skills or dementia. 10. Other invasive cancer within 5 years prior to breast cancer diagnosis

PO1-02-09

Efficacy of breast conserving treatment of minimal residual tumors after neoadjuvant therapy for breast cancer.

Presenting Author(s) and Co-Author(s):

R. Pesotsky. N.N. Petrov National Medical Research Center of Oncology, United States

V. Semiglazov. N.N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russian Federation, United States

P. Krivorotko. N.N. Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russia

T. Tabagua. N.N. Petrov National Medical Research Center of Oncology, United States

K. Zernov. N.N. Petrov National Medical Research Center of Oncology, United States

A. Emelyanov. N.N. Petrov National Medical Research Center of Oncology, United States

V. Mortada. N.N. Petrov National Medical Research Center of Oncology, United States

N. Amirov. N.N. Petrov National Medical Research Center of Oncology, United States

D. Ulrikh. NMRC of Oncology named after N.N.Petrov of MoH of Russia, Other, Russia

V. Levchenko. City Clinical Oncology Dispensary , St. Petersburg, Russia, Other, Russia

Y. Bondarchuk. N.N. Petrov National Medical Research Center of Oncology, United States

D. Enaldieva. N.N. Petrov National Medical Research Center of Oncology, United States

N. Bekkeldieva. NMRC of Oncology named after N.N.Petrov of MoH of Russia, Kyrgyzstan

K. Zirov. Russian Biotechnological University (ROSBIOTECH), Moscow, Russia, Other, Russia

S. Yerechshenko. N.N. Petrov National Medical Research Center of Oncology, United States

V. Evseev. LLC MEDSI, St. Petersburg, Russia, Other, Russia

K. Rychagov. NMRC of Oncology named after N.N.Petrov of MoH of Russian Federation, Other, Russia

S. Novikov. N.N. Petrov National Medical Research Center of Oncology, United States

M. Kazantseva. NMRC of Oncology named after N.N.Petrov of MoH of Russian Federation, Other, Russia

L. Gigolaeva. N.N. Petrov National Medical Research Center of Oncology, United States

E. Zhiltsova. N.N. Petrov National Medical Research Center of Oncology, United States

D. Nesterov. NMRC of Oncology named after N.N.Petrov of MoH of Russian Federation, Other, Russia

O. Ivanova. NMRC of Oncology named after N.N.Petrov of MoH of Russian Federation, Other, Russia

T. Semiglazova. N.N. Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russia

Background. Determining the most effective drug therapy regimens is one of the top priorities in the individualization of the treatment of patients with breast cancer (BC). Achievement of pathological complete response (pCR) is important prognostic factor, and used as the surrogate primary end point in many clinical trials. According to the literature, the achievement of pCR after neoadjuvant systemic treatment (NST) in breast cancer varies from 30 to 70%. Patients

who do not achieve pCR require post-neoadjuvant treatment, even when reaching minimal size of residual tumors. Initially, primary minimal tumors are characterized by high survival rates, which are proved by international and domestic studies. It is required to clarify the survival rates in the presence of a minimal residual tumor (ypT < 10mm) after neoadjuvant systemic therapy and to compare with primary minimal forms of breast cancer (pT1a-b N0M0), characterized by the most favorable prognosis. Objective. Improvement of the effectiveness of treatment of residual minimal forms (ypT1a-b) of BC after NST. Determination of the correlation between the schemes of NST and the rates of tumor response based on the results of postoperative pathological reports including RCB scale. Methods. The study included 602 patients aged 18–65 years with early and locally advanced I–IIIC stage T1-3N1-3M0 breast cancer, who underwent complex or combined treatment. This study included patients treated at the N.N. Petrov National Medical Research Center of Oncology from 2015 to 2021 Conclusion. After reaching a complete pathomorphological response of the tumor to NST (RCB 0), the 5-year disease-free (DFS) and overall (OS) survival rates (DFS – 78.5%; OS 90.4%) were inferior to the survival rates of patients with primary minimal breast cancer (pT1ab N0M0) [DFS – 86.4%; OS – 98.6%]. Neoadjuvant chemotherapy regimens that allow achieving a pathological complete response in triple-negative and HER2- positive breast cancer have been defined. An assessment of adverse factors that affect the effectiveness of breast conserving treatment and correlate with a deterioration in overall survival was performed. Results. Our data analysis revealed that the survival rates (DFS and OS) of patients with minimal residual tumor after neojuvant systemic therapy were not comparable with those in the group of patients with primary minimal breast cancer. Data analysis revealed the most effective combinations of drugs expressed in the rates of pathomorphological response according to the RCB scale. An assessment of adverse factors that affect the effectiveness of organ-preserving treatment and correlate with a deterioration in overall survival was performed. Clinical demography characteristics of patients included in this study.

Clinical demography characteristics of patients included in this study.

	RCB 1	RCB 0	mm	RCB2-3
Age	58	54	56	55
c T				
c T1	2	117	147	31
c T2	68	53	-	82
c T3	21	17	-	64
c N				
cN0	26	95	147	39
cN+ (verified)	65	92	-	138
G				
I	9	2	26	15
2	39	108	84	64
3	43	77	57	156
IHC subtypes				
ER -	30	77	28	18
HER 2+ - FISH +	6	8	10	2
HER 3 +	22	54	40	28
ER+/ HER 2-	33	48	69	132
NST				
AC4-T12	26	47	-	56
CAP6	7	16	-	-
AC4 - TCarb 4	16	38	-	8
AC4 - DH 4	14	32	-	21
AC4 - DHP 6	8	16	-	4
TCHP 6	6	14	-	2
FAC 4	14	24	-	49
ET	-	-	-	37
Mutations	10	7	-	2
BRCA 1	8	7	-	1
BRCA 2	1	-	-	-
Others	1	-	-	1
yp T1a	40	-	83	13
yp T1b	51	-	64	25
yp > T1b	-	-	-	139
DCIS	27	43	57	79
LVI	11	-	30	66
Adjuvant				
Treatment				
AC-T	-	-	30	3
TC (DC)	-	-	13	4
Capecitabine	30	-	-	15
TDMI	21	-	-	19
Trastuzumab	-	62	-	-
Trastuzumab +	7	-	-	5
Petruzumab				
Facitaxel +			21	-
Trastuzumab				
ET	48	88	54	125
Adjuvant radiotherapy	91	181	96	168

The rates of pathomorphological response after neoadjuvant therapy (NAT) in various surrogate subtypes of breast cancer

The rates of pathomorphological response after neoadjuvant therapy (NAT) in various surrogate subtypes of breast cancer

RCB	ER-	HER2 3+	ER + / HER2 -	Total
RCB 0	77 (61,6%)	62 (52,7%)	48 (22,5 %)	187 (41,9 %)
RCB 1	30 (24 %)	28 (23,9 %)	33 (15,4 %)	91 (20 %)
RCB 2-3	18 (4,4%)	27 (23,0 %)	132 (61,9 %)	177 (38,9 %)
Total	125	117	213	455

5-year survival rates in the study groups depending on the rates of pathomorphological response, those who received NST and with primary minimal breast cancer.

5-year survival rates in the study groups depending on the rates of pathomorphological response, those who received NST and with primary minimal breast cancer.

RCB	N	DFS % (n)	OS % (n)
RCB 0 or pCR	187	78,6% (147)	90,4% (169)
RCB 1	91	72,5% (66)	86,8% (79)
RCB 2-3	177	66,7% (118)	71,8% (127)
Min	147	86,4% (127)	98,6% (145)

PO1-02-11

Characterization of MammaPrint UltraLow Risk tumors in more than 1400 patients from the real-world evidence FLEX study

Presenting Author(s) and Co-Author(s):

C. Graham. Emory University, United States

K. Hoskins. University of Illinois Chicago, United States

V. Gadi. University of Illinois, United States

S. Hoekstra. Northern Light Mercy Breast Care, United States

G. Srkalovic. Sparrow Hospital System, United States

D. Marks. NYU Long Island School of Medicine; NYU Langone Hospital-Long Island, United States

B. Sieling. Trinity Health of New England, United States

P. Dauer. Agendia Inc., United States

A. Menicucci. Agendia Inc, United States

W. Audeh. Agendia Inc., United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

F. Investigators' Group. Agendia, United States

BACKGROUND: MammaPrint is a gene expression signature used to determine the risk of distant recurrence for patients with early-stage breast cancer. Previous studies from MINDACT, FOCUS, IKA, and STO-3 trials have demonstrated that postmenopausal node-negative patients with MammaPrint UltraLow Risk tumors are considered indolent and patients have excellent long-term survival outcomes up to 20 years with little to no endocrine treatment. These studies suggest that patients with UltraLow Risk tumors are ideal candidates for treatment optimization which has resulted in the inclusion of the UltraLow Risk result in the NCCN guidelines. Here, we characterized patients with UltraLow Risk tumors from the real-world evidence FLEX study.

METHODS: FLEX (NCT03053193) is a prospective, observational registry study with 99 sites open in the United States, Canada, Greece, and Israel. Patients enrolled in FLEX have early-stage breast cancer and receive MammaPrint testing as standard of care (with or without BluePrint molecular subtyping), and consent to full transcriptome analysis and clinical data collection. MammaPrint is a gene expression signature of 70 genes that classifies tumors as having a Low Risk or High Risk of distant recurrence. Within Low Risk tumors, a subcategory of UltraLow Risk (MammaPrint Index > 0.355) has been defined in previous studies. Clinical data for this analysis was locked February 2023. Clinical risk was defined as low risk or high risk based on Adjuvant Online criteria. **RESULTS:** Among the 12,328 patients enrolled in FLEX, 1465 (11.9%) have UltraLow Risk tumors. All tumors with available BluePrint molecular subtyping were classified as Luminal-Type. Of the patients with detailed clinical data, the majority had clinically low risk tumors (78.8%; Table 1). Notably, 34.6% of patients with UltraLow Risk tumors had Ki67 tumor staining of greater than 10%, 16.7% were pre- or perimenopausal, 43.6% had grade 2-3 tumors, and 20.1% had tumors > 2 cm (Table 1). Among patients with treatment information, 6.5% received a combination of chemotherapy with or without endocrine and HER2-targeted therapy, 82.4% received endocrine therapy, 4.8% received other treatment (endocrine with targeted therapy (CDK4/6), radiation alone, novel treatment regimen, or supporting agents), and 6.3% did not receive treatment (Table 1).

CONCLUSIONS: Previous trials have demonstrated the utility of MammaPrint UltraLow Risk in

patients with clinically low risk features. In this large real-world evidence study of patients with early-stage breast cancer, UltraLow Risk tumors can be identified across all clinical categories. Overall, we report a substantial number of premenopausal patients with UltraLow Risk tumors, and these young women would be good candidates for treatment optimization. Future studies will assess long-term outcomes in this cohort further stratified by treatment.

Table 1. Clinical and genomic characteristics of UltraLow Risk tumors

Clinical and genomic tumor characteristics	Patients (n = 1465)
Clinical subtype	
HR+ HER2-	1153 (98.3)
HR+ HER2+	19 (1.6)
TNBC	1 (0.1)
Age	
≤ 50	215 (17.0)
> 50	1046 (83.0)
Menopausal status	
Pre-/peri-	202 (16.7)
Post-	1004 (83.3)
Race	
AAPI	28 (2.3)
American Indian/Alaskan Native	4 (0.3)
Black	65 (5.4)
Latin American/Hispanic	47 (3.9)
White	1048 (87.8)
Mixed race/Other	1 (0.1)
Grade	
G1	670 (56.4)
G2	499 (42.0)
G3	19 (1.6)
T stage	
T1	754 (79.7)
T2	171 (18.1)
T3	19 (2.0)
T4	2 (0.2)
N stage	
N0	790 (87.5)
N1	106 (11.7)
N2	5 (0.6)
N3	2 (0.2)
Clinical risk , AOL	
Clin low	614 (78.8)
Clin high	165 (21.2)
Ki-67	
0 - 10%	553 (65.4)
11 - 20%	224 (26.5)
> 20%	69 (8.2)
Treatment arm	
Adjuvant	782 (90.4)
Neoadjuvant	51 (5.9)
Non-surgical	32 (3.7)
Treatment type	
Chemotherapy +/- targeted therapy	4 (0.5)
Chemoendocrine +/- targeted therapy	50 (6.0)
Endocrine therapy	689 (82.4)
Endocrine + targeted therapy	1 (0.1)
Other	39 (4.7)
None	53 (6.3)

Data are presented as n (%).

Patients with unknown or missing data for each category have not been included.

PO1-02-12

Nutritional guidance effect on anthropometric and inflammatory parameters in young women with breast cancer

Presenting Author(s) and Co-Author(s):

A. Barranco-Cortés. Universidad Anáhuac México, United States

F. Fajardo-Espinoza. Universidad Anáhuac México, United States

A. Espadas-Vargas. Universidad Anáhuac México, United States

D. Pérez-Camargo. Insituto Nacional de Cancerología, United States

S. Cabrera-Nieto. Universidad Anáhuac México, United States

M. Cruz-Ramos. Instituto Nacional de Cancerología, United States

A. Mohar. Instituto Nacional de Cancerología, United States

I. Labra Alvarado. Insituto Nacional de Cancerología, United States

C. Villarreal Garza. Tecnológico de Monterrey, Mexico, United States

Background Young women with breast cancer (YWBC) debut with more aggressive and advanced diseases; it may be related to chronic inflammation caused by the tumor. However, in Latin America, breast cancer is also related to malnutrition conditions such as obesity.

Malnutrition is commonly associated with physiological adaptations to stress and inflammation resulting in muscle catabolism and loss of functionality, which may affect oncology outcomes. Our research group had previously reported that YWBCs in Mexico are overweight or obese at diagnosis. Although they received educational support, this malnutrition prevalence continues or increases during the follow-up. A limitation of this previous study is that we only have data such as weight and height and miss other anthropometric parameters to measure the metabolic impact of weight gain. Body composition assessment is valuable for measuring malnutrition, obesity, and sarcopenia. The body composition assessment with Bioimpedance analysis (BIA) provides valuable parameters such as phase angle (PhA), which correlates with nutritional status, disease prognosis, inflammation, cell health, and metabolic activity. BC patients with a PhA >5.6 show a better survival rate. Another accessible tool to evaluate systemic inflammation is the neutrophil-lymphocyte ratio (NLR). Higher NLR (>2.12) is associated with worse disease-free and overall survival. This pilot study aims to measure the importance of PhA and NLR in YWBC with early breast cancer at diagnosis and at 12 months to evaluate the effects of personal nutritional guidance on these parameters. **Methods** Patients included in the “Joven & Fuerte (J&F) navigator program” of the National Institute of Cancerology (INCan) from 2021 to 2022 were invited to participate in this observational study. To evaluate the efficacy of personal nutritional guidance in anthropometric and NLR parameters, basal and 12-month BIA and anthropometric measures such as the Waist-Hip index were assessed, and NLR was obtained from the patient's records. **Results** Eleven early breast patients agreed to participate in the pilot intervention. The median age of the participants was 37 years. The majority had local advanced disease (54.5%), regarding molecular subtype luminal was the more frequent subtype (45.5%), followed by HER2 (36.4%), triple-negative (18.2%). According to BMI at diagnosis, 18.2% had normal-weight, 63.6% were overweight, and 18.2% had obesity. At follow-up, 9.1% had normal-weight, 63.6% were overweight, and 27.3% had obesity. A significant change in body composition parameters was observed, the percentage of patients with excess adipose tissue increased from 54.5% at baseline to 81.1%. All patients exhibited cardiovascular risk, as indicated by a Waist-Hip ratio greater than 0.80, and maintained a PhA (5.2 at baseline, 5.5 final) associated with overall survival risk. No significant changes were observed in the NLR

ratio (2.14 baseline, 2.34 final), maintaining the related risk for this parameter. Conclusions This pilot analysis suggests that a nutritional intervention based only in nutritional guidance and support seems inefficient in impacting nutritional or inflammatory parameters. A multidisciplinary intervention involving multidisciplinary healthcare teams, including rehabilitation, and psychology, may be required to achieve therapeutic effectiveness in this population. Further studies with larger sample sizes are necessary to confirm these findings and determine the most effective strategies to improve the nutritional status, cardiovascular health, and clinical outcomes of YWBC.

Anthropometric and inflammatory parameters

<i>n</i> =11	Baseline	Final	<i>p</i>
Body Mass Index (BMI)(Kg/m ²)	27.2(21.4,27.9) ^a	28.6(25.4,31.1) ^a	0.092
Lymphocyte/Neutrophil ratio (NLR)	1.96(1.41,2.27) ^a	2.37(1.35,3.07) ^a	0.859
Phase Angle	5.35(5.27,5.73) ^a	5.45(5.1,5.92) ^a	0.799
Body fat (%)	35.3(27.9, 41.6) ^a	40.2 (32.8,47.6) ^b	0.026
Muscle, kg	23.79(4.22) ^b	22.80(4.39) ^b	0.173

a The values presented as median and interquartile range, Wilcoxon.

b The values presented as mean and standard deviation, paired t-test.

PO1-02-13

Germline mutation status of BRCA1/2 and other breast cancer predisposition genes as predictive and prognostic biomarker: Results of the GeparX study (GeparX-BRCA)

Presenting Author(s) and Co-Author(s):

R. Schmutzler. Zentrum Familiärer Brust- und Eierstockkrebs, Uniklinik Köln, Germany, United States

T. Link. Department of Gynecology and Obstetrics, Technische Universität Dresden, Dresden, Germany

E. Hahnen. Zentrum Familiärer Brust- und Eierstockkrebs, Uniklinik Köln, Germany, United States

M. Reinisch. Interdisciplinary Breast Cancer Center/ Breast Unit, Essen, Germany, United States

J. Hauke. Zentrum Familiärer Brust- und Eierstockkrebs, Uniklinik Köln, Germany, United States

M. Just. Onkologische Schwerpunktpraxis Bielefeld, Bielefeld, Germany

M. Untch. AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany, Berlin, United States

C. Ernst. University Cologne, Center of Familial Breast and Ovarian Cancer, Cologne, Germany, United States

O. Stötzer. Group Practice Hematology/ Intern. Oncology, Munich, Germany, United States

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

M. Kayali. Universität Köln, Zentrum familiärer Brust- und Eierstockkrebs, Germany, United States

P. Wimberger. Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Sachsen, Germany

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

S. Schmidt. University Cologne, Center of Breast and Ovarian Cancer, Cologne, Germany, United States

S. Seiler. German Breast Group, Neu-Isenburg, Germany, Hessen, Germany

C. Jackisch. Department of Obstetrics and Gynecology, Sana Klinikum Offenbach, Germany, Germany

M. Thill. Agaplesion Markus Krankenhaus, 60431 Frankfurt a.M., Hessen, Germany

K. Rhiem. Zentrum Familiärer Brust- und Eierstockkrebs, Uniklinik Köln, Germany, United States

C. Denkert. Institut für Pathologie, Philipps Universität Marburg und Universitätsklinikum Marburg (UKGM), Germany

V. Nekljudova. German Breast Group, Neu-Isenburg, Germany, United States

J. Holtschmidt. German Breast Group, Neu-Isenburg, Germany

J. Blohmer. Charité - Universitätsmedizin Berlin, Germany

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

Germline mutation status of BRCA1/2 and other breast cancer predisposition genes as predictive and prognostic biomarker: Results of the GeparX study (GeparX-BRCA) Background: There is accumulating evidence that the RANK/RANKL signaling pathway plays a pivotal role in breast tumorigenesis, particularly in the development of BRCA1-mutated tumors. Targeting the RANK pathway has been shown to attenuate breast cancer (BC) proliferation in vitro and in vivo. Studies using bone modifying agents as adjuvant therapy showed reduced rates of bone metastases and improved BC survival, as well as prevention of treatment-induced skeletal events. The GeparX clinical trial assessed the use of denosumab in patients with primary BC as an adjunct to neoadjuvant chemotherapy for its ability to enhance pathological complete response (pCR) rate and improve outcome. The trial randomized 780 patients twice to a total of 4 treatment groups (to receive or not receive denosumab; to receive nab-paclitaxel 125 mg/m² weekly for 12 weeks or days 1 and 8 every 3 weeks for 4 cycles, both followed by 4 cycles of epirubicin/cyclophosphamide, 90/600 mg/m² every 2 weeks/every 3 weeks according to the investigator's choice). Carboplatin was given in triple-negative breast cancer (TNBC), and trastuzumab biosimilar ABP980 plus pertuzumab was given in human epidermal growth factor-2-positive (HER2+) BC. Overall, the pCR (ypT0 ypN0) rate was 41% with denosumab vs 43% without; nab-paclitaxel at a dosage of 125 mg/m² weekly resulted in a significantly higher pCR rate of 45% vs 39% with a dosage of 125 mg/m² days 1 and 8 every 3 weeks. Research question: Does the germline mutation status of BRCA1/2 and other BC predisposition genes affect treatment outcome in the GeparX study? Methods: Genetic germline analyses assessing pathogenic variants in BRCA1/2 and 16 other BC predisposition genes were performed at the Center for Familial Breast and Ovarian Cancer, Cologne, Germany; 767 patients were included in this secondary investigation (308 TNBC, 306 HER2-/hormone receptor positive [HR+], 153 HER2+). Findings: Germline BRCA1/2 mutations were present in 91/767 patients (11.9%), with a higher mutation prevalence in TNBC (50/308, 16.2%) and HER2-/HR+ BC (37/306, 12.1%), and a low mutation prevalence in HER2+ BC (4/153, 2.6%). Overall, the pCR rate (ypT0 ypN0) was elevated in BRCA1/2 mutation carriers vs non-carriers (49.5% vs 41.1%, respectively; overall: OR 1.40, 95% CI 0.90-2.17; TNBC: OR 1.24, 95% CI 0.67-2.32; HER2-/HR+: OR 1.83, 95% CI 0.86-3.88). Highest pCR rates were observed in TNBC in BRCA1/2 mutation carriers vs non-carriers (60% vs. 54.7%, respectively). Highest pCR rate differences were observed HER2-/HR+ BC in BRCA1/2 mutation carriers vs non-carriers (32.4% vs. 20.8%, respectively). Regarding treatment arms, both BRCA1/2 mutation carriers and non-carriers benefitted most from nab-paclitaxel at a dosage of 125 mg/m² weekly vs 125 mg/m² days 1 and 8 every 3 weeks (BRCA1/2 mutation carriers: 55.3% vs 43.2%, respectively; OR 1.63, 95% CI 0.71-3.73; non-carriers: 43.7% vs 38.6%, respectively; OR 1.24, 95% CI 0.91-1.68). No beneficial effect was observed for denosumab vs no denosumab (51.1% vs 47.8% for BRCA1/2 mutation carriers, respectively; OR 1.14, 95% CI 0.50-2.60; 40.3% vs 41.9% for non-carriers, respectively; OR 0.94, 95% CI 0.69-1.27). Of the 617 BRCA1/2-negative patients, 59 patients carried mutations in other BC predisposition genes which did not predict therapy response compared to patients without any mutation. Conclusions: Irrespective of the treatment arm, higher pCR rates were observed in BRCA1/2 mutations carriers vs non-carriers. Both BRCA1/2 mutation carriers and non-carriers benefitted most from weekly nab-paclitaxel. No pronounced effect was observed for denosumab in either group. Key words: GeparX, denosumab, BRCA1/2 germline mutations, therapy response Funding: GeparX was financially supported by Amgen and BMS (Celgene).

PO1-02-14

Breast cancer in older women - long-term prognosis by age and subtype in a large population-based cohort

Presenting Author(s) and Co-Author(s):

A. Chiorescu. Karolinska Institutet, Enebyberg, Sweden

A. Johansson. Karolinska Institutet, Stockholms Lan, Sweden

A. Valachis. Örebro University Hospital, Örebro, Sweden

A. Matikas. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Breast Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden

J. Frisell. Karolinska Institutet, Stockholm, Sweden

L. Holmberg. King's College, London, United Kingdom

I. Fredriksson. Department of Molecular Medicine and Surgery, Karolinska Institutet, and Department of Breast-, Endocrine Tumors and Sarcoma, Karolinska University Hospital, Stockholm, Sweden, Stockholms Lan, Sweden

Background Compared to middle-aged women, older women have a higher risk of breast cancer death. Whether the increased risk of breast cancer death is present in all subgroups of older adults with breast cancer, or negligible in the subgroups receiving adequate surgical and oncological treatment, has been debated. We studied long-term prognosis by age and subtype, adjusting for stage, treatment, socioeconomic status and comorbidity, clarifying which subgroups of older patients that are at increased risk of breast cancer death. **Methods** In a nation-wide cohort of 45,949 women aged ≥ 60 years at diagnosis of breast cancer 1997-2014, we estimated crude probabilities of breast cancer death and from other causes using competing risk methods. Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) with 95% confidence intervals (CI). **Results** In this large population-based cohort study of older women with breast cancer, we found an increasing risk of breast cancer death with increasing age at diagnosis, both at 5- and 10-year follow up. The strong association between age and breast cancer death was found for all breast cancer subtypes, being most prominent in Her2-positive breast cancer. The age effect was also significant in Luminal A breast cancer where treatment opportunities are not necessarily affected by age. High-risk tumors were equally common in all age groups above 60 years. In multivariable analysis, stage, subtype, grade and treatment were important explanatory variables to the age-related differences in survival, while comorbidity and socioeconomic status contributed minorly. After adjustments, older age remained an independent risk factor for both overall and breast cancer survival. Older women with triple-negative (60-79 years) or Her2-positive (60-84 years) tumors had a 5-year risk of breast cancer death exceeding the risk of death by other causes. **Conclusions** Older women had a significantly higher risk of breast cancer death irrespective of breast cancer subtype, also in Luminal A disease where treatment opportunities are not necessarily affected by age.

Crude probabilities of breast cancer specific death and death by other cause (competing cause of death) at 5, 10 and 15 years.

Table 3. Crude probabilities of breast cancer specific death and death by other cause (competing cause of death) at 5, 10 and 15 years.

	At risk				Probabilities of BC death			Probabilities of other death		
	0y N	5y N	10y N	15y N	5y Percent [95% CI]	10y Percent [95% CI]	15y Percent [95% CI]	5y Percent [95% CI]	10y Percent [95% CI]	15y Percent [95% CI]
Age										
60-64	10765	8911	3853	1477	5.8 [5.3, 6.2]	3.3 [3, 3.7]	10.1 [9.5, 10.7]	8.7 [8.1, 9.4]	13.3 [12.4, 14.2]	16.6 [15.5, 17.7]
65-69	10763	8407	2949	1036	6.3 [5.8, 6.8]	5.0 [4.6, 5.4]	10.0 [9.4, 10.7]	13.1 [12.3, 13.9]	13.2 [12.3, 14.2]	25.5 [24.1, 27]
70-74	8159	5943	1889	594	8.0 [7.4, 8.6]	8.2 [7.6, 8.8]	13.1 [12.3, 14.0]	20.8 [19.7, 22.0]	16.7 [15.6, 17.9]	39.3 [37.3, 41.2]
75-79	5562	3511	1137	270	15.4 [14.4, 16.3]	15.5 [14.6, 16.5]	20.4 [19.2, 21.5]	35.8 [34.3, 37.2]	23.6 [22.2, 24.9]	54.7 [52.8, 56.6]
80-84	5285	2664	609	72	17.3 [16.2, 18.3]	27.8 [26.6, 29]	21.5 [20.3, 22.7]	53.2 [51.6, 54.7]	22.9 [21.6, 24.1]	70.6 [68.9, 72.2]
85-89	3588	1263	152	12	20.0 [18.8, 21.4]	40.9 [39.3, 42.5]	24.1 [22.6, 25.6]	65.3 [63.5, 67.1]	24.6 [23.1, 26.2]	73.6 [71.9, 75.2]
90+	1827	340	24	0	24.1 [22.2, 26.1]	54.9 [52.5, 57.1]	N/A	70.3 [68.0, 72.5]	27.0 [24.9, 29.2]	N/A
	45,949	31,039	10,163	3,460						

N/A: Not available due to no women at risk.

Multivariable analysis of prognostic factors affecting 15-year overall (OS) and breast cancer-specific survival (BCSS)

Table 4. Multivariable analysis of prognostic factors affecting 15-year overall (OS) and breast cancer-specific survival (BCSS). Imputation analysis (complete case analysis in Table S1).

	Patients N	Deaths n	M1 HR [95% CI]	M2 HR [95% CI]	M3 HR [95% CI]	M4 HR [95% CI]	M5 HR [95% CI]
OS							
Age							
60-64	10656	1986	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
65-69	10636	2309	1.32 [1.24,1.40]	1.27 [1.19,1.35]	1.23 [1.16,1.31]	1.30 [1.22,1.38]	1.27 [1.20,1.35]
70-74	7997	2485	2.04 [1.93,2.17]	1.87 [1.76,1.99]	1.78 [1.67,1.89]	1.82 [1.71,1.93]	1.73 [1.63,1.84]
75-79	5414	2984	4.07 [3.85,4.31]	3.62 [3.41,3.84]	3.26 [3.07,3.46]	2.92 [2.75,3.10]	2.55 [2.39,2.72]
80-84	5152	3657	6.78 [6.41,7.16]	5.86 [5.54,6.21]	5.13 [4.85,5.44]	4.43 [4.18,4.71]	3.37 [3.15,3.60]
85-89	3349	2734	10.67 [10.06,11.32]	9.04 [8.50,9.61]	7.64 [7.18,8.13]	5.73 [5.36,6.12]	3.80 [3.53,4.10]
90+	1454	1314			11.83		
Total	44658	17469	17.71 [16.48,19.03]	14.81 [13.75,15.95]	[10.97,12.75]	8.33 [7.55,9.19]	4.60 [4.17,5.08]
BCSS							
Age							
60-64	10656	1019	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
65-69	10636	976	1.04 [0.95,1.14]	1.01 [0.92,1.10]	1.00 [0.91,1.09]	1.10 [1.01,1.21]	1.09 [1.00,1.20]
70-74	7997	936	1.40 [1.28,1.53]	1.30 [1.19,1.43]	1.28 [1.17,1.40]	1.32 [1.20,1.45]	1.29 [1.17,1.42]
75-79	5414	1071	2.60 [2.38,2.83]	2.36 [2.15,2.57]	2.26 [2.06,2.47]	1.70 [1.55,1.87]	1.52 [1.38,1.68]
80-84	5152	1060	3.22 [2.95,3.51]	2.85 [2.60,3.12]	2.68 [2.45,2.94]	1.87 [1.69,2.06]	1.52 [1.36,1.69]
85-89	3349	761	4.43 [4.03,4.87]	3.85 [3.48,4.25]	3.58 [3.23,3.96]	1.97 [1.76,2.20]	1.45 [1.28,1.64]
90+	1454	380	6.97 [6.18,7.86]	5.99 [5.29,6.78]	5.43 [4.79,6.16]	2.73 [2.29,3.25]	1.69 [1.41,2.01]
Total	44658	6203					

M1: adjusted year, region

M2: + socioeconomic status (level of education, income)

M3: + comorbidity

M4: + tumor characteristics (TNMstage (clin/path), grade, subtype)

M5: + treatment (breast surgery, axillary surgery, chemotherapy, trastuzumab, radiotherapy, endocrine therapy)

Multivariable analysis of prognostic factors affecting 15-year overall (OS) and breast cancer-specific survival (BCSS) by age at diagnosis and subtype.

Table 5. Multivariable analysis of prognostic factors affecting 15-year overall (OS) and breast cancer-specific survival (BCSS) in a cohort of 44, 658 women aged 60 y or more at diagnosis of primary breast cancer in 1997-2014, by age at diagnosis and subtype. 17,469 OS deaths, 6203 BCS deaths during follow-up. Imputation analysis.

	Lum A HR [95% CI]	Lum B HR [95% CI]	HER2 pos HR [95% CI]	TNBC HR [95% CI]
OS				
Age				
60-64	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
65-69	1.34 [1.21,1.47]	1.19 [1.05,1.35]	1.37 [1.11,1.69]	1.18 [1.00,1.40]
70-74	1.88 [1.71,2.06]	1.59 [1.41,1.80]	1.77 [1.43,2.20]	1.55 [1.31,1.83]
75-79	2.70 [2.45,2.97]	2.38 [2.10,2.69]	2.53 [2.05,3.12]	2.43 [2.07,2.86]
80-84	3.60 [3.26,3.98]	3.05 [2.69,3.46]	3.51 [2.79,4.42]	3.18 [2.68,3.77]
85-89	4.06 [3.66,4.51]	3.42 [2.97,3.95]	4.25 [3.31,5.44]	3.45 [2.86,4.16]
90+	5.03 [4.40,5.76]	4.03 [3.35,4.86]	4.92 [3.60,6.71]	4.09 [3.18,5.26]
BCSS				
Age				
60-64	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
65-69	1.18 [0.99,1.41]	1.04 [0.87,1.23]	1.13 [0.87,1.48]	1.02 [0.83,1.26]
70-74	1.40 [1.18,1.66]	1.16 [0.97,1.38]	1.58 [1.18,2.13]	1.15 [0.92,1.45]
75-79	1.55 [1.29,1.86]	1.46 [1.23,1.73]	1.75 [1.33,2.29]	1.47 [1.18,1.82]
80-84	1.54 [1.28,1.86]	1.28 [1.05,1.56]	1.86 [1.36,2.56]	1.70 [1.35,2.15]
85-89	1.47 [1.20,1.79]	1.34 [1.06,1.69]	1.84 [1.34,2.52]	1.37 [1.05,1.80]
90+	1.79 [1.41,2.29]	1.31 [0.92,1.86]	2.09 [1.35,3.25]	1.87 [1.30,2.68]

Model adjusted for year, region, tumor characteristics (TNM stage (clin/path), grade, subtype), treatment (breast surgery, axillary surgery, chemotherapy, trastuzumab, radiotherapy, endocrine therapy), socioeconomic status (level of education, income) and comorbidity
All models include non-missing observations on all covariates.

PO1-03-01

Barriers, facilitators, and challenges for the implementation of a hybrid multidisciplinary lifestyle intervention

Presenting Author(s) and Co-Author(s):

D. Martinez-Palacios. Universidad Anáhuac México, Miguel Hidalgo, Distrito Federal, Mexico

M. Cruz-Ramos. Instituto Nacional de Cancerología, United States

F. Fajardo-Espinoza. Universidad Anáhuac México, United States

Y. Rodriguez-Fonseca. Instituto Nacional de Cancerología, United States

A. Gonzalez-Perez. Universidad Anáhuac México, United States

A. Barranco-Cortés. Universidad Anáhuac México, United States

D. Pérez-Camargo. Instituto Nacional de Cancerología, United States

A. Mohar. Instituto Nacional de Cancerología, United States

C. Villarreal Garza. Tecnológico de Monterrey, Mexico, United States

Background. Breast cancer is the leading cause of cancer-related death and disability among young women in Mexico. The physical and psychological symptoms they experience affect their quality of life, physical functioning, and psychological well-being. To address this, the National Cancer Institute in Mexico City developed a program called "Joven & Fuerte" that provides services for young women with breast cancer. Due to the COVID-19 pandemic, the program has migrated to virtual attention and now offers hybrid attention to meet the needs of these patients. The research group developed the "Joven, Fuerte & Saludable" intervention, which is a hybrid (face-to-face and virtual) multidisciplinary lifestyle intervention that includes nutrition, rehabilitation, psychological support, mindfulness intervention, and lifestyle education for early disease young women undergoing oncology treatments. This study aims to evaluate the barriers and facilitators for implementing this lifestyle intervention. **Methodology.** The study involved young women with early breast cancer enrolled in the "Joven & Fuerte" program in 2022. They were invited to participate in a study to evaluate the barriers, facilitators, and challenges of a hybrid multidisciplinary lifestyle intervention during the first months since the diagnosis (3 months). The intervention included face-to-face consultations for anthropometric and biochemical assessments, interdisciplinary team evaluations, and virtual support through WhatsApp and Zoom. Educational materials such as printed or digital healthy lifestyle guides and educational videos were available on a private Facebook and YouTube group. Follow-up sessions were conducted via phone, video, or on-site visits. To evaluate lifestyle habits and quality of life status, distress, anxiety, and depression validated questionnaires were used. The CFIR and RE-AIM questionnaires were used to identify the barriers and facilitators among the program staff and patients while adopting the intervention. **Results.** The study found that patients were satisfied with the intervention and educational materials, but there were some barriers for implementation. One of the main barriers was the patients' geographical location, as 62.5% of patients were foreign and lived far from the hospital. Additionally, patients only sometimes used the educational materials due to forgetfulness, lack of time, not having internet access, or low digital literacy. Patients also had difficulty recognizing the impact of a "healthy lifestyle" and prioritized other consultations before the program schedule. Institutional barriers included a lack of human resources, which led to a loss in follow-up and patient motivation due to waiting-list periods. Undergraduate and postgraduate training students were introduced to support the multidisciplinary team in overcoming this challenge. Despite these obstacles, patients reported feeling supported by the multidisciplinary team and experienced benefits such

as reduced stress and anxiety and better management of treatment side effects upon completing program activities. An important institutional success was achieved by reducing service waiting times from three months to just 1-2 weeks for all services. Conclusions. Cultural behavior and emotional distress at diagnosis and during the first 3 months of intervention are the major challenges for patients. A hybrid educational intervention seems convenient to make follow-up more practical and accessible. Patients feel motivated because they are in touch with their clinicians and receive fast resolutions to their concerns. Many talented and enthusiastic human resources are needed to implement these interventions, but it is possible for a Latin American public hospital, considering the essential benefits for the patients.

PO1-03-02

Impact of Body Mass Index (BMI) on the efficacy of different adjuvant chemotherapy schedules in patients with breast cancer: analysis from the randomized phase III GIM2 trial

Presenting Author(s) and Co-Author(s):

- M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy
- F. Poggio. IRCCS Ospedale Policlinico San Martino, United States
- E. Blondeaux. IRCCS Ospedale Policlinico San Martino, United States
- M. Tagliamento. Department of Internal Medicine and Medical Sciences (DiMI), School of Medicine, University of Genova, Genova, Italy, United States
- M. Perachino. IRCCS Ospedale Policlinico San Martino, Genova, Italy, United States
- S. Nardin. IRCCS Ospedale Policlinico San Martino, Genova, Italy, United States
- B. Conte. Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute, Barcelona, Italy, United States
- S. De Placido. Department of Clinical Medicine and Surgery, University of Naples "Federico II, Napoli, Italy, United States
- M. Giuliano. Department of Clinical Medicine and Surgery, University of Naples "Federico II, Napoli, Italy, United States
- V. Forestieri. Department of Clinical Medicine and Surgery, University of Naples "Federico II, Napoli, Italy, United States
- M. De Laurentiis. Fondazione Pascale IRCCS, United States
- A. Gravina. Clinical Trial Unit, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Napoli, Italy, United States
- G. Bisagni. IRCCS AUSL Reggio Emilia, United States
- A. Rimanti. Azienda Ospedaliera Carlo Poma, United States
- A. Turletti. Ospedale Martini ASL Città di Torino, United States
- C. Nisticò. Medical Oncology Unit, ASL Frosinone, Frosinone, Italy, United States
- A. Vaccaro. Medical Oncology Unit, ASL Frosinone, Frosinone, Italy, United States
- F. Cognetti. Regina Elena National Cancer Institute, United States
- A. Fabi. Precision Medicine in Breast Cancer, Fondazione Policlinico Universitario A. Gemelli, IRCCS Rome - Italy, Rome, Italy
- S. Gasparro. Division of Medical Oncology 1, Regina Elena National Cancer Institute, Roma, Italy, United States
- O. Garrone. Medical Oncology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano, Italy, United States
- Y. Urracci. Hospital Businco, United States
- M. Alicicco. Department of Oncology, U.O.C. Oncologia, Azienda Ospedaliera Universitaria, Sassari, Italy, United States
- M. Mansutti. Department of Medical Oncology, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC) Udine, Italy

P. Poletti. Department of Medical Oncology, Ospedale Papa Giovanni XXIII, Bergamo, Italy, United States

P. Correale. Medical Oncology Unit, Grand Metropolitan Hospital "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy, United States

C. Bighin. University of Genova, Genova, United States

F. Puglisi. Department of Medicine (DAME), University of Udine, Udine, Italy and Department of Medical Oncology - CRO Aviano, National Cancer Institute, IRCCS, Aviano, Friuli-Venezia Giulia, Italy

F. Montemurro. Breast Surgery Strategic Program, Candiolo Cancer Institute, Fondazione del Piemonte per l'Oncologia - IRCCS, Torino, Italy, United States

G. Colantuoni. Medical Oncology, Azienda Ospedaliera S Giuseppe Moscati, Avellino, Italy, United States

L. Boni. IRCCS Ospedale Policlinico San Martino, Genoa, Genova, Italy

L. Del Mastro. University of Genova - IRCCS Ospedale Policlinico San Martino, United States

Background: The long-term results of the Italian randomized phase III GIM2 study showed that, in women with node-positive breast cancer (BC), dose-dense (DD) chemotherapy significantly improved both disease-free survival (DFS) and overall survival (OS) compared with standard-interval (SI) chemotherapy. Obesity has been identified as an independent poor prognostic factor in patients with BC, with a potential negative impact on the efficacy and toxicity of systemic therapies. Nevertheless, the specific influence of body mass index (BMI) on the efficacy of different adjuvant chemotherapy schedules (DD or SI) remains a subject of debate. This analysis aimed to investigate this hypothesis in patients enrolled in the GIM2 trial.

Methods: GIM2 was a randomized multicentric phase III trial that compared different chemotherapy schedule (DD vs SI) and regimen (FEC-P vs EC-P) in 2091 node-positive early breast cancer patients. BMI (kg/m^2) was categorized as follows: < 18.5 (underweight), 18.5 to < 25 (lean), 25 to < 30 (overweight), and ≥ 30 (obese). The primary endpoint was to assess association between BMI and DFS and OS. Survival estimates were compared using the Kaplan-Meier method and log-rank test. Univariate and multivariable Cox proportional hazard models, adjusted for relevant prognostic factors, were used. **Results:** A total of 1925 patients were included in the present analysis, of whom 31.6% (n=632) were overweight and 19.3% (n=386) obese. Median age was 52 years. Overweight-obesity condition was significantly associated with postmenopausal status, greater representation of T2-T4 tumors with N > 2 in both patients in the DD and SI arm. After a median follow-up of 15.0 years (IQR 8.4-16.3), compared to patients with normal BMI, those who were overweight or obese at diagnosis had a higher risk of experiencing a DFS event (Hazard Ratio [HR] 1.11 95% CI 0.94-1.31 and HR 1.37 95%CI 1.14-1.65, respectively, p=0.003) and OS event (HR 1.11 95% CI 0.89-1.38 and HR 1.59 95%CI 1.26-2.01, respectively, p=0.0003). No significant interaction was found between BMI and treatment schedule in terms of DFS (p for interaction=0.56) nor OS (p for interaction=0.19). At the multivariate analysis, in the DD arm, adjusted HR (aHR) for DFS and for OS were 1.01 (95% CI 0.75- 1.35) and 1.04 (95% CI 0.72-1.52) for obese vs. normal BMI groups, and 0.88 (95% CI 0.68- 1.15) and 0.77 (95%CI 0.54-1.10) for overweight vs. normal BMI groups, respectively. In the SI arm, aHRs for DFS and OS were 1.24 (95% CI 0.94- 1.63) and 1.35 (95%CI 0.96- 1.90) for obese vs. normal BMI groups, and 1.04 (95%CI 0.82- 1.33) and 1.01 (95% CI 0.74-1.40) for overweight vs. normal BMI groups, respectively. Similar results were observed when considering hormone receptor-positive and negative BC separately. **Conclusion:** In the GIM2 trial, BMI was prognostic but not predictive of different benefit to adjuvant chemotherapy. In high-risk patients, DD schedule should be considered the preferred schedule irrespective of BMI.

PO1-03-03

STEEP criteria v2.0 validation: A multi-trial analysis using GEICAM and TRIO adjuvant trials to evaluate surrogate endpoints for overall survival

Presenting Author(s) and Co-Author(s):

S. López-Tarruella. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

M. Pollán. Centro Nacional de Epidemiología. Instituto de Salud Carlos III. CIBERONC.CIBERESP. GEICAM Spanish Breast Cancer Group, Spain

A. Urruticoechea. Oncologikoa, United States

E. Carrasco. GEICAM Spanish Breast Cancer Group, Spain

G. Spera. Translational Research in Oncology, Medical Affairs, Uruguay

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

B. Bermejo. Hospital Clínico Universitario de Valencia, Valencia, Spain, Comunidad Valenciana, Spain

L. Chap. Beverly Hills Cancer Center, United States

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

J. Crown. Saint Vincent's University Hospital, United States

J. García-Sáenz. Instituto de Investigación Sanitaria Hospital Clinico San Carlos (IdISSC), United States

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

A. Guerrero. Fundación Instituto Valenciano de Oncología (FIVO). GEICAM Spanish Breast Cancer Group., Valencia, Comunidad Valenciana, Spain

V. Bee. Project Management Department. Translational Research in Oncology (TRIO), France

L. Calvo. Oncology Department-University Hospital A Coruña, A Coruña, Galicia, Spain

R. Fresco. Translational Research in Oncology (TRIO), Medical Affairs Department, Montevideo, Uruguay

A. Blasco. GEICAM Spanish Breast Cancer Group, Spain

A. Hernando. GEICAM Spanish Breast Cancer Group, United States

D. Slamon. UCLA David Geffen School of Medicine, Los Angeles, California, United States

Background: Standardized definitions of efficacy endpoints are needed to improve clinical trial designs, data reporting and interpretation of results, and to allow cross-trial comparisons. STEEP (Standardized Definitions for Efficacy Endpoints) criteria were proposed in 2007 by an expert panel from the National Cancer Institute (NCI) to provide common definitions for clinical trials in early breast cancer (BC). Invasive disease-free survival (IDFS) was selected as a candidate surrogate endpoint for overall survival (OS) in adjuvant trials and has been widely used in the last 15 years. Advances in BC systemic treatment led to review these criteria (STEEP v2.0), with the definition of a new modified endpoint: invasive BC-free survival (IBCFS). IBCFS excludes second primary non-breast invasive cancers from IDFS which may better detect efficacy effects when the toxicity profile of the intervention is well-known and the risk of second primary cancer is small. Methods: We proposed a multi-trial analysis of 8 adjuvant chemotherapy (CT) trials from GEICAM and TRIO to evaluate the different surrogate

endpoints defined in the STEEP v2.0. Trial-level surrogacy was assessed through correlation between the ln hazard ratio (HR) of OS and the ln HR of the different studied endpoints across trials. The correlation was estimated by the weighted, by trial size, least squares regression (WLS) line and evaluated comparing the R² values between OS and the corresponding endpoint tested.

Primary analyses evaluated the correlation of OS with IDFS/IBCFS. Secondary analyses evaluated the correlation of OS with other STEEP v2.0 endpoints (distant disease-free survival [DDFS], distant relapse-free survival [DRFS], recurrence-free survival [RFS], recurrence-free interval [RFI] and distant recurrence-free interval [DRFI]) and explored the surrogacy between OS and all endpoints in specific groups of patients (pts) according to their risk of relapse: hormone receptors positive (HR+)/HER2-negative (HER2-) pts with intermediate/high and high-risk and triple negative (TN) pts. Results: A total of 14,473 pts were included. Median age was 50 years (range, 20–82). All were female, and 51.8% were postmenopausal. With a median follow-up of 115 months (range, 0.0–188) we found 2,504 OS events, 4,146 IDFS events (60.9% being distant recurrences) and 3,810 IBCFS events (62.4% being distant recurrences).

For each trial, HR of OS, IDFS and IBCFS indicated same conclusions. If HR < 1 for OS, it was also for IDFS and IBCFS and the same was true when HR > 1. R² results of the weighted linear correlations between the ln HR of OS versus (vs) IDFS and OS vs IBCFS were 0.86 and 0.89, respectively. Confidence intervals (CI) at 95% were both overlapping. All other efficacy endpoints showed strong correlation with OS in the overall analysis.

R² values for HR+/HER2- intermediate/high and high-risk pts were 0.89 (OS vs IDFS) and 0.84 (OS vs IBCFS). For TN pts the correlations were weaker, being 0.63 (OS vs IDFS) and 0.73 (OS vs IBCFS). All WLS R² values are described in the table. Conclusions: All tested STEEP v2.0 endpoints were strongly correlated with OS (R² close to 1), meaning that their use as surrogate endpoints for adjuvant CT trials is appropriate. Notably, no differences were found between them in this multi-trial analysis. Therefore, none of them is more appropriate than other to discriminate the value of a new intervention vs comparator in adjuvant CT studies with mature data and long-term follow-up.

Table:

WLS R ² values (95% CI)	Number of pts	OS vs IDFS	OS vs IBCFS	OS vs DDFS	OS vs DRFS	OS vs RFS	OS vs RFI	OS vs DRFI
All pts	14,473	0.86 (0.74 - 0.90)	0.89 (0.79 - 0.90)	0.94 (0.89 - 0.99)	0.96 (0.92 - 1.00)	0.81 (0.66 - 0.97)	0.81 (0.66 - 0.97)	0.97 (0.94 - 1.00)
Intermediate/high and high-risk HR+/HER2- pts*	2,265	0.89 (0.81 - 0.90)	0.84 (0.71 - 0.97)	0.72 (0.62 - 0.93)	0.62 (0.36 - 0.88)	0.64 (0.39 - 0.89)	0.51 (0.21 - 0.82)	0.29 (0.00 - 0.62)
TN pts	3,868	0.63 (0.36 - 0.89)	0.73 (0.53 - 0.94)	0.72 (0.0 - 0.93)	0.86 (0.75 - 0.90)	0.72 (0.50 - 0.93)	0.72 (0.51 - 0.93)	0.86 (0.74 - 0.90)

*Intermediate/high-risk: T1c to T3 N0 with Grade 3; High-risk: i) 1-3 positive axillary lymph nodes (N+) and T ≥ 5cm or Grade 3, ii) ≥ 4 N+

PO1-03-05

Tolerance of adjuvant radiotherapy combined with pembrolizumab for triple negative breast cancer

Presenting Author(s) and Co-Author(s):

Y. Kirova. Institut Curie, Paris, Ile-de-France, France

T. Tison. Institut Curie, United States

P. Loap. Institut Curie, United States

E. ARNAUD. Medical Oncology Department, Institut Curie, United States

K. Cao. Institut Curie, United States

S. Bringer. Institut Curie, United States

M. Kissel. Institut Curie, United States

S. Maaradji. Institut Curie, United States

J. Mainguene. Institut Curie, United States

J. Pierga. Institut Curie, United States

F. Lerebours. Institut Curie, United States

A. Salomon. Institut Curie, United States

M. Mirabelle. Institut mutualiste montsouris, United States

D. Loirat. Institut Curie, Medical Oncology Department and D3i, Paris, France

F. Bidard. Institut Curie, Paris, France

BACKGROUND AND PURPOSE: The current standard-of-care management of locally advanced triple negative breast cancer (TNBC) is based on neoadjuvant chemo-immunotherapy with pembrolizumab, surgery, radiotherapy and adjuvant pembrolizumab. However, the safety of combining pembrolizumab with adjuvant breast radiotherapy has never been evaluated. This study evaluated the tolerance profile of concurrent pembrolizumab (P) with adjuvant radiotherapy (RT) in locally advanced TNBC patients.

METHODS: This bicentric ambispective study included the first prospectively registered patients with non-metastatic TNBC treated with the KEYNOTE-522 regimen in our institution. They received P in combination with carboplatin and paclitaxel chemotherapy and a second chemotherapy with doxorubicin and cyclophosphamide, followed by surgery and locoregional RT with or without P as adjuvant treatment. RT was normo- or hypofractionated, for the breast or chest wall, with or without lymph node irradiation according to institutional guidelines. Adjuvant P was administered at a total dose of 1800 mg at 200 mg once every 3 weeks or 400 mg once every 6 weeks. The safety profile was evaluated during and after the end of RT (until the last contact) with CTCAE V.5 scale.

RESULTS: A total of 55 patients (pts) were prospectively included between July 2021 and March 2023. The median age was 49 years (29-69). The median follow-up was 12 months (range, 10-26). Of them, 27 (49%) did not receive P concomitantly with RT (RT-only group) because of neo-adjuvant treatment related toxicities, and 28 (51%) received P concomitantly with RT (P-RT group). There was no statistical difference in population and toxicity between the RT-only group and the P-RT group. Nine patients were diagnosed with cardiac toxicities before the beginning of the RT and did not receive P during the RT. No RT-induced grade ≥ 4 toxicities

were observed. Early toxicities were mainly grade 1-2. Two grade 3 toxicities occurred (1 case of axillary pain in the P-RT group and 1 radiodermatitis in the RT-only group). No cardiac or pulmonary toxicities \geq grade 2 were observed with adjuvant therapy. The toxicity profile is given in table 1.

DISCUSSION: In these series, the main cause of discontinuation of pembrolizumab was related to suspicion of cardiac adverse events occurring during the neoadjuvant treatment and related to the injection of pembrolizumab or of the chemotherapy. All myocarditis happened before radiotherapy and did not affect the administration of radiotherapy. In this context, the optimal radiotherapy technique and cardiac dose constraints after ICI-induced myocarditis is unknown and late cardiotoxicity studies will be needed to precise these points. Cardiac sparing techniques, such as deep-inspiration breath hold, proton therapy, or alternative positioning (such as isocentric lateral decubitus) could be considered.

CONCLUSION: Adjuvant radiotherapy can be combined with pembrolizumab for TNBC patients without increasing the risk of radiation-induced adverse events, allowing maintaining a systemic treatment in these high-risk patients. Longer follow-up and prospective studies are needed to validate these results.

Adjuvant treatment-related adverse events

Toxicity	CTCAE v5 Grade	Whole population (n=55)	Withheld pembrolizumab (n=27)	Concurrent pembrolizumab (n=28)	p value
Radio-dermatitis	1	37 67.27 %	19 70.37 %	18 64.29 %	0.570
	2	9 16.36 %	3 11.11 %	6 21.43 %	
	3	1 1.82 %	1 3.7 %	0 0 %	
	4	0 0 %	0 0 %	0 0 %	
asthenia	1	22 40 %	10 37.04 %	12 42.86 %	0.478
	2	4 7.27 %	1 3.7 %	3 10.71 %	
	3	0 0 %	0 0 %	0 0 %	
	4	0 0 %	0 0 %	0 0 %	
pain	1	10 18.18 %	7 25.93 %	3 10.71 %	0.281
	2	0 0 %	0 0 %	0 0 %	
	3	1 1.82 %	0 0 %	1 3.57 %	
	4	0 0 %	0 0 %	0 0 %	
myocarditis	1	0 0 %	0 0 %	0 0 %	1.000
	2	0 0 %	0 0 %	0 0 %	
	3	0 0 %	0 0 %	0 0 %	
	4	0 0 %	0 0 %	0 0 %	
dyspnea	1	3 5.45 %	0 0 %	3 10.71 %	0.631
	2	1 1.82 %	0 0 %	1 3.57 %	
	3	0 0 %	0 0 %	0 0 %	
	4	0 0 %	0 0 %	0 0 %	
cough	1	4 7.27 %	2 7.41 %	2 7.14 %	1.000
	2	0 0 %	0 0 %	0 0 %	
	3	0 0 %	0 0 %	0 0 %	
	4	0 0 %	0 0 %	0 0 %	
odynophagia	1	3 5.45 %	2 7.41 %	1 3.57 %	0.837
	2	2 3.64 %	1 3.7 %	1 3.57 %	
	3	0 0 %	0 0 %	0 0 %	
	4	0 0 %	0 0 %	0 0 %	
lymphoedema	1	5 9.09 %	3 11.11 %	2 7.14 %	1.000
	2	0 0 %	0 0 %	0 0 %	
	3	0 0 %	0 0 %	0 0 %	
	4	0 0 %	0 0 %	0 0 %	

PO1-03-06

Older patients with Early Stage Triple Negative Breast Cancer: The Memorial Sloan Kettering Cancer Center experience.

Presenting Author(s) and Co-Author(s):

J. Singh. Memorial Sloan Kettering Cancer Center, West Harrison, New York, United States

D. Lake. Memorial Sloan Kettering Cancer Center, New York, New York, United States

W. Dente-Ferguson. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Y. Chen. Memorial Sloan Kettering Cancer Center, United States

F. Erlich. Memorial Sloan Kettering Cancer Center, United States

B. Korc-Grodzicki. Memorial Sloan Kettering Cancer Center, United States

M. Robson. Memorial Sloan Kettering Cancer Center, New York, United States

L. Norton. Memorial Sloan Kettering Cancer Center, United States

W. Zhi. Memorial Sloan Kettering Cancer Center, United States

INTRODUCTION Approximately 15% cases of TNBC are diagnosed in individuals over the age of 70. Older patients remain under-represented in clinical trials. We conducted a retrospective review of patients 70 years of age and older with stage I-III TNBC who were treated at Memorial Sloan Kettering Cancer Center (MSKCC), with the goal of describing the clinical practice patterns and outcomes. **MATERIAL AND METHODS** A retrospective record review of patients 70 years of age and older with a diagnosis of stage I-III TNBC between January 2015-December 2019 was performed. We report the data on the utilization of systemic chemotherapy and survival analyses. We compared patient characteristics by chemotherapy type using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test. Overall Survival (OS), Breast Cancer Specific Survival (BCSS), and Recurrence Free BCSS (RF-BCSS) were examined using Cox proportional hazards models. All statistical analyses were conducted using R. **RESULTS** A total of 147 patients were included. The median age was 75 years (range 70-96). The number of patients with stage I, II, and III disease was 64 (44%), 66 (45%), 17 (12%), respectively. Twenty-five (18%) patients underwent comprehensive geriatric assessment. Out of total patients, 93 (63%) patients received systemic Chemotherapy (C) while 54 (37%) received no chemotherapy (NC). Patients receiving C were younger (median age 74 years with C vs. 78 years with NC, $p < 0.001$) and had a higher disease stage (Stage II-III: 66% (C) vs. 41% (NC), $p = 0.005$). There were no significant differences in Activities of Daily Living (ADL) difficulty between both arms. Amongst Instrumental ADL (IADL) assessment, patients in the NC group reported statistically significant greater difficulty with meal preparation (17% in NC and 4.3% in C, $p = 0.016$). The most common reasons for not receiving chemotherapy were low-risk disease i.e. pT1aN0 or microinvasive (33%), patient preference (29%), and frailty per the treating oncologist (19%). Rate of mastectomy was higher in the NC group (35% in NC vs. 20% in C, $p = 0.029$). Among the 32 patients who had radiation data, breast irradiation rates were higher in the C group (70% in C and 17% in NC, $p = 0.003$). Thirty patients (20%) received neoadjuvant chemotherapy (NAC) and 65 (44%) received adjuvant chemotherapy. Anthracycline-based chemotherapy was the most common NAC ($n = 17$, 57%). Patients who received Cyclophosphamide-Methotrexate-5-Fluorouracil (CMF) were older (age ≥ 75 years: 51% (CMF) vs. 17% (ACT), $p = 0.010$), more likely treated in an adjuvant setting (87% CMF vs. 61% ACT, $p = 0.017$), had earlier-stage disease (Stage 1: 54% (CMF) vs. 26% (ACT), $p = 0.028$), and reported more ADL (31% in CMF vs. 0% in ACT, $p = 0.002$) and IADL difficulties (31% CMF

vs 4.3% in ACT, $p=0.021$). The use of Docetaxel/Cyclophosphamide (TC) and platinum-based regimens was low (8% and 5%, respectively). In the univariate analysis between the C and NC groups, there was no difference in OS (Hazard Ratio (HR) 0.78, 95% Confidence Interval (CI) 0.42-1.43; $p=0.4$), BCSS (HR 1.39, 95% CI 0.57-3.39; $p=0.5$), and RF-BCSS (HR 1.60, 95% CI 0.67-3.83; $p=0.3$). There was no difference in OS (HR 0.60, 95% CI 0.23-1.55; $p=0.3$), BCSS (HR 0.48, 95% CI 0.17-1.32; $p=0.2$), and RF-BCSS (HR 0.71, 95% CI 0.30-1.73; $p=0.5$) in patients receiving CMF vs. ACT. CONCLUSIONS In our single institutional experience, we observed that two-thirds of older patients with early-stage TNBC received systemic polychemotherapy. A third of patients with NC were very low risk (pT1a or microinvasive disease) which could explain lack of chemotherapy benefit in our study population. Use of CMF was more prevalent in patients aged ≥ 75 , stage I disease, ADL/IADL difficulties, and in the adjuvant setting. We observed no difference in survival outcomes between the two chemotherapy regimens. CMF remains an efficacious option and a potentially viable alternative to ACT in TNBC, especially in the setting of early stage and advanced age.

PO1-03-07

Revisiting the potential of pathological complete response as a surrogate for long-term survival outcomes in triple-negative breast cancer at the trial-level

Presenting Author(s) and Co-Author(s):

T. Yoshino. Nakagami Hospital, United States

Z. Zhang. The Queen's Medical Center, United States

R. Sato. The Queen's Medical Center, United States

S. Lipkowitz. Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States

T. Fujii. National Cancer Institute, National Institutes of Health, Bethesda, Maryland, United States

Background: Pathological complete response (pCR) has been used as a primary endpoint in neoadjuvant clinical trials for non-metastatic breast cancer and as a surrogate endpoint for long-term survival outcomes. The U.S. Food and Drug Administration (FDA) accepted pCR as a surrogate endpoint for the approval of new drugs in the neoadjuvant setting in high-risk early-stage breast cancer. However, though the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) pooled analysis in 2014 showed that at the patient level achieving pCR was associated with longer overall survival (OS) and event-free survival (EFS), at the trial-level the association between high pCR rate and better OS and EFS outcomes was weak (coefficient of difference [R^2]; 0.03 and 0.24, respectively) among all subtypes of breast cancer. A recent study reported that this association at the trial-level was similarly weak among Human Epidermal Growth Factor Receptor-2 (HER-2) positive breast cancer (R^2 ; 0.02 and 0.23, respectively). However, the potential surrogacy of pCR rate for OS and EFS in triple-negative breast cancer (TNBC) in the neoadjuvant setting has not been well studied in a comprehensive manner. Moreover, because of significant advances in systemic treatment strategies in TNBC over the past decade including a combination of immune checkpoint inhibitors (ICIs) with conventional cytotoxic agents, the trial-level surrogacy needs to be reassessed in recently published neoadjuvant clinical trials for TNBC. Our primary objective is to assess the association between pCR rate and survival outcomes in neoadjuvant clinical trials for TNBC by collecting data from articles published after the CTNeoBC article in 2014. Methods: We performed a systematic literature search based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in the PubMed, Cochrane Library, and Web of Science databases. Articles published between January 1, 2014, and March 31, 2023, were searched. We included only randomized control trials of neoadjuvant treatments for clinical stage I-III TNBC that compared two or more regimens followed by curative intent breast surgery. The selected trials had data for odds ratio (OR) for pCR and hazard ratios (HRs) either for OS or for EFS or disease-free survival (DFS). We excluded trials including estrogen receptor positive, progesterone receptor-positive, or HER-2 positive diseases, and those without data enough to obtain ORs for pCR, HRs for OS, EFS, or DFS. Unpublished data as a full article was also excluded. If EFS could not be obtained from the articles, DFS was used in place of EFS. Two independent investigators (TY and TF) searched and extracted data. Any disagreement was resolved by discussion with the third author (ZZ). A linear regression model on a logarithmic scale weighted by the sample size of each trial was performed and the R^2 was used to assess the trial-level association between OR for pCR and HRs for OS or EFS. Results: We identified eight trials with a total of 2,926 patients. Three of the eight trials used ICIs in the intervention arm. One trial did not provide OS data and was not included in the OS

analysis. In four trials, EFS was not available and DFS was used for EFS analysis. The R^2 was 0.191 (95% confidence interval [CI], 0.165 to 0.218) for OS and 0.193 (95% CI, 0.167 to 0.219) for EFS. Conclusions: Similarly to the previous reports, our findings suggest that the surrogacy of the pCR rate for OS and EFS in recent neoadjuvant clinical trials for TNBC is weak. At this moment, there is no strong evidence to support using pCR as a surrogate for long-term survival outcomes in neoadjuvant clinical trials for TNBC.

PO1-03-08

Association of patient-reported triple-negative breast cancer (TNBC) knowledge with clinical trial participation

Presenting Author(s) and Co-Author(s):

M. Tesch. Dana-Farber Cancer Institute, United States

N. Graham. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Ryan. DFCI, United States

M. Hughes. Dana Farber Cancer Institute, United States

E. Wrabel. Dana-Farber Institute, United States

N. Tung. Beth Israel Deaconess Medical Center, Boston, United States

S. Lo. Stamford Hospital, United States

T. Fynan. Berkshire Medical Center, United States

M. Faggen. Dana-Farber Cancer Institute, United States

N. Sinclair. Dana-Farber Cancer Institute Milford & Foxborough, United States

M. Constantinou. Lifespan Comprehensive Cancer Center, United States

S. Sinclair. Eastern Maine Medical Center, United States

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Garrido-Castro. Dana-Farber Cancer Institute, and Harvard Medical School, Brookline, Massachusetts, United States

Background: Patients with TNBC are highly encouraged to participate in clinical trials given the lack of targeted treatment options for this breast cancer subtype. Yet little is known regarding barriers to trial participation in this population, including the impact of patients' understanding about TNBC biology. We examined whether disease knowledge and other patient-level factors were associated with TNBC patients' participation in trials. Methods: From a multicenter, prospective cohort study of patients enrolled from 2019-present with newly diagnosed TNBC (ER/PR \leq 10% also eligible), we identified those with stage I-III tumors who completed at least one survey. Surveys assessed demographics, TNBC knowledge, risk perceptions, and participation in clinical trials. Patients were assigned to Cohort A if surgery was the first intervention and Cohort B if neoadjuvant therapy was given. Medical records were reviewed to verify the accuracy of tumor characteristics reported by patients. Data was summarized with descriptive statistics and logistic regression was used to identify factors associated with trial participation. Results: Of the 137 patients included, median age was 56 years (IQR 46-63), 104 (82%) were non-Hispanic White, 10 (8%) Black, 5 (4%) Hispanic. and 110 (86%) had at least some college education. Overall, 55 (41%) had stage I tumors, 65 (48%) stage II, and 14 (10%) stage III. Among 116 patients with available clinical trial participation data, 55 (47%) reported trial participation, 59 (51%) reported no trial participation, and 2 (2%) were unsure. The majority (36/55, 65%) of trial participants were in Cohort B. Among 129 patients with TNBC knowledge data, 82 (64%) and 73 (57%) correctly reported their tumor stage and grade, respectively. Most

(104/129, 81%) knew TNBC was defined as ER/PR/HER2-negative, but only 16% (21/128) knew the ER/PR-negative cut off was $\leq 1\%$. Of 98 patients with risk perception data, 30 (31%) estimated their likelihood of recurrence within the next 5 years as 0%, 60 (61%) between 10-50%, and 8 (8%) between 60-100%. When asked if TNBC patients who remain cancer-free after 3 years will most likely not experience recurrence, 44 (45%) said "True," 13 (13%) said "False," and 40 (41%) were unsure. On univariate analysis, trial participation was less likely in Cohort A patients (OR 0.42, 95% CI 0.20 – 0.89, $P=0.02$) and more likely in stage II patients (vs. stage I, OR 2.43, 95% CI 1.09 – 5.39, $P=0.03$). On multivariable analysis, patients with at least some college education had higher odds of trial participation compared to patients with a college degree or higher (OR 3.21, 95% CI 1.11 – 9.28, $P=0.03$). No associations were found for other factors, including TNBC knowledge. Conclusions: About half of TNBC patients surveyed reported participating in clinical trials. Most of these patients were undergoing neoadjuvant therapy, likely reflective of greater study availability in this setting. While TNBC knowledge was not significantly associated with trial participation in this small sample, a considerable number of patients reported their tumor characteristics incorrectly and/or appeared to underestimate their recurrence risks. This highlights the need for enhanced informational support for TNBC patients during treatment decision-making. More research is needed to understand barriers to trial participation in this population to leverage patient engagement and accelerate progress towards more effective treatments for TNBC.

	OR (95% CI)	P
Cohort^a		
B	Ref	
A	0.51 (0.13 – 1.98)	0.33
Age		
<50 years	Ref	
≥ 50 years	1.98 (0.75 – 5.22)	0.17
Non-Hispanic White		
Yes	Ref	
No	1.10 (0.36 – 3.37)	0.86
Education		
College graduate	Ref	
Some college	3.21 (1.11 – 9.28)	0.03
\leq High school	2.60 (0.64 – 10.48)	0.18
Stage		
I	Ref	
II	1.67 (0.45 – 6.26)	0.44
III	2.50 (0.34 – 18.17)	0.36
Number of TNBC knowledge questions answered correctly (0-4)^b	1.01 (0.59 – 1.71)	0.98

PO1-03-09

Transcriptomic profiling of ER-negative and ER-low, HER2-negative breast cancer and its implications on immune regulation

Presenting Author(s) and Co-Author(s):

G. Griguolo. Department of Surgery, Oncology and Gastroenterology, University of Padua; Division of Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy

C. Vernieri. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Lombardia, Italy

D. Massa. Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy, United States

L. Nicolè. Department of Medicine (DIMED), University of Padua, Padova, Italy, United States

c. Pinato. Veneto Institute of Oncology IOV-IRCCS, Veneto, Italy

F. Miglietta. Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy, United States

A. Vingiani. Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori, United States

S. Brich. Fondazione IRCCS Istituto dei Tumori, Italy

R. Lobefaro. Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, United States

F. Schiavi. Veneto Institute of Oncology IRCCS, United States

M. Fassan. University of Padua, Department of Medicine (DIMED), United States

G. Pruneri. University of Milan, Fondazione IRCCS Istituto Nazionale dei Tumori, Spain

V. Guarneri. Department of Surgery, Oncology and Gastroenterology, University of Padua; Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Veneto, Italy

M. Dieci. University of Padova, United States

Background: The recommended cut-off of < 1% positive cells to define estrogen receptor (ER) negative status in breast cancer (BC) is highly debated. Few data exist on transcriptomic features of ER-low BC, suggesting no major differences vs ER-neg.

Among HER2-negative BCs, we compared gene-expression profiling (including PAM50 intrinsic subtyping) according to ER status (ER-neg: 0% vs. ER-low: 1-9%) and assessed its impact on Tumor-infiltrating lymphocytes (TILs) levels.

Methods: Across two cancer centers, stage I-III HER2-negative BCs FFPE samples were reviewed for ER status. All ER-low (ER 1-9%) samples were identified and a cohort of ER-neg BC samples, matched for age and stage, was also retrieved. A small cohort of pts with intermediate ER expression (ER-int: 10-50%) was included as a control cohort.

Expression of 776 BC-related genes was evaluated by nCounter® (Breast Cancer 360TM Panel) and intrinsic molecular subtyping was determined using the PAM50 subtype predictor. A False Discovery Rate (FDR) corrected unpaired two-class SAM was used to identify genes differentially expressed in different subgroups.

TILs were evaluated on archival H&E slides following guidelines.

Results: Of 116 stage I-III HER2-neg BC pts included, 39 had ER-neg BC, 65 had ER-low BC, and 12 had ER-int disease. PAM50 intrinsic subtype distribution was similar in ER-neg and ER-low BCs, (with an enrichment in basal-like tumors), while both subgroups differed significantly from ER-int samples (Table). As compared to ER-neg tumors, ER-low BCs showed significantly higher expression of GATA3 gene and lower expression of EDN1 and PROM1 genes by SAM analysis (FDR < 5%); however, when the analysis was limited to PAM50 basal-like tumors (N=77) we only identified two genes that were downregulated in ER-low BCs (EDN1, PROM1) as compared to ER-neg BCs.

On the contrary, significant differences in transcriptomic regulation were observed between ER-low and ER-int BCs, with ER-low BCs showing significantly higher expression of 53 genes and lower expression of 398 genes, as compared to ER-int (SAM analysis FDR < 5%).

We previously reported similar TIL levels in ER-low and ER-neg tumors. In both ER-low and ER-int BCs, PAM50 basal-like subtype was associated with significantly higher TILs: median TIL levels 20 (range 0-80) and 6 (range 1-40) for PAM50 Basal-like BCs versus other PAM50 subtypes respectively in ER-low samples ($p < 0.001$); median TIL levels 53 (range 25-80) and 5 (range 0-10) for PAM50 Basal-like BCs versus other PAM50 subtypes respectively in ER-int samples ($p = 0.036$). No significant difference in TIL levels according to PAM50 subtyping were observed in ER-neg tumors.

No significant difference in mRNA levels for PD-1 (PDCD1) and PD-L1 (CD274) genes was observed between ER-low and ER-neg tumors.

Conclusions: Among patients with HER2-neg BC, gene-expression profiling is similar in ER-neg (i.e., < 1%) vs. ER-low tumors with a high prevalence of PAM50 Basal-like tumors and few differentially expressed genes.

In both ER-low and ER-int HER2-neg BCs, PAM50 Basal-like subtype is also associated with higher TIL levels.

Our results strongly indicate that HER2-neg/ER-low BCs and HER2-neg/ER-neg BCs are similar biological entities, thus further supporting the use of similar treatments in patients with early-stage ER-low and triple-negative BC, including immune checkpoint inhibitors.

PAM50 intrinsic subtype distribution according to ER levels

PAM50 Intrinsic Subtype	ER-neg (n=39)	ER-low (n=65)	ER-int (n=12)	Fisher test p-value
Basal-like	31 (79%)	46 (71%)	3 (25%)	ER-neg vs ER- low: 0.396 ER-neg vs ER-int: <0.001 ER-low vs ER-int: 0.002
HER2-enriched	1 (3%)	6 (9%)	0	
Luminal B	0	1 (2%)	0	
Luminal A	0	3 (5%)	4 (33%)	
Normal-like	7 (18%)	9 (14%)	5 (42%)	

PO1-03-10

Differential microbial metabolic pathways associated with resistance to neoadjuvant immunotherapy in locally advanced triple negative breast cancer

Presenting Author(s) and Co-Author(s):

H. Sarfraz. Moffitt Cancer Center/University of South Florida, Tampa, Florida, United States

B. Czerniecki. H. Lee Moffitt Cancer Center, United States

Z. Jameel. Moffitt Cancer Center/University of South Florida, United States

M. Jaglal. Moffitt Cancer Centre/ University of South Florida, United States

M. Eysha. Duke Cancer Institute, United States

T. Ozkul. Istanbul Medicana Atasehir Hospital, United States

J. Muzaffar. Duke Cancer Institute, United States

A. Saha. Moffitt Cancer Center/University of South Florida, United States

S. Sarfraz. Combined Military Hospital, United States

F. Zahra. Moffitt Cancer Center/University of South Florida, United States

M. Liu. Moffitt Cancer Centre/ University of South Florida, United States

K. Jhaveri. Moffitt Cancer Center/University of South Florida, United States

M. Sur. university of south florida, United States

A. Bagos-Estevez. university of south florida, United States

S. Bari. Duke Cancer Institute, United States

Differential microbial metabolic pathways associated with resistance to neoadjuvant immunotherapy in locally advanced triple negative breast cancer Background: It has previously been shown that microbial metabolic pathways are differentially activated in immunotherapy resistance, hence can serve as potential targets for therapeutic intervention. With the advent of Immune Checkpoint Blockers in the neoadjuvant setting of locally advanced (LA) TNBC, we hypothesized that similar microbial metabolite mediated resistance may be at play. We are presenting the real world data for neoadjuvant treatment in early TNBC along with a subset of tumor metabolite analysis. Method: 35 patients who received neoadjuvant pembrolizumab and chemotherapy for LA TNBC were identified at Moffitt Cancer Center between July 2019 to January 2023. These included 22 Caucasian, 5 African American, 2 Hispanic and 6 patients with undisclosed race. The age range was 33-78 years. The weight and Body Mass Index range was 55.3 kg-127.3 kg and 20.96-45.43 kg/m² respectively. Nine patients had stage III disease while 24 had stage II breast cancer.

The response was assessed in 33 patients; 20 patients (60.6%) achieved pathological complete response (pCR) and 13 (39.4%) had residual disease (RD). 1 patient developed severe immune mediated toxicity with colitis, hepatitis, myasthenia gravis leading to death while 1 patient had disease progression leading to drug discontinuation. Six patients developed immune mediated adverse events. We conducted untargeted metabolomic profiling on 24 patients to identify differentially abundant metabolites associated with pCR (ypT0/is ypN0) vs RD; 16 vs 8 patients respectively. Formalin fixed paraffin embedded (FFPE) slides from tumor tissue vs tumor bed were retrieved and histopathological evaluation of tumor cells was performed. 20 µm sections of FFPE block were used for untargeted metabolomics via liquid chromatography/mass spectrometry. Among the 200 metabolites detected, 63 were differentially abundant between pCR and tumor samples with RD. After correcting for false

discovery rate, we observed striking differential activation of two microbial metabolic pathways. Samples with RD had significantly elevated kynurenine (OR-3.64 X10³⁴, P-1.94 X 10⁻⁷⁴ and kynurenine /Tryptophan ratio). The tryptophan, kynurenine pathway has been known to be overexpressed in patients resistant to immunotherapy and modulated by the microbiome. Similarly, the purine metabolic pathway, specifically microbiota-derived immunostimulatory metabolites- inosine, hypoxanthine, uric acid were significantly depleted in patients with RD (Inosine OR-0.54, p-0.007, Hypoxanthine OR-0.5, p-0.00039, uric acid OR: 0.41, P-0.003). Previously Inosine has been shown to increase the anti-tumor effects of immune checkpoint blockade by enhancing CD8⁺ effector T-cell function. Hence depletion of inosine, hypoxanthine and uric acid signals lack of an effector CD8 T cell response. Conclusion: Despite being a small study, it corroborates pCR rates noted in KEYNOTE 522 in the real world setting but shows significant concern for serious immune mediated adverse effects. This highlights the importance of stratifying patients who might be resistant to ICB or develop significant toxicities, thus deriving little to no benefit from standard neoadjuvant treatment. This underscores the need to develop precision-based treatment algorithms. The study represents one of the first investigations of differential abundance of microbial metabolites with immunotherapy resistance in LA TNBC. Our results highlight two microbially mediated mechanisms that could be targeted to improve pCR rates in LA TNBC. We are working to identify microbial metabolic pathways associated with immune mediated toxicity.

PO1-03-11

Camrelizumab in Combination with Nab-Paclitaxel and Carboplatin versus Nab-Paclitaxel and Carboplatin as Neoadjuvant Therapy for Triple Negative Breast Cancer: A Multicenter, Open-Label, Randomized Controlled Study

Presenting Author(s) and Co-Author(s):

W. Zhao. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

X. Wang. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

B. Zhang. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

Y. Shi. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

C. Wang. Tianjin Medical University Cancer Institute and Hospital, United States

X. Wang. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

S. Li. Tianjin Medical University Cancer Institute and Hospital, United States

c. Hao. Tianjin Medical University Cancer Institute & Hospital, United States

N. Lu. Tianjin Medical University Cancer Institute and Hospital, United States

Y. Jia. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

L. Zhang. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

L. Zhang. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

W. Sun. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

X. Cao. Tianjin Medical University Cancer Institute and Hospital, United States

Z. Tong. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

Background: Triple-negative breast cancer (TNBC) is recognized for its aggressive nature and unfavorable prognosis. Immune checkpoint inhibitors have demonstrated promising antitumor activity in both neoadjuvant and metastatic settings. This study aimed to assess the efficacy and safety of camrelizumab, an anti-PD-1 antibody, in conjunction with chemotherapy as a neoadjuvant treatment for early-stage TNBC. Methods: This two-phase prospective, multicenter, randomized controlled study was initiated with the enrollment of previously untreated stage II-III TNBC patients in the first phase. They received neoadjuvant therapy comprising six 3-week cycles of camrelizumab (200 mg, q3w), along with nab-paclitaxel (220 mg/m², q3w) and carboplatin (AUC 5, q3w). In the second phase, patients were enrolled and randomized 1:1 to either the camrelizumab plus nab-paclitaxel and carboplatin group or the nab-paclitaxel plus carboplatin group. The present report covers the data from the first phase of the study. The primary endpoint was the total pathological complete response (tpCR, ypT0/is ypN0) rate. Secondary endpoints included breast pathological complete response (bpCR, ypT0/is) rate, objective response rate (ORR), event-free survival (EFS), residual cancer burden

(RCB), and safety. This study is registered with ClinicalTrials.gov, under the identifier NCT04907344. Results: Between September 2021 and March 2023, 39 patients were enrolled in the first phase. A total of 35 (89.7%) were node-positive. Among the 32 patients with evaluable efficacy, the tpCR rate was 59.4% (19/32), and the bpCR rate was 68.8% (22/32). The ORR at the end of neoadjuvant treatment stood at 87.2% (34/39). Among the 39 patients, 11 (28.2%) experienced grade 3 or higher treatment-related adverse events, the most common of which were thrombocytopenia (6 [15.4%]), leucopenia (5 [12.8%]), neutropenia (5 [12.8%]), alanine aminotransferase increased (2 [5.1%]), aspartate aminotransferase increased (1 [2.6%]), and hypothyroidism (1 [2.6%]). Adverse events leading to discontinuation of any agent occurred in 5 (12.8%) patients, while adverse events leading to delay in treatment occurred in 7 (17.9%) patients. Serious treatment-related adverse events were reported by 4 (10.4%) patients. Conclusions: In patients with early TNBC, the neoadjuvant treatment of camrelizumab in combination with nab-paclitaxel and carboplatin demonstrated a high pCR rate with an acceptable safety profile. The second phase of the study is currently in progress to validate these findings.

PO1-04-01

Phase 1 dose escalation study of ARX788, a next-generation anti-HER2 antibody drug conjugate, in heavily pretreated breast cancer patients

Presenting Author(s) and Co-Author(s):

S. Frentzas. Monash Health, United States

H. Park. Dana Farber Cancer Institute, United States

G. Budd. Cleveland Clinic, Cleveland, Ohio, United States

V. Ganju. PSEHOG (Peninsula & South Eastern Haematology and Oncology Group), Frankston, Victoria, Australia

C. Shannon. Mater Cancer Care Centre, United States

S. Hurvitz. Fred Hutchinson Cancer Center/University of Washington, Los Angeles, California, United States

K. Cuff. Princess Alexandra Hospital, Brisbane, Queensland, Australia

P. Lau. Linear Clinical Research, Perth, Australia and University of Western Australia, Perth, Washington, Australia

R. Eek. Border Medical Oncology and Hematology, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

F. Boyle. University of Sydney and Mater, United States

S. Aung. Ambrx, United States

C. Hessel. Ambrx, United States

J. Lu. Northwestern University Lurie Comprehensive Cancer Center, Chicago, Illinois, United States

Introduction: ARX788 is a next-generation anti-HER2 antibody-drug conjugate (ADC) conjugated to amebstatin269 (AS269), a potent cytotoxic tubulin inhibitor. ARX788 is highly stable with nearly identical PK profiles for the total ADC and the total antibody due to proprietary site-specific oxime conjugation chemistry. The stability of ARX788 results in limited systemic toxicity and increased targeted delivery of payload to tumor cells. Clinical benefit of ARX788 has been observed in patients (pts) with HER2-positive (HER2-pos) breast cancer (BC) in multiple clinical trials and recently in a randomized, controlled, phase 3 registrational trial conducted in China.

Methods: ARX788-1711 (NCT03255070) was a phase 1 dose-escalation study of ARX788 monotherapy in pts with advanced solid tumors with HER2 expression. There was no limit to the number of prior therapies. An objective of the trial was investigating the safety and tolerability of ARX788 in pts with BC.

Results: Between August 2020 and June 2023, 42 pts with HER2-pos and HER2-low BC with a median of 6 prior lines of therapy received intravenous ARX788 at either 1.5, 1.6, or 1.7 mg/kg every 21 days (Q3W) or every 28 days (Q4W). Treatment regimens were combined for these analyses. ARX788 was generally well tolerated. Most adverse events (AEs) were grade (Gr) 1 or 2, the most common being ocular, alopecia, nausea, and fatigue. Gr3 treatment-related AEs (TRAEs) occurred in 23.8% of pts and included nausea, ocular, AST and ALP increase (4.8% each); one pt (2.4%) had Gr3 pneumonitis/interstitial lung disease. A Gr3 ocular SAE occurred

48 days after the pt's last study dose and was resolving 9 days after onset. There were no Gr4 or Gr5 events. Treatment discontinuation due to drug-related AEs occurred in 7.1% of pts. Overall response rate (ORR) per RECIST v1.1 was analyzed in groups by HER2-low or HER2-pos tumor status. In pts with HER2-pos BC (n=11) the ORR was 54.5% (4 confirmed, 2 unconfirmed); in pts with HER2-low BC (n=30) the ORR was 23.3% (5 confirmed, 2 unconfirmed). The disease control rate (confirmed complete or partial response + stable disease) was 81.8% and 76.7%, for HER2-pos and HER2-low BC, respectively. Six of 9 pts with confirmed responses had a duration of response greater than 5 months. Six of eight pts with prior trastuzumab deruxtecan (T-DXd) exposure also had prior trastuzumab emtansine (T-DM1). Two pts with prior T-DM1 and T-DXd had significant target lesion reductions of 55% and 32%; these were a HER2-low pt with 6 prior cancer therapy regimens and a HER2-pos pt with 9 prior cancer therapy regimens, respectively. Both pts came off treatment before response confirmation. As of the data cut-off (19 Jun 2023), 4 of 9 confirmed responders remain on treatment and continue to experience clinical benefit including one pt with prior T-DM1 exposure with a durable response of 15.8 months. Importantly, significant target lesion reductions were observed in heavily pretreated pts who also received prior T-DXd and T-DM1.

Discussion: Based on the promising safety and antitumor activity of ARX788 in this heavily pretreated pt population, a phase 2 study is open (NCT04829604) and enrolling pts with HER2-pos BC who have been previously treated with T-DXd.

PO1-04-02

ACE-Breast-03: A phase 2 study of ARX788, a novel next-generation anti-HER antibody-drug conjugate in HER2-positive metastatic breast cancer patients previously treated with trastuzumab deruxtecan

Presenting Author(s) and Co-Author(s):

K. Ali. Maryland Oncology Hematology, United States

L. Agrawal. Norton Cancer Institute Resource Center – St. Matthews, United States

A. Thummala. Comprehensive Cancer Centers of Nevada - Las Vegas - Peak Drive, United States

K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

S. Ali. The Oncology Institute of Hope and Innovation, United States

S. Blau. Northwest Medical Specialties, United States

M. Block. Nebraska Cancer Specialists, Omaha, Nebraska, United States

M. Danso. Virginia Oncology Associates, Norfolk and Virginia Beach, VA, USA, United States

D. Yardley. Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, United States

J. Andersen. Compass Oncology, United States

A. Gropper-Waks. Dana-Farber Cancer Institute, United States

P. Jayachandran. University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, United States

I. Makhlin. University of Pennsylvania, Philadelphia, Pennsylvania, United States

P. Nikolinakos. University Cancer and Blood Center, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

S. Aung. Ambrx, United States

C. Hessel. Ambrx, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

W. Gradishar. Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background: HER2 overexpression and/or amplification confers aggressive tumor behavior and decreased survival in patients with breast cancer. Targeting of HER2 is a validated therapeutic strategy, and trastuzumab deruxtecan (T-DXd) has emerged as a preferred treatment in the second-line setting. However, effective treatment following progression on T-DXd remains a major unmet medical need. ARX788 is a next-generation antibody-drug conjugate (ADC) using a technology platform whereby a HER2-specific monoclonal antibody is conjugated to amberstatin 269 (AS269), a potent cytotoxic tubulin inhibitor. Site-specificity, high homogeneity, and stable covalent conjugation of ARX788 leads to the slow release and prolonged peak of serum pAF-AS269, which may contribute to the lower systemic toxicity and increased targeted delivery of payload to tumor cells, at a lower effective dose compared with other HER2 ADCs.

Methods: ACE-Breast-03 (NCT04829604) is a global, phase 2 study designed to assess anticancer activity and safety in approximately 40 patients with unresectable or metastatic HER2 positive breast cancer who have been previously treated with T-DXd. Eligibility criteria include measurable disease by RECIST v1.1, radiographically stable brain metastases, no more than three prior lines of treatment in the metastatic setting, and HER2 positivity as determined by central review. If recently progressed on T-DXd or trastuzumab emtansine (T-DM1), a new biopsy for HER2 status is required. Patients will be administered 1.5 mg/kg of ARX788 every three weeks. Efficacy will be assessed using RECIST v1.1 at nine-week intervals after starting ARX788 until progression or start of new cancer treatment. Objective response rate is the primary endpoint, with disease control rate, progression-free survival, overall survival, best overall response, duration of response, and time to response as additional endpoints. The safety and tolerability profile will also be evaluated. PK analysis will determine serum concentrations of ARX788, total antibody, and pAF-AS269. Potential predictive and/or prognostic biomarkers will be analyzed for exploratory purposes. Descriptive statistics will be used to evaluate anticancer activity, safety, and tolerability. The study is currently recruiting patients.

PO1-04-03

Phase I/II Trial of Ibrutinib Plus Trastuzumab in HER2-Positive Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

A. Glidden. Sarah Cannon Research Institute, Nashville, TN, United States

T. Locke. Sarah Cannon Research Institute, Nashville, TN, United States

A. Scales. Sarah Cannon Research Institute, Nashville, TN, United States

Background: Ibrutinib is a first-in-class inhibitor of Bruton's tyrosine kinase that has demonstrated potent inhibition of ErbB/HER family receptor tyrosine kinases in preclinical models. Ibrutinib also displays immunomodulatory effects, shifting the profile of the immune response from Th2-type to Th1-type cytokines (Dubovsky et al. 2013), resulting in enhanced antitumor immunity. As there is a need for novel HER2-targeted therapies following progression on established anti-HER2-directed therapies, and as combining multiple HER2-directed agents is more effective than single-agent therapy (Blackwell et al. 2012), this study explored the safety and efficacy of ibrutinib in combination with trastuzumab in patients (pts) with HER2-positive metastatic breast cancer (MBC) (NCT03379428). Trial design: Phase I was a dose-escalation study to define the recommended Phase II dose (RP2D) of ibrutinib plus trastuzumab. The primary objective of Phase II was to define the clinical benefit rate (CBR = complete response [CR] + partial response [PR] + stable disease [SD] \geq 6 months) of ibrutinib plus trastuzumab; secondary objectives were to determine objective response rate (ORR = CR + PR), overall survival (OS), progression-free survival (PFS), and safety/tolerability. Pts had HER2-positive MBC with measurable disease per RECIST v1.1, disease progression on or within 6 months of completing ado-trastuzumab emtansine (T-DM1) therapy, and \leq 4 (Phase I) or \leq 5 (Phase II) prior chemotherapy regimens for MBC, with no limit on prior endocrine therapies. Results: 26 pts were treated in Phases I and II: median age, 65.1 y; 15.4% Asian, 15.4% Black, 46.2% Caucasian, 19.2% Hispanic, and 3.8% Other; 46.2% with ECOG performance status (PS) of 0, 42.3% with PS of 1, and 7.7% with PS of 2. Median prior lines of therapy for MBC was 2 (range: 0, 6); median prior lines of therapy in any setting was 4 (range: 1, 9). In any setting, 88.5% of pts had prior treatment (Tx) with trastuzumab, 80.8% had prior Tx with pertuzumab, and 100% had prior Tx with T-DM1. 0% of pts had brain, 38.5% had bone, 23.1% had liver, and 42.3% had lung metastases. All pts were HER2+ by local pathology, 61.5% positive by IHC and 42.3% by FISH; 12 pts had ER+ and/or PR+ and 14 pts had ER-/PR- cancers. The starting dose of ibrutinib for Phase I was 560 mg. Of the 3 pts enrolled at this dose level, all experienced grade 3 or higher adverse events (AEs), with 2 of the pts experiencing serious AEs (grade 4 alanine aminotransferase [ALT] increased and grade 5 respiratory failure). As such, 420 mg of ibrutinib was selected as the RP2D. At the time of data extraction, across Phase I/II, 16 pts (61.5%) experienced a Tx-related adverse event (TRAE). The most common (\geq 5%) TRAEs of any grade were bruising and rash (each 19.2%); fatigue and thrombocytopenia (each 15.4%); anemia, diarrhea, and edema (each 11.5%); and ALT increased, aspartate aminotransferase increased, blurred vision, ecchymoses, mucositis, nausea, pruritus, and vomiting (each 7.7%). A total of 5 pts (19.2%) experienced grade 3 or 4 TRAEs; no grade 5 TRAEs were reported. 26 pts were treated with ibrutinib and trastuzumab, and 26 pts were in the evaluable population. 1 pt had CR for an ORR of 3.8% (95% CIs: 0.1, 19.6); 9 pts had SD, and 4 pts had SD for \geq 6 months for a CBR of 19.2% (95% CIs: 6.6, 39.4). Median OS was 27.1 months (range: 0.30, 27.1), and median PFS was 2.0 months (range: 0.03, 27.1). The PFS rate at 12 months was 34.6% (95% CIs: 15.6, 54.6). Conclusion: Ibrutinib

plus trastuzumab had a manageable safety profile; however, the CBR did not reach the protocol-specified goal of 28%, and these results do not support further clinical investigation. An in-depth evaluation of the immune effects of ibrutinib in these pts is ongoing.

PO1-04-04

Inetetamab combined with pyrotinib and oral vinorelbine for patients with HER2-positive metastatic breast cancer: a single-arm phase 2 trial

Presenting Author(s) and Co-Author(s):

X. Huang. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

N. Jin. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

C. Sun. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

X. Yan. Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, United States

F. Yang. Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, United States

Y. Liang. Department of Breast Surgery, Jiangsu Province Hospital, Nanjing, United States

W. Li. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

Y. Yin. The First Affiliated Hospital of Nanjing Medical University, United States

Aim: The efficacy and safety of inetetamab in combination with pyrotinib and oral vinorelbine was investigated in patients with human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer. **Methods:** In this prospective, single-arm, phase 2 trial, patients with HER2-positive metastatic breast cancer after progression on trastuzumab were recruited. Patients received combined treatment of inetetamab (loading dose of 8 mg/kg, subsequent doses 6 mg/kg, intravenously once every 3 weeks) plus pyrotinib (400 mg orally once daily) plus vinorelbine (60 mg/m² orally once weekly) until disease progression or intolerable toxicity. The primary endpoint was progression free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), disease control rate (DCR) and safety. The study was retrospectively registered in ClinicalTrials.gov on March 23rd, 2023. The registration number is NCT05823623. **Results:** Between Jan 1, 2022, and Dec 31, 2022, thirty patients were screened and enrolled to this study. The patients' median age at enrollment was 54 years, twelve patients (40.0%) had hormone receptor-positive disease and 23 patients (76.7%) had visceral metastasis. The median PFS was 8.63 months (95% confidence interval [CI] 4.15 to 13.12 months). ORR was 53.3% (16/30) and DCR reached 96.7% (29/30). The most common grade III/IV adverse events included leukopenia (5[16.7%]), neutropenia (4[13.3%]) and diarrhea (3[10%]). No treatment-related serious adverse events or treatment-related deaths occurred. **Conclusions:** The combination regimen of inetetamab plus pyrotinib plus oral vinorelbine showed an encouraging efficacy and favorable safety in patients with HER2 positive metastatic breast cancer.

PO1-04-05

Effectiveness and safety of inetetamab + pyrotinib + vinorelbine in ≥second-line treatment of HER2-positive metastatic breast cancer

Presenting Author(s) and Co-Author(s):

F. wu. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

M. Chen. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

W. Huang. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

L. Wang. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

N. Li. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

X. Wu. Department of Breast Surgery, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

X. Chen. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

Y. Hong. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

L. Lin. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

K. Chen. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

J. liu. Department of Medical Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, Fujian Province, China, United States

Background: In real-world settings, Patients with HER2-positive metastatic breast cancer (MBC) who cannot receive antibody-drug conjugates (ADCs) as standard second-line therapy due to cost–benefit ratios and who have no preferred options as ≥third-line regimen by NCCN guidelines, require new regimens to meet their clinical needs. This study aims to explore the effectiveness and safety of inetetamab + pyrotinib + vinorelbine for ≥second-line treatment of HER2-positive MBC. **Methods:** Patients with HER2-positive MBC who received ≥second-line treatment at our hospital from June 2020 to December 2022 were enrolled. Progression-free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR) and adverse reactions were assessed. Patients received inetetamab + pyrotinib + vinorelbine until disease progression or unacceptable toxicity were evaluated every two cycles according to the RECIST 1.1 criteria. **Results:** 89 patients were included based on the inclusion and exclusion criteria. Among them, 45 patients received second-line treatment who couldn't use T-DM1 or T-DXd, and 44 patients received ≥third-line treatment. The median PFS of the second-line treatment subgroup was 17months, the ORR and CBR were 60.0% and 86.7%, respectively, which were significantly higher than those in the ≥third-line treatment subgroup and numerically superior to T-DM1 as a second-line treatment option. Additionally, the ORR and CBR of patients with baseline brain metastasis who did not receive radiotherapy were 27.3% and 72.7%, respectively. The most common adverse events observed were leukopenia (37.1%), neutropenia (42.7%), anemia (34.8%) and diarrhea (67.4%). The incidence of grade 3-4

leukopenia, neutropenia, anemia and diarrhea were 11.2%, 15.7%, 55.6% and 27.0%, respectively. A total of 8 patients (8.9%) discontinued medication due to adverse reactions. Conclusions: Inetetamab + pyrotinib + vinorelbine demonstrates good efficacy and controllable toxicity as a second-line treatment for HER2-positive MBC. This therapeutic regimen provides a viable alternative option for patients who are unable to receive ADCs as the second-line treatment.

PO1-04-06

Exposure-response analyses of sacituzumab govitecan efficacy and safety in patients with metastatic breast cancer

Presenting Author(s) and Co-Author(s):

I. Singh. Gilead Sciences, Inc., United States
A. Sathe. Gilead Sciences, Inc., United States
P. Diderichsen. Certara USA, Inc, United States
H. Witjes. Certara USA, Inc, United States
A. Van Schanke. Certara USA, Inc, United States
J. Maringwa. Certara USA, Inc, United States
W. Verret. Gilead Sciences Inc, Foster City, CA, United States
S. Girish. Gilead Sciences, Inc., United States
A. Othman. Gilead Sciences, Inc., United States

Background: Sacituzumab govitecan (SG) is an antibody-drug conjugate that is composed of an anti Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolysable CL2A linker. SG (10 mg/kg on D1 and D8 of every 21D cycle) is approved for patients (pts) with metastatic triple-negative breast cancer (mTNBC) who received ≥ 2 prior systemic therapies (≥ 1 in the metastatic setting). The relationship between exposure of SG, free SN-38, and total antibody (tAB) following SG administration and its efficacy and safety were evaluated in pts with HR+/HER2- metastatic breast cancer (mBC) and all pts with mBC (mTNBC or HR+/HER2- mBC), respectively. Methods: Available exposure and efficacy outcomes from HR+/HER2- mBC pts from phase 3 study TROPiCS-02 (n=260) and safety outcomes from mBC pts in phase 1/2 study IMMU-132-01, phase 3 study ASCENT and TROPiCS-02 (total n=569) were analyzed. Exposure-response (ER) models were developed to characterize the relationship between exposure and efficacy (complete response [CR], overall response rate [ORR], clinical benefit rate [CBR], overall survival [OS] and progression-free survival [PFS]) and safety (adverse events [AEs] of vomiting, diarrhea, hypersensitivity reactions, nausea, neutropenia, febrile neutropenia, time to first dose reduction and first dose delay) endpoints. Exposure metrics of SG, free SN-38, and tAB were evaluated as predictors and effect of clinically relevant covariates was characterized within the modeling framework. Results: Average SG-related serum exposures over the duration of treatment (until the event) were associated with significantly increased efficacy (probability of CR, ORR, CBR and longer OS and PFS) and safety events (probability of any grade AE). Neutropenia was the only AE where the increase in exposure was significantly associated with the increased probability of Grade ≥ 3 and Grade 4 events. Baseline Trop-2 expression level was not correlated with assessed efficacy and safety endpoints. Conclusions: Within the exposure range achieved with the 10 mg/kg regimen, higher exposure values were associated with a higher probability of achieving better efficacy. The 10 mg/kg SG dose achieved an acceptable balance between efficacy and safety which supports the appropriateness of this regimen in pts with HR+/HER2- mBC.

PO1-04-07

Disitamab vedotin, a clinical stage HER2-directed antibody-drug conjugate, shows potent antitumor activity as a monotherapy and in combination with tucatinib in preclinical breast cancer models

Presenting Author(s) and Co-Author(s):

K. Willis. Seagen, United States

R. Hein. Seagen, United States

K. Snead. Seagen, United States

R. Thurman. Seagen, United States

A. Kulukian. Seagen, United States

Disitamab vedotin (DV, RC48-ADC) is an antibody-drug conjugate (ADC) that targets cancers expressing HER2. DV consists of an anti-HER2 monoclonal antibody, disitamab, conjugated with the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a cleavable vedotin linker. DV has multimodal antitumor mechanisms of action that include direct cytotoxicity of HER2-expressing cancer cells and bystander effect-based cytotoxicity of neighboring cells, both of which are mediated by the intracellular release of MMAE. Released MMAE can also induce immunogenic cell death, which promotes immune cell recruitment to the tumor. In addition, DV stimulates Fc-gamma receptor mediated antibody-dependent cellular cytotoxicity, which can lead to target cell death. DV also inhibits HER2-activated downstream signaling pathways, further blocking cell growth, survival, and proliferation. Previously, we showed the cytotoxic activity of DV against a panel of breast cancer cell lines with varying levels of HER2 expression, including the HER2-low range. Here, we sought to further characterize the preclinical antitumor activity of DV in patient-derived 3D models and patient-derived xenographs (PDX). In cultured breast cancer cells, DV was more potent and internalized to a greater magnitude than the HER2-directed ADCs trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd). In patient-derived 3D models, DV had superior activity compared to T-DXd. We further explored whether dual HER2 targeting with DV in combination with the HER2-selective oral TKI tucatinib improved the antitumor outcomes. In PDX models with varying HER2 IHC levels and models refractory to T-DXd, DV as a monotherapy and in combination with tucatinib showed significant tumor growth inhibition. This result is consistent with previous in vitro results that showed increased cytotoxicity of the combination of DV and tucatinib in cell lines with a wide range of HER2 expression, which may be mechanistically attributed to elevated HER2 cell surface levels upon treatment with tucatinib. Overall, these findings provide scientific rationale to explore DV in HER2-positive and HER2-low breast cancer patients as a monotherapy or in combination with tucatinib.

PO1-04-10

Body Mass Index and Treatment Efficacy in advanced Luminal Breast Cancer: Insights from the GEICAM/2013-02 (PEARL) trial

Presenting Author(s) and Co-Author(s):

M. Alva. Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain, United States

S. López-Tarruella. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

C. Zielinski. Vienna Cancer Center, Medical University of Vienna and Vienna Hospital Association. CECOG, Austria

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

M. Muñoz. SOLTI Breast Cancer Research Group, Hospital Clínic of Barcelona, Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, Catalonia, Spain

B. Bermejo. Hospital Clínico Universitario de Valencia, Valencia, Spain, United States

M. Margelí. SOLTI Cancer Research Group. Medical Oncology Department, ICO Badalona, B-ARGO Group. GEICAM Spanish Breast Cancer Group., Catalonia, Spain

A. Antón. Miguel Servet University Hospital, Zaragoza, Aragon, Spain

Z. Kahan. Department of Oncotherapy, University of Szeged. CECOG., Hungary

T. Csösz. Department of Oncology, Jasz-Nagykun-Szolnok Megyei Hetenyi Geza Korhaz-Rendelőintezet, Szolnok, Hungary. CECOG, Hungary

M. Casas. GEICAM Spanish Breast Cancer Group, Spain

L. Murillo. Hospital Clínico de Zaragoza Lozano Blesa, Zaragoza, Spain. GEICAM Spanish Breast Cancer Group., United States

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

E. Alba. Hospital Regional Universitario y Virgen de la Victoria, Málaga, Andalucía, Spain

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

A. Guerrero. Fundación Instituto Valenciano de Oncología (FIVO). GEICAM Spanish Breast Cancer Group., Valencia, Comunidad Valenciana, Spain

L. Calvo. Oncology Department-University Hospital A Coruña, A Coruña, Galicia, Spain

J. de la Haba-Rodríguez. Instituto Maimonides de Investigación Biomedica, Hospital Reina Sofía, Universidad de Córdoba. GEICAM Spanish Breast Cancer Group., Spain

M. Ramos. Centro Oncológico de Galicia, A Coruña, Spain. GEICAM Spanish Breast Cancer Group., United States

I. Álvarez. Hospital Universitario Donostia-BioDonostia. GEICAM Spanish Breast Cancer Group., Spain

A. García-Palomo. Hospital de León, León, Spain. GEICAM Spanish Breast Cancer Group., United States

M. Koehler. Repare Therapeutics, Cambridge, Massachusetts, USA, United States

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

J. Chacón. Hospital Universitario de Toledo. GEICAM Spanish Breast Cancer Group., Spain

C. Swift. The Royal Marsden Hospital, London, England, United Kingdom

C. Thallinger. Medical University of Vienna, Department of Oncology Währingergürtel 18-20, 1090 Vienna, Austria. CECOG Central European Cooperative Oncology Group, Vienna, Austria, United States

M. Gil-Gil. Institut Català d'Oncologia, Institut d'Investigació Biomèdica Bellvitge. GEICAM Spanish Breast Cancer Group, United States

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

Background: Endocrine therapy (ET) and treatment directed against molecular targets (CDK 4/6, PI3K, mTOR) constitute the basis of initial treatments for patients with advanced luminal breast cancer. Most of these treatments are oral and have been developed at a fixed dose, without weight adjusted dosing. There is little evidence on the influence that patients' weight might have on clinical outcomes of these oral drugs in the context of a randomized clinical trial. The present study analyzes the potential impact of the weight of patients treated in the two cohorts of the PEARL trial (NCT02028507) on Progression-Free Survival (PFS), Overall Survival (OS) and the incidence of side effects in each treatment arm.

Methods: GEICAM/2013-02 (PEARL) is a multicenter, phase III randomized clinical trial that enrolled patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer (MBC) who progressed to a prior aromatase inhibitor. Patients were randomized 1:1 to receive ET + palbociclib or capecitabine. Patient weight was assessed based on baseline body mass index (BMI) categories: normal (BMI ≤ 25 Kg/m²), overweight (BMI 25-29.9 Kg/m²) and obesity (BMI ≥ 30 Kg/m²). Cox's stratified proportional hazard model was used for survival analysis. Adverse events were assessed and graded according to National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) version 4.0.

Results: A total of 600 patients were included in the study and all were evaluable for the weight-based analysis, including 301 in the ET +palbociclib arm and 299 in the capecitabine arm. The distribution of patient's weights is shown in Table 1. For the Intention-to-treat (ITT) population, no significant difference in the median OS was found between the different weight categories (Normal: 32.8 months vs overweight: 31.9 months, [p=0.467]; obese: 32 months [p=0.407]). Specifically, for patients with normal weight, the median PFS was 9.3 months in the ET + palbociclib group compared to 9.0 months in the capecitabine group (hazard ratio (HR) 0.83, 95% confidence interval [CI]: 0.61-1.13; p=0.23). In the overweight group, the PFS was 7.5 months in the ET+palbociclib group and 11.1 months in the capecitabine group (HR 1.17, 95% CI: 0.87-1.58; p=0.30) while for the obese group, the PFS was 5.7 months vs 11.7 months (HR 1.14, 95% CI: 0.82-1.59; p=0.43), respectively.

No substantial differences in the incidence of grade ≥ 3 events were observed when considering weight categories in the different treatment groups (capecitabine arm (Normal: 60%, Overweight: 70.4%, Obese: 61.6%) and ET+palbociclib arm (Normal: 74.5%, Overweight: 76.1%, Obese: 51.6%).

Conclusions: Our findings, despite not finding statistically significant differences, suggest a potentially clinically relevant trend towards improved PFS with capecitabine in overweight and

obese patients compared to those receiving palbociclib plus ET. The impact of weight on the outcomes with fixed-dose oral drugs warrants further investigation in future studies.

Table 1.

	Cohort 1 (ET+Palbociclib) n=302	Cohort 2 (Capecitabine) n=299
Normal (BMI \leq 25 Kg/m ²).	95 (31.5%)	110 (36.8%)
Overweight (BMI 25-29.9 Kg/m ²)	115 (38.1%)	99 (33.1%)
Obesity (BMI \geq 30 Kg/m ²).	91 (30.1%)	90 (30.1%)

PO1-04-12

Palbociclib versus ribociclib in first-line treatment of patients with hormone-receptor positive HER2 negative advanced breast cancer – real world outcome data from the German registry platform OPAL

Presenting Author(s) and Co-Author(s):

M. Thill. Agaplesion Markus Krankenhaus, 60431 Frankfurt a.M., Hessen, Germany

M. Zahn. MVZ Onkologische Kooperation Harz, Goslar, Germany, United States

A. Welt. Universitätsklinikum Essen, Innere Klinik, Tumorforschung, 45147 Essen, Nordrhein-Westfalen, Germany

A. Nusch. Practice for Hematology and Medical Oncology Velbert, Velbert, Germany, Germany

M. Zaiss. Oncology Practice, Freiburg, Germany, United States

K. Engelken. Klinik Dr. Hancken, Mammazentrum, 21680 Stade, Niedersachsen, Germany

G. Kaltenecker. Städtisches Klinikum Karlsruhe, Frauenklinik, 76133 Karlsruhe, Baden-Württemberg, Germany

K. Ringwald. iOMEDICO AG, 79106 Freiburg, Baden-Württemberg, Germany

K. Gratzke. iOMEDICO AG, 79106 Freiburg, Baden-Württemberg, Germany

L. Kruggel. iOMEDICO AG, 79106 Freiburg, Baden-Württemberg, Germany

M. Jänicke. iOMEDICO AG, 79106 Freiburg, Baden-Württemberg, Germany

H. Schulz. Praxis für internistische Onkologie und Hämatologie (PIOH), 50226 Frechen, Nordrhein-Westfalen, Germany

C. Losem. TZN - Tumorzentrum Niederrhein, 41462 Neuss, Nordrhein-Westfalen, Germany

V. Hagen. St. Johannes-Hospital, Innere Medizin, 44137 Dortmund, Nordrhein-Westfalen, Germany

R. Fricker. Klinikum Hanau, Gynäkologisches Krebszentrum, 63450 Hanau, Hessen, Germany

E. Stickeler. Klinik für Gynäkologie und Geburtsmedizin, Uniklinik RWTH Aachen, Germany, United States

N. Harbeck. University of Munich, Munich, Bayern, Germany

A. Wöckel. Department of Obstetrics and Gynecology, University Hospital Würzburg, Würzburg, Germany, Germany

T. Decker. Oncology Ravensburg, Ravensburg, Germany

Introduction CDK4/6 inhibitors (CDKi) plus endocrine therapy (ET) are standard of care in first-line (1L) treatment of hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (ABC). In the pivotal trials the three CDK4/6i (palbociclib, ribociclib and abemaciclib) + ET showed similar progression-free survival (PFS) benefit over ET alone. However, other than ribociclib, palbociclib failed to demonstrate overall survival (OS) benefit. As patient (pts) characteristics differed between the trials, especially in the number of pts with treatment-free interval (TFI) of < 12 months after end of adjuvant ET, head-to-head comparisons of the CDKi are of clinical interest. Here we analyze the outcome of pts treated with palbociclib + ET or ribociclib + ET with real-world data from OPAL. Methods OPAL (NCT03417115) is a prospective observational, open, longitudinal multicenter cohort study (clinical registry) in Germany. Pts with ABC and early breast cancer can be recruited at start of their first systemic treatment. There are no treatment restrictions. Sites from all medical sectors

can participate in OPAL (medical and gynecologic oncologists from outpatient centers and hospitals). Details on all (sequential) treatments, patient and tumor characteristics, biomarker testing, clinical and patient-reported outcomes are collected. Follow-Up is until death or up to 5 years. Between 01/2018 and 07/2021 1049 pts with HR+ HER2- ABC were recruited by 143 sites. Database cut was on 31/08/2022. 384 pts received palbociclib + ET and 231 pts received ribociclib + ET as 1L treatment. All endocrine combination partners including switch of ET during first line therapy was allowed, whereas switch of CDK4/6i (n=25) were excluded. PFS in registries can differ from PFS in clinical trials, since the RECIST criteria are usually not applied in routine care. PFS in registries represents the time to clinically relevant progression in routine care. PFS and OS were estimated using the Kaplan-Meier method. To adjust for confounding, inverse probability of treatment weighting (IPTW) by propensity score analysis was used to compare PFS and OS between 1L palbociclib+ET and ribociclib+ET. IPTW was performed for the following variables: age, menopausal status, ECOG, any comorbidity, Charlson comorbidity index, metastatic stage, type of metastasis, number of metastatic sites, estrogen-/progesterone status, IHC status, previous chemo-/endocrine therapy, kind of endocrine combination partner, disease-free interval, and treatment-free interval. Results From 2018 to 2021, the proportion of CDK4/6i increased from 68% to 86% in 1L of HR+HER2- ABC. Overall, palbociclib was used in 44% and ribociclib in 26% of all first-line treatments in OPAL. Median age of pts receiving palbociclib/ribociclib was 66/68 years and for 77/81% of pts at least one comorbidity was documented. 37/35% of pts already had metastasis at diagnosis (M1) and 25/26% of pts had a TFI < 12 months. After IPTW, the two treatment groups were comparable for all tested characteristics. 42/46% of patients had a progression (palbociclib/ribociclib group). IPTW-adjusted median PFS was 25.1 months (95% Confidence interval (CI) 20.1 – 30.1) for the palbociclib and 27.0 months (95%-CI 21.1 – 31.6) for the ribociclib group. Hazard ratio was 0.91 (0.71 – 1.17) for palbociclib versus ribociclib. 26/29% of patients had an OS event (palbociclib/ribociclib group). IPTW-adjusted median OS was 36.7 months (95%-CI 33.0 – NA) for the palbociclib and 36.6 months (95%-CI 33.1 – NA) for the ribociclib group. Hazard ratio was 0.95 (0.69 - 1.30) for palbociclib versus ribociclib. Conclusions This analysis of real word data in the OPAL registry platform showed similar PFS and OS for palbociclib + ET compared to ribociclib + ET, when adjusted for a wide range of potential confounding variables. Further analyses will investigate whether one drug showed favorable results in certain subgroups of pts.

PO1-04-13

CARDIAC-STAR: Prevalence of Cardiovascular Comorbidities in Hormone Receptor Positive Human Epidermal Growth Factor Negative metaStatic breast cAnceR

Presenting Author(s) and Co-Author(s):

S. Dent. Duke University, Durham, North Carolina, United States

A. Guha. Augusta University, United States

H. Moore. Duke Cancer Institute, Durham, North Carolina, United States

R. McCaleb. Pfizer Inc., United States

I. Arias. Pfizer Inc., United States

S. Stergiopoulos. Pfizer Inc., United States

B. Li. Pfizer Inc, United States

D. Makari. Pfizer Inc., New York, New York, United States

M. Fradley. Perelman School of Medicine, University of Pennsylvania, United States

BACKGROUND: Baseline cardiovascular (CV) comorbidities can impact treatment decisions for patients (pts) with metastatic breast cancer (mBC). There is limited data on the prevalence of CV comorbidities at the time of hormone receptor positive human epidermal growth factor negative (HR+/HER2-) mBC diagnosis. The primary objective of this study is to describe the prevalence of pre-existing CV comorbidities in women and men with newly diagnosed HR+/HER2- mBC. A secondary objective is to describe the first documented cancer treatment for patients with or without CV comorbidities. **METHODS:** Women and men ≥ 18 years of age with newly diagnosed HR+/HER2- mBC from 01/2016 to 12/2021 were included in this retrospective, observational study using the Merative™ Marketscan® Commercial and Medicare Databases which is nationally representative. Evidence of mBC was defined as having two or more claims containing one or more diagnosis code for BC at least 30 days apart and at least two secondary malignancy diagnosis codes. Previously published claims-based algorithms were used to identify the HR+/HER2- molecular subtype. The index date is defined as the date of first mBC diagnosis. Patients had a 1-year pre-index period for observation of CV comorbidities and a 6-month post-index period for first documented cancer treatment. **RESULTS:** We identified 5,452 pts with HR+/HER2- mBC, 99% of whom were female, with a median age of 58 years (yrs) (IQR 13), and 83% having a health plan from an employer; i.e., are still employed. At mBC diagnosis, 3,335 pts (61.2%) had at least one pre-existing CV comorbidity (see Table). The most reported CV comorbidities were hypertension (50.7%), hyperlipidemia (33.7%), and diabetes (19.2%). The median age of pts with or without a CV comorbidity was 61 and 52 yrs, respectively; 16.2% with CV comorbidities were ≥ 75 yrs. Additional data, including first documented treatment, will be presented at the meeting. **CONCLUSIONS:** The prevalence of CV comorbidities in pts with HR+/HER2- mBC is often underrecognized. In this analysis, more than half of pts had at least one CV comorbidity by mBC diagnosis. CV comorbidities may impact treatment decisions in the HR+/HER2- mBC population, particularly in older pts.

Table

Table: Cardiac-STAR Patient Population

Characteristics	Total N = 5,452		Patients without CVD N = 2,117		Patients with CVD N = 3,335	
	N	%	N	%	N	%
Overall	5,452	100.0	2,117	100.0	3,335	100.0
Female at index date	5,399	99.0	2,106	99.5	3,293	98.7
Age Category (yrs)						
<55	2,092	38.4	1,258	59.4	834	25.0
55-64	2,158	39.6	713	33.7	1,445	43.3
65-74	611	11.2	94	4.4	517	15.5
75+	591	10.8	52	2.5	539	16.2
Geographic Region*						
Northeast	1,130	20.7	433	20.5	697	20.9
North Central	1,305	23.9	448	21.2	857	25.7
South	2,207	40.5	826	39.0	1,381	41.4
West	799	14.7	407	19.2	392	11.8
Unknown	11	0.2	3	0.1	8	0.2
Cardiovascular Comorbidities [‡]						

Table (continued)

Hypertension	2,765	50.7	0	0.0	2,765	82.9
Hyperlipidemia	1,839	33.7	0	0.0	1,839	55.1
Diabetes	1,049	19.2	0	0.0	1,049	31.5
Ischemic Heart Disease	268	4.9	0	0.0	268	8.0
Heart Failure (Includes Congestive Heart Failure)	255	4.7	0	0.0	255	7.7
Cerebrovascular disease Ischemic Stroke/Hemorrhagic Stroke	214	3.9	0	0.0	214	6.4
Atrial Fibrillation/Heart Flutter	163	3.0	0	0.0	163	4.9
Bradycardia (and other cardiac arrhythmias)	157	2.9	0	0.0	157	4.7
Peripheral Artery Disease	106	1.9	0	0.0	106	3.3
Cardiomyopathy	85	1.6	0	0.0	85	2.6
Acute Coronary Syndrome	57	1.1	0	0.0	57	1.7
Supraventricular tachycardia	61	1.1	0	0.0	61	1.8
Myocardial Infarction	31	0.6	0	0.0	31	0.9
Coronary Artery Bypass Graft	18	0.3	0	0.0	18	0.5
Severe Heart Valvular Heart Disease	9	0.2	0	0.0	9	0.2

*Region of residence:

Northeast: Connecticut, Maine, Massachusetts, New Hampshire, Vermont, Rhode Island, New Jersey, New York, and Pennsylvania;

Table (continued)

Midwest: Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota;

South: Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Alabama, Kentucky, Mississippi, Tennessee,

West Virginia, Arkansas, Louisiana, Oklahoma, and Texas;

West: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington

[†]Complete CV Comorbidities to be reported in poster/manuscript

PO1-04-14

PLK1 Inhibitor Onvansertib Extends the Response and Overcomes Resistance to Paclitaxel in Palbociclib-resistant HR+ Breast Cancer Patient-derived Xenografts.

Presenting Author(s) and Co-Author(s):

M. Ridinger. Cardiff Oncology, United States

P. Painsec. Institut Curie, United States

S. Sreekumar. Cardiff Oncology, United States

D. Gonzalez. Cardiff Oncology, United States

D. Klein. Cardiff Oncology, United States

L. Sourd. Institut Curie, United States

E. Montaudon. Institut Curie, United States

P. Cottu. Institut Curie, Paris, Paris, Ile-de-France, France

T. Smeal. Cardiff Oncology, United States

E. Marangoni. Institute Curie, United States

Paclitaxel is a first-line chemotherapy for hormone receptor positive (HR+) metastatic breast cancer patients after progression on a combination of endocrine and CDK4/6 inhibitor therapy. Response rate to paclitaxel ranges between 20-40%, and most patients progress due to intrinsic or acquired resistance, leaving them with limited treatment choices. Therapeutic strategies to overcome paclitaxel resistance and extend its clinical benefit are urgently needed. Paclitaxel-resistant tumors have increased expression of polo-like kinase 1 (PLK1), a serine-threonine-protein kinase that regulates mitosis and cell cycle progression. PLK1 has also been shown to mediate resistance to CDK4/6 inhibitor palbociclib in HR+ breast cancer. Onvansertib is an orally bioavailable, highly potent, and selective PLK1 inhibitor in clinical development. Onvansertib exhibited synergy in vitro and showed potent anti-tumor activity in vivo in combination with paclitaxel in ovarian cancer and triple negative breast cancer (TNBC) preclinical models. A phase 1b/2 clinical trial is ongoing to evaluate the safety and efficacy of onvansertib plus paclitaxel in advanced TNBC (NCT05383196). Here we investigated whether the potential of onvansertib and paclitaxel combination could be extended to HR+ breast cancer.

Co-treatment with onvansertib and paclitaxel synergistically inhibited the viability of HR+ breast cancer cell lines (MCF-7, T-47D, EFM-19, CAMA-1, ZR-75-1). Compared to the single agents, the combination induced increased apoptosis. The combination was further tested in vivo in patient-derived xenograft (PDX) models. To this end, six HR+ breast cancer PDXs with intrinsic or acquired resistance to palbociclib were established from primary breast tumors (n=1) or metastatic bone biopsies (n=5). The PDX tumors were engrafted subcutaneously in nude mice and the effect of onvansertib (45 mg/kg, oral, 5 days a week) and paclitaxel (15-25mg/kg, IP, once a week) was investigated as monotherapy and in combination.

The combination of onvansertib and paclitaxel was tolerated with minimal toxicity and showed enhanced anti-tumor activity compared to either agent alone in all 6 PDX models. Paclitaxel and onvansertib monotherapies had little to no anti-tumor activity in 4 out of 6 PDX models (HBCx124palboR25, HBCx-139 palboR5, HBCx-202 and HBCx-131). Importantly, the combination of onvansertib and paclitaxel induced strong anti-tumor activity in these 4 models. Tumor regression was observed in the 2 PDX models with acquired resistance to palbociclib,

HBCx-124palboR25 and HBCx-139palboR5, with 62% (5/8 mice) and 54% (6/11 mice) complete response rates, respectively. The combination showed tumor stasis in HBCx-131 and induced tumor regression in HBCx-202, established from patient resistant to palbociclib. In 2 of the 6 PDXs, paclitaxel exhibited anti-tumor activity, inducing tumor regression in HBCx-137paboR26 and tumor stasis in HBCx-86. In comparison, the combination of onvansertib and paclitaxel had greater activity, inducing tumor regression in both models with a higher rate of complete response than the monotherapy. Complete response rates for paclitaxel versus the combination were 62% and 100% in the HBCx-137palboR26 model and 0% and 67% in the HBCx-86 model. Notably, the antitumor activity of the onvansertib and paclitaxel combination was very durable, showing a robust delay in tumor relapse after stopping therapy.

Together, our data strongly support that combining paclitaxel with the PLK1 inhibitor onvansertib extends its benefit and overcomes paclitaxel resistance, and represents a promising therapeutic strategy for HR+ breast cancer patients after progression on a combination of endocrine and CDK4/6 inhibitor therapy.

PO1-05-01

Cyclin-dependent Kinase 4/6 Inhibitors Combined with Radiotherapy in the Management of Brain Metastases in HR-positive/HER2-negative Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

M. Kubeczko. Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, United States

D. Gabryś. Department of Radiotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, United States

A. Polakiewicz-Gilowska. Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, United States

A. Krzywon. Department of Biostatistics and Bioinformatics, Maria Sklodowska-Curie National Research Institute of Oncology, United States

D. Gräupner. IIIrd Radiotherapy and Chemotherapy Department, Maria Sklodowska-Curie National Research Institute of Oncology, United States

B. Łanoszka. Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, United States

M. Mianowska-Malec. Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, United States

A. Leśniak. Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, United States

K. Świdzka. Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, United States

K. Chomik. Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, United States

B. Grandys. Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, United States

M. Jarząb. Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, United States

Purpose: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) plus endocrine therapy demonstrated overall survival benefits in advanced breast cancer patients (ABC), hormone receptor-positive, HER2-negative (HR+/HER2-) and remains the mainstay in the first and second-line treatment. Brain metastases are rare at the beginning of treatment in this group of patients and are found more often during subsequent lines of treatment and other subtypes of breast cancer. However, there is a paucity of data on the safety and efficacy of multimodality CDK4/6i and radiotherapy treatment in the management of brain metastases. Thus, we performed a retrospective analysis of ABC patients (pts) treated at our institution with radiation therapy to the brain and CDK4/6i. Pts who received radiotherapy before CDK4/6i initiation or concurrently with CDK4/6i (group 1) were compared to the patients who progressed in the brain during CDK4/6i treatment and then received radiotherapy (group 2). The primary endpoint was progression-free survival (PFS) in group 1 vs. group 2; the secondary endpoints were local control (LC) within the brain in group 1 vs. group 2 and severe toxicity. Materials/Methods: Among 379 pts who received CDK4/6i, 26 pts (6.9%) received radiotherapy to the brain. 17 pts received radiotherapy before or concurrent with CDK4/6i and were included in group 1. Nine pts received radiotherapy after CDK4/6i discontinuation due to disease progression and comprised group 2. Results: The median age was 51.5 years (IQR range 41-62). Six pts had de novo

metastatic disease. The majority of patients were treated in the first-line setting (15 pts, 58%). 17 pts received ribociclib, 7 palbociclib, and 2 abemaciclib. 15 pts received letrozole as an endocrine compound and 11 pts fulvestrant. 19 pts (73%) received previous chemotherapy. Six pts had an ECOG performance status of 0, 15 pts ECOG 1, and 5 pts ECOG 2. The most common local treatment was whole-brain radiotherapy with a total dose of 20 Gy delivered in 5 fractions (fr) (11 pts: 4 pts VMAT, 2 pts IMRT, 3 pts 3D, and 2 pts 2D). Eight pts received stereotactic radiation therapy (6 pts with Linac: 2 pts 24 Gy/2 fr, 2 pts 24 Gy/3 fr, 2 pts 25 Gy/5 fr; 1 pt GammKnife 20 Gy/1 fr, 1 pt Cyberknife 15 Gy/3 fr). Six- and 12-month PFS in group 1 was 88.2% (95% CI: 74.1-100) and 58.8% (95% CI: 37.7- 91.8), respectively, whereas in group 2, six- and 12-month PFS was 55.6% (95%CI: 31- 99.7) and 44.4% (95% CI: 21- 92.2), respectively. Six- and 12-month LC in group 1 was 92.3% (95%CI: 78.9-100) and 83.9% (65.7-100), respectively. LC in group 2 was poor: 3-month LC was only 66.7 (30-100). At a median follow-up of 8.8 months, no unanticipated toxicity was reported. Conclusion: Multimodality treatment with CDK4/6i and radiotherapy to the brain is safe and effective. Patients who developed metastases during CDK4/6i treatment tend to have a worse prognosis in comparison to those who received prior radiotherapy. CDK4/6i following radiotherapy seems to be an effective and valuable treatment option in this particular metastatic breast cancer population.

PO1-05-02

CDK4/6 inhibitors in advanced breast cancer (aBC). Preliminary results of the CDK4/6i choice and sequence of treatments in a series of 174 patients. GOIRC-04-2019 retro/prospective observational study

Presenting Author(s) and Co-Author(s):

L. Moscetti. Universitaria Policlinico Modena, Modena, Italy, Italy

F. Canino. Oncology Department Azienda Ospedaliero Universitaria Policlinico Modena, GOIRC, United States

S. Natalizio. Oncology Department Azienda Ospedaliero Universitaria Policlinico Modena, United States

I. Sperduti. U.O. di Biostatistica e Bioinformatica - Direzione Scientifica Biostatistical Unit - Clinical Trials Center , Rome, Italy, United States

E. Barbieri. Oncology Department Azienda Ospedaliero Universitaria Policlinico Modena, GOIRC, United States

F. Piacentini. University of Modena and Reggio Emilia, MODENA, Emilia-Romagna, Italy

C. Omarini. AOU Policlinico Modena - Italy, United States

L. Cortesi. Oncology Department Azienda Ospedaliero Universitaria Policlinico Modena, GOIRC, United States

M. Barbolini. Oncology Department Azienda Ospedaliero Universitaria Policlinico Modena, GOIRC, United States

A. Musolino. University of Parma, United States

A. Frassoldati. Azienda Ospedaliero Universitaria di Ferrara-Arcispedale Sant'Anna, United States

F. Caggia. Oncology Department Azienda Ospedaliero Universitaria Policlinico Modena, GOIRC, United States

G. Zoppoli. Department of Internal Medicine and Medical Specialties DiMI, University of Genoa, Italy

M. Dominici. Oncology Department Azienda Ospedaliero Universitaria Policlinico Modena, United States

A. Toss. Oncology Department Azienda Ospedaliero Universitaria Policlinico Modena, GOIRC, United States

Background: The sequence of treatments in aBC after a CDK4/6 inhibitor (i) is not defined yet. Fulvestrant (FUL), everolimus (E) combinations, and chemotherapy (CT) represents the main treatment options in Europe. Neither of these options has proven to be superior to the others. We conducted a retro/prospective, observational, non-randomized study, to evaluate the impact of subsequent treatments options after a 1st or 2nd line CDK4/6i in real-world clinical practice. Preliminary result in the retrospective series are presented. Methods: All patients (pts) who met the criteria to receive CDK4/6i plus aromatase inhibitors (AIs) or FUL, from market availability, were enrolled. 400 pts will be included; data from 200 pts will be collected retrospectively and 200 prospectively. Results: To date, 293 pts receiving CDK4/6i have been enrolled and the outcomes of 174 are available for a preliminary analysis. Characteristics of pts were as follow: M/F 1/173; ductal carcinoma 69%, lobular carcinoma 24%; de novo disease 28.6% In the relapse group, 46.5% pts were endocrine sensitive; 22% were endocrine resistant (7.9% and 14.1% secondary). 29.3% had bone-only disease, 46% visceral metastases only; 36% were

Her2 score 0 and 64% score 1-2. 77% received CDK4/6i in 1st line, 23% in 2nd line.

In pts receiving 2nd line CDK4/6i, prior therapies (tx) were as follow: 34.5% taxanes, 43% other CT, 15% FUL, 8% E, 8% FUL. In the 1st line, 46% received palbociclib (P), 37% ribociclib (R) 21% abemaciclib (A). In the second line P76%, R10%, A14%.

The subsequent treatments in the 49 pts who progressed after 1st line CDK4/6i was: 26% AIs/FUL +/-E, 74% CT. In the 28 pts who progressed after a 2nd line CDK4/6i tx: 20% FUL+/-E, 80% CT. The median lines of post CDK4/6i was 3 for both group (range 1-8 and 1-7).

Median progression free survival (mPFS) after 1st line CDK4/6i tx was 31 months (mo) (95% CI 21-39) and 22 mo (65% CI 14-21) after 2nd line CDK4/6i tx.

mPFS per CDK4/6i 1st line was as follow: P 23 mo, R 39.9 mo, A 23.2 mo. In 2nd line mPFS was: P 20 mo, R 14 mo, A 5 mo. No differences were observed between the three CDK4/6i but, if considering 1st and 2nd line together there was a difference in favor of R ($p=0.009$). Across five variables (ductal vs lobular; Her 2 score 0 vs 1/2, ki 67 < 20 vs >20, de novo vs recurrence, bone only vs other sites, type of CDK4/6i) no differences were observed in mPFS, except for bone only disease in 1st line setting (mPFS 46.7 vs 22,9 mo, $p=0.007$)

Median PFS in second line in the group who received 1st line CDK4/6i, was 5 mo in pts receiving CT and 7 mo in pts treated with FUL/E whereas, for pts receiving further tx after 2nd line CDK4/6i tx, was 7 mo in CT and 4 mo with FUL/E ($p=ns$).

Following the Sonia trial results, an analysis of PFS2 has been performed and in pts receiving CDK4/6i vs other therapies in 1st line (57 vs 91 pts), PFS2 was 24 mo vs 35 mo ($p=0.014$). Conclusion: The sequence of treatments after a CDK4/6i is far to be defined. In this preliminary analysis conducted in pts treated mainly in the years 2017-2019, CT represents the main choice after CDK4/6i failure. These data show the picture of the initial approach in the daily practice in an evidence-absent scenario. The increasing skill in the management of the CDK4/6i has changed in the last 5 years and we will proceed to complete the enrollment, in order to evaluate the difference in the choice of CDK4/6i and the sequence of tx in the prospective part of the study.

PO1-05-04

CDK4/6 inhibitor-induced Interstitial Lung Disease (ILD) - A Case Series

Presenting Author(s) and Co-Author(s):

A. Chitalia. MedStar Washington Hospital Center, United States

K. Shah. Medstar Washington Hospital Centre, United States

Introduction:

CDK4/6 inhibitors interrupt cell cycle by inhibiting intracellular and hormonal signals responsible for proliferation of malignant cells, making them an effective treatment for patients with HR+ advanced breast cancer. Pre-clinical data demonstrates that CDK4/6 inhibitors allow for inflammatory cell recruitment, inducing pulmonary inflammation and thereby increasing the risk of ILD. The overall risk of ILD was 1.6% in a meta-analysis of over 16,000 patients treated with CDK4/6 inhibitors while individual reported risk was 1%, 1.6% and 3% for palbociclib, ribociclib, and abemaciclib respectively.

Objective:

The aim of this case series is to add to the body of literature about this rare but possibly serious side effect of CDK4/6 inhibitor associated ILD. Early detection and prompt management are essential for improved patient outcomes.

Case 1

A 61 year-old female was diagnosed with metastatic breast cancer to brain and bones after being admitted for evaluation of acute vision loss. She started on palbociclib and letrozole and subsequently had 2 hospitalizations for acute hypoxemic respiratory failure with unremarkable infectious workup. CT scan was significant for bilateral pulmonary infiltrates raising suspicion for CDK4/6 inhibitor-induced pneumonitis; subsequently palbociclib was discontinued and the patient was started on steroid taper resulting in improvement of her respiratory status.

Case 2

A 71 year-old female with a remote history of left breast cancer and sarcoidosis presented with respiratory symptoms. She was found to have metastatic breast cancer with CT scan revealing hilar and mediastinal adenopathy. The patient initially received taxol with near resolution of disease on imaging. The patient was subsequently started on palbociclib + letrozole. After 9 months of treatment, the patient was admitted for pneumonia and discharged home with oxygen. PFTs at the time were suggestive of restrictive pathology related to obesity hypoventilation. Six months later, the patient was admitted for worsening respiratory failure; CT scan revealed interstitial changes likely due to multifactorial etiologies including palbociclib-induced pneumonitis. The patient subsequently passed away.

Case 3

An 81 year-old female diagnosed with remote history of L. breast cancer presented with shortness of breath and weakness. CT scan revealed a nodule and lymphadenopathy; biopsy of nodule was consistent with breast primary. The patient was initially started on ribociclib which was discontinued after 4 cycles due to transaminitis. She was switched to palbociclib, however 2 months after initiation, the patient presented with flu-like symptoms. CT revealed scattered subpleural ground-glass opacities. Infectious workup was negative; pulmonary consultation believed this was likely due to drug-induced pneumonitis and palbociclib was discontinued and she was treated with a steroid taper. Patient was switched to fulvestrant; and after 9 months she was diagnosed with stage IV tongue cancer and her breast cancer therapy was

discontinued.

Discussion

CDK4/6 inhibitors have improved survival in patients with metastatic breast cancer, however they are associated with rare but serious adverse effects like ILD. ILD is a challenging clinical diagnosis as it refers to a cluster of disorders of varying presentation and pathophysiology, and as a result can be missed.

Conclusion

This case series demonstrates that CDK4/6 inhibitor-associated ILD may be more prevalent than originally reported. It is important to identify early by performing a thorough workup, including a detailed history and physical exam, medication list review, infectious work-up, chest imaging, PFTs and pulmonology consultation. Publishing a set of standardized guidelines to diagnose and treat CDK4/6 inhibitor-induced ILD is necessary as more cases are identified.

Characteristics	Patient 1	Patient 2	Patient 3
Race	African American	African American	Caucasian
Age	61	71	81
Specific CDK4/6 inhibitor	palbociclib	palbociclib	palbociclib
ER, PR (%)	99, 20	95, 10	90, 10
HER 2	negative	equivocal (By IHC and FISH)	negative
Time to ILD from start of tx (Days)	43	727	80
Adjunct medications	letrozole	letrozole	letrozole
Prior Chemo or hormone regimen	none	tamoxifen + 8 - week taxol	ribociclib
Infectious workup	yes	no	yes
Pulmonology consult	no	no	yes
PFTs	no	yes	no
Chest Imaging	yes	yes	yes

PO1-05-05

Overall survival (OS) and subsequent therapy patterns in Japanese patients with HR+/HER2- advanced breast cancer (ABC) treated with palbociclib (PAL) plus letrozole (LET) in first-line setting (1L)

Presenting Author(s) and Co-Author(s):

M. Takahashi. Hokkaido University, Sapporo, Japan

T. Osako. Breast Center, Kumamoto Shinto General Hospital, United States

H. Yasojima. Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

K. Inoue. Saitama Cancer Center, Saitama, Japan

M. Kawashima. Kyoto University, Japan

H. Maeda. Department of Breast Surgery, National Hospital Organization Hokkaido Cancer Center, United States

M. Ito. Hiroshima City Hiroshima Citizen's Hospital, United States

Y. Sagara. Hakuaiikai Sagara Hospital, Kagoshima, Kagoshima, Japan

K. Yonemori. Medical Oncology, National Cancer Center Hospital,, United States

M. Hattori. Aichi Cancer Center, United States

N. Yamamoto. Division of Breast Surgery, Chiba Cancer Center, United States

E. Tokunaga. Breast Oncology, National Hospital Organization Kyushu Cancer Center, United States

S. Ohsumi. Breast Oncology, National Hospital Organization Shikoku Cancer Center, United States

Y. Yamamoto. Kumamoto University Hospital, Kumamoto, Kumamoto, Japan

A. Ichikawa. Oncology Medical Affairs, Pfizer Japan Inc., United States

Y. Muramatsu. Pfizer Japan Inc., Japan

N. Masuda. Nagoya University Graduate School of Medicine, Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

Background: PAL is a first-in-class cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) for the treatment of HR+/HER2- ABC. In PALOMA-2 study, PAL plus LET demonstrated a numerically, not statistically significant, prolonged OS versus placebo plus LET (53.9 vs 51.2 months; HR, 0.956; 95% CI, 0.777-1.177) in patients with HR+/HER2- ABC in 1L. Subgroup analyses showed a similar trend in Asia/Pacific region (73.4 vs 55.1 months; HR, 0.744), however, data specific to Japanese subgroup have not been reported. An open-label, single-arm, multicenter Japanese phase 2 study (J-Ph2) investigated the efficacy and safety of PAL plus LET in postmenopausal Japanese women with HR+/HER2- ABC in 1L and showed a median progression-free survival (PFS) of 35.7 months (95% CI, 21.7-46.7) in the final analysis of PFS. However, OS data were immature at the data cutoff. Here, we report the findings from a follow-up study of J-Ph2 (NCT04735367) evaluating OS and subsequent therapy in these Japanese patients.

Methods: Patients (N=42) who participated in J-Ph2 were enrolled in this follow-up study. The primary endpoint was OS, defined as the time from the first dose of PAL plus LET in J-Ph2 to date of death due to any cause. Secondary endpoints included chemotherapy-free survival

(CFS) and type and duration of subsequent therapy. Median OS, CFS, duration of subsequent therapy and associated 95% CIs were estimated using the Kaplan–Meier method. Outcomes were also assessed for baseline demographic and disease characteristic subgroups including visceral or nonvisceral metastatic disease, disease-free interval (DFI; ≤12 months, >12 months, de novo metastatic), and duration of 1L PAL use (≤24 months or >24 months).

Results: Patients had a median age of 62.5 years; 48% had visceral metastases; 33% had de novo disease; 48% had a TFI >12 months; 93% had an ECOG performance status (PS) of 0. At a median follow up of 89.7 months, the median OS was 85.4 months (95% CI, 64.3–not estimable [NE]). Median OS was longer in patients with nonvisceral versus visceral metastases (not reached [NR] vs 67.3 months), with TFI >12 months versus ≤12 months (85.4 vs 45.4 months), or with duration of 1L PAL use >24 months versus ≤24 months (NR vs 47.5 months). Median CFS was 69.1 months (95% CI, 24.2–85.4), and that was longer in patients with nonvisceral versus visceral metastases (77.5 vs 37.5 months). At the data cutoff, 3 patients (7.1%) were still receiving PAL plus LET (90.9–93.2 months). Subsequent therapy after disease progression was administered to 34 of 42 patients (81%). Of these patients, 28 (82%) received endocrine-based therapy, while 3 (9%) patients each received chemotherapy and other therapy, respectively. The median duration of the first subsequent therapy was 8.3 months (95% CI, 3.9–12.2), and that was similar among patients with nonvisceral versus visceral metastases (7.8 vs 8.3 months).

Conclusion: This interim analysis showed a median OS of >7 years with 1L PAL plus LET. Patient demographics (geographic, racial factors), disease characteristics (ECOG PS, visceral metastases), and subsequent therapy decisions may have contributed to the extended median OS observed in this study. Further, this report provides insight into real-world subsequent treatment patterns following PAL plus ET.

Table

	Overall (n=42)	Nonvisceral (n=22)	Visceral (n=20)
Median OS (95%CI), months	85.4 (64.3–NE)	NR (64.3–NE)	67.3 (48.3–NE)
Median CFS (95%CI), months	69.1 (24.2–85.4)	77.5 (49.2–NE)	37.3 (13.6–76.8)
Median PFS (95%CI), months	35.7 (21.7–46.7)	46.7 (31.9–46.7)	16.7 (5.3–44.1)

PO1-05-06

Health-related QOL and physical activity collected via wearable device in patients with HR+/HER2- advanced breast cancer in Japan treated with palbociclib+endocrine therapy (ET) or ET alone: 6-month longitudinal study (JBCRG-26)

Presenting Author(s) and Co-Author(s):

H. Bando. University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan

M. Oba. Department of Clinical Data Science, National Center of Neurology and Psychiatry, United States

A. Ueda. Department of Breast-Thyroid-Endocrine Surgery, University of Tsukuba Hospital, United States

K. Terata. Department of Breast and Endocrine Surgery, Akita University Hospital, United States

M. Doi. Department of Clinical Oncology, Hiroshima Prefectural Hospital, United States

S. Nagai. Division of Breast Oncology, Saitama Prefecture Cancer Center, United States

M. Hattori. Aichi Cancer Center, United States

K. Watanabe. NHO Hokkaido Cancer Center, Sapporo, Japan

N. Tamura. Toranomom Hospital, Japan

M. Futamura. Department of Breast Surgery, Gifu University Hospital, Japan

K. Koizumi. Department of Breast Surgery, Hamamatsu University Hospital, United States

N. Niikura. Tokai University School of Medicine, Isehara-shi, Isehara, Kanagawa, Japan

T. Miyaji. Meaningful Outcome Consulting, United States

Y. Muramatsu. Pfizer Japan Inc., Japan

L. Xu. Heath & Value, Pfizer Japan Inc., United States

N. Masuda. Nagoya University Graduate School of Medicine, Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

S. Saji. Fukushima Medical University, Fukushima, Japan

Background: Palbociclib (PAL) is a first-in-class cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) for the treatment of HR+/HER2- advanced breast cancer (ABC). In phase 3 clinical trials, PAL+ET prolonged progression-free survival and maintained health-related quality of life (HRQOL) compared with placebo+ET. However, few studies have evaluated the day-to-day effects of PAL+ET treatment on patients' HRQOL and daily activities in a real-world setting. Here, we report the daily life of the patients treated with PAL+ET or ET alone evaluated with a mobile application and wearable device.

Methods: This is a prospective, observational, multicenter study conducted in Japanese women with HR+/HER2- ABC initiating PAL+ET (Group 1) or ET alone (Group 2) in first- or second-line setting. HRQOL was assessed with the EORTC-QLQ-C30 at baseline and Day 15 of each cycle via a smartphone-based application for 6 treatment cycles (24 weeks). Physical activity (PA) data were collected via wearable device (CentrePoint Insight Watch®, ActiGraph LLC, the USA). Patients were instructed to wear the device at all-times, except of while bathing and sleeping, during the baseline period (at least 4 days prior to treatment initiation was recommended) and 6 cycles. PA metrics were averaged on a weekly basis. Patient data, including baseline characteristics, treatment, and adverse events, were collected via electronic

case report forms. As primary endpoints, change in Global health status (GHS) of EORTC-QLQ-C30 and “sedentary time” from baseline were evaluated at each time point. No formal hypothesis testing or comparisons between groups was planned.

Results: Ninety-nine patients were enrolled (Group 1: 78 patients, Group 2: 21 patients). Patients had a median age of 56/52 years (Group 1/Group 2); 51%/33% had visceral metastases; 86%/86% had ECOG performance status of 0; 76%/91% initiated first-line treatment; 36%/33% were fully employed. Seventy-four of 78 patients (95%) in Group 1 and 20 of 21 patients (95%) in Group 2 completed the 6-cycle observation period. Baseline mean GHS score was 60.9 and 64.3 in Group 1 and 2, respectively. The change from baseline to Cycle 6 in GHS score was 4.6 and 1.2 in Group 1 and 2, respectively, not reaching the deterioration-threshold of 8 points in either treatment group. Results for each functional subscale are summarized in Table 1. Baseline mean “sedentary time” was 580.7 and 565.1 min/day in Group 1 and 2, respectively. The change from baseline to Cycle 6 in “sedentary time” was —67.2 and —139.4 min/day in Group 1 and 2, respectively. Results of other PA metrics are summarized in Table. No new safety signals were identified.

Conclusion: In this study, PAL+ET or ET alone did not have any significant adverse impact on HRQOL and PA measured by wearable devices in patients with HR+/HER2- ABC. (NCT04736576)

Table 1 Summary score of EORTC-QLQ-C30 functional scales and PA metrics

	Group 1 (PAL+ET)		Group 2 (ET alone)	
	Baseline (n=77)	Cycle 6 (n=74)	Baseline (n=21)	Cycle 6 (n=20)
EORTC-QLQ-C30*, mean (SD)				
Physical functioning	77.9 (21.3)	79.2 (19.5)	81.6 (14.9)	83.0 (15.7)
Role functioning	79.2 (26.5)	80.6 (23.9)	82.5 (26.1)	80.0 (17.6)
Emotional functioning	72.6 (22.0)	81.0 (16.6)	80.6 (15.9)	77.1 (14.3)
Cognitive functioning	82.0 (20.5)	79.3 (20.4)	85.7 (16.1)	78.3 (20.3)
Social functioning	84.2 (23.4)	82.2 (22.0)	81.7 (25.2)	82.5 (19.1)
PA metrics, mean (SD)	Baseline (n=78)	Cycle 6 (n=65)	Baseline (n=21)	Cycle 6 (n=17)
Moderate-to-vigorous PA time (min/day)	102.2 (59.9)	109.4 (69.3)	90.6 (46.9)	92.4 (39.7)
Steps	3918 (2463)	4466 (2453)	3821 (2161)	4202 (1803)
Calories	1488 (442)	1512 (476)	1532 (489)	1535 (444)

*A higher score indicates better HRQOL.

SD, standard deviation.

PO1-05-07

Circulating tumor DNA dynamics in acELERA Breast Cancer: a Phase II study of giredestrant for estrogen receptor-positive, HER2-negative, previously treated advanced breast cancer

Presenting Author(s) and Co-Author(s):

A. Collier. Genentech, Inc., South San Francisco, CA, USA, South San Francisco, California, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

E. Lim. Garvan Institute of Medical Research, St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia

M. Chavez. UT MD Anderson Cancer Center, Houston, Texas, United States

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

J. Martinalbo. F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States

P. Perez-Moreno. Genentech, Inc., South San Francisco, California, United States

H. Moore. Genentech, Inc., San Francisco, California, United States

BACKGROUND Giredestrant (GIR) is a highly potent, oral, selective estrogen receptor antagonist and degrader (SERD) that exhibits robust estrogen receptor (ER) occupancy. The Phase II, randomized, open-label acELERA Breast Cancer (BC) study (NCT04576455) assessed GIR vs physician's choice of endocrine therapy (PCET) in second- or third-line ER-positive, HER2-negative advanced BC (ER+, HER2- aBC). The study did not reach statistical significance for the primary endpoint of investigator-assessed progression-free survival (PFS); however, the benefit of GIR was of larger magnitude among patients (pts) with ESR1-mutated tumors (ESR1m; a common cause of acquired resistance to endocrine therapy [ET]). We present an exploratory biomarker analysis of circulating tumor (ct)DNA dynamics. **METHODS** Pts (n = 303) were randomized 1:1 to GIR or PCET (75% of pts had fulvestrant [FUL]; 25%, an aromatase inhibitor). Partial response (PR), stable disease (SD), and progressive disease (PD) were categorized by RECIST v1.1. Plasma samples taken at Cycle 1, Day 1 (C1D1; n = 229), while on treatment (tx) at C2D1 (n = 220), and at the end of therapy (EOT; n = 155) were evaluated with the FoundationOne Liquid CDx next-generation sequencing assay. Gene mutations were defined as variants with known or likely impact on protein function. Composite tumor fraction (cTF) was defined as the total estimated tumor ctDNA content in each sample, and was only evaluable for a subset of samples (137 C1D1; 136 C2D1; 99 EOT). cTF or ESR1 mutant allele frequency (MAF) changes were calculated as a percent change from C1D1. ESR1m clonality was estimated as variant tumor fraction/estimated tumor fraction. Statistical significance was evaluated using the Mann-Whitney test. **RESULTS** The overall mutation landscape remained relatively unchanged with GIR tx at C2D1 or EOT, except for ESR1m prevalence, which declined from 43% at C1D1 to 26% on tx and 27% at EOT. With PCET, ESR1m prevalence decreased from 34% at C1D1 to 29% on tx, but increased to 43% by EOT. There were no concordant changes for other top mutated genes in this study, including PIK3CA, TP53, or DNMT3A. cTF decreased on tx in 38/65 (59%) and 32/59 (54%) of evaluable pts with GIR and PCET, respectively; the median change from C1D1 was -23% with GIR compared with -5% with PCET or -15% with FUL. The median change in cTF levels on tx with GIR was significantly greater in pts with a PR (-88%) vs PD (+6%, p = 0.002) or SD (-19%, p =

0.004). The degree of cTF decline on tx with GIR was significantly higher in pts with baseline ESR1m (median change -58%) vs no ESR1m detected (+5%, $p = 0.012$). Pts with a clonal ESR1m had higher levels of cTF decline on tx vs pts with subclonal ESR1m, suggesting cTF dynamics are a function of tumor heterogeneity. ESR1 MAF decreased on tx in 93% of pts with baseline ESR1m on GIR, vs 60% with PCET and 70% with FUL. ESR1 MAF decline on tx was significantly higher with GIR vs PCET at both C2D1 and EOT ($p < 0.0001$). The average ESR1 MAF decline on tx with GIR was greater in pts with a PR (-97%) vs PD (-54%, $p = 0.025$) or SD (-48%, $p = 0.051$), and all seven GIR-treated pts with a PR showed a near or total loss of ESR1 MAF by C2D1. The ESR1m variants D538G and Y537X had a significantly greater decline in MAF on tx with GIR vs PCET or FUL ($p < 0.0001$). CONCLUSIONS Data show that cTF and ESR1m ctDNA dynamics were associated with clinical response to GIR in ER+, HER2- aBC. ESR1 MAF decline was significantly greater with GIR vs PCET or FUL. ESR1 MAF declined to a greater degree with GIR compared with cTF, which is consistent with the larger magnitude of PFS benefit seen with GIR in pts with ESR1m tumors. The specific ESR1 variants D538G and Y537X showed greater sensitivity to GIR compared with PCET or FUL.

PO1-05-08

Enhanced ER+ tumor growth inhibition of fulvestrant from effective oral delivery yielding elevated plasma concentrations

Presenting Author(s) and Co-Author(s):

D. Godfrin. VeraMorph, Mansfield, Massachusetts, United States

M. Butchbach. Nemours Children's Biomedical Research, United States

Fulvestrant has been a backbone of endocrine therapy (ET) for ER+/HER2- metastatic breast cancer (mBC) for over 20 years due to its nanomolar potency, purely antagonistic behavior, and well-tolerated adverse event (AE) profile. It remains the only selective estrogen receptor degrader (SERD) approved in ER+/HER2- mBC regardless of ESR1 mutation status. While ESR1 mutations reduce fulvestrant binding affinity, they do not implicitly lead to acquired resistance as with aromatase inhibitors (AIs) and can be overcome by increasing exposure.¹ Further, preclinical evidence suggests that higher exposure to fulvestrant correlates with higher efficacy in rodents.² Unfortunately, fulvestrant is currently delivered at its maximum feasible dose due to its poor solubility and a lack of effective drug delivery technologies. In response, several novel oral SERDs have been brought into clinical development to improve upon the efficacy of fulvestrant. However, multiple have failed to prove superior to fulvestrant in its intramuscular (IM) injection formulation and improvements from elacestrant (EMERALD) and camizestrant (SERENA-2) are largely attributed to patients with ESR1 mutations after prior ETs. Therefore, enabling higher exposure of fulvestrant could prolong progression-free survival and improve quality of life for ET-naïve mBC patients and those that have progressed on ETs.

VeraMorph has leveraged a proprietary oral drug delivery technology to overcome the limitations of fulvestrant's poor solubility and potentially help mitigate acquired resistance by improving exposure via daily oral dosing. The oral dosages, which consist of a novel polymer-based soft gummy, stabilize fulvestrant in simulated intestinal media up to 5 mg/mL without influencing fulvestrant permeability or causing cytotoxic effects. Pharmacokinetic (PK) studies of oral fulvestrant in rodents have demonstrated maximum plasma concentrations up to 450 ng/mL, a level roughly 20 times that of the average exposure from the monthly IM formulation in clinical settings. PK studies also demonstrated that oral exposure increased with a roughly dose-proportional relationship, with a reduction in AUC from day 1 to day 8 upon repeat dosing. In a cell-derived xenograft (CDX) study utilizing ER+ MCF-7 tumors implanted in athymic nude mice, once daily dosing via oral gavage of oral fulvestrant at 125 mg/kg was able to achieve a statistically significant 55% reduction in tumor growth by day 42 relative to a 50 mg/kg dose of the IM formulation delivered subcutaneously once per week, which was determined to create an equivalent exposure to the monthly IM human dose in separate studies. Oral fulvestrant yielded no observed adverse effects up to 125 mg/kg in both the 42-day CDX study in mice or an 8-day safety study in rats. Further, onset of action and acquired resistance are being tested by monitoring cell viability (via the MTT assay) with MCF-7 cells exposed to time profiles of fulvestrant exposure resembling oral and monthly intramuscular delivery. The study demonstrated that oral dosing reaches minimal cell viability 1-2 weeks faster than IM dosing. Also, preliminary data suggests that the onset of acquired resistance (as demonstrated by a resumption of cell growth) may occur faster from the steady exposure of IM dosing relative to the modulation of daily oral dosing. These results suggest that oral fulvestrant has the potential to finally realize the full potential of fulvestrant as an effective ET for metastatic breast cancer with a well-tolerated AE profile, enhanced efficacy, and reduced susceptibility to acquired resistance with applicability across all mBC patients.¹ Brett JO, Spring LM, Bardia A, Wander

SA (2021) Breast Cancer Research, 23(1):1–15. ² Wardell SE, et. al. (2020) Breast Cancer Research and Treatment, 179(1):67–77.

PO1-05-09

ASCENT-07: A phase 3, randomized, open-label study of sacituzumab govitecan versus treatment of physician's choice in patients with HR+/HER2- inoperable, locally advanced, or metastatic breast cancer post-endocrine therapy

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

K. Punie. Department of Medical Oncology, GZA Hospitals Sint-Augustinus, United States

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

A. Young. Gilead Sciences, Inc., United States

X. Ren. Gilead Sciences, Inc., United States

P. Cinar. Gilead Sciences, Inc., United States

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Approximately 70% of all breast cancer (BC) cases are hormone receptor positive/human epidermal growth factor receptor 2-negative (HR+/HER2-), with ~65% of these being HR+/HER2-low (immunohistochemistry [IHC]1+, IHC2+/in situ hybridization [ISH]-). Despite an increasing number of available endocrine and targeted treatments for metastatic disease, tumors eventually develop resistance to endocrine therapy (ET). Chemotherapy, the standard of care for patients (pts) whose cancers no longer respond to ET, is associated with poor outcomes, representing a high unmet need in the first-line endocrine-resistant setting. Sacituzumab govitecan (SG) is a Trop-2-directed antibody-drug conjugate (ADC) that delivers SN-38 (the active metabolite of the topoisomerase inhibitor irinotecan) to tumor cells via internalization, and to the surrounding tumor microenvironment via the bystander effect. SG demonstrated a significant and clinically meaningful survival benefit in the phase 3, randomized TROPiCS-02 trial, and is approved in the US for inoperable, locally advanced, or metastatic HR+/HER2- BC after ET and ≥ 2 systemic therapies in the metastatic setting. ASCENT-07 will examine the efficacy and safety of SG in the first-line chemotherapy setting, ie, in patients with inoperable, locally advanced, or metastatic ET resistant HR+/HER2- BC. **Study design:** ASCENT-07 (NCT05840211) is a randomized, open-label, global study evaluating SG versus treatment of physician's choice (TPC) chemotherapy in pts with HR+/HER2- inoperable, locally advanced, or metastatic BC who have received ET and are eligible for their first chemotherapy for advanced/metastatic disease. Pts aged ≥ 18 years with histologically confirmed HR+/HER2- (HER2 IHC0 or HER2-low [IHC1+, IHC2+/ISH-]) according to ASCO/CAP criteria, measurable disease per RECIST v1.1, and ECOG performance status of 0 or 1 will be included. Pts are eligible if they meet ≥ 1 of the following criteria: progressive disease (PD) in the metastatic setting on ≥ 2 lines of ET (± targeted therapy) (disease recurrence within the first 24 months of starting adjuvant ET is considered a line of therapy), PD within 6 months of first-line ET (± CDK 4/6 inhibitor) in the metastatic setting, or disease recurrence within 24 months of adjuvant ET

with CDK 4/6 inhibitor initiation and no longer a candidate for additional ET. PD on the most recent therapy will be documented by CT or MRI per RECIST v1.1. Key exclusion criteria include prior treatment targeting topoisomerase I. Pts will be randomized to SG 10 mg/kg IV on days 1 and 8 of a 21-day cycle or TPC (capecitabine, paclitaxel, nab-paclitaxel). The primary endpoint is progression-free survival (PFS) assessed by blinded independent central review (BICR) per RECIST v1.1 criteria or death from any cause, whichever comes first. Secondary endpoints include PFS (assessed by the investigator), overall survival, objective response rate and duration of response per BICR and investigator, and quality of life (QoL) assessed using the EORTC QLQ-C30 cancer questionnaire (primarily change in the Physical Functioning domain at week 16 and time to deterioration in the Global Health Status/QoL domain). Pharmacokinetics and immunogenicity analyses will be undertaken in pts receiving SG. Incidence of adverse events and serious adverse events, including relationship to study drug(s), will be reported. Laboratory and vital signs will be monitored. ASCENT-07 is currently open for recruitment and requires ~654 eligible pts to provide adequate power for assessment of the primary and key secondary endpoints.

PO1-05-10

Clinical effectiveness of CDK4/6 inhibitors in HER2-low metastatic breast cancer

Presenting Author(s) and Co-Author(s):

F. Zhang. Montefiore Medical Center, United States

J. Anampa Mesias. Albert Einstein College of Medicine, Bronx, NY, United States

Introduction: There is growing evidence indicating that human epidermal growth factor 2 (HER2)-low is a unique subtype of breast cancer that comprises a substantial share of patients historically classified as HER2 negative. Cyclin-dependent kinase 4/6 inhibitors (CDK4/6is) are important in the treatment of hormone receptor-positive (HR+)/HER2-negative metastatic breast cancer (MBC). Whether HER2-low status or the level of HER2 gene amplification have prognostic significance for HR+/HER2-negative MBC patients treated with ET and CDK4/6i remains an area of active investigation. **Methods:** Patients diagnosed with HR+/HER2-negative MBC and who were treated with palbociclib, ribociclib, or abemaciclib from 6/10/2015 to 12/28/2022 were selected from the Montefiore Health system database and followed until 3/24/2023. HER2-0 was defined as immunohistochemistry (IHC) 0, and HER2-low was defined as IHC 1+ or IHC 2+/*in situ* hybridization negative by 2018 ASCO/CAP guidelines. Median values were used to establish cutoffs for HER2/CEP17 ratio and HER2 gene copy number (GCN). Characteristics of the patients and tumors in the subgroups were compared using chi-squared/Fisher's exact test for categorical data and Kruskal-Wallis/Wilcoxon signed rank tests for continuous data. Kaplan-Meier and Cox proportional hazards analysis were used to compare overall survival (OS) and progression free survival (PFS). **Results:** 239 patients received CDK4/6i, with 46 HER2-0 and 193 HER2-low patients. There was no statistically significant difference in clinicopathological characteristics between both cohorts. No significant differences were observed in median OS (36 vs 34 months, $P > 0.9$) and median PFS (44 vs 35 months, $P = 0.4$) between HER2-0 and HER2-low patients. Adjusting for HER2 status, multivariable analysis showed no statistically significant association between HER2-low status and worse OS (HR: 1.03, $P = 0.9$) or worse PFS (HR: 1.37, $P = 0.4$). The median HER2/CEP17 ratio was 1.25 (Interquartile range (IQR): 1.18-1.39), and the median HER2 GCN was 2.58 (IQR: 2.10-3.18). Median OS (25 vs 37, $P = 0.15$) and median PFS (35 vs 37, $P = 0.15$) showed no significant differences between ratio-below vs above-median patients. However, patients with GCN-below-median had significantly worse OS (25 vs 37 months, $P = 0.026$), with no significant difference in median PFS (38 vs 35 months, $P = 0.3$). Multivariate analysis revealed a significant effect of GCN-below-median on OS (HR: 0.50, $P = 0.022$) but not on PFS. **Conclusion:** The clinical effectiveness of CDK4/6i is not influenced by HER2-low status; however, the extent of HER2 gene amplification may have a substantial impact on therapy responsiveness in MBC patients undergoing CDK4/6i treatment.

Table 1

Characteristic	HER2			HER2/CEP17 Ratio			HER2 GCN		
	HER2-0, N = 45 ¹	HER2-low, N = 137 ¹	p-value ²	Low, N = 71 ¹	High, N = 72 ¹	p-value ²	Low, N = 72 ¹	High, N = 72 ¹	p-value ²
Ethnicity									
Hispanic	13 (29%)	72 (52%)	0.3	26 (37%)	29 (40%)	0.9	26 (36%)	29 (40%)	0.8
Non-Hispanic	31 (70%)	57 (42%)		42 (60%)	44 (60%)		43 (60%)	43 (60%)	
Unknown	2	4		3	0		3	0	
Race			>0.9			>0.9			0.8
White	10 (22%)	39 (28%)		12 (17%)	10 (14%)		12 (17%)	10 (14%)	
Black	21 (46%)	86 (62%)		35 (50%)	37 (51%)		36 (51%)	36 (51%)	
Asian	2 (4.3%)	11 (8.0%)		3 (4.3%)	3 (4.2%)		4 (5.6%)	2 (2.8%)	
Other	13 (29%)	54 (39%)		20 (28%)	22 (31%)		19 (27%)	23 (32%)	
Unknown	0	7		3	1		1	1	
Gender			>0.9			>0.9			0.3
Female	46 (100%)	131 (96%)		70 (99%)	72 (99%)		72 (100%)	70 (97%)	
Male	0 (0%)	2 (1.5%)		1 (1.4%)	1 (1.4%)		0 (0%)	2 (2.8%)	
Age	66 (53, 72)	61 (53, 69)	0.4	60 (54, 72)	62 (54, 69)	0.6	61 (54, 69)	60 (53, 71)	0.8
Hormone Status			0.3			0.5			0.2
ER+/PR+	34 (75%)	131 (96%)		49 (69%)	51 (70%)		44 (61%)	52 (72%)	
ER+/PR-	12 (27%)	61 (45%)		26 (37%)	22 (30%)		20 (28%)	20 (28%)	
ER-/PR+	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)	
ER-/PR-	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Tumor Grade			0.8			0.2			0.15
1	1 (2.2%)	10 (7.3%)		6 (8.5%)	2 (3.3%)		6 (8.3%)	2 (3.4%)	
2	20 (45%)	61 (45%)		27 (38%)	30 (42%)		32 (44%)	30 (41%)	
3	14 (31%)	44 (32%)		21 (29%)	23 (32%)		17 (23%)	27 (37%)	
Unknown	11	30		17	13		17	13	
Charon Comorbidity Index	8.00 (7.00, 9.00)	8.00 (7.00, 10.00)	0.7	8.00 (7.00, 10.00)	8.00 (7.00, 9.00)	0.5	8.00 (7.00, 10.00)	8.00 (7.00, 9.00)	0.2
Visceral Metastases			>0.9			0.3			0.6
FALSE	17 (37%)	79 (58%)		31 (44%)	24 (33%)		27 (37%)	30 (42%)	
TRUE	29 (63%)	120 (87%)		40 (56%)	47 (65%)		45 (63%)	42 (58%)	
Prior Chemotherapy			0.7			0.058			>0.9
FALSE	37 (82%)	163 (119%)		45 (63%)	56 (77%)		42 (58%)	61 (84%)	
TRUE	8 (18%)	29 (21%)		6 (8.5%)	14 (19%)		10 (14%)	10 (14%)	
Unknown	1	1		0	1		0	1	
Number of Lines of Chemotherapy			0.7			0.078			0.4
0	37 (82%)	163 (119%)		45 (63%)	56 (77%)		42 (58%)	61 (84%)	
1	4 (8.9%)	19 (14%)		4 (5.6%)	8 (11%)		6 (8.3%)	6 (8.3%)	
2	3 (6.7%)	5 (3.6%)		0 (0%)	3 (4.2%)		2 (2.8%)	1 (1.4%)	
3	1 (2.2%)	3 (2.2%)		0 (0%)	3 (4.2%)		0 (0%)	3 (4.2%)	
4	0 (0%)	1 (0.7%)		0 (0%)	1 (1.4%)		0 (0%)	1 (1.4%)	
5	0 (0%)	1 (0.7%)		0 (0%)	1 (1.4%)		0 (0%)	1 (1.4%)	
Unknown	1	1		0	1		0	1	
Prior ET			0.3			0.13			0.2
FALSE	33 (73%)	125 (91%)		51 (72%)	43 (58%)		51 (71%)	43 (58%)	
TRUE	12 (27%)	67 (49%)		20 (28%)	29 (40%)		21 (29%)	29 (39%)	
Unknown	1	1		0	1		0	1	
Number of Lines of ET			>0.9			0.2			0.3
0	33 (73%)	125 (91%)		51 (72%)	43 (58%)		51 (71%)	43 (58%)	
1	7 (16%)	33 (24%)		9 (13%)	14 (19%)		8 (11%)	13 (18%)	
2	4 (8.9%)	20 (15%)		6 (8.5%)	12 (17%)		6 (8.3%)	10 (14%)	
3	1 (2.2%)	6 (4.4%)		3 (4.2%)	2 (3%)		4 (5.6%)	1 (1.4%)	
4	0 (0%)	3 (2.2%)		0 (0%)	0 (0%)		1 (1.4%)	1 (1.4%)	
5	0 (0%)	1 (0.7%)		0 (0%)	1 (1.4%)		0 (0%)	1 (1.4%)	
6	0 (0%)	1 (0.7%)		0 (0%)	1 (1.4%)		0 (0%)	1 (1.4%)	
7	0 (0%)	1 (0.7%)		0 (0%)	1 (1.4%)		0 (0%)	1 (1.4%)	
Unknown	1	1		0	1		0	1	
CDK4/6			0.7			0.7			0.4
Abemaciclib	9 (20%)	31 (23%)		10 (14%)	11 (15%)		10 (14%)	9 (12%)	
Palbociclib	30 (66%)	141 (103%)		52 (73%)	50 (68%)		53 (73%)	57 (77%)	
Ribociclib	3 (6.7%)	17 (12%)		6 (8.5%)	4 (5.5%)		4 (5.6%)	6 (8.3%)	
ET			0.5			0.2			0.9
Aspirin/Statins	9 (20%)	29 (21%)		12 (17%)	12 (17%)		11 (15%)	14 (19%)	
Estrogen/anti	1 (2.2%)	4 (3.0%)		0 (0%)	4 (5.6%)		1 (1.4%)	2 (2.8%)	
Fulvestrant	11 (24%)	69 (50%)		22 (31%)	28 (39%)		24 (33%)	28 (38%)	
Letrozole	23 (51%)	89 (65%)		34 (48%)	30 (42%)		33 (46%)	29 (40%)	
Tamoxifen	0 (0%)	2 (1.5%)		2 (2.8%)	0 (0%)		1 (1.4%)	1 (1.4%)	

Baseline characteristics of patients with MBC comparing HER2-0 vs HER2-low, above/below median HER2/CEP17 ratio, and above/below median HER2 GCN.

Table 2

Characteristic	OS		PFS	
	50% Percentile	p-value ¹	50% Percentile	p-value ¹
HER2		>0.9		0.4
HER2-0	36 (19, 49)		44 (42, -)	
HER2-low	34 (27, 38)		35 (32, 43)	
HER2/CEP17 Ratio		0.15		0.15
Low	25 (21, 44)		35 (20, 45)	
High	37 (26, 50)		37 (35, -)	
HER2 GCN		0.026*		0.3
Low	25 (19, 40)		38 (19, 45)	
High	37 (34, 50)		35 (25, -)	

¹p<0.05; **p<0.01; ***p<0.001

Median OS and PFS in patients with MBC comparing HER2-0 vs HER2-low, above/below median HER2/CEP17 ratio, and above/below median HER2 GCN.

Table 3

Characteristic	HER2 OS			HER2 PFS			HER2/CEP17 Ratio OS			HER2/CEP17 Ratio PFS			HER2 GCN OS			HER2 GCN PFS			
	N	HR	p-value ¹	N	HR	p-value ¹	N	HR	p-value ¹	N	HR	p-value ¹	N	HR	p-value ¹	N	HR	p-value ¹	
HER2	180			180															
HER2-0	33	-		33	-														
HER2-low	147	1.03	0.9	147	1.07	0.4													
HER2/CEP17 Ratio																			
Low							110			110									
High							51	-		51	-								
							59	0.74	0.3	59	0.58	0.2							
HER2 GCN													110			110			
Low													52	-		52	-		
High													58	0.50	0.022*	58	0.70	0.5	
Race	180			180			110			110			110			110			
White	32	-		32	-		14	-		14	-		14	-		14	-		
Black	87	1.11	0.7	87	0.85	0.7	59	0.63	0.3	59	0.62	0.8	59	0.70	0.4	59	0.85	>0.9	
Asian	10	1.40	0.4	10	1.08	>0.9	4	0.40	0.2	4	0.13	0.14	4	0.35	0.14	4	0.17	0.2	
Other	51	1.18	0.7	51	1.27	0.7	33	1.24	0.7	33	4.27	0.3	33	1.47	0.5	33	4.39	0.3	
Ethnicity	180			180			110			110			110			110			
Hispanic	63	-		63	-		44	-		44	-		44	-		44	-		
non-Hispanic	117	0.98	>0.9	117	1.50	0.5	66	1.95	0.2	66	7.01	0.11	66	2.25	0.14	66	6.68	0.12	
Age	180	1.00	0.7	180	1.02	0.4	110	1.01	0.8	110	1.03	0.3	110	1.01	0.7	110	1.03	0.3	
Visceral Metastases	180			180			110			110			110			110			
FALSE	66	-		66	-		43	-		43	-		43	-		43	-		
TRUE	114	0.81	0.3	114	0.67	0.2	67	0.58	0.060*	67	0.38	0.052*	67	0.56	0.043*	67	0.37	0.040*	
Hormone Status	180			180			110			110			110			110			
ER+/PR+	125	-		125	-		74	-		74	-		74	-		74	-		
ER+/PR-	55	0.87	0.5	55	1.27	0.6	36	1.03	>0.9	36	2.36	0.2	36	1.09	0.8	36	2.60	0.12	
ER-/PR+	0	-		0	-		0	-		0	-		0	-		0	-		
ER-/PR-	0	-		0	-		0	-		0	-		0	-		0	-		
Tumor Grade	180			180			110			110			110			110			
1	11	-		11	-		8	-		8	-		8	-		8	-		
2	97	1.27	0.5	97	1.63	0.5	59	1.15	0.8	59	1.87	0.5	59	1.24	0.6	59	1.61	0.6	
3	72	0.95	0.9	72	1.02	>0.9	43	0.98	>0.9	43	1.57	0.7	43	1.33	0.6	43	1.49	0.7	
Charlson Comorbidity Index	180	1.13	0.2	180	1.04	0.8	110	1.08	0.5	110	0.93	0.7	110	1.06	0.6	110	0.97	0.8	
Prior Chemotherapy	180			180			110			110			110			110			
FALSE	151	-		151	-		95	-		95	-		95	-		95	-		
TRUE	29	0.93	0.8	29	0.72	0.6	15	1.24	0.7	15	1.22	0.9	15	1.15	0.8	15	1.12	>0.9	
Prior ET	180			180			110			110			110			110			
FALSE	119	-		119	-		71	-		71	-		71	-		71	-		
TRUE	61	0.62	0.037*	61	0.60	0.2	39	0.44	0.016*	39	0.44	0.13	39	0.52	0.061	39	0.48	0.2	

¹HR = Hazard Ratio
*p<0.05, **p<0.01, ***p<0.001

Multivariable analysis of OS and PFS for patients with MBC comparing HER2-0 vs HER2-low, above/below median HER2/CEP17 ratio, and above/below median HER2 GCN.

PO1-05-11

Efficacy of metformin as adjunctive therapy in patients with de novo metastatic breast cancer: a retrospective cohort study

Presenting Author(s) and Co-Author(s):

R. Chongxi. Cangzhou Clinical College of Integrated Traditional Chinese and Western Medicine of Hebei Medical University, China (People's Republic)

S. Jianna. Cangzhou Clinical College of Integrated Traditional Chinese and Western Medicine of Hebei Medical University, United States

K. Lingjun. Cangzhou Clinical College of Integrated Traditional Chinese and Western Medicine of Hebei Medical University, United States

H. Yu. Cangzhou Clinical College of Integrated Traditional Chinese and Western Medicine of Hebei Medical University, China (People's Republic)

Background: Metformin, an oral biguanide used for the treatment of type-2 diabetes mellitus (DM), has been shown in a considerable number of studies to have an anti-tumorigenic impact against breast cancer cells through several mechanisms, thereby improving breast cancer outcomes. However, the impact of metformin treatment on survival outcomes in patients with non-diabetic breast cancer is still under debate, with very few data available regarding metformin administration in de novo metastatic breast cancer (dnMBC). This study was conducted to investigate and evaluate the impact on survival outcomes of patients with dnMBC treated with metformin as adjunctive therapy at our institutes. **Methods:** All dnMBC women who received chemotherapy-based systemic therapy or combined with metformin administered orally in our hospitals between March 2007 and November 2016 were enrolled in the study. Data were retrospectively extracted from the patients' case records. Data were analyzed according to the clinicopathological features and treatment outcomes. All specimens were rechecked for the purpose of the research. Overall survival (OS), as the study endpoint, was defined as the time from pathologically confirmed diagnosis to all-cause death or end of the follow-up time. Kaplan-Meier estimate was used to calculate the survival rates. The difference between metformin and non-metformin groups was compared by the log-rank method. Cox regression analysis (uni- and multivariate analysis) was used to assess the effect of variables on survival outcomes. Analyses were performed by Stata 17 software for windows version. **Results:** A total of 252 women with dnMBC were included with an average age of 54.41 ± 11.61 years. Among them, 97 patients (including 11 DM patients) received chemotherapy-based systemic therapy plus oral administration of metformin 850-1000mg twice daily (metformin group), and 155 patients received chemotherapy-based systemic therapy (non-metformin group). There was no significant difference in body mass index, age, N-stage, P53 index, ER/PR status, HER-2 expression and initial metastatic sites between metformin group and non-metformin group. But there were differences in T-stage and Ki67 index between the two groups (Table 1). The median follow-up was 70 months. The median OS was 24 months. The 3-year and 5-year OS rates for all patients were 29.8% (95% CI: 24.2% to 35.4%) and 11.6% (95% CI: 7.5% to 16.7%), respectively; Log-rank test showed that the metformin group had a significant advantage over the non-metformin group in OS rates ($p=0.0002$). The 3-year and 5-year OS rates in the metformin group were 42.3% (95% CI: 32.4% to 51.8%) and 21.2% (95% CI: 12.8% to 31.1%), respectively; the same rates for non-metformin group were 21.9% (95% CI: 15.8% to 28.7%) and 5.6% (95% CI: 2.4% to 11.1%), respectively. Results of proportional hazards model, after adjustment for T-stage and Ki67 index, depicted an independent prognostic value of metformin use with multivariate hazard ratio of 0.61 (95% CI: 0.45 to 0.81) for OS compared to non-metformin group ($p=0.001$). No survival advantage was found for DM patients (0.59; 95%

CI:0.29 to 1.22; p=0.159). Conclusions: Our data support a favorable outcome for survival associated with metformin use in dnMBC patients. However, the retrospective nature and small sample size of the current study are major limitations to reliable conclusions about metformin's potential to improve OS in patients. Therefore, prospective evidence from phase-3 randomized controlled trials on the feasibility of metformin use in dnMBC is required before its routine use can be recommended. Keywords: Metformin; De novo metastatic breast cancer; Adjunctive therapy; Survival outcomes

Tables:

Table 1. Cost-effectiveness of the multigene assays compared to clinical-pathological risk alone.

Test	Δ Cost	Δ QALYs	Δ life-years	ICER	NMB
The Oncotype DX [®] test	-\$13,395	0.25	0.29	Dominant	\$38,492
MammaPrint [®]	\$1,079	0.04	0.05	\$27,760	\$2,808
EndoPredict [®]	\$392	0.05	0.06	\$7,942	\$4,544
Prosigna ROR [®]	-\$2,410	0.07		Dominant	\$9,768

Dominant = the multigene assay is less costly and more effective compared to using clinico-pathologic risk alone

ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life-year

PO1-05-12

Pooled clinical trial data analyses comparing the biology of HER2-low vs HER2-0 breast cancer in patients with metastatic breast cancer following treatment with standard single agent chemotherapy

Presenting Author(s) and Co-Author(s):

E. Lamont. Medidata AI, Medidata Solutions, Boston, Massachusetts, United States

E. Stein. Medidata AI, Medidata Solutions, United States

P. Tarantino. Breast Oncology Program, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

C. Ahlberg. Medidata AI, Medidata Solutions, United States

K. Chinnathambu. Medidata AI, Medidata Solutions, United States

J. Qi. Medidata AI, Medidata Solutions, United States

K. Tummagunta. Medidata AI, Medidata Solutions, United States

J. Bilan. Medidata AI, Medidata Solutions, United States

R. Davi. Medidata AI, Medidata Solutions, United States

L. Ensign. Medidata AI, Medidata Solutions, United States

Background: Prior analyses of observational data suggest that for patients with metastatic breast cancer (MBC), tumor biology does not vary by HER2-low vs. HER2-0 expression given similar overall survival (OS) times after accounting for patients' clinicopathologic features including hormone receptor (HR) status. We sought to evaluate potential differential biology by HER2-low status by (1) studying data pertaining to patients treated in historic clinical trials (i.e., data collected to measure associations between protocol defined treatments and outcomes) and (2) evaluating the endpoint of progression-free survival (PFS) in addition to OS following treatment with standard single agent chemotherapy for MBC. Methods: Pooling anonymized clinical trial data from studies within the Medidata Enterprise Data Store, we identified 142 women with HER2-negative MBC who received treatment with an NCCN recommended single agent chemotherapy in the context of a clinical trial. Using patient-level immunohistochemistry (IHC) results, we categorized patients as either HER2-low (IHC 1+/2+ and not amplified by in situ hybridization) or HER2-0 (IHC 0). We compared patients' baseline demographic and clinicopathologic features according to HER2-low vs HER2-0 status. We used Cox proportional-hazard models stratified by HR status to estimate OS and PFS according to HER2-low vs HER2-0 classification while adjusting for patients' baseline demographic and clinicopathologic attributes. Results: Patients with HER2-low disease represented 20% (28/142) of the HER2-negative cohort. Twenty-five percent (7/28) of HER2-low patients had tumors that expressed hormone receptors compared with 17% (19/114) of HER2-0 patients ($p=0.31$). In this cohort, the maximum follow up time was 38.4 months. For HER2-low patients vs HER2-0 patients, the median OS was 10.7 vs. 12.7 months ($p=0.37$), and the median PFS was 3.5 vs. 2.9 months (log rank test, $p=0.53$) respectively. In Cox proportional-hazard models that adjusted for patient demographic and clinicopathologic features and were stratified by HR status, patients with HER2-low tumors had an 16% elevated (non-significant) hazard of death compared with patients with HER2-0 tumors (HR 1.16, 95% CI: 0.69-1.95) and a 22% reduced (non-significant) hazard of progression or death (HR 0.78, 95% CI: 0.45-1.35). Conclusions: Analyses of pooled historic clinical trial data pertaining to women with HER2-negative MBC who were treated with single agent chemotherapy revealed no meaningful clinical differences in either OS or PFS

endpoints according to HER2-negative subtypes (i.e., HER2-low vs. HER2-0) after accounting for patient demographic and clinicopathologic features. These results support prior findings from observational research suggesting that there are no biological differences associated with HER2-negative subtypes. Table. Multivariable Cox Proportional Hazards Models for OS and PFS Stratified by Hormone Receptor Status, (N=134)

Variable	OS		PFS	
	HR*	95% CI	HR*	95% CI
Age (decade)	0.84	0.70-1.01	0.86	0.72-1.01
Race				
White	1.00	(referent)	1.00	(referent)
Black	1.75	0.84-3.63	1.57	0.66-3.73
Asian	0.93	0.47-1.80	1.33	0.71-2.51
Other	1.69	0.45-6.38	2.10	0.62-7.15
Ethnicity				
Non-Hispanic or Latino	1.00	(referent)	1.00	(referent)
Hispanic or Latino	2.10	0.95-4.64	1.02	0.44-2.35
HER2 Characterization				
HER2-0	1.00	(referent)	1.00	(referent)
HER2-1+/2+	1.16	0.69-1.95	0.78	0.45-1.35
Prior Lines of Chemotherapy for Metastatic Disease				
0	1.00	(referent)	1.00	(referent)

1	0.82	0.46-1.46	1.13	0.65-1.95
2	0.69	0.35-1.36	1.00	0.52-1.93
3	0.59	0.10-3.42	2.18	0.45-10.50
ECOG Performance Status				
0	1.00	(referent)	1.00	(referent)
1	1.65	1.07-2.54	1.57	1.02-2.43

Legend: OS=overall survival; PFS=progression-free survival; HR=hazard ratio; HER2=human epidermal growth factor receptor 2; ECOG=Eastern Cooperative Oncology Group. *Analyses adjusted for clinical trial membership (coefficients not reported)

PO1-05-13

Drop-out rates from line to line of treatment in metastatic breast cancer (MBC): Results from the Austrian AGMT_MBC-Registry

Presenting Author(s) and Co-Author(s):

S. Gampenrieder. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

G. Rinnerthaler. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

A. Pichler. Internal Medicine - Department for Haemato-Oncology, LKH Hochsteiermark, Leoben, Austria, United States

W. Herz. Department of Surgery, Breast Health Center, LKH Hochsteiermark, Leoben, Austria, United States

A. Petzer. Internal Medicine I for Hematology with Stem Cell Transplantation, Hemostaseology and Medical Oncology, Ordensklinikum Linz Barmherzige Schwestern – Elisabethinen, Linz, Austria, United States

C. Dormann. Internal Medicine I for Hematology with Stem Cell Transplantation, Hemostaseology and Medical Oncology, Ordensklinikum Linz Barmherzige Schwestern – Elisabethinen, Linz, Austria, United States

M. Balic. Division of Oncology, Department of Internal Medicine, Medical University Graz, Austria

C. Suppan. Clinical Division of oncology, Medical University of Graz, United States

S. Heibl. Department of Internal Medicine IV, Klinikum Wels-Grieskirchen GmbH, Wels, Austria, United States

L. Scagnetti. Department of Internal Medicine IV, Klinikum Wels-Grieskirchen GmbH, Wels, Austria, United States

M. Sandholzer. Department of Internal Medicine II, Academic Teaching Hospital Feldkirch, Feldkirch, Austria, United States

C. Schmitt. Department for haematology and internal oncology, Med Campus III, Kepler University Hospital Linz, United States

A. Zabernigg. Department of Internal Medicine, County Hospital Kufstein, Kufstein, Austria, United States

D. Egle. Department of Gynaecology, Medical University Innsbruck, Innsbruck, Austria, United States

P. Pichler. University Hospital St.Pölten, Department for Internal Medicine 1, St. Pölten, Austria, United States

C. Hager. Department of Gynecology and Obstetrics, City Hospital, Dornbirn, Austria, United States

F. Roitner. Department of Internal Medicine II, Hospital Braunau, Braunau, Austria, United States

J. Andel. Department of Internal Medicine II, Pyhrn-Eisenwurzen Klinikum Steyr, Steyr, Austria, United States

K. Strasser-Weippl. Department of Medicine I, Clinic Ottakring, Vienna, Austria, United States

R. Bartsch. Medical University of Vienna, Department of Medicine I, Division of Oncology, Vienna, Austria, Austria

M. Hubalek. Department of Gynecology, Breast Health Center Schwaz, Schwaz, Austria, United States

M. Knauer. Breast Center Eastern Switzerland, St. Gallen, Switzerland, United States

C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria

R. Greil. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

Background: In metastatic breast cancer (MBC) continuous treatment with sequentially administered cancer drugs is the standard of care. Lines of treatment (LoT) consisting of single drugs or drug combinations are usually administered until disease progression or unacceptable toxicity. To provide as many patients as possible access to the most effective therapies, the “best treatment first” strategy has been established as a subset of patients will be lost from LoT to LoT. To investigate drop-out rates in all subsequent LoT, high-quality real-world data are needed. Here, we present data from the Austrian Study Group of Medical Tumor Therapy (AGMT) MBC-Registry, a multicenter nationwide ongoing retrospective and prospective registry for MBC patients in Austria. Patients and methods: Patients with known hormone-receptor (HR) and HER2 status, available survival data and at least one LoT were included. Therapies administered between diagnosis or disease progression and subsequent disease progression were counted as one LoT. All types of antitumor drugs (endocrine therapy, targeted therapy, chemotherapy, immunotherapy) were considered. Results: As of 16-May-2023, 2,484 patients were included in the registry. Out of 2,044 evaluable patients, 1,330 (65.1%) were HR+/HER2-, 251 (12.3%) were HR+/HER2+, 146 (7.1%) were HR-/HER2+ and 317 (15.5%) were triple-negative, respectively. The median number of treatment-lines in the overall cohort was 3 (range 1-14; 95%CI 3-3). In patients with HR+/HER2-, HR+/HER2+, HR-/HER2+ and triple-negative tumors the median LoT were 3 (range 1-14; 95%CI 3-4), 4 (range 1-13; 95%CI 3-4), 3 (range 1-10; 95%CI 3-4) and 2 (range 1-9; 95%CI 2-3), respectively. Overall, 641 patients were still on treatment at data cut off. The estimated percentage of patients being treated in each LoT and the corresponding drop-out rates from 1st- to 5th-line are provided in Table 1.

		1 st -line	2 nd -line	3 rd -line	4 th -line	5 th -line
All	n	2044	1281	869	558	344
	Drop-out-Rate	/	23.8%	24.8%	30.9%	34.0%
HR+/HER2-	n	1,330	854	586	380	244
	Drop-out-Rate	/	19.6%	23.0%	29.6%	30.7%
HR+/HER2+	n	251	157	109	72	48
	Drop-out-Rate	/	23.4%	20.4%	25.0%	28.4%

HR-/HER2+	n	146	78	59	37	24
	Drop-out-Rate	/	36.6%	16.9%	36.2%	33.3%
Triple-negative	n	317	192	115	69	28
	Drop-out-Rate	/	34.0%	38.2%	39.5%	57.6%

Conclusion: Relevant drop-out rates even in the early treatment lines support a “best treatment first” strategy. An accelerated investigation of promising cancer drugs in early treatment lines in patients with MBC is warranted.

PO1-05-14

Outcomes of first-line chemotherapy for visceral crisis in metastatic breast cancer

Presenting Author(s) and Co-Author(s):

M. Andrade. University of São Paulo (USP), United States

V. Felix. University of São Paulo (USP), United States

R. Colombo Bonadio. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

L. Testa. Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil, United States

Background: Visceral crisis (VC) in metastatic breast cancer (BC) is defined as severe organ dysfunction, as assessed by signs and symptoms, laboratory tests, and rapid disease progression. The management of this condition is currently based on limited retrospective evidence and expert opinions, since VC has been a common exclusion criterion in clinical trials. There is a paucity of real-world data regarding the management of BC VC. We aim to evaluate the survival outcomes and prognostic factors of first-line palliative chemotherapy for VC in a tertiary cancer center in Brazil. Methods: Data were retrospectively collected from patients with metastatic BC diagnosed with VC between 2017 and 2022 in a single cancer center. Our analysis focused on patients receiving first-line chemotherapy for VC. Patients with hormone receptor-positive BC could have been previously treated with endocrine therapy for metastatic disease. CDK4/6 inhibitors were not available in the cancer center during the study period. Prognostic factors associated with survival were evaluated through univariate and multivariable analyses, using the Cox regression model. Results: A total of 106 patients with VC were evaluated. Among them, 58.5% (62 patients) had not received any previous line of chemotherapy in the metastatic setting before the diagnosis of VC (1st line cohort). Median overall survival (mOS) in the total population was 1.7 months, significantly distinct from the 1st line cohort, which had a mOS of 4.9 months ($p < 0.001$). Focusing on the 1st line cohort, the most common type of VC was pulmonary (40.3%), followed by hepatic (24.2%), and medullary infiltration (21%). 66.1% of patients had HR+HER2- (mOS 9.3 months), 19.3% HER2+ (mOS 4.5 months), and 11.3% triple-negative BC (TNBC) (mOS 1.5 months). Most patients were treated for VC based on systemic therapy combinations (59.7%), while 32.2% received monochemotherapy, and 8.1% were managed with best supportive care (BSC) alone. In the population receiving multidrug therapy, the mOS was 9.3 months, compared to 4.9 months with monochemotherapy and 0.7 months in patients undergoing BSC. Nevertheless, the type of treatment received was not associated with OS in the multivariable analysis. In the multivariable analysis, the prognostic factors associated with worse mOS were TNBC subtype, hepatic VC, and ECOG-PS > 2 . (Table). Among patients with hepatic VC, 73.7% died during the same hospitalization and 60.5% received chemotherapy within 30 days prior to death. Conclusions: Patients with VC due to BC have a poor prognosis, even in the context of first-line chemotherapy. Factors such as ECOG-PS, BC subtype, and VC type should be taken into account when discussing the expected outcomes of this life-threatening condition. Taking these factors into account can help physicians to differentiate patients who are more likely to benefit from systemic oncologic treatment from those for whom such therapy would be futile or potentially harmful.

Median overall survival according to baseline characteristics and multivariable analysis (1st line cohort, n=62)

Baseline factors	mOS, months (95% CI)	HR (95% CI)	p-value
<i>BC subtype</i>			
HR+HER2-	9.3 (3.2 – 15.7)	Reference	
HER2+	4.3 (1.1 – 10.4)	1.19 (0.5 – 2.86)	0.692
TNBC	1.5 (0.3 – 3.3)	3.41 (1.03 – 11.29)	0.044
<i>Type of visceral crisis</i>			
Lung	3.2 (1.2 - 8.3)	Reference	
Liver	1.4 (0.2 - 7.2)	2.81 (1.23 – 6.43)	0.014
Bone marrow	5.8 (3.1 - 48.5)	0.76 (0.31 – 1.83)	0.541
<i>VC treatment</i>			
Polychemotherapy	9.3 (3.1 - 37.2)	Reference	
Monochemotherapy	4.9 (2.0 - 10.4)	0.89 (0.38 – 2.08)	0.792
BSC	0.7 (0.1 - NR)	2.26 (0.55 – 9.21)	0.256
<i>ECOG-PS</i>			
1-2	9.3 (4.2 - 15.7)	Reference	
3-4	1.1 (0.3 - 2.1)	2.73 (1.2 – 6.19)	0.017

PO1-06-01

Clinical Efficacy of Tumor Organoid-Guided Cancer Therapy for Locally Advanced Unresectable or Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

Y. Lin. Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, United States

H. Gao. Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, United States

H. Li. Biomedical Laboratory, Jingke BioTech Group, United States

B. Du. Biomedical Laboratory, Jingke BioTech Group, United States

M. Cheng. Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, United States

J. Zou. Guangdong Medical University, United States

X. Zheng. Southern Medical University, United States

T. Zhu. Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, United States

T. Li. Biomedical Laboratory, Jingke BioTech Group, United States

S. Li. Biomedical Laboratory, Jingke BioTech Group, United States

K. Wang. Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, United States

Purpose: Patient-derived organoids (PDOs) may facilitate treatment selection, but the feasibility of using breast cancer PDOs to guide personalized treatment in clinical practice has not been fully investigated. This study aimed to assess the clinical efficacy of treatment guided by PDO drug sensitivity tests (OGT) versus treatment of physician's choice (TPC) in patients with locally advanced unresectable or metastatic breast cancer (MBC) and to explore the potential of PDOs to reveal mechanisms underlying treatment resistance. **Methods:** Patients diagnosed with MBC were recruited between January 2020 and August 2022. PDOs were established from biopsies specimens or malignant effusion samples. The efficacy of customized drug panels was determined by measuring cell mortality after drug exposure. Patients receiving OGT were matched 1:2 by nearest neighbor propensity scores with patients receiving TPC. The primary clinical outcome was progression-free survival. Secondary outcomes included objective response rate and disease control rate. Targeted gene sequencing and pathway enrichment analysis were performed. **Results:** 46 PDOs (46 of 51, 90.2%) were generated from 45 MBC patients. PDO drug screening showed an accuracy of 81.1% (95% CI 67.6%-91.9%) in predicting patients' clinical responses. 36 OGT patients were matched to 69 TPC patients. OGT was associated with prolonged median progression-free survival (11.0 months vs 5.0 months; unadjusted hazard ratio 0.53 [95% CI 0.33-0.85]; P=0.01) and improved disease control (88.9% vs 63.8%; unadjusted odd ratio 4.26 [1.44-18.62]) compared with TPC. The objective response rate of both groups was similar. Pathway enrichment analysis uncovered differentially modulated pathways implicated in DNA repair and transcriptional regulation in patients less sensitive to capecitabine/gemcitabine, and pathways associated with cell cycle regulation in patients less sensitive to palbociclib. **Conclusions:** MBC patients treated with OGT were associated with superior progression-free survival and disease control compared with TPC. PDO-based functional precision medicine is a feasible strategy for treatment optimization and

customization in MBC and may enhance our understanding of therapeutic resistance.

PO1-06-02

Solti-1716 TATEN phase II trial: Targeting non-Luminal disease by PAM50 with pembrolizumab and paclitaxel in Hormone Receptor-positive/HER2-negative advanced breast cancer (ABC)

Presenting Author(s) and Co-Author(s):

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

B. Conte. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain, United States

F. Brasó-Maristany. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), United States

N. Chic. Hospital Clínic of Barcelona, Barcelona, Spain ; August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain, Catalonia, Spain

M. Muñoz. SOLTI Breast Cancer Research Group, Hospital Clínic of Barcelona, Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, Catalonia, Spain

C. Hernando. Hospital Clínico Universitario de Valencia, Valencia, Spain

M. Alva. Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain, United States

S. Vazquez. Hospital Duran i Reynals-Institut Català d'Oncologia. Hospitalet de Llobregat, Barcelona, Spain., United States

S. Blanch. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US. Fundación Instituto Valenciano de Oncología, Valencia, Spain, United States

M. Oliveira. SOLTI Cancer Research Group, Barcelona, Spain / Vall d'Hebron University Hospital, Barcelona, Spain / Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, United States

E. Fernández. SOLTI Cancer Research Group, Barcelona, Spain., United States

O. Castillo. Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

P. Galván. Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

□. Aguirre. Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

E. Sanfeliu. SOLTI Breast Cancer Research Group, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Faculty of Medicine and Pathology Department, Hospital Clínic of Barcelona, University of Barcelona, Barcelona, Spain., Catalonia, Spain

L. Villanueva. SOLTI Cancer Research Group, Barcelona, Spain, United States

T. Pascual. SOLTI Cancer Research Group, Barcelona, Spain /Department of Medical Oncology, Hospital Clínic de Barcelona, Spain / Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

Background Within HR+/HER2-negative breast cancer, PAM50 non-luminal tumors (HER2-enriched [HER2-E] and Basal-like) have higher expression of proliferation and immune-related genes and tumor infiltrating lymphocytes and might benefit from immunotherapy. Here, we report the efficacy, safety, and correlative analysis data of the TATEN trial, the first study designed to evaluate pembrolizumab and paclitaxel in HR+/HER2-negative, PAM50 non-luminal, ABC. Methods TATEN trial (NCT04251169) is a single-arm, multicenter, phase II study evaluating pembrolizumab in combination with paclitaxel in patients with HR+/HER2-, PAM50 non-luminal ABC. Key inclusion criteria include progression to prior CDK4/6 inhibitors (CDK4/6i), presence of measurable disease, no prior chemotherapy for ABC, ECOG 0-1, and non-luminal metastatic disease by PAM50. Included patients received pembrolizumab at 200 mg every 3 weeks (beginning at cycle 1) in combination with weekly paclitaxel at 80 mg/m² beginning at cycle 2. The primary endpoint was overall response rate (ORR) according to RECIST V1.1. in patients who received at least one dose of combination treatment and had a first, post-baseline tumor assessment (evaluable population). Secondary endpoints included progression-free survival (PFS), clinical benefit rate (CBR), safety, and predictive biomarkers. The study was based on a Simon two-stage design. Stage I of the trial would be considered successful if at least 6 of 15 patients achieved a partial response and/or complete response. In that case, the trial would recruit up to 46 evaluable patients for a target ORR \geq 41%. Metastatic biopsies from patients enrolled in pre-screening were also evaluated for tumor infiltrating lymphocytes (TILs) and were further analyzed with an expression panel of 192 genes, including PDL1 and PD1. Results From July 2020 to December 2021, 132 tumors were screened, and 27 PAM50 non-luminal tumors were identified (20%). Non-luminal tumors trended to have higher PDL1 expression ($p=0.090$) and TILs ($p=0.084$) compared to luminal tumors, while no difference was observed for PD1 ($p=0.850$). Of 20 recruited patients in the study (stage I+II), 18 were evaluable for the primary endpoint. Baseline characteristics were as follows: median age 55 years, ECOG 0 55%, de novo MBC 22%, and visceral disease 72.2%. Eleven patients had received paclitaxel treatment in the adjuvant setting. Regarding PAM50 subtype, 2 patients had basal-like and 16 HER2-E tumors. At the time of data cut-off (June 2023), 13 patients (72.2%) had stopped their treatment because of progressive disease and 3 (16.6%) due to toxicity. Two patients (11.1%) were still on treatment. The ORR was 61.1 % (11 of 18, 95% CI 35.7-82.7). CBR was 88.9% (16 of 18, 95% CI 65.3-98.6), and median PFS was 8.3 months (95% CI 7.3 – 14.1). Treatment-related adverse events (TRAEs) of any grade (G) occurred in 19 patients (95%), while 45% of patients experienced G3 TRAEs. No G4 or G5 TRAEs were reported in the evaluable population. Gene expression analysis was successful for all recruited patients ($n=20$). High expression of the PAM50 luminal A signature ($p=0.049$), and the luminal genes PGR ($p=0.028$) and RRAGA ($p=0.038$) were associated with worse PFS (univariate analyses). The pan-leucocyte receptor CD84 ($p=0.028$) was associated with better PFS (univariate analysis). Conclusions Pembrolizumab in combination with paclitaxel is safe and exhibits promising efficacy outcomes in patients with CDK4/6i resistant HR+/HER2- ABC with a PAM50 non-luminal subtype. Although meeting the criteria for stage II, the enrollment was stopped prematurely due to the lack of funding and pembrolizumab supply. More correlative analyses will be presented at the conference. This study was funded in part by MSD.

PO1-06-03

Efficacy of First-line Treatments for Hormone Receptor-positive, Human Epidermal Growth Factor Receptor 2-positive Metastatic Breast Cancer: A Systematic Literature Review and Network Meta-analysis Feasibility Assessment

Presenting Author(s) and Co-Author(s):

P. Sharma. University of Kansas Medical Center Westwood, Westwood, Kansas City, Kansas, United States

C. Dang. Breast Medicine Service, Memorial Sloan-Kettering Cancer Center, United States

C. Drudge. EVERSANA, United States

A. Debnath. EVERSANA, United States

M. Rai. EVERSANA, United States

E. Gauthier. Pfizer Inc, San Francisco, California, United States

E. Broughton. Pfizer Inc, United States

Background:

A comprehensive summary of clinical evidence for first-line (1L) treatments for hormone receptor-positive, human epidermal growth factor receptor 2-positive (HR+/HER2+) advanced or metastatic breast cancer (mBC) is needed to understand which treatments have been evaluated and the outcomes associated with different treatments. Understanding the available clinical evidence for HR+/HER2+ mBC 1L treatments can also inform the feasibility of network meta-analyses (NMAs) to estimate relative treatment effects where head-to-head trials are not available. The objective was to prepare a systematic summary of clinical trials of 1L treatments for HR+/HER2+ mBC and assess the feasibility of NMAs for key efficacy outcomes.

Methods:

A systematic literature review (SLR) was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Clinical trials evaluating 1L treatments for adults with HR+/HER2+ mBC published between January 2000 and January 2023 were identified via predefined searches of databases (Embase, MEDLINE, Cochrane Library), relevant congress proceedings, and ClinicalTrials.gov (updating a previous SLR covering January 2000 to December 2020). Study design characteristics, patient characteristics, and efficacy outcomes were extracted from identified trials. An NMA feasibility assessment that considered network connectivity and cross-study heterogeneity was conducted for four efficacy outcomes of interest: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and clinical benefit rate (CBR).

Results:

After screening, 37 records reporting on 23 unique studies (11 randomized controlled trials [RCTs] and 12 single-arm trials; 35 study arms in total) were selected. Included trials were mostly phase II or phase III multi-country studies that evaluated a HR+ or HER2+ population, with outcomes being reported for the subgroup of patients with the HR+/HER2+ subtype. Treatments evaluated included one or two anti-HER2 therapies (AHTs) + endocrine therapy (ET) (5/35 study arms), AHTs + chemotherapy (CT) (20/35), AHTs + ET + CT (2/35), AHTs alone (5/35), and ET alone (3/35). For HR+/HER2+ patients, PFS and OS were reported by 17/23 and 10/23 studies, respectively. Reported median PFS and OS ranged from 2.4-23.7 months and 23.9-66.7 months, respectively. Among the 11 included RCTs, hazard ratios and/or Kaplan-Meier curves, which were considered a requirement for NMAs for time to event

outcomes, were reported for PFS and OS by 9 and 6 studies, respectively. Among these studies, reported median PFS and OS ranged from 2.4-19.2 months and 23.9-57.9 months, respectively. For HR+/HER2+ patients, ORR and CBR were reported by 13/23 and 6/23 studies, respectively. Assuming all CTs could be considered equivalent treatments and all ETs could be considered equivalent treatments, NMAs involving networks of 9, 6, 6, and 3 treatments were feasible for PFS, OS, ORR, and CBR, respectively. Some patient characteristics including time since mBC diagnosis and proportion with bone metastases were not reported consistently across trials. However, included studies were broadly comparable based on study design characteristics, outcome definitions and other reported patient characteristics such as age and Eastern Cooperative Oncology Group performance status.

Conclusion:

Clinical trials in 1L HR+/HER2+ mBC have evaluated various combinations of AHTs, CTs, and ETs, with most study arms being AHTs + CT. Although efficacy outcomes of interest were not consistently reported across trials, NMAs were found to be feasible for PFS, OS, ORR, and CBR based on available data.

PO1-06-04

Immune checkpoint inhibitors for triple-negative inflammatory breast cancer (INCORPORATE): an international multicenter retrospective analysis

Presenting Author(s) and Co-Author(s):

C. Valenza. European Institute of Oncology, IRCCS, University of Milano, Milan, Italy, United States

D. Trapani. European Institute of Oncology, IRCCS, University of Milano, Milan, Lombardia, Italy

P. Zagami. European Institute of Oncology, IRCCS, University of Milano, Milan, Italy, United States

G. Antonarelli. European Institute of Oncology, IRCCS, University of Milano, Milan, Italy, United States

L. Boscolo Bielo. European Institute of Oncology, IRCCS, University of Milano, Milan, Italy, United States

E. Nicolò. European Institute of Oncology, IRCCS, University of Milano, Milan, Italy, United States

J. Ribeiro. Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France/Paris-Saclay University, Gustave Roussy, INSERM U981, PRISM Center, F-94805, VILLEJUIF France, United States

L. Guidi. European Institute of Oncology, IRCCS, University of Milano, Milan, Italy, United States

C. REDUZZI. Weill Cornell Medicine, United States

M. Spotti. Research Department - Interdisciplinary Department for Patient Pathway Organization (DIOPP), Gustave Roussy Cancer Campus, Grand Paris, France, United States

E. Munzone. European Institute of Oncology, IRCCS, Milano, Italy

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Ueno. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

R. Layman. The University of Texas MD Anderson Cancer Center, United States

M. Cristofanilli. Weill Cornell Medicine, United States

L. Carey. UNC-Lindberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

W. Woodward. UT MD Anderson Cancer Center, Houston, Texas, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

Background: Inflammatory breast cancer (IBC) is an aggressive clinical presentation of breast cancer (BC). Immune checkpoint inhibitors (ICIs) combined with chemotherapy provided an overall survival (OS) benefit in the metastatic setting and an even-free survival (EFS) benefit in patients (pts) with early triple-negative (TN) BC, respectively. Patients with TN-IBC were under-

represented or excluded in pivotal trials and commonly not evaluated in subgroup analyses.

Methods: We conducted a retrospective, multicenter, international, observational study to evaluate the clinical benefit of ICIs in pts with TN-IBC (defined as cT4d per AJCC TNM, 8th ed., ER < 1% and PgR < 1%, HER2: negative). Pts with early-stage TN-IBC were included if they received an ICI combined with neoadjuvant chemotherapy (NACT) (Group 1). Pts with metastatic TN-IBC were included if they received ICI monotherapy or in association with first-line chemotherapy (Group 2). Treatment was administered according to guideline recommendations (in PD-L1+ metastatic IBC and regardless of PD-L1 in early IBC), in clinical trials, or off-label (regardless of PD-L1 expression status in metastatic IBC). Endpoints were pathological complete response (pCR) and 1-year EFS rate for group 1 (calculated from date of first cycle of NACT to any recurrence or death), and progression-free survival (PFS) for group 2. Correlative analyses were provided (significance at p-value < 0.05).

Results: We included 59 pts from 8 international referral centers. 15 pts had early IBC (Group 1), and 44 pts had metastatic disease (Group 2). Patient characteristics and outcomes are shown in Table 1.

Among the 15 pts from Group 1, 10 received anthracycline, taxane and carboplatin-based (AC-CbT) NACT with pembrolizumab, 3 neoadjuvant paclitaxel-carboplatin chemotherapy with pembrolizumab, 2 neoadjuvant nab-paclitaxel with atezolizumab. One pt progressed on NACT, 2 pts are still receiving NACT. Among 13 pts evaluable for response, 6/13 (46%) achieved a pCR. After a median follow-up of 7.1 months, the median EFS was 12.9 months and the 1-year EFS rate was 70%. The median OS was 15.7 months.

Among pts from Group 2, PD-L1 status was positive (IC \geq 1% or CPS \geq 10) in 27/44 pts (61%), negative in 5/44 pts (11%) and unknown in 6/44 pts (13%). At a median follow-up of 24.3 months, median PFS and OS were 4.1 and 15.7 months. As backbone chemotherapy in first line setting, 6 pts received AC-CbT regardless of PD-L1 status (mPFS: 8.6 months), 21 taxane-based/anthracycline-free chemotherapy (mPFS: 5.3 months), 14 other chemotherapy regimens (mPFS: 2.1 months) and 3 single-agent immunotherapy (mPFS: 50.1 months). Three of 6 patients who received AC-CbT underwent surgery and radiotherapy.

In Group 2, after adjusting for the number of metastatic sites (>1 vs. 0-1), PD-L1 status (positive vs. negative vs. unknown) and de novo metastatic disease (yes vs. no), AC-CbT chemotherapy (HR 0.05; 95% CI: 0.01-0.56; p=.015) and taxane-based chemotherapy (HR 0.20; 95% CI: 0.06-0.68; p=.009) were both associated with longer PFS.

Conclusions: This multicenter retrospective analysis of TN-IBC treated with combination of chemotherapy and IOs showed relatively low pathology response, EFS and clinical benefit suggesting need to further investigate the role of immunotherapy in this aggressive disease.

Patient characteristics and outcomes

Table 1. Patient characteristics and outcomes.

	Early (N=15)	Metastatic (N=44)
Age, median (IQR), n (%)	53 (48-65)	52 (46-59)
De novo metastatic disease, n (%)	NA	25 (57%)
HER2low, n (%)	5 (33%)	18 (41%)
Primary IBC, n (%)	15 (100%)	25 (57%)
PD-L1		
Positive IC ≥1% or CPS ≥10, n (%)	-	27 (61%)
Negative, n (%)	-	5 (11%)
Unknown, n (%)	-	6 (13%)
Visceral disease, n (%)	-	27 (61%)
>1 metastatic site, n (%)	-	30 (68%)
Treatment regimens		
Pembrolizumab + AC-CbT (Kn522), n (%)	10 (67%)	6 (14%)
Pembrolizumab + CT (Kn355), n (%)	0 (0%)	12 (27%)
Atezolizumab + nabP, n (%)	2 (13%)	14 (32%)
Other ICIs + CT, n (%)	3 (20%)	9 (21%)
ICIs monotherapy, n (%)	0 (0%)	3 (7%)
Chemotherapy backbone ^a		
AC-CbT, n (%)	10 (67%)	6/41 (15%)
Taxanes, n (%)	5 (33%)	21/41 (51%)
Other, n (%)	0 (0%)	14/41 (34%) ^b
Immune-checkpoint inhibitor, n (%)		
Pembrolizumab, n (%)	13 (87%)	24 (55%)
Atezolizumab, n (%)	2 (13%)	16 (36%)
Other, n (%)	0 (0%)	4 (9%) ^c
Curative/palliative surgery, n (%) ^d	12/13 (92%)	8 (18%)
Radiotherapy, n (%) ^e	11/13 (85%)	7 (16%)
Outcomes		
pCR/ORR, n (%)	6/13 (46%)	10 (23%)
DCR, n (%)	14 (93%)	22 (50%)
Median follow-up, months (95% CI)	7.1 (4.8-9.4)	24.3 (12.7-35.9)
EFS/PFS events, n (%)	4 (27%)	36 (82%)
median EFS/PFS, months (95% CI)	12.9 (9.6-16.2)	4.1 (2.3-5.8)
6 months EFS/PFS rate, %	84%	33%
12 months EFS/PFS rate, %	70%	18%
OS events, n (%)	3 (20%)	27 (61%)
mOS, months (95% CI)	15.7 (11.3-20.1)	15.7 (8.4-23.0)

^a Patients who received only immunotherapy in metastatic setting (N=3) were excluded

^b Platinum and gemcitabine (N=6), carboplatin (N=5), eribulin (N=2), cyclophosphamide (N=1)

^c Nivolumab (N=2), nivolumab plus ipilimumab (N=1), durvalumab and tremelimumab (N=1)

^d The two patients who are still receiving NACT have been excluded

- * Patients who received only immunotherapy in metastatic setting (Nf3) were excluded
- § Platinum and gemcitabine (Nf6), carboplatin (Nf5), eribulin (Nf2), cyclophosphamide (Nf1)
- # Nivolumab (Nf2), nivolumab plus ipilimumab (Nf1), durvalumab and tremelimumab (Nf1)
- + The two patients who are still receiving NACT have been excluded

PO1-06-05

Heterogeneity and prognostic characteristics of HER2-low breast cancer: A retrospective analysis of patients with HER2-negative metastatic breast cancer

Presenting Author(s) and Co-Author(s):

H. Lv. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China (People's Republic)

M. Yan. Henan Cancer Hospital, Henan, China

m. zhang. Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

L. Niu. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China (People's Republic)

H. zeng. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China (People's Republic)

H. Sun. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

s. zhao. Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

j. wang. Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

Background: It remains uncertain as to whether low levels of HER2 positivity have any prognostic implications in breast cancer patients, whether HER2 levels can be inconsistent between primary tumors and metastatic lesions in individuals with advanced HER2-negative breast cancer, and how such inconsistencies may impact patient prognosis. Methods: A retrospective analysis of advanced breast cancer patients admitted to our hospital from from January 1st, 2010 to January 1st, 2019 was performed, with all patients that underwent at least one metastatic lesion biopsy being screened. The hormone receptor (HR) and HER2 profiles of both primary and metastatic lesions from these patients were confirmed, and HER2-positive patients (HER2 3+ immunohistochemistry [IHC] results or HER2 2+ IHC results with positive in situ hybridization [ISH] results) were excluded from further analyses. To examine the prevalence of HER2-low status across primary and metastatic cancers, the current study set out to detect inconsistencies between these two tumor compartments with respect to HER2-low status and to examine the prognostic implications of these findings in patients. Results: The median follow-up duration for this study at the cutoff date (December 31, 2021) was 49.3 (45.8-52.8) months. The current study examined 1,031 participants with HER2 and HR status data from both primary and metastatic tumors. The proportion of HER2-low expression was significantly higher in metastatic lesions than primary tumors (34.7% vs 25.7%), with a corresponding drop in the proportion of HER2-zero metastatic lesions (FIGURE 1). In a multivariate analysis, HER-2 upregulation was linked to HR status, which was established as an independent influencing factor, with such upregulation being most common in HR-positive individuals ($P= 0.004$). With respect to HER2 status of primary lesions, the median survival of patients in the HER2-zero was similar to HER2-low patients, regardless of HR status [44.8 months (95% CI 38.2-54.1) vs 41.5 months (95% CI 35.0-48.0)] ($P = 0.954$)(FIGURE 2A). However, when the HER2 status of metastatic lesions was examined, patients with HER2-low

expression had a greater median OS than HER2-zero patients [47.6 months (95% CI 39.6-48.0) vs. 32.2 months (95% CI 24.6-40.0)] ($P < 0.001$)(FIGURE 2B). The median OS of patients that exhibited HER2 upregulation (zero→low) was longer than that of patients without such upregulation (zero-zero) (55.8 months (95% CI 45.0-66.6) vs. 32.4 months (95% CI 23.8-41.0)) ($P < 0.001$)(FIGURE 3A). Among HR-positive patients, HER2 upregulation was associated with significantly prolonged OS relative to patients without such upregulation [56.6 months (95% CI 44.6-68.6) vs. 41.7 months (95% CI 31.1-52.3)] ($P=0.006$)(FIGURE 3B), whereas survival outcomes were similar in these two groups in the HR-negative subgroup [44.8 months (95% CI 25.6-64.0) and 25.3 months (95% CI 20.4-30.3)] ($P=0.103$)(FIGURE 3C). However, independent of HR status, the median OS of patients who had HER2 downregulation (low→zero) was similar to those without downregulation (low→low)(FIGURE 3 D, E, F). Conclusion: These results support inconsistencies in HER2-low expression status between primary and metastatic lesions, with low HER2 levels in metastatic tumors being associated with improved survival outcomes. HR-positive patients are more likely to exhibit HER2 upregulation within metastatic lesions and experience corresponding prognostic benefits. Keywords: HER2-low, inconsistency, survival, prognosis, advanced breast cancer

The expressions of HR and HER2 in primary tumors and their matched metastases.

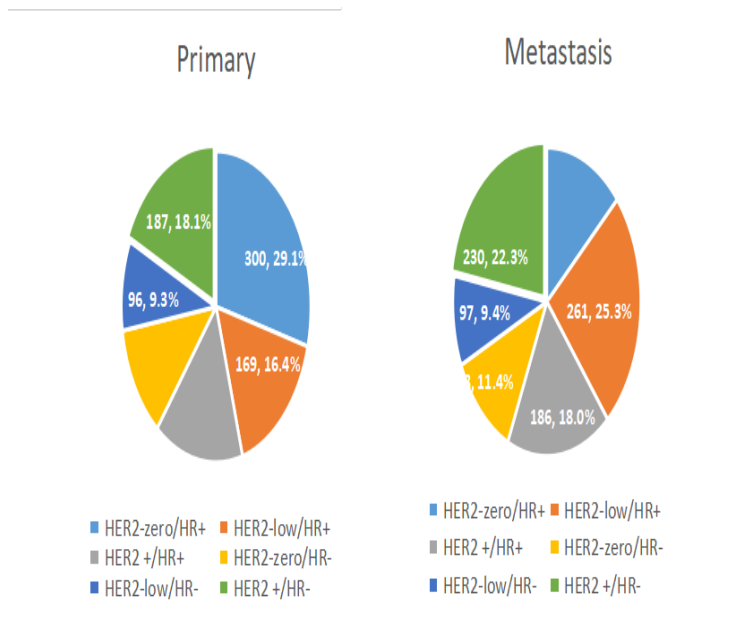


Figure 1. The expressions of HR and HER2 in primary tumors and their matched metastases.

HR, hormone receptor.

HR, hormone receptor.

Survival analysis of patients with HER2- low expression in primary tumors and their matched metastases

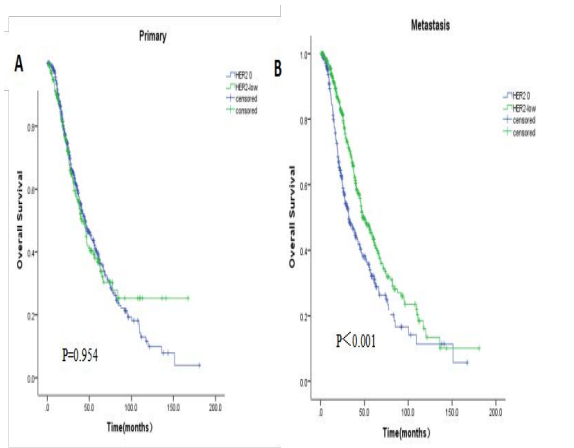


Figure 2. Survival analysis of patients with HER2- low expression in primary tumors and their matched metastases

The effect of HER2 up regulation and loss on survival in metastatic lesions.

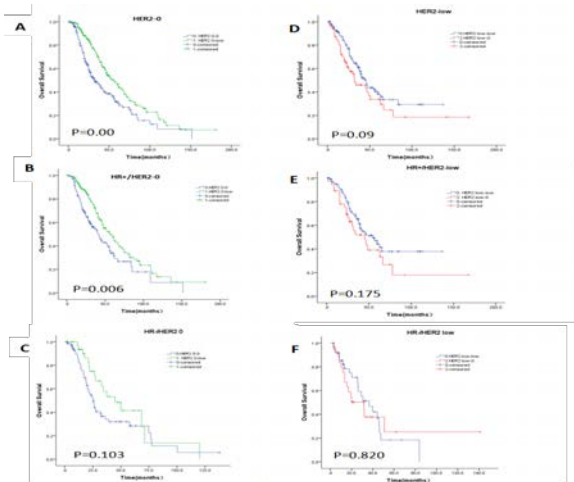


Figure 3. The effect of HER2 up-regulation and loss on survival in metastatic lesions. A. The effect of HER2 up-regulation on survival in primary HER2-zero patients; B. In patients with primary HR + / HER2-zero, the effect of HER2 up-regulation in metastatic lesions on survival; C. In patients with primary HR - / HER2-zero, the effect of HER2 up-regulation in metastatic lesions on survival; D. The effect of HER2 loss on survival in patients with primary HER2-low metastasis; E. The effect of HER2 loss on survival in patients with primary HR + / HER2-low metastasis; F. The effect of HER2 loss on survival in patients with primary HR - / HER2-low.

A. The effect of HER2 up regulation on survival in primary HER2-zero patients; B. In patients with primary HR + / HER2-zero, the effect of HER2 up-regulation in metastatic lesions on survival; C. In patients with primary HR - / HER2-zero, the effect of HER2 up-regulation in metastatic lesions on survival; D. The effect of HER2 loss on survival in patients with primary HER2-low metastasis; E. The effect of HER2 loss on survival in patients with primary HR + / HER2-low metastasis; F. The effect of HER2 loss on survival in patients with primary HR - / HER2-low.

PO1-06-06

Underestimation of metastatic spread in patients with lobular breast cancer: results from the post-mortem tissue donation program UPTIDER

Presenting Author(s) and Co-Author(s):

K. Van Baelen. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, Leuven, Vlaams-Brabant, Belgium

G. Zels. KU Leuven, United States

M. De Schepper. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium & Department of Pathology, University Hospitals Leuven, Leuven, Belgium, United States

M. Maetens. Laboratory for Translational Breast Cancer Research, KU Leuven, Leuven, Belgium, Belgium

J. Van Cauwenberge. KU Leuven, United States

T. Geukens. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, United States

K. Borremans. KU Leuven, United States

F. Richard. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, United States

A. Mahdami. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, United States

H. Nguyen. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Vlaams-Brabant, Belgium

S. Leduc. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, United States

A. Pabba. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, United States

A. Smeets. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, United States

I. Nevelsteen. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, Leuven, Belgium

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

H. Wildiers. University Hospitals Leuven, United States

V. Vandecaveye. Translational MRI, Department of Imaging and Pathology, KU Leuven, and Department of Radiology, University Hospitals Leuven, Leuven, Belgium, United States

W. Van Den Bogaert. Department of Forensic Medicine, University Hospitals Leuven, Leuven, Belgium, United States

G. Floris. University Hospitals Leuven, United States

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

Background: Invasive lobular carcinoma (ILC) accounts for 15% of all invasive breast cancers (BC) and has a peculiar metastatic spread in comparison to BC of no-special type. Since ILC is less likely to disrupt normal tissue architecture and is usually non-mass forming, imaging of ILC

lesions entails many challenges. Insights into pathologic versus radiological metastatic invasion can lead to better diagnostic and monitoring tools for patients with ILC. Here, we compare microscopical findings during autopsy with clinical findings prior to death in patients with metastatic ILC included in our post-mortem tissue donation program UPTIDER (NCT04531696). Methods: UPTIDER was started in November 2020 in University Hospitals Leuven/KU Leuven with inclusion of patients with stage IV BC who were willing to participate. One of the predefined subgroups consisted of patients with primary pure (i.e. not mixed) ILC. Samples were taken from different macroscopically invaded and non-invaded sites. Clinical data on disease progression, imaging, biochemistry and treatment regimens were extracted from patient files. The number of samples that were preregistered as pathological served as a surrogate for lesions that were seen on imaging performed during the treatment of the patient. These samples are compared to microscopical findings of the autopsy. Results: Since the start of UPTIDER, an autopsy has been performed on 6 patients with pure ILC (26.1% of all autopsies). Median age at initial diagnosis was 52 years (range: 37 – 80 years). Three patients (50.0%) had stage IV disease at diagnosis, the others relapsed on average 162.7 months (range: 55 – 358 months) after initial diagnosis. The average time between clinical occurrence of metastases and death was 44.8 months (range: 15 – 83 months). Median number of treatment lines for stage IV disease was 5 (median endocrine lines 2; median chemotherapy regimens 3.5). To follow disease evolution, computed tomography of thorax and abdomen was used for 4 (66.7%) patients and whole-body diffusion-weighted magnetic resonance imaging (WB-DWI/MRI) for the remaining 2 (33.3%). Median time between last premortem imaging and death was 5.9 weeks (range: 1.6 – 16.6 weeks). At autopsy, a median of 26 unique metastases (range: 12-36) were sampled per patient. Table 1 gives an overview on the unique microscopically invaded metastases that were sampled per patient. Only 47.3% of the sampled unique metastases was preregistered. Of all unique metastases, 26.7% appeared macroscopically normal during autopsy. Tissues that appeared normal but turned out to be microscopically infiltrated included liver, stomach, adrenal glands, heart, pericardium, visceral and subcutaneous fat tissue. There were 2 patients with normal appearing, microscopically infiltrated livers. In these patients, elevation of γ GT and transaminases was seen in the months prior to death. Conclusions: The disease burden of metastatic ILC reported on premortem imaging does not reflect the microscopical findings at autopsy. One of the priorities of metastatic ILC research should be the development of diagnostic tools to better estimate the extent of the disease. Future analyses of the performed postmortem MRIs in our study can aid in improving the interpretation of WB-DWI/MRI for patients with ILC. For now, clinicians should consider that unexplained clinical and/or biochemical findings might indicate progression of ILC.

Table 1: patient overview on performed imaging and unique metastases sampled during autopsy

Patient ID	Clinical subtype	Imaging technique mostly used	Last used imaging technique	Weeks between last imaging and death	Post-mortem MRI performed	Number of unique metastases sampled	Number of unique metastases preregistered as pathological (%)	Number of unique metastases only seen microscopically (%)
#2003	ER+ HER2+	CT thorax/abdomen	CT thorax/abdomen	1.6	Yes	28	13 (46.4)	2 (7.1)
#2005	ER+ HER2-	WB-DWI MRI	CT thorax/abdomen	16.6	No	12	5 (41.7)	4 (33.3)
#2011	ER+ HER2-	WB-DWI MRI	WB-DWI MRI	8.7	Yes	36	11 (30.6)	7 (19.4)
#2012	ER+ HER2-	CT thorax/abdomen	CT thorax/abdomen	3.1	No	23	NA	NA
#2023	ER+ HER2-	CT thorax/abdomen	CT thorax/abdomen	3.1	Yes	23	14 (60.9)	4 (17.4)
#2025	ER+ HER2-	CT thorax/abdomen	CT thorax/abdomen	11.3	Yes	32	19 (59.4)	18 (56.3)
Total	/	/	/	/	/	154 (131 with exclusion of samples pt #2012)	62 (47.3*)	35 (26.7*)
Median	/	/	/	5.9	/	26	46.4%	19.4%

CT = computed tomography; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; pt = patient; WB-DWI MRI = whole-body diffusion-weighted magnetic resonance imaging

*exclusion of samples of patient 2012 since no preregistration was performed for this patient due to unexpected death

PO1-06-07

EMSY enhances cancer stem cell self-renewal and tumorigenesis by reshaping methionine metabolism in triple-negative breast cancer

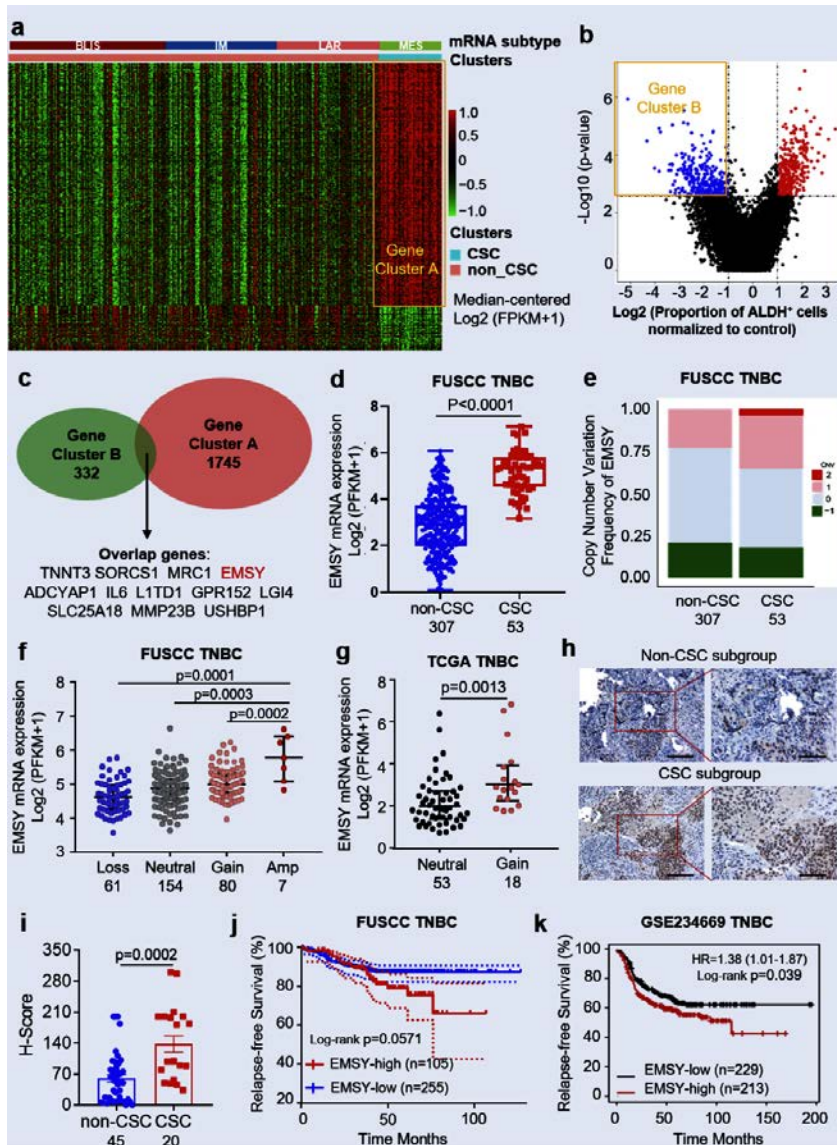
Presenting Author(s) and Co-Author(s):

C. Liu. Cancer Center and Cancer Institute, Shanghai Medical College, Fudan University, United States

K. Yu. Cancer Center and Cancer Institute, Shanghai Medical College, Fudan University, United States

Treatment of triple-negative breast cancer (TNBC) remains challenging. Cancer stem cells (CSCs) are the most intractable subpopulation of TNBC cells, which has associated with a high risk of relapse and poor prognosis. However, eradication of CSCs continues to be difficult. Here, we integrated the multiomics data of our large TNBC cohort (n=360) to identify vital markers of CSCs. We discovered that EMSY, inducing a BRCAness phenotype, was preferentially expressed in breast CSCs, promoted the enrichment of ALDH⁺ cells and was positively correlated with poor relapse-free survival. Mechanistically, EMSY competitively bound to the JmjC domain, which was critical for the enzyme activity of the KDM5B-specific H3K4 demethylase to reshape methionine metabolism and promote CSC self-renewal and tumorigenesis in an H3K4 methylation-dependent manner. Moreover, EMSY accumulation in TNBC cells sensitized them to PARP inhibitors against bulk cells and methionine deprivation against CSCs. These findings indicate that clinically relevant eradication of CSCs could be achieved with a strategy that targets CSC-specific vulnerabilities in amino acid metabolism.

EMSY was highly expressed in BCSCs and positively correlated with TNBC malignancy



a. Heatmap with mRNA expression characteristics of non-CSC and CSC subtypes. The top 2,000 most differentially expressed genes used for clustering are plotted. Samples are also annotated on top by the FUSCC subtypes. b. Volcano plot showing genes targeted by a siRNA inducing a significant change (Fold change (FC) represented the proportion of ALDH+ cells compared to the control). c. Overlap analysis of the upregulated genes in CSC subtype (Gene cluster in A) and the genes via siRNA (Gene cluster in B) inducing a significant reduction of the ALDH+ cell ratio. d. The mRNA expression of EMSY in non-CSC and CSC TNBC transcriptomic subtypes (n = 360, Mann-Whitney's test). Each boxplot showed the median and 95% confidence intervals (95% CI). e. The CNV frequency of EMSY in non-CSC and CSC subtypes. f, g. EMSY mRNA expression of samples with different EMSY copy number in FUSCC (n=302) and TCGA (n=71) TNBC cohorts. h, i. Immunohistochemistry analysis of EMSY expression in specimens of patients between non-CSC (n=45) and CSC (n=20) subtypes. Representative images (h) and the graph of H Scores (i, mean \pm SEM, Mann-Whitney's test) were shown. Scale bar, 4 μ m (left), 20 μ m (right). j, k. Kaplan-Meier RFS plots of EMSY in FUSCC (n=360) and GSE234669 (n=442) TNBC (<https://kmplot.com/analysis/>).

Accumulation of EMSY enhanced CSC self-renewal and tumorigenesis

a. The mRNA (left) and protein (right) expression of EMSY in FACS sorted ALDH⁺ and ALDH⁻ cells. b-d. ALDH activity detected by ALDEFLUOR assay and shown as mean \pm SEM (n=3/group, one-way ANOVA's test) in EMSY-knockdown cells (b, c) and EMSY-overexpressing cells (d). e, f. Self-renewal ability determined by primary mammosphere formation (e, n=6 biological independent experiments, one-way ANOVA's test) and secondary mammosphere formation (f, n=6 biological independent experiments, one-way ANOVA's test) in EMSY-knockdown SUM149 and MDA-MB-453 cells. Scale bar, 200 μ m. g. Self-renewal ability determined by primary mammosphere formation and secondary mammosphere formation in EMSY-overexpressing SUM159 (n=6 biological independent experiments, one-way ANOVA's test). Scale bar, 200 μ m. h-l. EMSY-knockdown SUM149 were injected into mammary fat pads with extreme limiting dilutions (5×10^4 , 5×10^3 cells/ fat pad). Tumor growth curves (n=5/group, two-way ANOVA's test) (h, i) were shown. Tumor cell ALDH activity was determined by ALDEFLUOR assay and the bar plot was shown as mean \pm SEM (n=5/group, one-way ANOVA test) (j). Frequency of breast CSC was calculated based on the positive tumor sites per group by ELDA (ELDA: Limiting Dilution Analysis for stem cell research (wehi.edu.au)) (k, l).

Dairy methionine deprivation, alone or in combination with PARPi, as a therapeutic strategy for EMSY-amplification tumors.

a. Immunohistochemistry analyses of EMSY expression in specimens of patients and representative images were shown. b. Patient-derived organoid (PDO) models were performed with fresh isolated primary tissues derived from four independent TNBC patients according to the mRNA level of EMSY. PDO was cultured with fresh medium with (Complete) or without methionine (methionine deprivation, MD) and tumor sphere numbers were determined (n=6/group, two-way ANOVA test). c-e. Effect of MD and olaparib on CSCs and tumor progression. Mice bearing patient-derived xenograft model (PDX, FD-009) were treated with PARPi (50mg/kg, i.p., once every day), dairy MD, and their combination. Tumor volume (c), tumor cell ALDH activity (d) and absolute ALDH⁺ cancer cells in tumor tissue (e) were assessed (n=5/group, one/two-way ANOVA test). f. Single breast cancer cells from the primary tumors were implanted for a second tumor formation in a limited dilution assay (1000 and 10,000 cells/fat pad); frequency of breast CSC was calculated based on the positive tumor sites per group by ELDA (ELDA: Limiting Dilution Analysis for stem cell research (wehi.edu.au)).

PO1-06-08

Treatment utilization by race and insurance type among triple negative breast cancer patients

Presenting Author(s) and Co-Author(s):

N. Sadetsky. Gilead Sciences, Inc., United States

L. Bakhuluma-Ncube. Trinity Life Sciences, United States

E. Fox. Trinity Life Sciences, United States

L. Okpala. Gilead Sciences, Inc., United States

M. O'Hara. Trinity Life Sciences, United States

J. Parr. Trinity Life Sciences, United States

Introduction

Triple negative breast cancer (TNBC) is associated with poorer prognosis and its lower long-term survival rates disproportionately affect people of racial and ethnic minority groups.

Ensuring timely and effective treatment for all patients regardless of race or insurance status is critical. The objective of this study is to describe treatment patterns by line of therapy, race, and insurance type to identify barriers to accessing healthcare using a physician survey and patient-chart review. **Methods**

This study employed a 60-minute physician survey and linked retrospective chart review of patients' charts conducted June-July 2022. Participating oncologists across the US (34% Central; 19% Southeast; 18% Northeast; 21% West; 9% East Coast) were required to be board-certified, in practice 3 to 30 years post-residency, and managing at least 7 patients with TNBC in the past 3 years. Oncologists extracted patient-level data from 2-4 patient records for the chart review. A convenience sample of charts oversampled patients on Medicaid, Black and Latina patients, and patients with later stage TNBC to allow for robust disparities analysis. Data collection included provider characteristics, treatment by line of therapy (LOT), rationale for treatment decisions, barriers experienced in accessing care, and support services used.

Results

Participating oncologists (n=101, 73% male; 62% community vs 39% academic setting) provided data on 283 patients with TNBC [99% female; median age = 46.0 years; race = Black (42%), Latina (31%), White (25%) or Other (2%); geographic location = Urban (53%), Suburban (39%), Rural (8%)]. White patients were more likely to be covered by private insurance (73%) compared to Black (25%) and Latina patients (32%). Black and Latina patients were more likely to be covered by Medicaid (White, 16%; Black, 71%; Latina, 52%). Over half of patients needed prior authorization for first-line (1L) treatment; mean wait time for prior authorization was 1.5 weeks. Black patients (58%) were more likely to require prior authorization in 1L as compared to White patients (49%); There were no significant differences in prior authorization requirements based on type of insurance (Medicaid, Medicare, Private/Commercial Insurance). Of the 283 patients treated with 1L therapy, 111 patients received second-line (2L) treatment [Black (n=52, 44%), Latina (n=29, 32%), White (n=26, 37%), Other (n=4, 71%)], and 45 patients received third-line (3L) treatment [Black (n=25, 21%), Latina (n=9, 10%), White (n=9, 13%), Other (n=2, 33%)]. Chemotherapy was the most common 1L (75%) and 2L (51%) treatment. Targeted therapy (TT), defined as immunotherapy, hormone therapy or antibody–drug conjugates, was most common in 3L (64%). A smaller proportion of Black patients who progressed to 3L received TT (n=13, 52%) compared to White (n=8, 89%) and Latina (n=7, 78%) patients. A larger proportion of patients with private/commercial insurance (n=18, 95%) received TT in 3L as compared to patients with Medicaid (n=10, 42%) or Medicare (0%).

Conclusions

Findings indicated disparities both in pre-treatment barriers (specifically prior authorization) and the utilization of targeted therapy in later lines of therapy among Black patients. Although treatment patterns did not seem to differ by race in early lines of therapy, numerical differences in treatment patterns by race and insurance type emerged in later lines of therapy. Given the poor prognosis for patients diagnosed with TNBC and its disproportionate impact on communities of color, future policy efforts should be focused on achieving equity in treatment initiation and use of TT in TNBC patients.

PO1-06-09

Phase 2 Trial with Safety Run-In of Gedatolisib Plus Talazoparib in Advanced Triple Negative or BRCA1/2 Positive, HER2 Negative Breast Cancers Big Ten Cancer Research Consortium BTCRC-BRE18-337

Presenting Author(s) and Co-Author(s):

S. Phadke. University of Iowa, Iowa city, Iowa, United States

K. Wisinski. University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, United States

O. Danciu. University of Illinois Cancer Center, Chicago, United States

A. Shah. Northwestern University - Feinberg School of Medicine, United States

M. Yu. University of Wisconsin Carbone Cancer Center, United States

Y. Chen. University of Wisconsin-Madison, United States

K. Miller. Indiana University, United States

M. Burkard. DEPARTMENT OF MEDICINE University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States

Up to 2/3 of triple negative breast cancers (TNBC) have acquired defects in homologous recombination (HR) DNA repair, yet poly (ADP-ribose) polymerase inhibitor (PARPi) monotherapy has been largely ineffective in the absence of a germline BRCA 1/2 mutation (gBRCA1/2). Phosphoinositide-3-kinase (PI3K)/mTOR pathway alterations are also common in breast cancers. Preclinical data suggest that PI3K/mTOR inhibition may disrupt normal function of the HR complex and increase dependency on PARP enzymes for HR DNA repair. Thus, combining a PI3K/mTOR inhibitor with a PARPi may result in a synergistic anti-neoplastic effect. The run-in portion of this study evaluated the safety of weekly IV gedatolisib (PI3K/mTORi) and continuous daily talazoparib to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). A 3+3 design for dose escalation explored two dose levels. The phase II study began once the MTD and R2PD were confirmed. Eligibility required age \geq 18, 1-2 prior lines of therapy (protocol later amended to allow up to 3 lines), and advanced TNBC or advanced HER2-negative BC with gBRCA1/2 mutation. The sample size for the phase II study was determined based on a 1-sided binomial test under the null and alternative ORR of 5% vs 20% with a type I error rate of 0.1 and power level of 80%. The primary endpoint was overall response rate (ORR) in TNBC without known gBRCA1/2 with secondary endpoints of progression-free survival (PFS) and overall survival (OS). Patients with a gBRCA1/2 mutation were not included in the primary endpoint analysis. Correlative studies are planned to evaluate HR deficiency mutations, PIK3CA mutations, and other exploratory genomics. A total of 33 patients were enrolled: 14 in the safety run-in phase of the trial and 19 in the phase II study (17 TNBC, 2 with gBRCA2 mutation). In the safety run-in, 6 patients were enrolled at dose level 1 (0.75 mg talazoparib po daily and 180 mg gedatolisib IV weekly) and 8 at dose level 2 (1 mg talazoparib po daily and 180 mg gedatolisib IV weekly). 42% of the cohort developed hyperglycemia, which was mostly grade 1. There was 1 DLT of grade 3 neutropenia at dose level 1. There were 3 patients who experienced grade 4 AEs, thrombocytopenia (2) and lymphopenia (1) which were outside of the DLT window. The MTD was 1 mg of talazoparib daily and 180 mg of gedatolisib weekly, and this was selected as the RP2D. A protocol amendment was made during the phase II portion to allow for a 3 week on/1 week off schedule for gedatolisib due to emerging data showing a more favorable safety profile and enhanced antitumor activity with this dosing schedule. In the 17 patients with TNBC and no gBRCA mutation in the phase II cohort, the ORR was 12%. Best response was partial response (PR) in

2 patients (12%), stable disease (SD) in 7 patients (41%), and progressive disease (PD) in 8 patients (47%). The clinical benefit rate (ORR+SD) at 16 weeks was 23.5%. The most common adverse events (AEs) in all 33 patients were anemia (70%), fatigue (67%), oral mucositis (64%), nausea (60%), neutropenia (45%) and anorexia (45%). Of these, most were grade 1-2 other than anemia (35% grade 3), neutropenia (20% grade 3), fatigue (18% grade 3), and oral mucositis (10% grade 3). There were no grade 4 AEs in the phase II study. Median PFS was approximately 3 months and median OS was approximately 6.4 months. Although this study did not meet its primary endpoint, there were 2 TNBC patients without a gBRCA1/2 mutation who achieved a partial response to this non-chemotherapy regimen. Future biomarker testing may help elucidate these findings and possible predictors of response.

PO1-06-10

Overall survival results from EVER-132-001, a phase 2b single-arm study of sacituzumab govitecan in Chinese patients with metastatic triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

F. Ma. Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

S. Wang. Sun yat-sen university cancer center, United States

Z. Tong. Tianjin Medical University Cancer Institute & Hospital, United States

W. Li. The First Hospital of Jilin University, Changchun, United States

X. Wu. Hubei Cancer Hospital, United States

X. Wang. Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, United States

T. Sun. Cancer Hospital of China Medical University/Liaoning Cancer Hospital, United States

Y. Pan. Department of Medical Oncology, The First Affiliated Hospital Of USTC, Hefei, Anhui, China (People's Republic)

H. Yao. Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, United States

X. Wang. Sir Run Run Shaw Hospital, Zhejiang University, School of Medicine, United States

T. Luo. West China Hospital, Sichuan University, Chengdu, United States

J. Yang. First Affiliated Hospital of Xi'an Jiaotong University, United States

X. Zeng. Chongqing University Cancer Hospital, Chongqing, Chongqing, China (People's Republic)

W. Zhao. Chinese PLA General Hospital, United States

K. Komatsubara. Gilead Sciences, Inc., United States

R. Nakamura. Gilead Sciences, Inc., United States

C. Lai. Gilead Sciences, Inc., United States

B. Zhang. Gilead Sciences, Inc., United States

X. Cong. Gilead Sciences, Inc., United States

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

Background

Breast cancer is the most frequently diagnosed cancer and the 5th most common cause of cancer-related death in Chinese women with over 416,000 new cases and over 117,000 deaths estimated in 2020. Triple-negative breast cancer (TNBC) represents 10%-20% of cases in women with breast cancer. Sacituzumab govitecan (SG) is a Trop-2-directed antibody-drug conjugate and is approved for second-line or later (2L+) treatment of metastatic (m)TNBC in multiple countries, including the US and China. In the pivotal phase 3 study ASCENT, which enrolled predominantly non-Asian patients (pts), SG demonstrated improved efficacy outcomes vs treatment of physician's choice (TPC) in pts with mTNBC treated in 2L+, with a manageable safety profile. For pts treated with SG, median progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) were improved vs TPC (Bardia A et al, 2021). The single-arm phase 2b EVER-132-001 study was conducted to assess the efficacy and safety of 2L+ SG in Chinese pts with mTNBC. In preliminary findings from EVER-132-001, SG

demonstrated substantial clinical activity and a manageable safety profile (Xu B et al, 2023). Here, we present additional efficacy and safety results from EVER-132-001, including the first report of median OS.

Methods

Pts with mTNBC who had received at least 2 prior lines of chemotherapy for mTNBC received SG (10 mg/kg IV on days 1 and 8, Q3W). The primary end point was ORR per independent review committee (IRC). Secondary end points included duration of response (DoR) per IRC, clinical benefit rate (CBR) per IRC, PFS per IRC, OS, and safety.

Results

Eighty pts were enrolled, with a median age of 48 years (range 24-70). Pts had received a median of 4 prior treatment regimens (range 2-8), and 59% of pts had ECOG performance status of 1. At the data cutoff, September 19, 2022, with a median follow-up of 14.7 mo (range 1.2-25.3), median OS was 14.7 mo (95% CI 10.3-18.3) and the OS rate at 12 months was 54% (95% CI 42-64) (Table). ORR was 40% (95% CI 29-52) with median DoR of 11.6 mo (95% CI 7.0-13.8), and CBR was 46% (95% CI 35-58) (Table). Median PFS was 5.6 mo (95% CI 4.1-8.3) (Table). Grade \geq 3 treatment-emergent adverse events (TEAEs) occurred in 79% of pts, and TEAEs leading to dose reduction, treatment interruption, and treatment discontinuation occurred in 20%, 48%, and 8% of patients, respectively (Table). The most common TEAEs of any grade were decreased neutrophil count (85%), anemia (84%), and decreased white blood cell count (83%). The most common grade \geq 3 TEAEs were decreased neutrophil count (64%), decreased white blood cell count (50%), and anemia (23%).

Conclusions

SG continued to demonstrate substantial clinical activity, with OS, ORR, DoR, CBR, and PFS results in the EVER-132-001 trial, consistent with the phase 3 ASCENT trial of SG in mTNBC. TEAEs were manageable and no new safety signals were identified. These results support the use of SG as a new standard of care for Chinese pts with pretreated mTNBC.

Table

Efficacy, ITT	SG (n = 80)
ORR^a (95% CI), %	40 (29-52)
DoR^a (95% CI), mo	11.6 (7.0-13.8)
CBR^a (95% CI), %	46 (35-58)
Median PFS^a (95% CI), mo	5.6 (4.1-8.3)
Median OS (95% CI), mo	14.7 (10.3-18.3)
Landmark OS rate (95% CI), %	
3 mo	94 (86-97)
6 mo	83 (72-89)
9 mo	70 (59-79)
12 mo	54 (42-64)
Safety, all treated	SG (n = 80)
Any grade TEAEs, n (%)	80 (100)
Grade \geq 3	63 (79)
TEAEs leading to dose reduction	16 (20)
TEAEs leading to treatment interruption	38 (48)
TEAEs leading to treatment discontinuation	6 (8)
^a Per independent review committee.	

PO1-06-11

Exosomal HMGB1 induce PD-L1+-tumor associated macrophages through glycometabolic reprogramming to promote lung-tropic metastasis of triple negative breast cancer

Presenting Author(s) and Co-Author(s):

W. Chen. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, Changzhou, Jiangsu, China (People's Republic)

J. Wu. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, United States

T. Cheng. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, United States

S. Yang. The First Affiliated Hospital with Nanjing Medical University, United States

Background: Lung metastasis occurs in 30% of triple negative breast cancer (TNBC), the detailed molecular mechanism remains largely unexplored. Accumulating evidence suggests that PD-L1+-tumor associated macrophages (PD-L1+-TAMs) are closely related to immune suppression, invasion, and metastasis. Tumor-derived exosomes have been reported to remodel tumor microenvironment and accelerate metastasis via packing and delivering a variety of biologically active molecules. Our previous studies found that exosomes from breast cancer cells polarized macrophages toward TAMs within the primary tumor nest. The aim of this study was to reveal whether TNBC-derived exosomes were able to polarize lung macrophages towards PD-L1+-TAMs and generate a pre-metastatic immunosuppressive niche, therefore discovering the underlying mechanism of lung-tropic metastasis. Methods: Exosomes isolated from EO771 TNBC cell line (EO771/exo) and HC11 normal breast epithelial cell line (HC11/exo) were characterized. Uptake of exosomes by macrophages was visualized by confocal microscopy. Mass spectrometry was applied to identify the significantly highly expressed HMGB1 protein in EO771/exo, and ligands of HMGB1 on lung macrophages were detected by co-immunoprecipitation. Functions of EO771/exo and HMGB1 in inducing PD-L1+-TAMs and generating a pre-metastatic immunosuppressive niche were confirmed by both in vitro and in vivo studies. Roles of EO771/exo and HMGB1 on glycolysis and lactate production were evaluated by metabolism assays. Associations between PD-L1+-TAMs and CD3+CD8+ T lymphocytes within TNBC axillary lymph nodes and lung metastasis specimens were analyzed by immunofluorescence and immunohistochemistry. Results: Confocal microscopy showed constant internalization and absorption of EO771/exo by macrophages. EO771/exo could polarize macrophages toward PD-L1+-TAMs and generate a pre-metastatic immunosuppressive niche, with respect to HC11/exo. Mass spectrometry, clinical samples, and bioinformatics analysis revealed that HMGB1 was highly expressed in EO771/exo and was involved in cellular communication and metabolism processes. Co-immunoprecipitation and 3-dimensional modeling indicated a strong binding of HMGB1 with Tim-3 ligand on lung macrophages. Macrophages treated with EO771/exo displayed an enhanced glycolysis and lactate production. Flow cytometry demonstrated that green fluorescent protein (GFP)-EO771 tumor-bearing mice had more lung micro-metastases than brain and liver. Immunofluorescence and laser confocal microscopy confirmed that EO771/exo, with respect to HC11/exo, were able to increase lung micro-metastases and escalate PD-L1 expression on lung macrophages. Moreover, elevated PD-L1+-TAMs and reduced CD3+CD8+ T lymphocytes were found in TNBC positive axillary lymph nodes and lung metastasis specimens than TNBC negative axillary lymph nodes. Conclusions: Exosomal HMGB1 from TNBC could target Tim-3 ligand on

lung macrophages and accelerate glycolysis and lactate production to induce PD-L1⁺-TAMs, thereby suppressing CD3⁺CD8⁺ T lymphocytes immunity and generating a pre-metastasis immune-suppressive niche. Our research would uncover a novel mechanism of lung-tropic metastasis and provide a new therapeutic approach for TNBC treatment. Keywords: breast cancer; lung metastasis; exosomes; tumor-associated macrophages; metabolic reprogramming

PO1-06-12

Phase II study of sitravatinib plus tislelizumab with or without nab-paclitaxel in patients with locally recurrent or metastatic triple negative breast cancer

Presenting Author(s) and Co-Author(s):

L. Fan. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

X. Liu. Fudan University Shanghai Cancer Center, United States

Y. Xu. Fudan University Shanghai Cancer Center, United States

X. Sui. Fudan University Shanghai Cancer Center, United States

W. Zhang. Fudan University Shanghai Cancer Center, United States

L. Ma. Fudan University Shanghai Cancer Center, Shanghai, China, United States

X. Jin. Fudan University Shanghai Cancer Center, United States

S. Wu. Fudan University Shanghai Cancer Center, China (People's Republic)

H. Wang. Fudan University Shanghai Cancer Center, United States

Y. Xiao. Fudan University Shanghai Cancer Center, United States

L. Chen. Fudan University Shanghai Cancer Center, United States

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

K. Yu. Cancer Center and Cancer Institute, Shanghai Medical College, Fudan University, United States

G. Liu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China, United States

X. Hu. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

Z. Wang. Fudan University Shanghai Cancer Center, United States

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Fudan University Shanghai Cancer Center, United States

Background:

The combination of a PD-(L)1 inhibitor plus chemotherapy demonstrated promising anti-tumor activity as first-line therapy for patients (pts) with locally recurrent inoperable or metastatic PD-L1 positive triple-negative breast cancer (TNBC). However, for pts without PD-L1 expression and for those who have failed prior lines of treatment, therapeutic options are still limited. This multi-cohort, phase II trial aimed to evaluate the safety and antitumor activity of 70 mg (cohort A) or 100 mg (cohort B) sitravatinib plus tislelizumab in pts with locally recurrent or metastatic TNBC, and their combination (70 mg sitravatinib plus tislelizumab) with nab-paclitaxel in untreated locally recurrent inoperable or metastatic TNBC pts (cohort C). The efficacy of sitravatinib plus tislelizumab in cohort A and B has been reported with objective response rate (ORR) of 38.1% and 45.0%, respectively. Herein, the preliminary results of cohort C and updated results of cohort A and B were reported. Methods:

Pts with untreated locally inoperable or metastatic TNBC were included in cohort C and received 70 mg sitravatinib orally once daily plus 200 mg tislelizumab intravenously on day 1 and 100mg/m² nab-paclitaxel on days 1 and 8 every three weeks until disease progression or intolerable toxicity. The primary endpoint was ORR. Secondary endpoints included disease

control rate (DCR), progression-free survival (PFS), duration of response (DOR), 1-year overall survival (OS) rate and safety/tolerability. Based on Simon's two-stage design, > 9 responders were need in stage 1 (n=18) for the study to continue, and > 19 responders were needed by the end of study (n=35) to demonstrate statistical superiority with sitravatinib plus tislelizumab and nab-paclitaxel (assumed to be around 65%) to a historical control of 46% (1-sided alpha of 0.1, power of 80%). Updated analyses were provided for cohort A (Simon's 2 stage design) and B (Bayesian optimal phase II design). Results:

Among the 18 pts in stage 1 of cohort C, 12 of them achieved confirmed response, and therefore the study proceeded to the enrollment in stage 2. As of April 30, 2023, a total of 32 pts were enrolled, with a median age of 51 years. Among the 23 efficacy evaluable pts, unconfirmed ORR was 87.0% (95% CI 66.4-97.2) (including 3 CRs and 17 PRs), with 7 pts not reaching next tumor assessment after reaching CR/PR, and confirmed ORR was 52.2% (95% CI 30.6-73.2). DCR was 95.7%. Any grade of treatment-related adverse events (TRAEs) occurred in 31 (96.9%) pts, and grade ≥ 3 TRAEs occurred in 5 (15.6%) pts. One (3.1%) patient experienced grade ≥ 3 immune-related adverse events. SAEs were reported in 3 (9.4%) pts. At the data cut-off date, the median follow-up duration for cohort A and B was 20.4 (range 1.3–24.3) months and 13.3 (range 5.1-19.1) months, respectively. The median PFS in cohort A was 8.2 (95% CI 2.8-12.4) months, and in cohort B was 5.4 (95% CI 4.2-10.9) months. Median OS was not reached in both cohorts. RNA-seq analysis showed that the suppression of immune regulatory pathways and the activation of metabolic pathways promoted early progression. Besides, baseline angiogenesis associated pathway held the potential to predict the favorable response to tislelizumab plus sitravatinib. Conclusion:

In the first-line treatment of locally recurrent or metastatic TNBC, preliminary analysis of cohort C showed that sitravatinib combined with tislelizumab and nab-paclitaxel had promising anti-tumor activity with a high ORR, and the combination was generally well tolerated. In TNBC pts with less than three lines of therapy, the chemotherapy-free regimen with sitravatinib plus tislelizumab demonstrated promising PFS after a longer follow-up duration.

PO1-06-13

Plasma Exosomes in Obesity-driven Diabetes Exacerbate Progression of Triple Negative Breast Cancer: Insights from Animal Models

Presenting Author(s) and Co-Author(s):

P. Llevenes. Boston University, United States

Objective: Our objective is to examine how obesity and type 2 diabetes (T2D) drive systemic and local metabolic changes in adipose tissue to promote progression of triple negative breast cancer (TNBC). We investigate the role of plasma exosomes as significant mediators of gene expression and functional changes, increasing TNBC progression and metastasis. We hypothesize that T2D and obesity alter the payload of plasma exosomes. These modified exosomes, specifically differentially expressed microRNAs in T2D, critically reshape the tumor microenvironment, ultimately promoting epithelial to mesenchymal transition (EMT) and distant metastasis of TNBC cells. Our goal is to gain a deeper understanding of the underlying mechanisms connecting T2D, obesity and TNBC metastasis, through the novel factor of exosome crosstalk. Our findings shed light on novel therapeutic targets and strategies to mitigate the impact of metabolic disorders on cancer outcomes.

Methods: We subjected C57BL/6J female mice to high-fat diet (HFD; 60% Kcal fat) for 12 weeks with weight monitoring, whereupon oral glucose tolerance test confirmed glucose intolerance and insulin resistance. Plasma exosomes were then isolated from peripheral blood and used to treat E0771 cells, as a TNBC model, for 72 hours for in vitro and in vivo analysis. To assess gene expression changes, we employed a commercial EMT array kit and performed qPCR. Gene expression data were uploaded to Qiagen software, specifically the Ingenuity Pathway Analysis tool, for analysis. To evaluate cell migration as a functional test of aggressiveness, a migration assay was conducted using 24-hour FBS deprivation, followed by 24-hour migration, utilizing transwell plates with 8µm pores. For in vivo analysis, mice were injected with 50k E0771-GFP cells in the 4th mammary fat pad. Tumors were allowed to grow for 28 days, at which time histology and flow cytometry analyses were performed with harvested brain, lung, and spleen.

Results: In-vitro analysis showed that HFD-derived exosomes reprogram gene expression in E0771 cells, driving a strong EMT signature, compared to LFD control or exosome-free negative control. This reprogramming elicited a pro-metastatic phenotype and upregulated signaling pathways associated with metastasis. Furthermore, HFD exosomes upregulated PD-L1 receptor expression compared to negative controls, linking EMT to immune tolerance. In-vivo analysis confirmed these findings, demonstrating increased metastatic burden in both lung and brain in the HFD context.

Conclusions: Plasma exosomes derived from HFD fed mice dramatically reprogram EMT gene networks in E0771 cells, exerting genomic alterations that persist for at least 28 days. These induced changes in cellular gene expression likely promote the development of brain metastases and immune evasion. The model suggests that TNBC patients with obesity-driven diabetes should be evaluated for increased risk of distant metastases. Plasma exosomes miRNA profiling may be a valuable biomarker in cancer disparities populations where the prevalence of obesity and diabetes are high.

PO1-06-14

Preliminary results of a phase I dose escalation study of eribulin in combination with copanlisib in patients with metastatic triple negative breast cancer (TNBC)

Presenting Author(s) and Co-Author(s):

N. Bagegni. Washington University in St Louis School of Medicine, United States

B. Haas. Washington University in St Louis School of Medicine, United States

L. Nehring. Washington University in St Louis School of Medicine, United States

J. Luo. Washington University in St Louis School of Medicine, United States

L. Kennedy. Vanderbilt University Medical Center, Nashville, Tennessee, United States

M. Trivedi. Columbia University Irving Medical Center, United States

M. Bhave. Emory University School of Medicine, Atlanta, Georgia, United States

R. Said. National Cancer Institute Cancer Therapy Evaluation Program, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

Background: Aberrant PI3K pathway signaling is frequently observed in TNBC. Increasing evidence indicate that PI3K pathway activation maintains the stemness and chemoresistance of breast cancer stem cells (CSCs). PI3K inhibition sensitizes CSCs to chemotherapy. Eribulin (E), a non-taxane microtubule dynamics inhibitor, showed overall survival benefit in metastatic HER2 negative BC. Preclinically, the addition of copanlisib (C), a potent pan-class I PI3K inhibitor that is highly selective against α and δ PI3K isoforms, improved anti-tumor effect in both E-sensitive and resistant TNBC patient-derived xenograft models, irrespective of PIK3CA/PTEN alteration status. Here we report the preliminary data of the phase I dose escalation trial of E+C in patients with metastatic TNBC.

Methods: This trial includes a phase I study to determine the dose limiting toxicity (DLT) and recommended phase 2 dose (RP2D) of E+C, followed by a randomized phase II study of E+C (at RP2D) versus E (stratified by tumor PIK3CA/PTEN mutation status) with progression-free survival (PFS) as the primary endpoint. Key eligibility included patients with: metastatic TNBC who progressed on ≤ 5 lines of chemotherapy, prior anthracycline/taxane chemotherapy (unless contraindicated), ECOG 0-1, adequate organ function and known tumor PIK3CA/PTEN/AKT mutation status. Key exclusions include: prior receipt of E or any PI3K/mTOR/AKT inhibitor, grade ≥ 2 neuropathy, presence of tumor AKT mutation, and uncontrolled diabetes, hypertension or congenital QT prolongation. A 3+3 design was used to determine the DLT and RP2D. Dose level 1 (DL1) started with E at 1.1 mg/m² mg IV and C at 45 mg IV on days (D) 1/8 of 21-D cycle, with the potential to escalate to 2 additional dose levels – DL2: E 1.4 mg/m² and C 45 mg on D 1/8; DL3: E 1.4 mg/m² and C 60 mg on D 1/8.

Results: Eight patients were enrolled in the phase I study and received at least 1 dose of E+C. The median age was 48.5 (range, 26-67) years. The majority of patients identified as White (additionally 2 Hispanic, 1 Black) and had an ECOG performance status of 1 (n=6, 75.0%). Tumor PIK3CA and PTEN alterations were each observed in 1 patient. Median number of cycles received were 2 (range, 1-5). All 8 patients had at least 1 treatment-related adverse event (TRAE). The most common TRAEs across all dose levels were: lymphopenia (n=5, 62.5%), neutropenia (n=5, 62.5%), hyperglycemia (n=4, 50.0%), anemia (n=4, 50.0%) and fatigue (n=4, 50.0%); most toxicities were grade (G) 1-2. G3 hyperglycemia and hypertension were observed in 1 patient each, were medically managed and did not lead to treatment

interruption. 1 patient was diagnosed with pulmonary embolism, possibly attributed to study therapy and breast cancer. DLTs were reported in 2 of 2 patients treated at DL2 - 1 patient developed G3 rash responsive to oral corticosteroids, and 1 patient developed G3 acute kidney injury in the setting of hypovolemia and discontinued study therapy. No additional patients were enrolled in DL2. No DLTs were observed in all 6 patients treated at DL1. 1 patient treated at DL1 had possible G1 non-infectious pneumonitis that resolved spontaneously on short interval imaging. Stable disease was observed in 2 of 6 response-evaluable patients (33.3%). 1 patient achieved regression of cutaneous disease following 1 cycle of therapy as assessed by the treating investigator. DL1, E at 1.1 mg/m² plus C at 45 mg IV, was determined to be the RP2D. Tumor tissue biomarker analysis is underway.

Conclusion: These data indicate that E+C at DL1 is a well-tolerated regimen warranting further investigation. The study is actively enrolling patients to the phase II study.

Clinical trial information: NCT04345913.

Funding Source: National Cancer Institute.

PO1-07-01

Artificial intelligence-based prediction of Oncotype DX Score from whole slide images using human-interpretable features and breast biomarkers

Presenting Author(s) and Co-Author(s):

N. Le. PathAI, Inc, Boston, Massachusetts, United States

J. Van Arnam. Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio, United States

C. Kirkup. PathAI, Boston, Massachusetts, United States

Y. Gerardin. PathAI, Boston, Massachusetts, United States

M. Drage. PathAI, Boston, Massachusetts, United States

N. Khaitan. Cleveland Clinic, United States

A. Sharma. Cleveland Clinic, United States

G. Galev. Cleveland Clinic, United States

N. Indorf. PathAI, United States

E. Sansevere. PathAI, United States

I. Wapinski. PathAI, Boston, Massachusetts, United States

S. Hennek. PathAI, Boston, Massachusetts, United States

G. Zhang. Cleveland Clinic, United States

Background The Oncotype DX Breast Recurrence Score assay (ODX) is a commonly used genomic test for patients with estrogen receptor (ER)-positive, HER2-negative, early-stage invasive breast cancer. While ODX predicts patients' recurrence risk and benefit from chemotherapy, it is tissue and time-consuming, and expensive. Previous deep-learning or non-linear ODX prediction models achieved promising performance using whole-slide images (WSI) or with other covariates (e.g., ER, progesterone receptor (PR), HER-2, Ki-67 scores and tumor stage) but systematic quantification of the contribution of individual histological features to the ODX score remained challenging. Here, we extracted a rich set of human-interpretable features (HIFs) quantifying nuclear morphology and the distribution of cells and tissues in the tumor microenvironment. We used these HIFs, along with manually assessed ER, PR, HER-2 scores, and tumor stage, to predict ODX scores. We also explored the role of Ki-67 features in augmenting our model predictions. **Methods** We developed machine learning models to extract cell, tissue, and nuclear HIFs from WSI stained with hematoxylin and eosin (H&E) and immunohistochemistry (IHC) against Ki-67. These models were deployed on 353 H&E WSI to extract 276 HIFs quantifying cell densities, tissue areas, relative cell counts, and nuclei size, shape and color. Hierarchical agglomerative clustering was applied to cluster these features into 11 groups. Univariate regression was performed to identify correlations between ODX scores and feature clusters. To predict ODX score using HIFs, a multivariable regression model was fitted to the data where regressors are representative features from each cluster, in addition to ER, PR, HER-2 scores and stage as covariates. The model was fitted on the training set (N=266 slides) and evaluated on the held-out test set (N=87 slides). To examine the utility of Ki-67 IHC features in ODX prediction, a Ki-67 model was deployed on a subset of 194 matched Ki-67 IHC WSI to extract count proportions and densities of Ki-67 positive cells in cancer epithelium and stroma. **Results** Significant positive correlations were identified between ODX scores and feature clusters corresponding to cancer cell density ($p < 10^{-7}$), macrophage density ($p < 10^{-4}$), immune cell density ($p < 10^{-16}$), and variations in cancer nuclear size ($p <$

10-5) and color ($p < 10^{-3}$). Significant negative correlations were observed between ODX scores and clusters related to fibroblast density ($p < 10^{-3}$), and variations of non-cancer cell nuclear color ($p = 0.02$). Evaluation of our model's ability to predict ODX scores revealed an association between predicted and observed scores (Pearson $r = 0.74$). The AUROC for model predictions of high/low classifications (with reference to a cutoff ODX score of 20) was 0.80. Ki-67 features were clustered together with H&E cancer cell density features and showed a stronger correlation with ODX scores compared to the H&E features alone. Combining Ki-67 cell density features with H&E features led to increased performance of the multivariable regression model on the test set compared to H&E features only ($r = 0.62$ vs. $r = 0.59$). However, a model combining Ki-67, H&E and covariates performed similarly to a model with H&E and covariates ($r = 0.73$), suggesting that Ki-67 features may not be needed for ODX prediction when H&E and covariate information is available. Conclusions Our model predicts ODX recurrence scores with comparable performance to other black-box approaches using WSI and breast biomarker status and without the need for, Ki-67 features. Using readily available information, our model has the potential to be a convenient screening tool for patient stratification, which may lead to better patient care, lower costs, and faster treatment.

PO1-07-02

Sensitive tumor detection, accurate quantification, and ER subtyping using low-pass methylome of liquid biopsy samples from patients (pts) with metastatic breast cancer (mBC)

Presenting Author(s) and Co-Author(s):

M. Paoli. Department of Cellular, Computational, and Integrative Biology, University of Trento, Trento, Italy

A. Nardone. Translational Research Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

F. Galardi. Translational Research Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

C. Biagioni. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

D. Romagnoli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

F. De Luca. Translational Research Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

G. Franceschini. Department of Cellular, Computational, and Integrative Biology, University of Trento, United States

I. Migliaccio. Translational Research Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

M. Pestrin. Medical Oncology Unit, Hospital of Gorizia, United States

G. Sanna. Medical Oncology Unit, Hospital of Alghero, United States

E. Risi. Medical Oncology Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

L. Livraghi. Medical Oncology Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

E. Moretti. Medical Oncology Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

L. Biganzoli. Medical Oncology Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

L. Malorni. Translational Research Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

F. Demichelis. Department of Cellular, Computational, and Integrative Biology, University of Trento, United States

M. Benelli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

Background The presence and amount of blood circulating tumor DNA (Tumor Content, TC) is emerging as a clinically relevant factor in many cancers, including BC. In the metastatic setting, a commonly used tumor tissue agnostic approach involves analyzing Copy Number Alterations (CNA) from low-pass whole-genome sequencing (lpWGS) by ichorCNA. However, with a lower limit of detection of 3%, it is unsuitable for low TC applications, such as monitoring disease in response to treatment. Here we report on the use of low-pass whole genome bisulfite sequencing (lpWGBS) coupled with a novel tool, METER (METHylation analyzER), to overcome current limitations of lpWGS, enabling sensitive TC detection, accurate quantification, and ER subtyping from mBC liquid biopsies. **Methods** METER is a computational tool to analyse TC

exploiting BC-specific Differentially Methylated Sites (DMS) and Regions (DMR) in IpWGBS data. To define BC DMSs and DMRs, Roker-meth was applied to the WGBS profiles of 30 BC tissue (BASIS dataset) and 23 healthy donor cell free DNA (cfDNA) (Fox-Fisher 2021). METER consists of three modules: 1) METER-quant, a DMS-based quantifier of TC; 2) METER-detect, a DMR-based z-score method to classify samples as TC+ (METER+) or TC- (METER-); 3) METER-subtype, to infer ER status via Robust Partial Correlation applied to ER+ vs. ER- BC DMR. We generated IpWGBS data (coverage 0.5-1X) of 135 cfDNA samples from 58 pts (45 ER+, 13 ER-, 55 (95%) up to 3 previous lines of treatment; before starting treatment (T0, n=58), after the first cycle (T1, n=25), and at progression (T2, n=22)) and 30 from healthy individuals as controls. ichorCNA using sensitive parameters (allowing normal fraction up to 0.99) was used to estimate reference TC. A leave-one-out strategy applied to the control samples was used to estimate the false discovery rate (FDR) of METER-detect classification. METER+/- pts were tested for association with OS and PFS using the log-rank test and compared with ichorCNA detection (TC by ichorCNA above or below 3%, ichorCNA+/-). Results TC of 105 cfDNA BC samples by METER-quant was concordant with estimates from the state-of-the-art tool ichorCNA ($R > 0.90$, $p < 1e-10$). In 22 pts with complete longitudinal data, METER-quant median TC of 0.05 at T0 (IQR 0.02-0.12), 0.02 at T1 (0.01-0.07), and 0.06 at T2 (0.03-0.11) were obtained, with significant difference observed for T0 vs T1 and T2 vs T1 (paired Wilcoxon $p < 0.05$). Across all time points, METER-detect classified 43% of the n=42 ichorCNA- samples as METER+. The reliability and prognostic performance of METER and ichorCNA detection classification were then compared using clinical outcome data. Based on T0 data, METER+ pts had significantly worse OS than METER- (HR=4.2 CI=2.0-8.9, $p < 0.001$). This effect was stronger than using ichorCNA (HR=2.3 CI=1.3-4.0, $p=0.006$). Worse PFS at T0 was observed for METER+ compared with METER- pts (HR=3.7 CI=1.8-7.9, $p < 0.001$), while no significant association was observed for ichorCNA+ pts (HR=1.4 CI=0.8-2.5, $p=0.2$). Of note, ichorCNA-/METER+ pts (N=11) at T0 had worse PFS compared with ichorCNA-/METER- (N=11) (HR=3.7 CI 1.4-9.7, $p=0.005$). Considering the 73 METER+ and 53 samples with METER-quant $> 5\%$, METER-subtype showed an accuracy of 0.84 (CI=0.73-0.92) and 0.94 (CI=0.83-0.99) respectively in classifying ER status based on IHC. Discussion IpWGBS enables tumor tissue agnostic analysis and concurrent investigation of complementary molecular features, including CNA and DNA methylation patterns. In a small and heterogeneous cohort, METER showed comparable performance to state-of-the-art tools in terms of TC quantification (ichorCNA) and ER subtyping (IHC), while offering enhanced sensitivity and ensuring a low FDR. METER showed promising prognostic stratification capabilities, particularly for patients with low TC. Validation in an extended prospective cohort is currently ongoing.

PO1-07-03

An Accurate Breast Cancer Diagnosis Method Using a Multi-Feature Fusion Neural Network on Contrast-Enhanced Spectral Mammography

Presenting Author(s) and Co-Author(s):

Y. Song. Yantai Yuhuangding Hospital, United States

W. Jiang. Yantai Yuhuangding Hospital, United States

Objectives: Our study aims to develop an accurate and comprehensive deep neural network capable of classifying CESM images to aid in the early detection and diagnosis of breast cancer in clinical settings. **Methods:** We enrolled diagnostic CESM examinations conducted between January 1, 2019 and January 17, 2021. We developed and tested the performance of a multi-feature fusion network for breast lesion classification by combining low-energy (LE) and dual-energy subtracted (DES) images, dual-view, and bilateral information using a large and diverse CESM dataset. We have evaluated the ability of the proposed network to generalize on external datasets and the results were reported using the area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, and specificity. **Results:** In the study period 1973CESMs were included. Mean age was 53 years \pm 12 (standard deviation). In the internal test dataset, the model with CESM (LE +DES) inputs combined not only bilateral information (left and right breasts) but also dualview information (CC and MLO), achieved best diagnosis performance with AUC of 0.96 [95% confidence interval (CI): 0.95–0.97], accuracy of 0.9 [95% confidence interval (CI): 0.88–0.92], sensitivity of 0.84 [95% confidence interval (CI): 0.80–0.88] and specificity of 0.93 [95% confidence interval (CI): 0.91–0.95], while the model with LE inputs only got an AUC of 0.94 [95% (CI): 0.93–0.95], accuracy of 0.88 [95% confidence interval (CI): 0.86–0.90], sensitivity of 0.79 [95% confidence interval (CI): 0.74–0.83] and specificity of 0.93 [95% confidence interval (CI): 0.91–0.95] (external dataset: an AUC of 0.90 [95% (CI): 0.85–0.94], accuracy of 0.84 [95% confidence interval (CI): 0.78–0.89], sensitivity of 0.77 [95% confidence interval (CI): 0.61–0.88] and specificity of 0.87 [95% confidence interval (CI):0.80–0.92]). **Conclusion:** CESM is a promising technique in breast cancer diagnosis due to its high feasibility and potential. The results demonstrate that left-right breast fusion and dual-view fusion are helpful for accurate diagnosis on CESM images. Specifically, dual-energy subtracted (DES) images generated by CESM improve diagnostic accuracy when compared to low-energy (LE) images alone. **Keywords:** Contrast-enhanced spectral mammography; Deep neural network; Breast cancer diagnosis; Multi-feature fusion

PO1-07-04

Multomics analysis reveals the landscape of PD-L1 expression in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

H. Wang. Fudan University Shanghai Cancer Center, United States

X. Ding. Fudan University Shanghai Cancer Center, United States

C. Liu. Fudan University Shanghai Cancer Center, United States

Y. Xiao. Fudan University Shanghai Cancer Center, United States

R. Shui. Fudan University Shanghai Cancer Center, United States

Y. Li. Fudan University Shanghai Cancer Center, United States

C. Chen. Fudan University Shanghai Cancer Center, United States

W. Yang. Department of Oncology, Fudan University Shanghai Cancer Center, United States

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Background: Tumor-infiltrating lymphocytes (TILs) and programmed death ligand 1 (PD-L1) remain controversial in predicting clinical outcomes of triple-negative breast cancer (TNBC), as outcomes do not always correlate with the expression of these biomarkers. Genomic and transcriptomic alterations that might contribute to the expression of these biomarkers remain incompletely uncovered. **Methods:** We evaluated PD-L1 immunohistochemistry (IHC) scores (SP142 and 28-8) and TILs in our TNBC multiomics dataset and two immunotherapy clinical trial cohorts. Then, we analyzed genomic and transcriptomic alterations correlated with TILs, PD-L1 expression and patient outcomes. **Results:** Despite TILs serving as a decent predictor for TNBC clinical outcomes, there remained exceptions. Our study revealed that several genomic alterations were correlated with unexpected events. Particularly, PD-L1 expression may cause a paradoxical relationship between TILs and prognosis in certain patients. Consequently, we classified TNBCs into four groups based on PD-L1 and TIL levels. The TIL-PD-L1+ and TIL+PD-L1- groups were not typical “hot” tumors; both were associated with worse prognoses and lower immunotherapy efficacy than TIL+PD-L1+ tumors. Copy number variation of PD-L1 and oncogenic signaling activation were correlated with PD-L1 expression in the TIL-PD-L1+ group, whereas GSK3B-induced degradation might cause undetectable PD-L1 expression in the TIL+PD-L1- group. These factors have the potential to affect the predictive function of both PD-L1 and TILs. **Conclusions:** Several genomic and transcriptomic alterations may cause paradoxical effects among TILs, PD-L1 expression and prognosis in TNBC. Investigating and targeting these factors will advance precision immunotherapy for TNBC patients. **Keywords:** Triple-negative breast cancer, PD-L1 expression, Tumor-infiltrating lymphocytes, Multiomics, Immunotherapy

PO1-07-05

Preliminary Evaluation in Breast Cancer of PointCheck: a Noninvasive AI-Based Neutropenia Monitoring Device

Presenting Author(s) and Co-Author(s):

J. Garcia-Mosquera. Hospital Universitario Dexeus, United States

M. Alva. Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain, United States

T. Iwase. Translational Cancer Research, University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

G. Lamaj. Leuko Labs, United States

P. Tolosa. SOLTI Cancer Research Group, Barcelona, Spain/Medical Oncology Department, Hospital 12 de Octubre, Madrid., Madrid, Madrid, Spain

R. Sánchez-Bayona. Medical Oncology Department, Hospital 12 de Octubre, Madrid. SOLTI Cancer Research Group, Barcelona, Spain

J. Pelaez-Escobar. Leuko Labs, Spain

A. Pablo-Trinidad. Leuko Labs, Spain

R. Benasutti. Leuko Labs, United States

A. Bourquard. Leuko Labs, United States

I. Butterworth. Leuko Labs, United States

A. Sánchez-Ferro. Leuko Labs, United States

C. Castro-González. Leuko Labs, United States

J. Pérez-García. International Breast Cancer Center (IBCC), Pangaea Oncology, Qiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Catalonia, Spain

A. Martínez-Bueno. Hospital Universitari Dexeus, Barcelona, Spain

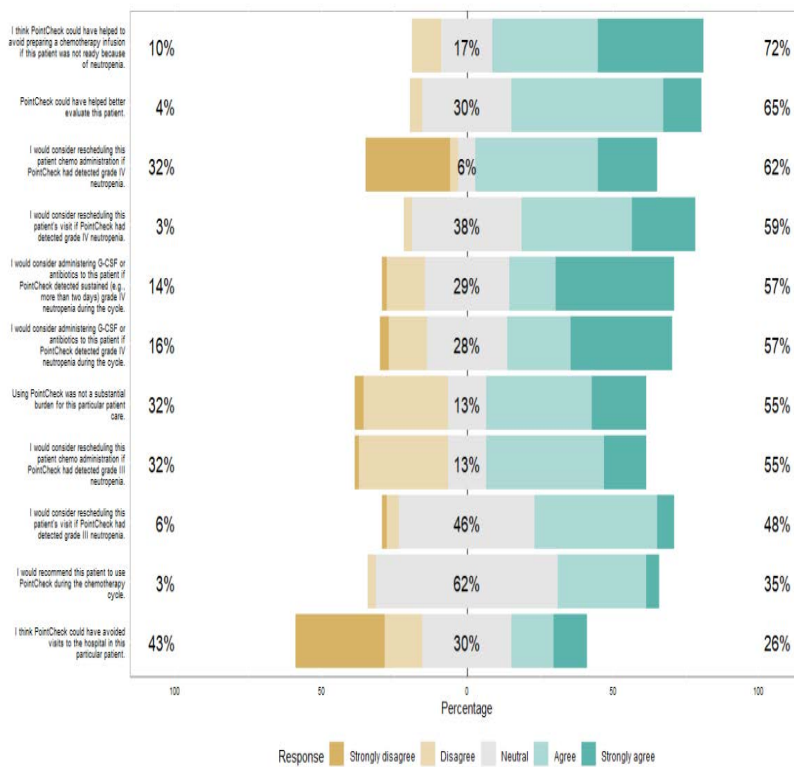
E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

A. Nasrazadani. Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background Febrile neutropenia (FN) is a common complication that can arise in breast cancer patients receiving myelosuppressive chemotherapy and increases the risk of fatal infections. Despite better preventive strategies there are between 140,000 to 200,000 FN-related hospitalizations yearly. Quick detection and awareness of grade III neutropenia (Absolute Neutrophil Count [ANC] < 1,000/ μ L) or greater can be critical to managing FN and treatment scheduling and dosing in patients with breast cancer. The current gold standard for neutropenia detection is a peripheral blood collection that requires patients to come into the clinic. PointCheck™ is a novel, noninvasive technology that can monitor for grade III neutropenia or greater and enable prompt detection in the home by acquiring microscopy videos of superficial capillaries through the nailfold skin and analyzing those videos with computer vision AI algorithms. To evaluate the usability, diagnostic performance, and preliminary clinical utility of PointCheck™ on FN detection we conducted a multi-center observational usability and diagnostic study. Methods The present study included an overall cohort of 175 diverse cancer patients, with 70 breast cancer patients. The primary endpoint was to achieve a score over 80.8 on a standardized System Usability Scale (SUS). Secondary endpoint was achievement of

diagnostic performance with an area under the curve (AUC) above 0.80. We also performed an exploratory analysis on the device's clinical utility. Eligible participants were introduced to the device, watched a tutorial video and were given a user manual. They used the device autonomously under the supervision of the clinical team. Usability data was collected using the SUS, the scoring system that has a scale between 0-100. PointCheck™ measurements were analyzed using AI algorithms and compared to same-day Complete Blood Counts (CBCs) collected within 90 minutes of the measurement to assess accuracy in classifying patients as grade III neutropenic or greater ($< 1,000/\mu\text{L}$), or non-grade III neutropenic ($\geq 1,000/\mu\text{L}$). In the exploratory clinical utility analysis, clinicians provided narrative insights by completing a Likert survey assessing how PointCheck™ would support or impact their clinical decisions. Results 81.4% of breast cancer patients scored above 80.8 on the SUS scale across all sites, with a mean SUS score of 87.7 (SD=13.2). Furthermore, the AI-based PointCheck™ classifier accurately discriminated neutropenia patients with an AUC = 0.90 in the overall cohort. In the exploratory analysis, a majority of clinicians (65.2%) agreed that the device could have helped better evaluate their patients (Table 1). Whereas almost 3 out of 4 clinicians (72.4%), described that the use of PointCheck™ could have avoided preparing a chemotherapy infusion if the patient was not ready due to grade III neutropenia or greater. Conclusions The present study showed that there is a high perception of usability of PointCheck™, indicating an above average user experience and falling within the top 10% of systems. Furthermore, we found that PointCheck™ can accurately detect grade III neutropenia or greater in a large cohort of patients including breast cancer patients. Application of PointCheck™ to clinical practice as a monitoring system can contribute to the early detection of FN and antineoplastic therapy management.

Table 1: Clinical Utility Survey Results



PO1-07-06

Sonographic assessment of breast implants using strain elastography and shear wave elastography in an animal model

Presenting Author(s) and Co-Author(s):

H. Fritsch. St. Franziskus Hospital Münster, United States

M. Celik. Universität Köln, United States

M. Warm. Breast Center, Municipal Hospital Holweide. Cologne, Cologne, Germany

F. Thangarajah. Universitätsklinikum Duisburg-Essen, United States

A. Pisek. St. Franziskus Hospital Münster, United States

C. Eichler. St. Franziskus Hospital Münster, United States

Purpose: To date, MRI remains the gold standard for the diagnosis of breast implant rupture. As MRI is an expensive procedure with limited availability, improvement in sonographic assessment is desirable. A potentially useful tool in this regard is the assessment of tissue stiffness using ultrasound elastography. Strain elastography provides a qualitative analysis by producing a coloured map in the B-mode image comparing the stiffness of adjacent tissues in the region of interest, whereas shear wave elastography provides a quantitative analysis. To evaluate the diagnostic utility of both methods under standardised conditions, we developed an animal model. Under natural conditions, the physiology of the patient (e.g. the amount and stiffness of the breast tissue covering the implant in question) can influence the measurements and alter the data. Therefore, the animal model provides an excellent opportunity to compare ruptured and intact implants of different types and sizes under exactly the same conditions, neglecting individual characteristics of real patients. **Methods:** An animal model was created by preparing an implant site in a chicken breast, mimicking the layers of tissue typically covering a breast implant after mastectomy (skin, fat, muscle). Different fractured and intact implants were inserted. Measurements were made using strain elastography and shear wave elastography by an investigator with no further experience of breast ultrasound. Implants were scanned in five pre-defined planes in both intact and ruptured conditions. For strain elastography, the resulting images were examined for repetitive patterns. Shear wave elastography data were analysed for significant differences between ruptured and intact implants. **Results:** The chicken breast animal model produced realistic images and measurements comparable to those of a human breast. Therefore, ruptured and intact implants could be compared under standardised conditions. Statistical analysis showed no significant difference between intact and ruptured implants in shear wave elastography data. However, qualitative analysis using strain wave elastography showed different patterns when comparing intact and ruptured implants in the animal model. Intact implants showed a characteristic three-layer sonographic image at certain levels. **Conclusion:** Shear wave elastography does not appear to provide reliable data for the evaluation of breast implants, whereas qualitative analysis using strain wave elastography may be a useful tool to improve diagnostic accuracy.

PO1-07-07

Radiomics features for distinguishing true recurrence versus new primary tumor following breast-conserving treatment

Presenting Author(s) and Co-Author(s):

F. Qu. Fudan University Shanghai Cancer Center, United States

G. Su. Fudan University Shanghai Cancer Center, United States

J. Li. Shanghai Cancer Center Fudan University, United States

C. You. Fudan University Shanghai Cancer Center, United States

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background Despite modern surgical and irradiation techniques, ipsilateral breast tumor recurrence (IBTR) accounts for 5-15% of all cancer recurrences in women treated with breast conservative treatment. Historically, the methods to define true recurrence (TR) and new primary tumor (NP) for IBTR mainly rely on clinical and pathological criteria, limiting the accuracy of the discernment and causing misclassification. This study aimed to develop a preoperative, noninvasive model for distinguishing IBTR by integrating clinicopathological review with paired dynamic contrast-enhanced breast magnetic resonance imaging (DCE-MRI) at diagnosis and following in-breast recurrence. **Methods** We retrospectively extracted radiomics features from MRI to develop a radiomic cohort of IBTR (n =46), among which all patients underwent paired preoperative DCE-MRI. This radiomic cohort was divided into a training cohort (n =27) and a validation cohort (n =19) with stratified random sampling. Classification of IBTR as TR or NP on the basis of tumor location, histologic subtype, estrogen receptor, and HER2 status was set as the gold standard. The least absolute shrinkage and selection operator (LASSO) regression and logistic regression were utilized to perform radiomics feature selection and model training, respectively. The clinical utility of the model was determined via decision curve analysis (DCA). **Results** We selected three radiomics features (first-order feature Kurtosis from the first postcontrast phase on IBTR DCE-MRI, GLCM feature l_{mc2} from the first postcontrast phase on IBTR DCE-MRI, and the delta feature Correlation from the precontrast phase of the change between IBTR and primary tumor DCE-MRI) to develop an IBTR-classification predicting radiomic model, which performed well in the validation cohort (AUC 0.867, 95% confidence interval (CI) 0.694-1). Further investigation for sensitivity (73.3%) and specificity (100%) verified a favorable concordance between the radiomic classification and the conventional standard, with a diagnostic accuracy of 79%. **Conclusions:** Our study demonstrated the feasibility of the radiomics model in predicting IBTR classification and provided preoperative information about the nature of “recurrence”. This might have important implications in surgical approaches and multidisciplinary care for IBTR. Further efforts are needed to improve the reproducibility of radiomics features and models in multiple centers.

PO1-07-08

Value of high resolution full field optical coherence tomography and dynamic cell imaging (D-FFOCT) for one-stop rapid diagnosis breast clinic

Presenting Author(s) and Co-Author(s):

a. simon. APHP, United States

y. badachi. APHP, United States

j. ropers. APHP, United States

i. laurent. APHP, United States

l. dong. APHP, United States

e. da maia. APHP, United States

a. bourcier. APHP, United States

g. canlorbe. APHP IUC Sorbonne University, Centre de Recherche Saint-Antoine (CRSA), INSERM UMR_S_938,, United States

C. Uzan. Hôpital Pitié-Salpêtrière Paris, United States

BACKGROUND: Full field optical coherence tomography combined to dynamic cell imaging (D-FFOCT) is a new, simple to use, nondestructive, quick technique than can provide sufficient spatial resolution to mimic histopathological analysis. The objective of this study was to evaluate diagnostic performance of D-FFOCT for one-stop rapid diagnosis breast clinic.

METHODS: D-FFOCT was applied to fresh untreated breast and nodes biopsies. Four different readers (senior and junior radiologist, surgeon and pathologist) analyzed the samples without knowing final histological diagnosis or ACR classification. The results were compared to conventional processing and staining (Hematoxylin-eosin). **RESULTS:** A total of 217 biopsies were performed on 152 patients. There were 144 breast biopsies and 61 lymph nodes with 101 infiltrative cancers (49,27%), 99 benign lesions (48,29%), 3 ductal in situ carcinoma (1,46%) and 2 atypias (0,98%). The diagnostic performances results were as follow: sensitivity: 77% [0.7;0.82], specificity: 64% [0.58;0.71], PPV: 74% [0.68;0.78] and NPV: 75% [0.72;0.78]. A large images atlas was created as well as a diagnosis algorithm from the readers experience.

CONCLUSION: D-FFOCT provides interesting results defining malignancy on fresh breast and nodes samples. By training with the diagnosis algorithm and the images atlas or by using machine learning, radiologists could obtain even better outcomes allowing quick detection of breast cancer and lymph node involvement.

diagnosis algorithm

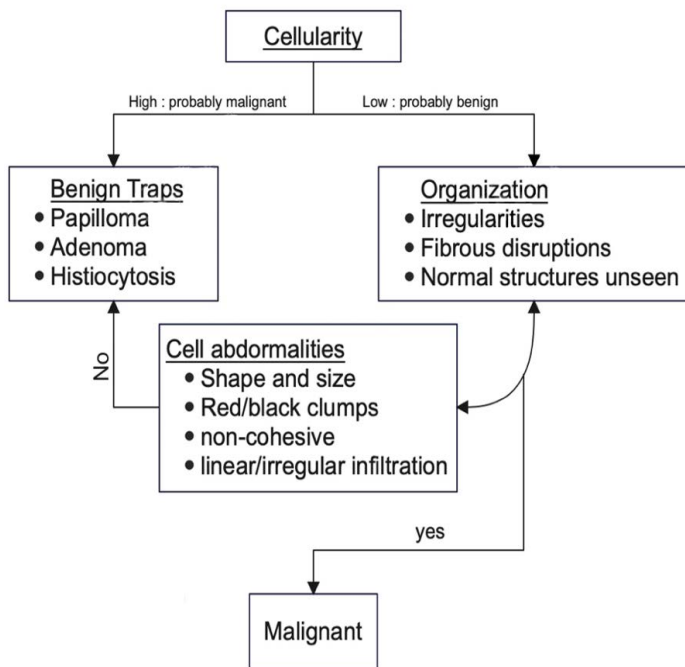
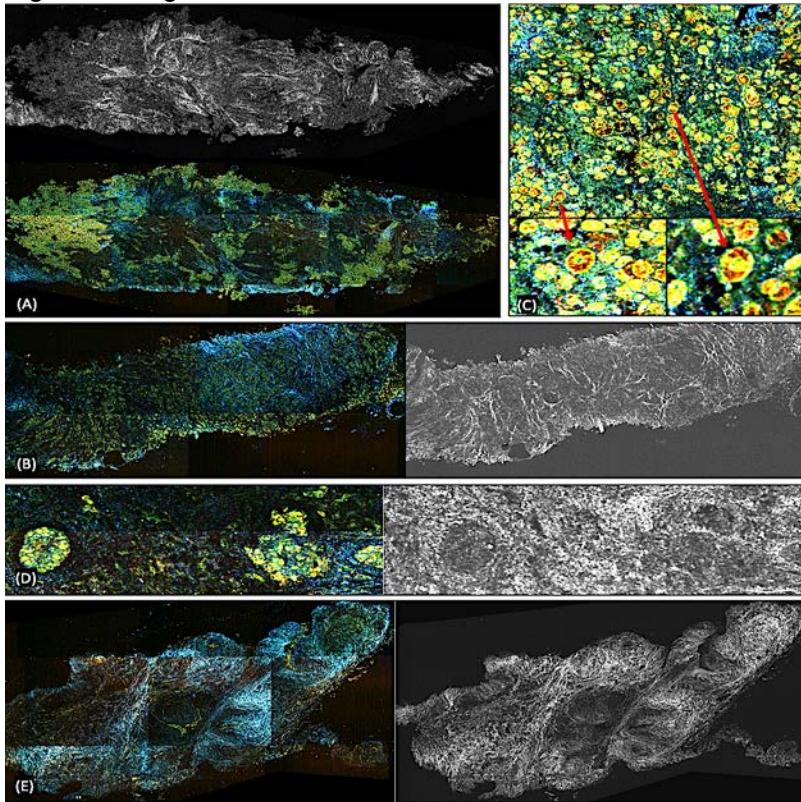


Figure 1 Images in DCI and FFOCT



Two infiltrating cancer diagnosed on pathology (A,B). Focusing on cells (C). Normal galactophoric duct (D). Adenofibroma (E)

PO1-07-09

Benefit of Adherence to Annual Mammography Screening: Results from 8,305 Cancers in an Institutional Database

Presenting Author(s) and Co-Author(s):

R. Nishikawa. University of Pittsburgh, United States

A. Bandos. University of Pittsburgh, United States

S. Duffy. Queen Mary University of London, London, England, United Kingdom

D. Logue. University of Pittsburgh, United States

M. Zuley. University of Pittsburgh, United States

Purpose: There is much debate on the starting age and frequency for asymptomatic mammographic breast cancer screening. We analyzed data from our medical center to determine the effect of the frequency of screening on the likelihood of a woman being diagnosed with a late-stage cancer and on the all-cause mortality. **Method:** For this study, we used our institutional breast cancer care data mart, which contains data for all patients who had breast imaging or were treated for breast cancer at a University of Pittsburgh Medical Center (UPMC) facility between 2004 and 2019 inclusive. Including only women 40 years and older, 8,145 had at least one screening mammogram prior to their diagnosis of breast cancer. Screening exams less than 260 days apart were considered to be from the same screening episode. For the 8,145 women, we determined the interval between their two most recent screening mammograms and grouped them into: (i) Baseline (only 1 prior screening episode prior to diagnosis); (ii) Compliant (less than or equal to 15 months between the two most recent screening episodes); (iii) Delayed (more than 15 months but less than 27 months between the two most recent screening episodes); and (iv) Missed (more than 27 months between the two most recent screening episodes). Late-stage cancer was defined as TNM stage 2b or worst. In cancers arising in those with at least two prior screening examinations, we estimated and tested significance of effects of adherence category on risk of late-stage cancer using logistic regression. We estimated the corresponding effects on survival to death from any cause using proportional hazards model. The effect of compliance was evaluated univariately followed by the multivariable analysis accounting for demographic and clinical characteristics including age, race, and menopausal status. Analysis within practically relevant subgroups was performed for additional illustration. **Results:** For all-cause death 5-year mortality rate post-diagnosis was 4.2% for the Compliant group (n=3369, median follow-up 5.13 years), 5.9% for the Delayed group (n=1340, median follow-up 4.64 years), and 12.2% for the Missed group (n=1129, median follow-up 3.36 years). The overall 5-year mortality rate was 6.1% (n=8145, median follow 5.12 years). Both unadjusted and adjusted for age, menopausal status, and ethnicity, the poorer survival with lesser compliance was highly significant (with the adjusted hazard ratios relative to the baseline group of 0.5, 0.8, and 1.3 for the three compliance groups respectively, $p < 0.001$). In the population overall, there was a significant trend of increasing risk of stage 2B or worse with lesser adherence to annual screening, the proportions being 9%, 14%, and 19% for the compliant, delayed, and missed groups respectively ($p < 0.001$). This remained significant when adjusted for age, menopausal status, or ethnicity ($p < 0.001$). The trend was significant within major demographic subgroups, except for a relatively small subpopulation of women with unknown menopausal status. **Conclusions:** Annual mammographic screening resulted in lower all-cause mortality and lower risk of late-stage cancers, for both white and black women and pre- and post-menopausal women. Our study clearly shows a benefit to screening all women over the age of 40 annually over longer periods between screens.

Table of Late-Stage Cancers by Screening Adherence and Demographic Factors

Table. Diagnosis of breast cancer at stage 2B or higher by screening adherence group and demographic factors

Subpopulation	Number (%) diagnosed at late stage for adherence groups				
	Baseline	Compliant	Overdue	Missed	Overall
Total	415/2307 (18)	311/3369 (9)	181/1340 (14)	214/1129 (19)	1121/8145 (14)
	Age				
40-49	105/644 (16)	54/458 (12)	41/201 (20)	35/167 (21)	235/1470 (16)
50-59	128/635 (20)	99/962 (10)	68/423 (16)	67/343 (20)	362/2363 (15)
60-69	115/641 (18)	89/1057 (8)	44/424 (10)	61/334 (18)	309/2456 (13)
70-79	44/271 (16)	53/686 (8)	19/231 (8)	31/196 (16)	147/1384 (11)
80 and older	23/116 (20)	16/206 (8)	9/61 (15)	20/89 (22)	68/472 (14)
	Race				
White	361/2052 (18)	277/3101 (9)	155/1187 (13)	171/947 (18)	964/7287 (13)
Black	50/196 (26)	29/207 (14)	20/126 (16)	34/147 (23)	133/676 (20)
Others	4/59 (7)	5/61 (8)	6/27 (22)	9/35 (26)	24/182 (13)
	Menopausal status				
Pre-	76/496 (15)	36/426 (8)	38/207 (18)	24/148 (16)	174/1277 (14)
Post-	283/1501 (19)	249/2733 (9)	133/1064 (13)	180/926 (19)	845/6224 (14)
Not known	56/310 (18)	26/210 (12)	10/69 (14)	10/55 (18)	102/644 (16)

Diagnosis of breast cancer at stage 2B or higher by screening adherence group and demographic factors

PO1-07-10

Blood Based Early Cancer Detection Assay

Presenting Author(s) and Co-Author(s):

A. Carson. Genece Health, United States

M. Wang. Genece Health, United States

B. Leatham. Genece Health, United States

K. Fathe. Genece Health, United States

E. Cho. GC Genome, United States

T. Lee. GC Genome, United States

J. Lee. GC Genome, United States

J. Ahn. GC Genome, United States

D. Kim. GC Genome, United States

B. Lee. Genece Health, United States

Background: Breast cancer screening programs utilizing mammography have been shown to be highly effective in identifying breast cancer in women over the age of 40. High breast density is an independent risk factor for breast cancer and makes mammograms more difficult to interpret, decreasing their sensitivity. In the spring of 2023, the FDA, who certifies all mammography facilities under the Mammography Quality Standards Act, updated its regulations to require that breast density status be reported to all individuals receiving a mammogram. The new guidelines now require individuals with dense breast tissue be notified of this status. The guidelines also recommend these women discuss additional screening options with their healthcare providers¹. These additional screening options may include breast tomosynthesis, breast MRI, breast ultrasound, and/or molecular breast imaging. Many of these options require additional exposure to radiation, are expensive, and are not equitably available across the country. In addition, they all require a follow-up appointment. Compliance can be challenging given the top barriers to mammography cited include the need for transportation, child-care, and the ability to take time off from work². Genece Health is developing a simpler and less expensive screening solution that identifies the presence of early to late-stage breast cancer using cfDNA from a single blood draw. The Genece Health assay utilizes an algorithm that leverages Artificial Intelligence and Machine Learning to analyze fragment size and end motif patterns in cfDNA as well as regional mutational density to detect presence of ctDNA originating from breast cancer. This algorithm provides highly sensitive and specific results in a preliminary data set. Methods: The preliminary data set, presented herein, is a cohort of over 50 retrospective breast cancer plasma samples and over 100 presumed normal samples. The breast cancer samples were collected at all stages of progression, from stage 0, or ductal carcinoma in situ (DCIS), through stage IV. The majority (>50%) were from stage I breast cancer. 400 µL of double spun plasma, collected in Streck BCT devices, was processed to purify and isolate cfDNA. cfDNA was used to create WGS libraries that were sequenced on a NovaSeq 6000. Sequence data were analyzed using a bioinformatics pipeline that yields an ensemble probability that correlates to the presence or absence of ctDNA from breast cancer. Results: The Genece Health assay and algorithm performed with a specificity greater than 85%. With this specificity, the assay had a sensitivity greater than 85% in samples from stages II to IV and a slightly lower sensitivity in stage 0 and I samples. Follow-up analyses were conducted to stratify performance based on breast cancer type (e.g. invasive ductal carcinoma vs invasive lobular carcinoma) and HR, PR, and HER2 status (e.g. HER2-negatives vs HER2-

positives). Conclusions: The presented preliminary data indicate that the Genece Health technology can be leveraged as a complement to mammography in indications, such as dense breast tissue, where there is an unmet need for an easy and cost-effective way to monitor for breast cancer. The ability to have a blood-based test to complement mammography could reduce the access barriers most cited by females in the United States. Follow-up studies with greater numbers of samples and additional training and optimizations of the algorithm will yield performance improvements that allow the assay to detect all types and stages of breast cancer. References: 1. FDA News Release 09 March 2023. FDA Updates Mammography Regulations to Require Reporting of Breast Density Information and Enhance Facility Oversight. 2. Henderson LM et al. The Role of Social Determinants of Health in Self-Reported Access to Health Care Among Women Undergoing Screening Mammography. *J Womens Health*. 2020 Nov;29(11):1437-1446.

PO1-07-11

Radiogenomic-based imaging intratumor heterogeneity model predicts breast cancer prognosis and unveils therapeutic targets

Presenting Author(s) and Co-Author(s):

G. Su. Fudan University Shanghai Cancer Center, United States

Y. Xiao. Fudan University Shanghai Cancer Center, United States

C. You. Fudan University Shanghai Cancer Center, United States

R. Zheng. Fudan University, United States

S. Zhao. Fudan University Shanghai Cancer Center, United States

H. Wang. Fudan University, United States

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Y. Gu. Fudan University Shanghai Cancer Center, United States

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background: Intratumor heterogeneity (ITH) refers to variations observed among cancer cells within a single tumor, posing significant challenges in clinical practice due to its contribution to treatment resistance and unfavorable outcome. However, the inconvenience of multi-region biopsy and limitations of genomic sequencing based on limited tissue impede the practical detection of ITH. Consequently, there is an urgent need for a non-invasive method that comprehensively captures ITH from a holistic perspective of the entire tumor. **Methods:** We utilized a large multicenter dataset comprising dynamic contrast-enhanced magnetic resonance images from breast cancer patients (n = 1423) along with matched multiomics data (n = 468) to develop a non-invasive machine learning approach for measuring ITH. We extracted quantitative radiomic features from both the entire tumor and peritumor regions, with a specific focus on features associated with imaging heterogeneity. Using these radiomic features, we established an imaging ITH (IITH) model. The robustness of IITH evaluation was determined by assessing its correlation with genomic ITH (employing the mutant-allele tumor heterogeneity [MATH] algorithm) and pathological cellular ITH (analyzing variation in quantitative nuclear features extracted through digital pathology). Prognostic power was evaluated using Kaplan-Meier and multivariate Cox proportional hazards analyses. Integrated multiomics analyses were performed to investigate the molecular basis of different IITH subgroups. **Results:** We developed a non-invasive radiomic signature to quantify imaging ITH (IITH) in the FUSCC cohort. Breast cancer patients were retrospectively categorized into high and low IITH groups. Multivariate Cox analysis identified high IITH as an independent predictor of poor prognosis in breast cancer patients, even after adjusting for clinical risk factors such as tumor size, positive lymph nodes, clinical subtype and lymphovascular invasion status. These findings were further validated in the DUKE cohort, confirming the prognostic value of IITH. Moreover, we substantiated the robustness of IITH by demonstrating its association with genomic and pathological ITH. Multiomics analysis revealed the activation of oncogenic pathways and metabolic dysregulation in high-IITH tumors. Intriguingly, our investigation also highlighted ferroptosis as a vulnerability and potential therapeutic target in high-IITH tumors, which was further supported by evidence from the TCGA cohort. **Conclusion:** Radiomic-based assessment of ITH provides a non-invasive approach to comprehensively capture ITH and predict the

prognosis of breast cancer patients. Targeting ferroptosis may hold promise as a treatment strategy for patients with high ITH.

PO1-07-12

Inverse modeling with surface temperature accurately detects the presence of breast cancer

Presenting Author(s) and Co-Author(s):

N. Sritharan. Rochester Regional Health, United States

C. Gutierrez. Rochester Institute of Technology, United States

I. Perez-Raya. Rochester Institute of Technology/ BiRed Imaging Inc, United States

J. Gonzalez-Hernandez. Rochester Institute of Technology, United States

A. Owens. Company/ Rochester Institute of Technology, United States

D. Dabydeen. Rochester Regional Health, United States

L. Medeiros. Rochester Regional Health, United States

S. Kandlikar. Rochester Institute of Technology/ BiRed Imaging Inc, United States

P. Phatak. Rochester Regional Health/ BiRed Imaging Inc, United States

Breast cancer affects over 250,000 women in the United States every year. Patient outcomes including overall survival significantly decline with large sized tumors and nodal involvement on initial presentation. The introduction of mammogram screening has been instrumental in the early detection of cancer. However, it has lower sensitivity in dense breast tissue and limited specificity which leads to unnecessary additional invasive testing. Several methods such as magnetic resonance imaging (MRI), computed tomography (CT) and ultrasound imaging are used as adjunctive methods. However, there is still a need for cost-effective techniques without additional radiation exposure for breast cancer screening for use with mammography. We propose an adjunctive screening method using surface temperature measurements and inverse breast modeling for early detection of breast cancer. Methods: We enrolled patients who presented with mammogram detected breast tumors that were confirmed to be cancerous lesions by biopsy. We used prone position steady state infrared imaging of bilateral breasts to measure surface temperatures and multi-view MRI images to create patient specific 3D breast models. The inverse technique applies Levenberg-Marquard algorithms (LMA) and utilizes commercial software for thermal transport modeling. The inverse technique predicts a heat generation map normalized for baseline surface temperatures to localize the presence of an underlying tumor. Results: A total of 25 breast tumors (diameter range from 5 to 27 mm) from 24 patients were included in the analysis with a median patient age of 67 years. One patient had bilateral breast tumors. Mammogram data showed inclusion of mixed breast tissue composition including dense and extremely dense breast tissue. LMA accurately detected the tumor in all 25 patients with maximum absolute errors of 7 mm in location of the tumor in the breast and 1.78 mm in diameter. The accuracy of detection was not affected by tumor histology which included invasive ductal and lobular carcinomas, ductal and lobular carcinoma in-situ and atypical ductal hyperplasia. No heat sensitive tumors were detected in the 23 contralateral breasts which acted as internal negative controls. Conclusion: Infrared temperature profiles and inverse modeling successfully detected malignant breast tumors with no missed tumors or false positive results and could be used as adjunctive screening along with mammography, especially in patients with dense breast tissue.

PO1-08-01

Identifying a founder BRCA1 variant in the Qatari population With unique genotype – phenotype correlations

Presenting Author(s) and Co-Author(s):

S. Al-Bader. National Center for Cancer Care and Research, Hamad Medical Corporation, United States

H. Habish. Hamad Medical Corporation Building, United States

R. Al Sulaiman. Hamad Medical Corporation Building, United States

H. Al-Mulla. Hamad Medical Corporation Building, United States

H. Ghazouani. Hamad Medical Corporation Building, United States

PURPOSE: Hereditary breast and ovarian cancer syndrome (HBOC) is the most common cause of hereditary breast & ovarian cancers in Qatar and worldwide which is caused by pathogenic variants in the BRCA1& BRCA2 genes. The aim of this retrospective study is to describe a common recurrent founder pathogenic variant in the BRCA1 gene that was observed in the native Qatari population with unique genotype-phenotype correlations.

METHODS: Medical records of Qatari patients (affected & unaffected) with personal and/or family history of breast & ovarian cancers who carry pathogenic/likely pathogenic mutations in the BRCA1 & BRCA2 genes were reviewed between 2013- 2020. Epidemiological information and clinical data were reviewed including age, gender, ethnic background, personal history of cancer, tumour characteristics and family history. We used frequencies and proportions to describe the data and used Kaplan-Meier curves and log-rank analysis to compare survival rates. For the analysis, we used Stata Corp. 2015. Stata Statistical Software: Release 14, College Station, TX: Stata Corp LP. **Result:** Our result confirms the presence of a common recurrent pathogenic variant in BRCA1 gene [(c.4787 C>A) (p. Ser 1596*)] among Qatari patients who belong to 8 consanguineous large families followed by BRCA1[c.4065_4068delTCAA]. BRCA1 c.4787 variant is highly associated with early onset breast cancer specifically Invasive ductal carcinoma (IDC) triple negative breast cancer (stage I, grade III), rather than ovarian cancer. In addition, the c.4787 C>A was found to be highly penetrant in families for young onset breast cancer. **Conclusion:** We showed that BRCA1 c.4787 C>A pathogenic variant is a highly recurrent variant among Qatari consanguineous families and contributes to the early onset breast cancer in Qatar. Early identification of this variant can aide to improve patient's survival & guide early personalized treatment and prevention.

PO1-08-02

Population-based screening of Uruguayan Ashkenazi Jews for recurrent BRCA1 and BRCA2 pathogenic sequence variants

Presenting Author(s) and Co-Author(s):

C. Castillo. Servicio de Oncología Clínica, Hospital de Clínicas, Montevideo, Uruguay, United States

N. Camejo. Servicio de Oncología Clínica, Hospital de Clínicas, Montevideo, Uruguay, United States

N. Artagaveytia. Departamento Básico de Medicina, Montevideo, Facultad de Medicina, Uruguay, United States

L. Brignoni. Departamento Básico de Medicina, Facultad de Medicina, Montevideo, Uruguay, United States

Y. Laitman. The Susanne Levy Gertner Oncogenetics Unit, Institute of Genetics, Sheba Medical Center, Tel Hashomer Israel, United States

A. Cayota. Laboratorio de Genómica Funcional, Institut Pasteur de Montevideo, Uruguay, United States

G. Krygier. Servicio de Oncología Clínica, Hospital de Clínicas, Montevideo, Uruguay, Uruguay

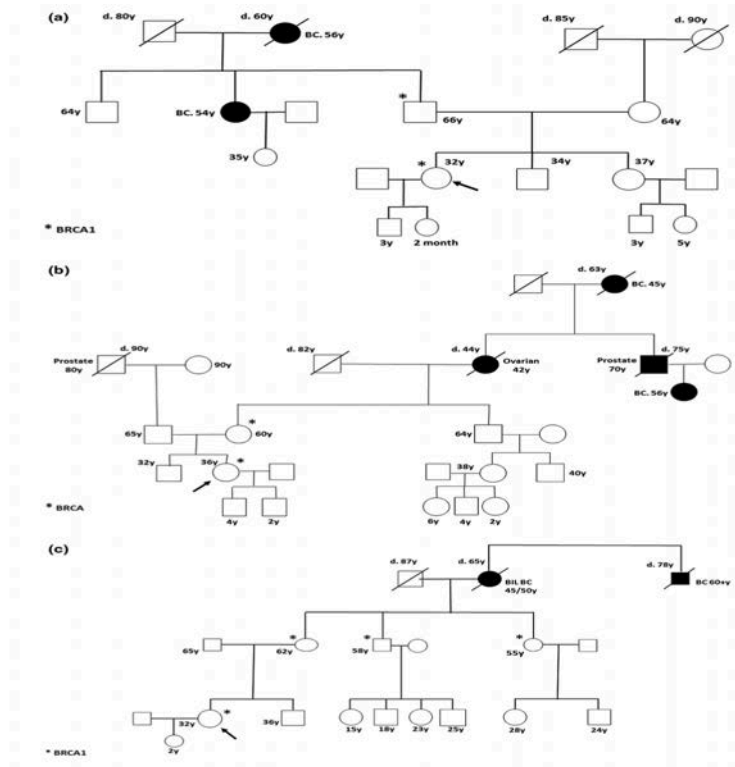
L. Delgado. Servicio de Oncología Clínica, Hospital de Clínicas, Montevideo, Uruguay, United States

E. Friedman. The Suzanne Levy-Gertner Oncogenetics Unit at the Sheba Medical Center, Israel, United States

In Ashkenazi Jews (AJ) three recurring pathogenic sequence variants (PSVs) are detected in ~2.5% of the general population in the BRCA1 (c.68_69del = 185delAG, c.5266dup = 5382insC), and BRCA2 (c.5946del = 6174delT). Population-based screening for these PSVs in AJ women is part of the health basket in Israel. To assess the feasibility and outcome of BRCA genotyping in the Jewish population of Uruguay, AJ in the greater Montevideo area were recruited using ethically approved protocol and without pretest counseling were genotyped for the three predominant AJ PSVs in the BRCA genes. Independently confirmed PSV carriers were counseled, and genetic testing was offered to additional family members. Overall, 327 participants were enrolled: 312 (95%) female, 261 (80%) had all four grandparents AJ, and 14 (4%) women were breast cancer survivors with a mean age \pm standard deviation (SD) 50 \pm 11.5 years. The BRCA1 c.68_69del PSV was detected in three cancer free participants (0.92%, CI 95% 0.31-2.6), all with a suggestive family history. No carriers of the other two recurrent PSVs were detected. Online oncogenetic counseling was provided for all carriers. In conclusion, the rate of the BRCA1 c.68_69del PSV was similar with the rate in other AJ communities. AJ population BRCA genotyping screens in Uruguay seem feasible and should be promoted.

Pedigrees of the carrier cases (a-c)

Characteristic	No. of patients	
	(N = 327)	%
Mean age (range) years	47 (22–83)	
<i>Age category</i>		
<40 yr	86	(26.3)
≥40to <60 yr	174	(53.2)
≥60 yr	67	(20.5)
Female sex	312	(95.4)
<i>Level of education</i>		
College	250	(76.4)
High school	63	(19.2)
Primary	1	(0.3)
No data	13	(4)
<i>Ethnicity</i>		
Four Ashkenazi grandparents	261	(79.8)
At least one Sephardic grandparent	34	(10.4)
At least one non-Jewish grandparent	11	(3.4)
At least one grandparent of unknown origin	8	(2.5)
No data	13	(3.9)
<i>Previous cancer diagnosis in women—no. (%)</i>		
Breast	14	(4.5)
Colon	3	(<1)
<i>Previous cancer diagnosis in men—no. (%)</i>		
Prostate	2	(13)
<i>Personal and/or family history for suggestive of inherited cancer</i>		
Yes	82	(15)
No	234	(80.6)
No data	11	(4.4)



PO1-08-03

Using Telehealth to Establish a High Risk Cancer Prevention Clinic over a large Geographic Area

Presenting Author(s) and Co-Author(s):

M. Purcell. Intermountain Health, United States

T. Reading. Intermountain Health, Salt Lake City, Utah, United States

G. Lee. Intermountain Health, United States

J. Tittensor. Intermountain Health, American Fork, Utah, United States

M. VanMeter. Intermountain Health, United States

There are health disparities in breast cancer screening based on urban, rural or frontier geographic designations. For instance, in Utah, the percentage of women who had no mammography in the last two years was 33.5% for urban, 33.8% for rural and 40.4% for frontier designations. Rural women are also diagnosed with breast cancer at later stages. Diagnosing breast cancer at earlier stages leads to improved survival, more affordable care, less toxic treatments, better quality of life and less time away from home and work.

We are presenting the innovative use of telehealth to establish a High Risk Cancer Prevention Clinic to effectively reach a large geographic area and mitigate obstacles to accessing care. The clinic's mission is to identify and care for individuals with increased cancer risk due to familial, genetic and/or high risk lesions. This initiative provides centralized comprehensive evaluation, counseling and screening planning as well as referral for risk-reducing interventions closer to home. With a collaborative approach involving surgical and medical oncology, genetics, radiology and women's health specialists, the teleclinic has successfully served 280 patients since Spring 2022. Recently our health care system has increased significantly in geographic reach due to mergers with other health systems. We think this teleclinic is nimble enough and easily scalable to accommodate caring for increased numbers of patients needing this service.

PO1-08-04

Universal Germline Genetic Testing for Breast Cancer: Implementation in a Rural Practice and Impact on Shared Decision Making

Presenting Author(s) and Co-Author(s):

C. Shelton. The Outer Banks Hospital, Nags Head, North Carolina, United States

S. Nielsen. Invitae, California, United States

A. Ruiz. Chesapeake Regional Medical Center, Chesapeake, Virginia, United States

L. Shelton. The Outer Banks, North Carolina, United States

K. Freas. The Outer Banks Hospital, United States

S. Poll. Invitae, United States

B. Heald. Invitae, United States

D. Pineda-Alvarez. Invitae, United States

E. Esplin. Invitae, United States

R. Ellsworth. Invitae, United States

H. Montgomery. Dana Farber Cancer Institute, United States

Background: Prior work from our group has shown a high rate of familial breast cancer (BC) among rural BC patients (pts), with 33% reporting > 1 first-degree family members with BC and 55% meeting NCCN germline genetic testing (GGT) criteria (Shelton CH et al. NC Med. J; 2022). In 2018, we increased GGT to include all BC pts and observed: 1) many pts were out-of-criteria per NCCN guidelines but had actionable pathogenic germline variants (PGVs) and 2) knowledge of GGT factored significantly into shared decision making by providers and patients, including for positive and negative results. Beginning in 2019, concurrent with the recommendation from the American Society of Breast Surgeons, we expanded this model of universal GGT to an IRB-approved study to measure the impact of prospective testing on shared decision-making. Herein we report the real-world implementation of universal GGT for patients with BC and genetics-informed treatment decision-making in a rural community practice. Methods: From 2019-2022 all BC pts at a small, rural community hospital were offered GGT. Demographics, clinical features, and GGT results were collected along with clinician-reported clinical recommendations for treatment based on GGT results. Descriptive statistics and two-tailed Fisher's exact test were employed and significance was set at $p < 0.05$. Results: 210 BC pts were offered GGT and 192 (91%) underwent testing [97% female, 95% non-Hispanic White, mean age at diagnosis of 62, 75% Stage I], with all but 7 pts completing GGT before primary treatment decisions. 104 (54%) of patients were in-criteria (IC) and 88 (46%) out-of-criteria (OOC) with NCCN GGT guidelines. PGVs were identified in 25 pts (13%) and 15 genes, most commonly BRCA1/2 (5 pts), PALB2 (3), monoallelic MUTYH (3) and ATM, BARD1, CHEK2 (2 pts each). PGV frequencies were 15% in IC and 11% in OOC patients ($p=0.495$). 46 (24%) pts had only a variant of uncertain significance (VUS) results. 70% of patients had > 1 clinical management change based on their GGT results. Changes in breast surgery, uptake of risk-reducing bilateral salpingo-oophorectomy, surveillance and clinical follow-up were significantly higher in patients with PGV compared to those with VUS/negative results ($p < 0.0001$). Compared to those with negative results, patients with PGVs in BRCA1 and BRCA2 were significantly more likely to undergo bilateral mastectomy (BLM) while those with PGVs in other genes or with VUS were not significantly more likely to elect for BLM than those with negative results. Clinicians reported that return of GGT reinforced their recommendation for 73/138 (53%) of patients who underwent breast-conserving therapy. GGT

results aided in radiation therapy strategy for 54% of pts, most often resulting in dose de-escalation (accelerated fractionation) for negative/VUS pts (Table). Conclusions: Universal GGT for patients with BC was successfully implemented in a rural community practice with >90% uptake. Treatment was enhanced in those with clinically actionable PGVs and de-escalated in those without PGVs. Universal GGT for patients with BC is feasible to implement as the standard of practice within rural populations, enabling optimization of clinical care to patients' genetic profile and may reduce unnecessary healthcare resource utilization.

Universal Germline Genetic Testing for Breast Cancer: Implementation in a Rural Practice and Impact on Shared Decision Making

Table: Genetics-informed Changes to Radiation Therapy

	Overall n=185 ^a	PGV- positive n= 25	VUS n=46	Negative n= 121	PGV vs. VUS/negative, p-value
Total w/ change in RT strategy (% of all pts tested ^a)	103 (55.7)	15 (60.0)	21 (45.7)	67 (55.4)	
Dose de-escalation (accelerated fractionation) (%) ^b	81 (76.7)	2 (13.3)	18 (85.7)	61 (91.0)	>0.001
Omission of RT (%) ^b	9 (8.7)	2 (13.3)	1 (4.8)	6 (9.0)	0.664
Dose escalation (conventional/ standard fractionation) (%) ^b	13 (12.6)	11 (73.3)	2 (9.5)	0 (0.0)	>0.001

RT, radiation therapy

^aexcludes 7 pts who had testing >3 months after diagnosis

^b% of pts with change in radiation therapy (RT) strategy

Changes in Radiation Therapy Strategy based on GGT

PO1-08-05

Using the CTS5 Score to Predict Late Recurrence in Male and Female Estrogen Receptor-Positive Breast Cancer Patients: a SEER database analysis of 65,729 cases

Presenting Author(s) and Co-Author(s):

F. Wang. Hangzhou Linping Maternal and Child Health Hospital, United States

F. Ren. Hangzhou Linping Maternal and Child Health Hospital, United States

J. Qian. Hangzhou Linping Maternal and Child Health Hospital, United States

Y. Xu. Hangzhou Linping Maternal and Child Health Hospital, United States

J. Wu. Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, United States

Y. Zong. Wayne State University, United States

X. Gu. Zhejiang Provincial Hospital of Chinese Medicine, United States

Purpose: The Clinical Treatment Score post-5 years (CTS5) score is a prognostic prediction tool to predict the risk of late distant recurrence in postmenopausal women with estrogen receptor-positive (ER+) breast cancer. Here we aimed to evaluate the prediction role of CTS5 in male breast cancer patients using the Surveillance, Epidemiology, and End Results (SEER) database. **Methods:** ER+ early male and female breast cancer patients from the SEER database 2010-2013 were included. Clinicopathological features and the CTS5 score between the gender groups were compared using chi-square test. Overall survival (OS) and breast cancer-specific survival (BCSS) were estimated by Kaplan-Meier plots and compared between the groups with Log-rank test and multivariate cox proportional hazard regression models was used to determine the relationship between the CTS5 score and breast cancer survival outcomes in different gender cohorts. **Results:** A total of 65,729 ER+ breast cancer patients were included in the study and 611 were men. Male breast cancer was more likely to be diagnosed later in life (>50 years old, 87.1% vs 73.6%, $p < 0.001$), with more aggressive biological features (grade II 51.6% vs 47.2%, $p < 0.001$; grade III 37.8% vs 28.3%, $p < 0.001$), and higher tumor burden (stage II 45.8% vs 32.9%, $p < 0.001$, stage III 17.5% vs 10.5%, $p < 0.001$) when compared to female counterparts. More male patients were CTS5 intermediate- or high-risk than female patients (high 7.9% vs 6.3%, intermediate 41.1% vs 24.6%, low 51.1% vs 69.1%, $p < 0.001$). Patients were divided into 0-5 year and >5 year cohorts based on whether they had a BCSS event within 5 years. In the >5 year cohort, patients with CTS5 high- or intermediate- risk had worse survival outcomes compared with low-risk cases in male and postmenopausal female patients but not in premenopausal female patients. In the 0-5 year cohort, the CTS5 score was not predictive for disease recurrence in male or postmenopausal patients. **Conclusion:** Male breast cancer patients were more likely to have aggressive tumors and worse survival outcomes. The CTS5 score could be applied to predict breast cancer-specific mortality risk beyond 5 years in male ER+ breast cancer patients.

PO1-08-06

Clinical-molecular correlation in breast cancer with pathogenic variants in CHEK2. Is there a relationship with HER2+ breast cancer?

Presenting Author(s) and Co-Author(s):

N. Pérez-Rodríguez. University Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Canarias, Spain

C. Prieto-Morin. University Hospital Nuestra Señora de Candelaria, Spain

M. Maeso. University Hospital Nuestra Señora de Candelaria, Spain

L. Pérez-Mendez. University Hospital Nuestra Señora de Candelaria, Spain

Background: The CHEK2 gene codes for checkpoint protein Kinase 2 (CHK2), an effector in the ATM-CHEK2-p53 DNA damage repair pathway in double-stranded DNA breaks. Initially, germline pathogenic variants were associated with moderate risk for breast carcinoma, but later studies linked alterations in the gene to other types of cancer. The aim of our study was to establish a clinical-molecular correlation of profiles of patients carrying pathogenic variants and variants of uncertain significance (VUS) in CHEK2 with a diagnosis of breast carcinoma, in patients treated in our hospital. And to describe whether the pathogenic variant c.1100del present different clinical or immunohistochemical characteristics than the rest, also considering the particularity of being an island population. Methodology: We have collected data from genetic studies performed in patients from our hospital, covering a population of 580,000 inhabitants, in Santa Cruz de Tenerife (Canary Islands, Spain), between 2017 and 2023. Out of 952 patients with suspected hereditary cancer, 81 had CHEK2 mutations. In patients with CHEK2 mutations and breast cancer we established three groups for clinical molecular analysis: 1) pathogenic variant c.1100del, 2) other pathogenic variants and 3) VUS, to be correlated with age, histology, ER, PR, Ki, grade (G), HER2, second tumour or recurrence, subtype, HER2 low, aggressive clinic, neuropathy, haematological and digestive toxicity. The germline genetic study performed covered 77 genes related to hereditary cancer using the SureSelect HS library preparation kit (Agilent Technologies). The classification of the variants identified was performed according to the American College of Medical Genetics (ACMG) criteria. Results: In the 952 genetic studies performed, 8.5% of cases had CHEK2 mutations, 2.62% were related to breast carcinoma (N=26) of which 54% had the pathogenic variant "c.1100del", 16% "other" pathogenic variants and 30% VUS. The mean age at diagnosis was 42 years, being lower than 38 years in pathogenic variants other than c.1100del. Histologically, infiltrating ductal carcinoma (85%) and mucinous carcinomas (12%), ER+ (93%), PR+ (77%), HER 2+ (31%), HER2 low (44%), G2-3 (84%) and Ki >15% (70%) were predominant. Second diagnoses were tumour or recurrence in 40%, being higher in the group of pathogenic variants other than c.1100del (50%), and showing aggressive clinical course in 26%. The predominant subtype was luminal B (50%), HER2+ (31%), luminal A (12 %) and triple negative (7%), although in the cluster analysis patients with pathogenic variant c.1100del HER2+ were higher (38%) and luminal B (38%), while in pathogenic variants other than c.1100del and VUS the luminal subtype was predominant (75%). Chemotherapy toxicity: neuropathy (35%), haematological and digestive toxicity (50%). Conclusion: Our results are consistent with other reported series, being related with all breast carcinoma subtypes, mainly luminal B and HER2+ and with triple negative at a lesser extend. Considering HER2 low patients were about 75% of patients with CHEK2 mutations, a molecular mechanism that correlates a truncating mutation in CHK2 and HER2 overexpression can be hypothesized. In the cluster analysis, HER2+ (38%), and luminal B (38%) subtypes predominate in patients with pathogenic variant c.1100del, while in pathogenic variants other than c.1100del and VUS the luminal B subtype predominates

(75%), as well as recurrence or second tumours in 50% of cases. On the other hand, considering that this is an island population, the possible effect of geographical isolation and the resulting inbreeding in the past, these facts do not seem to elicit differences comparing to the rest of the continental population, although the increase in pathogenic variants in CHEK2 were observed in patients from the small island of La Gomera. The relationship between CHEK2 and HER2 in breast cancer is an area of active research.

Relative frequency in groups of CHEK2 variants

GROUP		
	Frequency	Percentage
P. c.1100del	14	53,8
P. others	4	15,4
VUS	8	30,8
Total	26	100,0

Relative frequency in CHEK2 “pathogenic variants c.1100 del (53%)”, “other”pathogenic variants no c.1100 del (15 %)” and VUS (30%).

Relative frequency of breast cancer subtypes according to CHEK2 variants.

Subtype		
	Frequency	Percentage
HER2+	8	30,8
Luminal A	3	11,5
Luminal B	13	50,0
Triple -	2	7,7
Total	26	100,0

HER2+: 30,8%. Luminal A: 11,5% . Luminal B: 50%. Triple negative: 7,7% .

Histology, ER, PR, Ki, HER2 and HER2 low

Histology			Ki67		
	Frequency	Percentage		Frequency	Percentage
Infiltrating ductal carcinoma	22	84,6	<= 15	8	30,8
Mucinous carcinoma	3	11,5	> 15	18	69,2
Ductal carcinoma in situ	1	3,8	Total	26	100,0
Total	26	100,0			

ER			HER2		
	Frequency	Percentage		Frequency	Percentage
no	2	7,7	Negative	18	69,2
yes	24	92,3	Positive	8	30,8
Total	26	100,0	Total	26	100,0

PR			HER2low		
	Frequency	Percentage		Frequency	Percentage
no	6	23,1	no	15	57,7
yes	20	76,9	yes +1	7	26,9
Total	26	100,0	yes +2	4	15,4
			Total	26	100,0

Histology , infiltrating ductal carcinoma (84%), ER+ (92%), PR (77%), Ki >15% (70%), HER2+ (31%), HER2 low (45%)

PO1-08-07

Utilization Management: The Impact of Laboratory Genetic Counseling Oversight on BRCA1 and BRCA2 Targeted Analysis Orders

Presenting Author(s) and Co-Author(s):

R. Vanderwall. Labcorp Women's Health and Genetics, Ypsilanti, Michigan, United States

D. Noeth. Labcorp Women's Health and Genetics, United States

A. Goulbourne. Labcorp Women's Health and Genetics, United States

K. Goode. Labcorp Women's Health and Genetics, United States

T. Ruegg. Labcorp Women's Health and Genetics, United States

M. Hayden. Labcorp Women's Health and Genetics, United States

W. Spence. Labcorp Women's Health and Genetics, United States

INTRODUCTION: While multigene hereditary cancer testing has become a common order for individuals with personal and/or family histories of cancer, targeted genetic testing (TGT) remains a cost-effective test option for cascade testing of individuals with a known gene mutation in the family. In order to proceed with TGT, the genetic testing laboratory must receive documentation of the specific variant. Intervention of a genetic counseling team (GCT), which includes laboratory genetic counselors and genetic counseling assistants, can play a major role in utilization management for genetic testing companies, including obtaining and reviewing mutation reports and offering clinically appropriate and cost-effective test options. Given previously reported low rates of cascade testing for family members of mutation carriers and the potential barriers of ordering TGT testing, we sought to review the success of providers ordering BRCA1 and BRCA2 TGT testing and the GCT role in management of these orders.

METHODS: Per standard operating procedure at Labcorp, the GCT reviews all hereditary cancer genetic test orders before they begin processing through prior authorization and laboratory analysis. When societal guidelines dictate, GCT intervention may occur to request genetic testing reports and offer to update testing appropriately. A retrospective review of GCT notes on TGT orders was conducted, with review of all BRCA1 and BRCA2 TGT orders accessioned between January 1 and February 28, 2023. Orders that were updated or cancelled before GCT review were excluded from analysis. All other TGT orders were coded into one of seven categories: (1) ordered for TGT, mutation report provided, proceed without GCT intervention; (2) ordered for TGT, mutation report obtained after GCT intervention, proceed with TGT; (3) ordered for TGT, no report obtained, updated to BRCA1 and BRCA2 comprehensive sequencing and deletion/duplication analysis with or without other hereditary cancer genes (COMP) with authorization from ordering provider via GCT intervention; (4) ordered for TGT, report obtained, updated to COMP via GCT intervention; (5) ordered for TGT, no report or authorization to update testing obtained during GCT intervention, testing cancelled; (6) ordered for TGT and COMP, no report, TGT cancelled; and (7) ordered for COMP, mutation report obtained, updated to TGT with authorization from ordering provider after GCT intervention. Time between accessioning and initial GCT resolution was also collected.

RESULTS: A total of 198 TGT orders and associated GCT notes were reviewed. 24 orders (12.1%) proceeded with TGT without GCT intervention (category 1) with an average turn-around-time of 1 day. GCT intervention was required for 158 (79.8%) of TGT orders with an average turn-around-time of 5 days. After GCT review and/or intervention, 60 (30.3%) orders proceeded with TGT analysis (categories 1, 2, and 7); 23 (11.6%) of these were originally

ordered for COMP, then updated when a mutation report was obtained (category 7). Testing was updated from TGT to COMP because no mutation report was obtained in 78 (39.3%) cases (category 3). In 7 (3.5%) TGT orders, testing was updated to COMP even though a mutation report was obtained (category 4).

CONCLUSION: TGT analysis is beneficial for cascade testing, but access to a mutation report as a requirement to proceed can be a barrier. More strategies are needed to provide education for ordering providers and patients on the benefit of sharing familial mutation reports for cascade testing. Efficiency of testing increases when patients and providers have access to records and provide this information to laboratories up-front. Laboratory GCTs are invaluable resources in reviewing nuanced genetic test orders, educating providers in the strengths and limitations of different genetic test options, and working to ensure patients receive clinically appropriate and cost-effective testing.

PO1-08-08

Hereditary cancer genetic testing in Puerto Rican females

Presenting Author(s) and Co-Author(s):

H. Cox. Exact Sciences Laboratories, United States

D. Hartzfeld. Exact Sciences Laboratories, United States

S. Gessy. Exact Sciences Laboratories, United States

C. Zaleski. Exact Sciences Laboratories, United States

J. Machado. Exact Sciences Laboratories, United States

Background: Puerto Rico is a Caribbean Island and unincorporated United States territory with a population of approximately 3.2 million. The incidence of breast cancer in Puerto Rico is estimated at 57.5 per 100,000 females with a mortality rate of 13.0 per 100,000 females. A recent study of hereditary breast and ovarian cancer syndrome across countries in the Caribbean reported a combined positive detection rate of 14.2% using a similar multi-gene panel to the one described here. Positive rates ranged from 5.5% to 28.3% per country, but sample sizes were limited, ranged from 61 to 298 participants per country, and did not include Puerto Rico. To provide insight into the incidence of inherited tumor predisposition syndromes in less studied populations, we analyzed the demographics and germline genetic findings for a cohort of Puerto Rican females largely ascertained based on a personal and/or family history of breast cancer. Methods: This retrospective study includes 949 consecutive female individuals who underwent genetic testing at a single clinical laboratory (PreventionGenetics LLC) using a multi-gene panel test of 29 genes associated with hereditary cancer. Clinical information was obtained from health care provider-completed test requisition forms. Next Generation Sequencing (NGS) with copy number variant (CNV) detection was performed on patient-derived DNA using the Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA) and Sanger sequencing as necessary. Results: The median age at testing was 55.5 years and ranged from 19.1 to 90.0 years of age. Of the total cohort, 713 (75.1%) individuals had a personal history of breast cancer with or without additional cancer types; 43 (4.5%) individuals had non-cancerous breast findings, and 49 (5.2%) individuals had a personal history of other types of cancer(s). The remaining 144 (15.2%) individuals did not specify a personal history, but the vast majority did indicate a family history of cancer (n=133; 93.8%). Comparably, 572 (60.3%) of the individuals with a personal history of cancer or of non-cancerous breast findings reported a family history of cancer. The median age at onset for breast cancer was 53 years (n=472; range=24-89 years). A total of 90 (9.5%) individuals had a pathogenic (P) or likely pathogenic (LP) and 3 (0.3%) of individuals harbored the APC I1307K risk variant. Of the 90 individuals with positive findings, 31.1% had a P/LP variant in BRCA2, 28.0% in MUTYH, 11.8% in CHEK2, 7.5% in BRCA1, in 6.5% BRIP1, and 11.8% in ATM, CDKN2A, MSH6, NBN, PALB2, RAD51C, RAD51D, and RET. The most frequently reported pathogenic variants were MUTYH p.Gly396Asp (n=20), BRCA2 p.Glu1308* (n=16), and BRCA2 p.Asn1933Lysfs*29 (n=6). A recurrent pathogenic deletion of the upstream and exon 2 region of BRCA1 was also identified in three individuals. The indeterminate and negative rates were 36.5% (n=346) and 53.7% (n=510), respectively. Conclusion: Although the present study was limited to biological females and included individuals with broader personal and family cancer histories, the positive rate is within range of those reported for other countries in the Caribbean. Interestingly, P/LP variants have been reported to be enriched in BRCA1, BRCA2, and PALB2 across other Caribbean countries; however, this was not mirrored in the pattern of positive findings for this cohort of Puerto Rican females and may suggest a distinct background for hereditary cancer predisposition in this population. Further studies are needed to understand the landscape of

germline variants in this population to ensure proper surveillance and risk mitigation is applied.

PO1-08-09

Drynaria fortunei, a nutritional herb for prevention in triple negative breast cancer

Presenting Author(s) and Co-Author(s):

N. TELANG. Palindrome Liaisons Consultants, Montvale, New Jersey, United States

H. Nair. Dept. of OB-GYN, San Antonio, Texas, United States

G. Wong. American Foundation for Chinese medicine, New York, New York, United States

Study Rationale: The triple negative breast cancer (TNBC) lacks the expression of hormone and growth factor receptors and responds only to anthracycline/taxol-based conventional chemotherapy. Major therapeutic limitations include systemic toxicity and acquired resistance to chemo-therapeutics. Relatively non-toxic nutritional herbs from traditional Chinese medicine (TCM) may represent testable alternatives against TNBC. These herbs effectively target multiple signaling pathways (Yang et al: J. Ethno-pharmacology 264: 113249, 2021). Growth inhibitory efficacy of nutritional herbs in a cellular model for TNBC is associated with downregulation of RB, RAS, PI3K and AKT signaling pathways (Telang et al: Pharmaceuticals 14: 1318, 2021). *Drynaria fortunei* (DF) is a nutritional herb that is used in many TCM herbal formulations. The present study is designed to examine the effects of DF in a cellular model for TNBC and to identify mechanistic leads for its efficacy. Experimental Model, herbal extract and biomarkers: Estrogen receptor negative, progesterone receptor negative and human epidermal growth factor receptor-2 negative MDA-MB-231 human breast cancer cell line represented a cellular model for TNBC. Non-fractionated aqueous extract from the bark of DF represented the test agent. Cell cycle progression, RB signaling and caspase 3/7 activity represented quantitative end point biomarkers. Study Outcome: Treatment with DF at cytostatic concentrations induced S phase arrest and inhibited RB signaling via downregulated expression of cyclin E, CDK2, pRB and E2F1. DF treatment also induced caspase 3/7 activity, a marker for cellular apoptosis. Collectively, these data provide potential mechanistic leads for anti-proliferative and pro-apoptotic effects of DF in the present model. Conclusion: Present data validate a mechanism-driven experimental approach to prioritize efficacious nutritional herbs as testable alternatives for prevention/therapy of TNBC.

PO1-08-10

Impact of Oncologist-Led Genetic Counseling and Testing on Prophylactic Mastectomy Rates Among Multi-Ethnic Women with Operable Breast Cancer

Presenting Author(s) and Co-Author(s):

A. Michel. New York Presbyterian Columbia University Irving Medical Center, United States

K. Luo. Columbia University, Department of Epidemiology, Mailman School of Public Health, United States

V. Ro. Columbia University, Department of Medicine, Vagelos College of Physicians and Surgeons, United States

M. Fine. New York Presbyterian Columbia University Irving Medical Center, United States

M. Trivedi. Columbia University Irving Medical Center, United States

W. Chung. Columbia University, United States

R. Rao. Columbia University Vagelos College of Physicians and Surgeons, New York City, New York, United States

T. Jones. Christine E Lynn College of Nursing, Florida Atlantic University, Boca Raton, FL, United States

E. Levinson. Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, United States

C. Koval-Burt. Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, United States

D. Russo. Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, United States

I. Chilton. Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, United States

R. Kukafka. Columbia University, United States

K. Crew. Columbia University Irving Medical Center, United States

Introduction: Approximately 5-10% of breast cancers are attributed to an inherited pathogenic variant (PV) in breast cancer predisposition genes, such as BRCA1 and BRCA2. Identifying women with hereditary breast cancer syndromes is critical to inform risk-appropriate screening and prevention strategies. For example, contralateral prophylactic mastectomy (CPM) has been shown to reduce the risk of new breast primaries without a demonstrated survival benefit. In a prior study, we found that women with pathogenic/likely pathogenic (P/LP) variants were over four times more likely to undergo CPM compared to those with benign/likely benign (B/LB) variants. In recent years due to expanded indications for genetic testing and social distancing during the COVID-19 pandemic, oncologist-led genetic testing and telehealth genetic counseling has gradually replaced in-person genetic counseling visits. We aimed to understand how changes in the delivery of genetic counseling and testing services impacted CPM rates among multi-ethnic women with operable breast cancer in the post COVID-19 period. Methods: We conducted a retrospective cohort study among 1,080 women diagnosed with unilateral breast cancer who underwent germline genetic testing between 2013 and 2022 at Columbia University Irving Medical Center (CUIMC) in New York, NY. The pre COVID-19 period was defined as 2013-2019 and the post COVID-19 period as 2020-2022. Demographics, including age, race/ethnicity and marital status, and clinical characteristics, such as year of diagnosis, breast cancer stage, tumor hormone receptor status, family history of breast cancer, and

genetic test results, were extracted from the electronic health record (EHR). We used univariable and multivariable logistic regression analyses to estimate the odds ratio (OR) and 95% confidence interval (95% CI) associated with each variable and receipt of CPM. Results: Among 1080 evaluable women, mean age at diagnosis was 51.2 years old (SD, 12.3) with 39.6% non-Hispanic White, 27.8% Hispanic, 11.4% non-Hispanic Black, 9.0% Asian, and 12.2% multi-racial/other. Within the overall study population, 12.1% of women had P/LP variants and 21.4% had variants of unknown significance (VUS) results. Non-Hispanic Whites and Blacks had the highest frequency of P/LP variants, whereas VUS results were more common among Hispanics and Asians (see Table). Twenty-three percent of women in the study population underwent CPM. In multivariable analysis, younger age at diagnosis, more advanced stage breast cancer, family history of breast cancer, Hispanic race and P/LP results on germline genetic testing were associated with increased CPM rates. Hispanic women were over 60% more likely to undergo CPM compared to non-Hispanic White women (adjusted OR=1.63, 95% CI=1.07-2.47). No significant change in CPM rates was observed in the post-COVID era compared to the pre-COVID era. Conclusion: We aimed to understand how the transition to telehealth and oncologist-led genetic testing affected CPM rates. Although we did not observe a change in CPM rates in the post-COVID era, Hispanic women had significantly more VUS results and were over 60% more likely to undergo CPM compared to non-Hispanic White women. In future studies, we hope to improve risk communication of genetic test results and the risks and benefits of CPM, particularly in vulnerable and underserved populations.

Table 1

RACE/ETHNICITY	P/LP N (%)	VUS N (%)	# OF PTS RECEIVING CPM N (%)	OR OF CPM (95% CI)	P- VALUE
NON-HISPANIC WHITE N=428	64 (15.0)	54 (12.6)	102 (23.8)	Reference	
NON-HISPANIC BLACK N=123	15 (12.2)	26 (21.1)	35 (28.4)	1.13 (0.65, 1.95)	0.661
HISPANIC N=300	32 (10.7)	84 (28.0)	78 (26)	1.63 (1.07, 2.47)	0.022
ASIAN N=97	6 (6.2)	29 (29.9)	21 (21.6)	0.92 (0.49, 1.69)	0.778
OTHER OR UNKNOWN N=132	14 (10.6)	38 (28.8)	17 (12.8)	1.19 (0.49, 2.91)	0.703

Genetic testing results and rates of contralateral prophylactic mastectomy stratified by race/ethnicity in women diagnosed with operable breast cancer and undergoing germline genetic testing from 2013-2022 at Columbia University Irving Medical Center, New York, NY

PO1-08-11

The survival rate of hereditary breast cancer in young women of Kazakh population

Presenting Author(s) and Co-Author(s):

D. Kaidarova. Kazakh Institute of Oncology and Radiology, United States

N. Omarbayeva. Kazakh Institute of Oncology and Radiology, United States

A. Abdrakhmanova. Kazakh Institute of Oncology and Radiology, United States

O. Shatkovskaya. Kazakh Institute of Oncology and Radiology, United States

D. Omarov. Kazakh National Medical University, United States

Background

The study focused on determining survival rates between breast cancer patients with various germinal mutations and those without mutations among Kazakh women. Methods

The study included 222 female patients of Kazakh ethnic group diagnosed with stage I-IV stage breast cancer at the age up to 40 years old. DNA samples were tested by next-generation sequencing on the MiSeq Illumina platform using Trusight Cancer kit for the analysis of 94 genes and 287SNPs. Information about dates of diagnosis and death retried from cancer registry system. Survival analyses were performed and compared mutation carriers and non-carriers subgroups. The 5-year survival was calculated using the Kaplan-Meier method. Results

Next generation sequencing test identified 11 various pathogenic mutations in 57(25.7%) of overall 222 patients. The 5-year survival analysis for mutation carriers were 72.1%and 82.1% for non-carriers, with no statistically significant difference(P0.232). When stratified by mutational type, the 5-year survival rates were 71.8% for BRCA1 carriers, 81.3% for BRCA2, 53.35% for TP53 and 50% for moderate risk gene PALB2 mutation. These findings suggest that mutations in certain genes may be associated with differences in survival outcomes. Conclusions

In breast cancer patients of Kazakh population similar to the world prevalence and predictive value of germline mutations have been found. A subcohort of mutation carriers and non-carriers demonstrated no significant difference in 5-year survival rate which may be associated with an early onset of disease, high-risk predictor of poor prognosis. Long-term survival and detailed PFS will be published according to information of follow-up visits and the cancer register system.

PO1-08-12

Genomic Characterization of the Carolina Breast Cancer Study

Presenting Author(s) and Co-Author(s):

S. Van Alsten. UNC-Chapel Hill, United States

E. Butler. UNC-Chapel Hill, United States

B. Calhoun. UNC Chapel Hill, United States

M. Love. UNC Chapel Hill, United States

C. Perou. University of North Carolina, Chapel Hill, North Carolina, United States

K. Hoadley. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, United States

M. Troester. UNC-Chapel Hill, United States

Background: Breast cancer is a heterogeneous disease defined by distinct subtypes, mutational profiles, and genomic characteristics. Previous analyses in The Cancer Genome Atlas (TCGA) have been instrumental in understanding the genomic landscape of breast cancer, including identification of key driver mutations, mutational signatures, and distinguishing features of breast cancer subtypes. However, TCGA may not be representative of other population-based breast cancer cohorts, particularly those of earlier stage and including a more diverse set of patients. Our aim was to characterize the genomic landscape of breast cancer in the Carolina Breast Cancer Study (CBCS), a cohort which oversamples Black and young women. Methods: We used targeted sequencing to profile somatic alterations in 1,175 genes from 275 formalin fixed paraffin embedded primary breast tumors in CBCS, 52% of which came from Black women, 41% from women under age 50, and 29% of which were Basal-like based on bulk RNA profiling. We also evaluated TP53 mutation as a source of breast cancer heterogeneity, comparing the type and location of TP53 mutations in each cohort. We assessed chromosome arm-level gains and losses using GISTIC and defined genomic instability as the total number of aneuploid chromosome arms. Intratumoral heterogeneity was assessed with PyClone-VI and defined as the total number and Shannon's Diversity Index of tumor-specific subclones. For genes mutated in more than 5% of samples and chromosomal aberrations significantly enriched in GISTIC, we estimated the prevalence of alterations and compared to previous distributions in 981 TCGA tumors. Results: Seven genes [TP53 (N=101, 37%), PIK3CA (N=76, 28%), GATA3 (N=32, 12%), CDH1 (N=31, 11%), MAP3K1 (N=22, 8%), KMT2C (N=20, 7%), and CBF3 (N=19, 7%)] were mutated in more than 5% of CBCS tumors; all but CBF3 which were also highly prevalent in TCGA. While most TP53 hotspot mutations observed in CBCS were previously reported in TCGA, CBCS had twice as many Y220C mutations, one-third fewer R175H mutations, and a non-significantly higher proportion of nonsense mutations than TCGA (20% vs 12%, $p = 0.05$). Hotspot mutation prevalence in other Luminal-associated driver genes (e.g. PIK3CA, GATA3, CDH1) did not differ by dataset. CBCS tumors showed a higher degree of genomic instability (8 arms vs. 5 arms, $p < 0.001$) and subclonal diversity than TCGA (48% vs 12% comprised of two or more subclones, $p < 0.05$). Both datasets showed significant amplifications of 1q and 8q, and deletions of 13q and 17p (where BRCA2 and TP53, respectively, are located), with CBCS having non-significantly higher prevalence of each of these changes. Conclusions: While comparisons should be interpreted in light of technical and population differences between TCGA and CBCS, the overall results show that the suite of commonly altered genes and chromosome arms were highly consistent between TCGA and the diverse CBCS cohort. CBCS tumors tended to display higher genomic instability, intratumoral heterogeneity, and number and diversity of TP53 mutations. This may reflect distinctions in

tumor evolutionary state between CBCS and TCGA tumors, and/or could reflect differences in the study populations. Results underscore the importance of considering population characteristics – particularly stage and race – in large-scale genomic contexts, and highlight the importance of diverse cohorts in genomic research.

PO1-09-01

Patient Advocates, Oncologists & Research Scientists Collaborate to Address PostPartum Breast Cancer

Presenting Author(s) and Co-Author(s):

E. Landsberger. SHARE Cancer Support, NYC, New York, United States

P. Schedin. Oregon Health & Science University, United States

L. Weatherby. MBC Alliance, United States

V. Borges. University of Colorado Anschutz Medical Center, United States

The incidence of young women (YW= < 45) with aggressive breast cancer (BC) has been increasing and BC in younger women tends to be diagnosed in more advanced stages¹. A group of advocates, oncologists and scientists have established an advocate-researcher dialogue to address this. A key finding we are highlighting and sharing with the community is that postpartum BC (PPBC) is a "free biomarker" for increased risk of metastatic disease. We report our efforts to understand the biologic underpinnings of PPBC, strategize to disseminate information, and accomplish our longterm goals to reduce BC incidence and mortality in YW.

Interactions Between Childbirth & BC The interactions between the reproductive life phases and BC are complex. We are taught that having children and nursing them is protective against BC. What is complicated is the fact that after childbirth, women overall are at a 10-30% increased risk for getting early onset BC. For women < 30 at the time of their last baby, this increased risk converts to a protective effect about 10 years after childbirth, such that in later life they have a lower risk of getting BC in comparison to women who have not given birth. However for women who have children after 30, the risk remains increased for many decades. The peak window of time for YW to get BC is within 10 years after childbirth and diagnoses during this window are PPBC. The global trend of women delaying childbirth until they are older is one factor contributing to increased PPBC². While lactation can be protective, this protection is seen most robustly against triple negative BC (TNBC). This protective effect is seen most strongly in women who nurse for about 6 months. In some who do not nurse, especially black women, risk for TNBC can be increased³. When women get diagnosed with PPBC several things are known⁴:

- The frequency of the different subtypes of BC (ER+,PR+,Her2+) is similar to BC diagnosed in YW overall, so most PPBC is ER+ Her2-
- While there is no difference in the % of women who will have Her2+ or TNBC among PPBC cases, more women with PPBC will have + lymph nodes at diagnosis
- Of women who get diagnosed with BC < 45 , about half will occur in this PP window accounting for about 50% of all early onset BC

Studies have shown that PPBC has a higher tendency towards developing metastatic disease in comparison to BC in women without children or in women diagnosed more than 10 years since last childbirth⁴. Research is ongoing to identify why this increased risk is occurring and how treatment can be tailored to eliminate this risk. Adherence to therapy and participation in clinical trials is crucial. Clinical trials should capture when a woman had her last child as a routine datapoint so PPBC can be researched more broadly. This datapoint - age of her youngest child when she was diagnosed - is essentially a "free biomarker" indicating risk for metastasis. Advocate-Researcher Outreach Efforts

- Production of a podcast episode "Rising Rates of BC & MBC in YW" on www.OurMBCLife.org produced by SHARE Cancer Support
- Discussion with other advocates and organizations to raise awareness
- Approach donors to increase funding for research in PPBC

Summary

- BC in YW is increasing and YW with recent childbirth are at increased risk. Raising health awareness in a proactive, non-alarming manner is an important advocacy goal
- YW diagnosed within 10 years of a recent childbirth represent a unique subset of BC called PPBC
- Age of youngest child at time of diagnosis is an important free biomarker for risk and should be added to medical histories
- Increase funding is essential to determine why PPBC has different outcomes and how treatments can be tailored to ensure the wellness of our young mothers

References:

- 1 Thomas A JNCI 2019
- 2 Nichols HB AIM 2019
- 3 Jung AY JNCI 2022
- 4 Goddard ET JAMA 2019

PO1-09-02

Universal genetic testing for women with newly diagnosed breast cancer identified many mutations, impacted clinical management and caused no psychological distress to patients

Presenting Author(s) and Co-Author(s):

D. De Silva. Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia, United States

L. Stafford. Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia, United States

A. Skandarajah. The Royal Melbourne Hospital, United States

M. Sinclair. Royal Women's Hospital, Melbourne, VIC, Australia

L. Devereux. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, United States

K. Hogg. Murdoch Children's research Institute, United States

M. Kentwell. RMH Familial Cancer Centre, United States

A. Park. Royal Melbourne Hospital, Melbourne, VIC, Australia

I. Lal. Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia, United States

M. Zethoven. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, United States

M. Jayawardena. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, United States

F. Chan. Royal Children's Hospital Melbourne, Melbourne, VIC, United States

P. James. Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia, United States

G. Lindeman. Walter & Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia

I. Campbell. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, United States

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

Background: For newly diagnosed breast cancer (BC) patients, identification of pathogenic germline mutations in hereditary breast cancer (HBC) genes can inform clinical management and risk mitigation strategies and identify patients who would benefit from targeted therapy and clinical trials. Offering germline testing based on NCCN or other guidelines fails to identify all patients with germline HBC gene mutations, potentially with adverse consequences for patients and their families. As an integral part of the study, we have explored the acceptance of universal testing among patients and clinicians. **Methods:** This is the largest Australian multi-centre prospective study exploring the prevalence of hereditary pathogenic variants in the Australian BC population. 650 newly diagnosed consecutive, consented patients with non-metastatic breast cancer or high-grade DCIS were recruited from May 2020 to March 2023 in 2 phases. Phase 1 (n=157) offered a combination of germline and somatic sequencing. Germline testing was performed by whole genome sequencing on DNA from blood or saliva, and the data analyzed for actionable HBC gene mutations, including large genomic rearrangements. Germline variants were interrogated for pathogenic variants in BRCA1, BRCA2, PALB2, ATM, CHEK2, BARD1, BRIP1, RAD51B, RAD51C, RAD51D, MLH1, MSH2, MSH6, PMS2, CDH1, PTEN, STK11, TP53 and NTHL1. Tumour sequencing will be reported separately. Phase 2 (n=493) included germline exome sequencing with no somatic sequencing. The objectives were to assess the additional actionable HBC gene mutations identified by universal testing

PO1-09-03

Clinical Impact of Multigene Panel Testing in Patients with a Personal or Family History of Breast or Ovarian Cancer Previously Negative for BRCA1/2 Genes

Presenting Author(s) and Co-Author(s):

D. Miller. University of Wisconsin Hospitals and Clinics, United States

S. Pritzl. Mayo Clinic, United States

A. Tess. University of Wisconsin Carbone Cancer Center, United States

J. Gooding. University of Wisconsin Carbone Cancer Center, United States

L. Barroilhet. University of Wisconsin Hospitals and Clinics, United States

L. Dubenske. University of Wisconsin Hospitals and Clinics, United States

K. Wisinski. University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, United States

Rapid developments in cancer genetics and hereditary cancer risk assessments have enabled the identification of individuals at elevated risk for hereditary malignancies to guide enhanced cancer screening and prevention efforts. Multigene panel testing has emerged as the standard approach as emphasized in the National Comprehensive Cancer Network (NCCN) guidelines. The purpose of this study was to investigate the frequency of other pathogenic mutations identified through multigene panel testing in individuals who previously tested negative for germline BRCA1/2 and assess the clinical impact of panel testing. Patients either previously diagnosed with breast cancer or with a family history of breast or ovarian cancer that had also been seen by Oncology Genetics at a single institution and tested negative for BRCA1/2 genes but had not undergone prior multigene panel testing were invited via a letter to return for an additional genetic counseling visit to discuss multigene panel testing. Patients were also able to opt-in to a survey component of the study and received an email to fill out the Multidimensional Impact of Cancer Risk Assessment (MICRA) and Cancer Worry Scale (CWS). Surveys were completed prior to the initial genetic counseling appointment and repeated after discussion of the multigene panel test results. A total 24 women met with a genetic counselor of which 22 (92%) had a personal history of breast cancer, 1 (4%) had a family history of breast cancer, and 1 (4%) had a family history of ovarian cancer. The mean age was 52.6 years (range, 42-68) and 100% of women were Caucasian. Of the 24 women, 17 (71%) completed multigene panel testing. Of the women that underwent testing, 7 (41%) had negative results, 6 (35%) had variants of unknown significance (VUS), and 4 (24%) had a pathogenic mutation identified in another gene (CDKN2A, CHEK2, and CFTR). There was no significant change in MICRA or CWS scores after multigene panel results were reviewed in the 9 patients that completed both pre- and post-genetic testing surveys. The mean/median summary MICRA scores pre- and post-counseling were 30 (SD 12.4), median 26 (min 18, max 56), and 21.2 (SD 15.4), median 21 (min 3, max 43), respectively ($p=0.19$, Wilcoxon signed ranks test). The mean/median summary CWS scores pre- and post-counseling were 14.3 (SD 5), median 15 (min 7, max 24), and 13.6 (SD 2.59), median 14 (min 10, max 17), respectively ($p=0.53$, Wilcoxon signed ranks test). Of the 4 patients with newly identified pathogenic mutations, 2 started new screening protocols and 1 underwent a prophylactic mastectomy. In conclusion, multigene panel testing identified pathogenic mutations in a subset of individuals who previously tested negative for BRCA1/2 genes leading to changes in clinical management. The completion of multigene panel testing did not lead to a significant increase in MICRA or CWS scores. Key limitations of this study include a small sample size and an all Caucasian population.

PO1-09-05

Reversing Rural Disparity Through Increased Access to Breast Care Using Model of Academic-Community Collaboration

Presenting Author(s) and Co-Author(s):

C. Shelton. The Outer Banks Hospital, Nags Head, North Carolina, United States

A. Ruiz. Chesapeake Regional Medical Center, Chesapeake, Virginia, United States

Background: Rural disparity in Breast Cancer (BC) often relates to poor geographic access. We are small county in rural North Carolina with historically poor outcomes, including more advanced stages of BC at presentation, higher mastectomy rates, and higher BC-specific mortality rates than elsewhere. Beginning in 2002 we increased access to care by construction of a 19-bed Critical Access Hospital. With a higher median age population (10 years older), and cancer as the number one cause of death (30% of all deaths), we began to increase access to services with focus on cancer. Two decades later, we still do not provide all aspects of care locally, but through a model of collaboration we have increased access to all aspects of cancer care. Breast Cancer is the most common, and this report details the reversal in disparity seen rurally based on our model of collaboration with both a regional community cancer program and academic cancer program. Methods: We partnered with academic and community cancer centers in nearby counties to increase access to imaging, cancer specialists, radiation therapy and chemotherapy services, and support services for breast care. When we could not provide these services locally, we helped navigate patients to these other facilities to improve access. We invited dedicated breast surgeon from community cancer program to attend clinic weekly in our area. We created virtual breast-specific tumor boards to discuss 100% of cases prospectively, with improved access to pathologists, geneticists, fellowship-trained imaging specialists, breast surgeons and other multi-disciplinary care members (reconstructive surgery, PT/OT, integrative medicine, GYN). We became cancer accredited with both COC and NAPBC. We compare metrics pre/post-improvements. Results: Baseline:

1. Mortality rates: (2002-2006) 5-year BC mortality rates in our region averaged 32.3/100,000 population which was in the top quartile for the state, 30% higher than the state average.
2. Stages at presentation: 47% of BC stages were early (stages 0/1) in our service region compared to 62% elsewhere (NCDB data). Stage IV represented 6% in our region versus 4% elsewhere. 2500 mammograms/year at hospital at baseline.
3. Surgery/Radiation Therapy: Mastectomy rates averaged >50% in region, with correspondingly lower breast conserving rates than elsewhere due to lack of access to breast surgeons and radiation therapy services locally. Closest RT facility 80 miles.
4. Distances to high quality breast care averaged 150 miles. Closest Academic/Community Cancer Program 2-hour drive (one way). Post Collaboration: 1. Mortality rates: (2015-2019), 5-year BC mortality rates in our region averaged 16.3/100,000 population which is in the lowest quartile, 20% lower than the state average.
2. Stages at presentation: 74% of BC stages are early (stages 0/1) in our region versus 68% elsewhere. Stage IV now below parity with 3% locally versus 4% nationally. More than 5100 mammograms/year done currently at local hospital.
3. Surgery/Radiation Therapy: Mastectomy rates average 21%, with partial mastectomy rates of 79% in our area versus 70% elsewhere (NAPBC data) with RT services available locally.
4. Distances to quality breast care average 20 miles, and we are nationally accredited program in breast care as a critical access hospital. Analytic case load is now triple baseline numbers.

Conclusion:

We reversed the trend in rural disparity in breast cancer outcomes through model of

collaboration. We increased screening rates locally, doubling the number of screening/diagnostic exams, increased the percentage of early stage at diagnosis, halved our mastectomy rates, and reduced BC-specific mortality 50% relative to baseline (and now 20% lower than state). We are now at parity with most BC-specific quality metrics reflecting a huge shift in rural disparity, which could only be achieved rurally through collaboration.

Reversing Rural Disparity Through Increased Access to Breast Care Using Model of Academic-Community Collaboration

	BC Mortality Rate (per 100K)	Early Stage BC	Stage IV BC	Number of Mammograms/Yr.	Mastectomy Rate	Lumpectomy Rate
Baseline (2002-2006)	32.3	47%	6%	2500	52%	48%
Post Collaboration (2015-2019)	16.3	74%	3%	5100	21%	79%
Relative Change (RR)	0.5	1.57	0.50	2	0.4	1.65

BC= Breast Cancer RR = Relative Ratio

This table depicts the changes in our region over time, which have brought us to parity with Breast Care nationally.

PO1-09-06

Patient Barriers to Genetic Counseling

Presenting Author(s) and Co-Author(s):

K. Dirrigl. Dignity Health Cancer Institute, Phoenix, Arizona, United States

L. Hebert. Dignity Health Cancer Institute, Phoenix, Arizona, United States

L. WintonLi. Dignity Health Cancer Institute, Phoenix, Arizona, United States

M. Taylor. Dignity Health Cancer Institute, Phoenix, Arizona, United States

A. G. Wendt. Cancer Center at Saint Joseph's, Phoenix AZ; CORA CommonSpirit Health Research Institute, United States

Patient Barriers to Genetic Counseling Background: Access to genetic counseling is becoming more important as new targeted drugs are developed and as recommendations for testing for hereditary cancer syndromes expands. Yet, significant barriers hinder patients' access to these services leading to a certain percentage of patients declining a genetic counseling referral (Ochoa, O'Neill). Among one of the more often cited reasons for declining genetic counseling is the cost of the consultation when it is not covered by insurance or a patient is uninsured. This potentially limits patient treatment options and can result in a missed opportunity to identify at-risk relatives. There is scant data documenting why women do not accept genetic counseling referrals and our study sought to better identify these potential barriers. In doing so we hope to enable healthcare providers and policymakers to develop strategies to ensure equitable access to these crucial services. **Methods:** Breast cancer patients for whom a genetic counseling referral was placed and who self-declared the inability to pay our Cancer Center's genetic counseling fee (\$126) were approached about filling out an anonymous survey regarding their reasons for declining. The survey queried, in addition to cost, other patient-related barriers to genetic testing. The survey also captured the number of first-degree relatives who might be affected by an actionable pathogenic variant. After patients were consented and completed the survey, genetic testing, paid for by the study, was offered. **Results:** To date, 13 patients were approached about the study and 10 patients (77%) agreed to participate, were consented and filled out surveys. Women could choose more than one reason for declining a genetic counseling referral but the most prevalent reasons cited were cost (10), worried there is nothing to be done about inherited cancers (3), concern about genetic material being taken and/or results being used against them (2), too many appointments (2). Of these 10, all (100%) elected to proceed with genetic counseling and all 10 (100%) elected to proceed with genetic testing. Two of the 10 patients (20%) tested were found to have actionable pathogenic variants (one in BRCA2 and one in CHEK2) potentially impacting 13 adult first-degree relatives. **Conclusion:** These preliminary findings underscore the importance of access to genetic counseling in order to facilitate appropriate genetic testing. The identification of actionable genetic mutations allows for early detection, timely interventions, and tailored management plans, ultimately leading to improved patient outcomes. By identifying cost as the most often cited reason for declining genetic counseling, healthcare providers and policymakers can develop strategies such as the implementation of financial assistance programs and universal insurance coverage for genetic counseling services in order to alleviate the financial burden and ensure equitable access to these crucial services. **References** 1. O'Neill SM, Peters JA, Vogel VG, Feingold E, Rubinstein WS. Referral to cancer genetic counseling: Are there stages of readiness? *Am J Med Genet C Semin Med Genet.* 2006;142C(4):221-231. doi: 10.1002/ajmg.c.30109.

2. Ochoa D, Jean-Louis C, Stephenson K, Woods M, Kelsey J, Henry-Tillman R. What happens

after referral? completion rates of genetic counseling evaluations in breast cancer patients. *J Natl Med Assoc.* 2022;114(1):90-93. doi: 10.1016/j.jnma.2021.12.006.

PO1-09-07

Outpatient mastectomy is a safe surgical option for patients treated in a rural Appalachian tertiary facility

Presenting Author(s) and Co-Author(s):

G. Stimac. West Virginia University Department of Surgery, Morgantown, WV, USA, United States

K. Lupinacci. Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, United States

M. Cowher. Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, United States

H. Hazard-Jenkins. West Virginia University Department of Surgery, Morgantown, WV, USA, United States

Background The feasibility of the outpatient mastectomy in a rural setting is poorly characterized. Centers treating rural patient populations have unique challenges. Limited access to resources and distance to facilities that can care for post-surgical patients are two such challenges. The aim of this study is to analyze the efficacy and safety of an outpatient mastectomy program in our tertiary care facility treating rural Appalachian patients. **Methods** We performed a single-institution retrospective review of all patients with breast cancer over 18 years of age who underwent a mastectomy with or without immediate alloplastic breast reconstruction at JW Ruby Memorial Hospital from 2019-2022. Our primary objective was to determine the 30, 60, and 90-day readmission rates. Our secondary objective included an analysis of perioperative pain control variables to develop an enhanced recovery protocol. Data collected included age, ethnicity, prognostic factors, stage at diagnosis, surgical treatment, opioid and non-opioid based treatments pre- and postoperatively by milligram morphine equivalents (MMEs), comorbidities as analyzed by the Charlson comorbidity index (CCI) variables, and distance from the tertiary hospital. **Results** We identified thirty-two women between 2019-2022 who underwent same-day mastectomy at JW Ruby Memorial Hospital in Morgantown, West Virginia. The mean age was 55.4 years. The mean distance to the hospital was 22.1 miles with a maximum distance of 111 miles (SEM = 3.90). The mean CCI score was 2.9 (SEM = 0.51). Overall readmission rates at 30- 60- and 90-days were 6.3% (n = 2), 3.1% (n = 1) and 0%, respectively. One woman was readmitted eight days postoperatively from a unilateral mastectomy and sentinel lymph node biopsy without reconstruction for an expanding hematoma of the chest after resuming anticoagulation on postoperative day three. The other two patients were admitted for unrelated surgical reasons. Thus, readmission related to surgical complications alone was 3.1% (n = 1). Preoperatively, 90.6% (n = 29) of women received a local anesthetic block by the anesthesia provider. Neither a preoperative nor intraoperative block was given to the remaining three. Bilateral mastectomies occurred in 21.9% (n = 7) of women and 78.1% (n = 25) underwent unilateral mastectomy. Of these 32 women, 25.0% (n = 8) underwent immediate staged reconstruction with tissue expanders. There were no direct-to-implant reconstructions in this population. There were twenty-six sentinel lymph node biopsies and four axillary dissections performed. The mean MMEs received for the duration of the hospital encounter was 132 (SEM = 23.4). An enhanced recovery after surgery protocol was not used. **Discussion** Outpatient mastectomy is a safe and effective option for eligible patients living in rural settings. Factors such as the type of mastectomy, reconstruction, the patient's overall health status, and the availability of support at home can impact the feasibility of this approach. Careful patient selection and a multidisciplinary team including the patient, surgeon, and anesthesiologist should carefully assess the individual's circumstances to determine if

outpatient mastectomy is appropriate. Implementation of enhanced recovery after surgery protocols will be further investigated and guided by this study.

PO1-09-08

Mammography adherence modifies the relationship between multilevel social deprivation and tumor characteristics in the Carolina Breast Cancer Study

Presenting Author(s) and Co-Author(s):

M. Dunn. University of North Carolina - Chapel Hill, United States

M. Emerson. University of North Carolina - Chapel Hill, United States

L. Henderson. University of North Carolina - Chapel Hill, United States

K. Reeder-Hayes. UNC Lineberger Comprehensive Cancer Center, United States

T. Hyslop. Sidney Kimmel Cancer Center – Jefferson Health, United States

M. Troester. UNC-Chapel Hill, United States

Objective: To describe associations of individual and community socioeconomic status (SES) with breast cancer tumor and treatment characteristics, and to assess potential modification by mammography receipt. **Methods:** The Carolina Breast Cancer Study is a population-based cohort of women diagnosed with breast cancer between 2008 and 2013. We restricted this analysis to participants with stage 1-3 cancer (n=2,841). Socio-demographic information was obtained during in-home study interviews, and tumor characteristics were obtained from medical records and pathology reports. Community characteristics were obtained from American Community Survey census-tract level data. SES subgroups were identified using latent class analysis, a method for identifying group membership based on multiple shared characteristics. This was done separately using individual data (e.g. household income) and census-tract level data (e.g. poverty rate). We reported prevalence differences (PDs) and 95% CIs for each outcome. Finally, analyses were repeated with stratification by race (Black/non-Black) and receipt of at least one mammogram every 2 years (yes/no), based on self-reported mammography history. **Results:** Based on the latent class models, participants were sorted into 4 groups based on their individual/community SES: “high/high”, “high/low”, “low/high”, and “low/low”. Black women made up 81% of the low/low group compared to 26% of the high/high. All high individual-SES participants were combined as one referent group because they had similar clinical characteristics regardless of community status. We found that participants with low/low SES had more aggressive tumor characteristics at diagnosis compared to the referent group, such as stage 3 cancer (PD = 5.7%, 2.4-9.0), grade 3 tumor (PD = 9.9%, 5.3-14.4), and triple negative breast cancer (PD = 5.8%, 2.4-9.1). Low/low participants were also more likely to have an interval of at least 30 days between diagnosis and treatment (PD = 4.6%, 0.2-9.0). However, none of these associations were significant for low/high women. When reported separately by race, Black women with low/low SES had greater frequency of stage 3 cancer (PD = 6.3, 1.9-10.8) and prolonged treatment length (PD = 7.5%, 1.1-13.8) compared to high-SES Black women. Race-stratified SES differences were non-significant for genomic subtype and other tumor characteristics like grade and tumor size.

After stratifying by screening status, we found that associations of SES with stage and tumor size were only present among those with < 1 mammogram every 2 years. The low/low PDs were (7.9%, 1.5-14.3) for stage 3 and (7.8%, 2.2-13.3) for tumor size >5 cm. Low/low women also had greater frequency of lump detected cancer (PD = 12.6%, 4.0-21.2). In contrast, these associations were not present among women with biannual mammography. Finally, screening status did not modify PDs for genomic subtype (ER⁺/HER2⁻, ER⁻/HER2⁺, TNBC). **Conclusions:** Lower community-level SES is associated with less favorable tumor characteristics at diagnosis, mainly among those with low individual SES. Access to mammography may explain

part of the disparity in stage and tumor size, suggesting public health benefit for targeted screening initiatives in disadvantaged communities. Still, screening and SES are only 2 mechanisms that contribute to racial disparities; our future work will explore additional intervention points.

Demographic and clinical characteristics of CBCS participants by individual and community socioeconomic status (n=2,841)

	High Individual, High Community	High Individual, Low Community	Low Individual, High Community	Low Individual, Low Community	P value
Overall	1,148	357	659	677	
Race					<0.001
White	802 (70%)	144 (40%)	307 (47%)	115 (17%)	
Black	304 (26%)	207 (58%)	332 (50%)	550 (81%)	
Other	42 (4%)	6 (2%)	20 (3.0%)	12 (2%)	
Education					<0.001
Any college	1,052 (92%)	296 (83%)	357 (54%)	308 (45%)	
No college	96 (8%)	60 (17%)	302 (46%)	369 (55%)	
Urbanicity					<0.001
Urban	1,047 (91%)	282 (79%)	557 (85%)	569 (84%)	
Rural	101 (9%)	75 (21%)	102 (15%)	108 (16%)	
AJCC Stage					<0.001
1	527 (46%)	164 (46%)	275 (42%)	253 (37%)	
2	468 (41%)	155 (43%)	277 (42%)	299 (44%)	
3	153 (13%)	38 (11%)	107 (16%)	125 (18%)	
Grade					<0.001
1	262 (23%)	66 (19%)	120 (18%)	101 (15%)	
2	430 (38%)	133 (38%)	265 (41%)	234 (35%)	
3	445 (39%)	152 (43%)	266 (41%)	335 (50%)	
Clinical subtype					0.005
ER-/HER2+	55 (6%)	13 (4%)	38 (6%)	36 (6%)	
ER+/HER2-	750 (75%)	215 (72%)	430 (73%)	386 (66%)	
TNBC	193 (19%)	70 (23%)	125 (21%)	163 (28%)	

SES groups were derived from latent class models. P-values were assessed by chi-square tests. Participants with race classified as “other” includes all those not identifying as Black or White, including American Indian / Alaska Native, Asian, or another race not listed on the questionnaire. Urbanicity is defined at the census tract-level

PO1-09-09

The journey of HR positive, HER2 negative metastatic breast cancer's patients: heterogeneities and barriers in Brazilian public health system- a national survey

Presenting Author(s) and Co-Author(s):

H. Resende. Hospital Jardim Amália, United States

I. Soares. Hospital Hinja, Volta Redonda, Brazil, United States

A. Renó. Hospital Hinja, Volta Redonda, Brazil, United States

A. Cunha. Hospital Hinja, Volta Redonda, Brazil, United States

V. Aguiar. Centro Universitário de Volta Redonda (UniFOA), Volta Redonda, Brazil, United States

L. Tureta. Hospital Hinja, Volta Redonda, Brazil, United States

V. Pereira. Hospital Hinja, Volta Redonda, Brazil, United States

Background: Breast cancer is the most common neoplasm in Brazilian women, with high percent of patients diagnosed in advanced stages. Metastatic breast cancer (mBC) is a challenge in the country, where 75% of the population is covered by public health system (Sistema Único de Saúde, SUS). We conducted an on-line survey to describe the journey of human epidermal growth factor receptor 2-negative (HER2-), hormone receptor positive (RH+) mBC patients across public scenario in Brazil. Methods: An on-line survey comprised of 39 to 48 (depending on the kind of some questions, which could open another question in case of affirmative answer) objective questions were sent by e-mail to 180 oncologists working in public and private health care system. Questions were focused on assessing wait time for first treatment after admission in the hospital in both systems, availability of oncological drugs within SUS according to essential medicines list by World Health Organization, and presence of palliative and multidisciplinary teams in both systems. Continuous variables were measured by median and mean. The level of statistical significance adopted was 5% with Teste p two-sided. Analyses were performed using SAS statistical software (version 25.0). Results: We had 150 respondents working in SUS and private health system, which fulfilled the inclusion criteria to participate in this survey. The other 30 respondents were excluded from the study because they worked exclusively in SUS or exclusively in the private system, and their answers were not analyzed. Median wait time for surgery was 60 days in the SUS (N=150) and 30 days in the private health system (N=150) e ($p < 0,0001$). Regardless of chemotherapy provided, median waiting time was 30 and 15 days in the SUS (N=150) and the private health system (N=150), respectively ($p < 0,0001$). Most oncologists in the SUS (N=125, 83.3%) pointed to endocrine therapy as their first-choice treatment in mBC. Concerning endocrine therapy in the SUS, Gonadotropin-Releasing Hormone Agonist (GnRHa) was available, and it was prescribed by 54 (36.0%) and Fulvestrant for 72 (48.0%) of respondents. Considering chemotherapy, weekly paclitaxel alone or combined with platin were available and they were prescribed by 124 (82.6%) and 109 (72.6%) of oncologists respectively. Vinorelbine was available and it was prescribed according to oncologists' report by 109 (72.6%) and Pegylated liposomal doxorubicin (PLD) by 38 (25.3%) of oncologists. Oncologists answered agree or strongly agree that they had a multidisciplinary care team in SUS 77,3% (N =116) versus 87,3% (N=131) in the private system ($p=0.022$). Concerning palliative care 66,09% (N= 99) in the SUS versus 82,0% (N=123) in the private system answered that they agreed or strongly agreed that this service was available ($p=0.001$). Conclusions: The Brazilian government has continuously improved delivery of services and medicines via the public system (SUS), but there are still significant differences within this system and versus the private sector. Unavailability of

endocrine therapy agents as GnRH α and Fulvestrant, and some chemotherapy agents as PLD and Vinorelbine for high percentage of patients, raises the existence of disparities within SUS. Also, longer waiting times for treatment in the SUS, lower availability of support teams such multidisciplinary and palliative care, they point out disparities between SUS and private health systems. The lack of a National Cancer Control Program and low health investment by Brazilian government might explain the difference in cancer patients' access.

PO1-09-10

County-level Social Vulnerability and Survival among Women with Inflammatory Breast Cancer

Presenting Author(s) and Co-Author(s):

K. Hirko. Michigan State University, United States

E. Troll. DFCI, United States

S. Ryan. DFCI, United States

F. Nakhlis. Dana-Farber Cancer Institute, United States

J. Bellon. DFCI/BWH, Boston, Massachusetts, United States

O. Kantor. Brigham and Women's Hospital/Dana-Farber Cancer Institute, United States

C. Minami. Dana-Farber Cancer Institute, Massachusetts, United States

E. Yeh. DFCI/BWH, United States

I. Schlam. Tufts Medical Center, United States

L. Warren. DFCI/BWH, United States

C. Block. Dana-Farber Cancer Institute, United States

S. Schumer. Dana-Farber Cancer Institute, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Purpose: Inflammatory breast cancer (IBC) is an aggressive form of breast cancer with a poor overall prognosis compared to other forms of breast cancer. Advances in treatment have contributed to improvement in IBC survival rates in recent years, yet disparities in outcomes persist. It is unclear whether social determinants of health impact IBC prognosis independent of access to quality cancer care. Thus, the aim of this study was to examine whether the US county-level social vulnerability index (SVI) was associated with IBC stage at diagnosis and overall survival (OS) among women with IBC treated at a single institution. **Methods:** Patients enrolled in the IBC registry at Dana-Farber Cancer Institute (DFCI) were included in this study. We linked participant's residential zip codes to the 2020 CDC's county-level SVI, which is calculated from 15 social determinants of health attributes from the American Community Survey including socioeconomic status, household composition, language and minority status, and housing and transportation factors. The SVI value reflects the percentile of counties in the nation that are less vulnerable than the county of interest. We assessed associations between SVI and stage at diagnosis using t-tests. Kaplan-Meier curves and log-rank tests were used to assess survival across SVI quartiles based on distribution (1st [least vulnerable] and 4th [most vulnerable]). Using hierarchical logistic regression models and Cox proportional hazards models with mixed effects incorporating cluster-specific random effects that modify the baseline hazard function, we assessed whether SVI is associated with the presence of de novo metastatic disease and OS in IBC. **Results:** A total of 586 women (86% White) enrolled in the IBC registry at DFCI between 1986 and 2021 were included in this study. Of these, 69.1% had stage III and 30.9% had de novo metastatic disease. 280 deaths occurred in the study population over a mean follow-up of 4.1 years. SVI for the counties where study participants resided ranged from 2.6% to 95.8% (median=34.2%). The mean SVI did not significantly differ according to stage at diagnosis (41.6% in non-metastatic and 40.8% in metastatic at presentation; p=0.70). OS did not significantly differ across SVI quartiles (p-value=0.63). In the age-adjusted models, the SVI was not associated with the presence of de novo metastatic disease (odds ratio (OR (95% CI)=0.99 (0.84, 1.16)) or OS (HR (95% CI)=0.79 (0.46, 1.33)).

Conclusions: Our findings that residing in socially vulnerable US counties is not associated with the presence of de novo metastatic disease or IBC survival among a subset of women accessing high-quality cancer care suggest that improving access to quality cancer care may overcome underlying socioeconomic factors that contribute to disparities in IBC outcomes. Future studies are needed to confirm these findings in other settings.

PO1-09-11

Racial Differences in Pathologic Complete Response Rate and Overall Survival Following Neoadjuvant Chemotherapy for Breast Cancer

Presenting Author(s) and Co-Author(s):

C. Livasy. Atrium Health Levine Cancer Institute, Charlotte, North Carolina, United States

E. Donahue. Atrium Health Levine Cancer Institute, United States

B. Neelands. Atrium Health Levine Cancer Institute, United States

L. Hadzikadic-Gusic. Atrium Health Levine Cancer Institute, United States

T. Sarantou. Atrium Health Levine Cancer Institute, United States

M. Needham. Atrium Health Wake Forest Baptist, United States

A. Patrick. Atrium Health Levine Cancer Institute, United States

A. Heeke. Levine Cancer Institute, Atrium Health, United States

A. Tan. Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, United States

R. White. Atrium Health Levine Cancer Institute, United States

Background: Neoadjuvant chemotherapy (NAC) is increasingly used in the treatment of breast cancer and has been utilized in multiple clinical trials assessing the efficacy of novel therapies. Pathologic complete response (pCR) following NAC is associated with improved survival outcomes in breast cancer and pCR is a commonly used endpoint in clinical trials. Despite improvements in breast cancer survival using modern treatment regimens, Black women continue to experience worse survival outcomes as compared to White women. The objective of this study was to evaluate the association between race and clinical outcomes, specifically pCR rate, recurrence free survival and overall survival, in patients undergoing neoadjuvant chemotherapy at our institution. Methods: We conducted a retrospective review of patients who completed at least 75% of the recommended cycles of neoadjuvant chemotherapy for breast cancer between 2010 and 2016 and underwent surgery. Receptor subtypes were defined as HR+/HER2-negative, HER2+ or triple-negative. The association between race and pCR, defined as ypT0/ypTis ypN0, and survival endpoints of overall survival and recurrence free survival were analyzed using multivariable logistic regression and Cox proportional hazard models. Results: A total of 532 women met the inclusion criteria, 323 (60.7%) were White, 188 (35.3%) were Black and 21 (3.9%) were other/unknown. Median follow-up was 65 months. The receptor subgroups consisted of 195 (36.7%) HR+/HER2-negative cancers, 193 (36.3%) HER2+ cancers and 144 (27.1%) triple-negative cancers. No significant association between race and receptor subtype ($p=0.55$) or pre-treatment clinical stage ($p=0.96$) was observed. The overall observed pCR rate was 19% for Black patients and 27% for White patients, demonstrating a significantly different pCR rate by race in multivariate analysis (odds ratio of pCR White vs Black of 1.75; $p=0.02$). The largest discrepancy in pCR rate between White and Black patients was within subjects with triple-negative disease (pCR rate 44% White patients vs 27% Black patients, $p=0.03$). There was no association between recurrence free survival and race in univariate analysis ($p=0.15$). A significant difference in overall survival by race was observed using multivariable Cox proportions hazard model (hazard ratio Black vs White 1.77; $p=0.03$). Conclusions: In this retrospective analysis of patients receiving neoadjuvant chemotherapy, Black patients experienced a significantly lower pCR rate compared to White patients, with the biggest gap identified within triple-negative breast cancers. During the study period, Black patients also experienced a lower overall survival rate compared to White patients. Differences in the ability to achieve a pCR may be a contributing factor to the worse

survival outcomes of Black patients.

PO1-09-12

Cancer health disparities among patients with early-stage estrogen receptor-positive (ER+) breast cancer treated in public or private practices in Brazil

Presenting Author(s) and Co-Author(s):

- R. Barroso-Sousa. Dasa Oncology, United States
- D. Assad-Suzuki. Hospital Sírio-Libanês, Brasília, Brazil, Brazil
- D. Santos. Hemolabor, Goiânia, Goiás, Brazil, Goiânia, Goiás, Brazil
- F. Moura. Hospital Sírio-Libanês, Brasília DF, Brazil , Instituto Hospital de Base do Distrito Federal, DF, Brazil, Brazil
- S. Oliveira. Liga Norte Riograndense contra o Câncer , RN, Brazil, Brazil
- A. Galvão. Uniceub, DF, Brazil, Brazil
- B. Souza. DASA Oncologia/Hospital Brasília, Brasília, DF, Brazil, Brazil
- A. Castro. Hospital Sírio-Libanês, Brasília DF, Brazil, Brazil
- M. Andrade. Liga Norte Riograndense contra o Câncer , RN, Brazil, United States
- A. Shimada. Hospital Sirio Libanês, São Paulo , Brazil, Brazil
- Y. Beckedorff. Hospital Sirio Libanês, São Paulo, Brazil, Brazil
- M. Magalhães. Hospital Universitário Evangélico Mackenzie, CURITIBA, Parana, Brazil
- C. Souza. Hospital de Câncer de Barretos, Barretos, Brazil
- C. Paiva. Barretos Cancer Hospital, Barretos, Brazil
- H. Resende. Hospital Jardim Amália, United States
- D. Pereira. ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, Brazil
- A. Rodrigues. Universidade Federal de Minas Gerais, Brazil; ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, United States
- D. Rosa. Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul, Brazil

Background Cancer registries in Brazil are deficient and data about patients' profiles and cancer treatment patterns are scarce in the country. Moreover, while 30% of population has access to private insurance, almost 70% of population uses publicly health services. The objective of this work was to describe the sociodemographic and clinicopathological characteristics of women with early-stage ER+ breast cancer on adjuvant ET in different regions of Brazil, and to describe treatment patterns for this disease according public and private institutions. **Methodology:** We performed a real-world data analysis in different institution regions of Brazil. Women with a history of early-stage ER+ invasive carcinoma of the breast on adjuvant endocrine therapy for at least 6 months were invited to participate of this study in 12 centers in four different regions in Brazil. Demographic and clinicopathologic information was retrieved from medical records. In order to compare healthcare insurance type, we considered patients who were treated under the Brazilian public health system as publicly insured, and women who had private insurance or paid for their treatment as privately insured. High education level was defined by completed high school. Data collection was done with RedCap software. Qualitative variables were compared between groups using the Chi-square or exact Chi-square test and for quantitative variables the non-parametric Mann-Whitney test was used. $P < 0.05$ was considered significant. Analyzes were performed in SAS 9.4; **Results:** From June 2021 to May 2023, a total of 461 women with ER+, early BC, were included in this analysis. A total of 233 (50.6%) came from private institutions, the mean age was 56.02 years (range 22-

93), 47.69% were non-white, 61.3% were post-menopause, 61.7% lived with a partner, and 76.2% were highly educated and 66.81% had comorbidities. Tumor staging at diagnosis was classified as III, II and I respectively in 21.26%, 43.17% and 35.57% of all cases. Regarding treatment received, 62.4% of patients underwent lumpectomy, 32.2% had axillary dissection, 67.6% received (neo)adjuvant chemotherapy, 45.2% were on aromatase inhibitors and 14.19% were on ovarian function suppression plus ET. Median duration of ET use was 2.78 years (range 6 months- 9.61 years). Publicly health insurance was significantly associated with younger age at diagnosis (< 60 yo), premenopausal status, to live alone, lower educational level, more advanced tumors, prior mastectomy, prior axillary dissection, prior neo-adjuvant chemotherapy, prior radiotherapy, lower use of aromatase inhibitors, ovarian function suppression plus ET, and CDK4/6 inhibitors, while higher use of concomitant medications. Conclusion: The study shows significant health disparities among women with early-stage ER+ breast cancer treated in private versus public institutions in Brazil. Importantly, despite having more advanced tumors, women in public institution had less access to ovarian suppression, CDK4/6 inhibitors and were treated with more aggressive surgical procedures. A deep discussion involving government, lawmakers, health care providers and patients should be conducted to try to decrease the described disparities.

Patient's characteristic and patterns of treatment among patients with estrogen receptor-positive breast cancer on adjuvant therapy according to health insurance in Brazil

Patient's characteristic and patterns of treatment	Private health insurance		p-value
	Yes (n=233)	No (n=228)	
	n (%)	n (%)	
Age > 60 years old	92 (39.48)	67 (29.39)	0.0466
Premenopausal status	68 (29.18)	110 (48.46)	< 0.0001
Living with a partner	155 (67.69)	127 (55.70)	0.0084
High educational level	209 (93.72)	121 (57.62)	< 0.0001
Tumor stage III	28 (12.02)	70 (30.70)	< 0.0001
Modified radical mastectomy	33 (27.27)	44 (37.29)	0.0189
ALND	28 (23.14)	49 (41.53)	0.0024
Prior Chemotherapy	140 (60.09)	170 (75.56)	0.0004
Endocrine Therapy			< 0.0001
- Aromatase Inhibitors	120 (51.50)	87 (38.67)	
- Tamoxifen	62 (26.61)	124 (5.11)	
- OS plus ET	51 (21.89)	14 (6.22)	
Use of adjuvant CDK4/6i	8 (7.21)	1 (0.47)	0.0004
Prior Radiotherapy	178 (76.39)	197 (87.56)	0.0019
Concomitant medication	72 (30.90)	106 (46.49)	0.0006

ALND: axillary lymph node dissection; CDK4/6i: CDK4/6 inhibitors; ET: endocrine therapy; OS: ovary suppression.

PO1-10-01

Racial/Ethnic Disparities in Rates of Pathological Complete Response and Survival in Patients with Inflammatory Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Zasloff. Duke University School of Medicine, Durham, North Carolina, United States

S. Thomas. Duke University School of Medicine, Durham, North Carolina, United States

K. Parrish. Department of Surgery, Duke University Medical Center, Durham, NC, USA, United States

A. Botty van de bruele. Duke University School of Medicine, North Carolina, United States

G. DiLalla. Duke University School of Medicine, United States

M. DiNome. Duke University School of Medicine, RALEIGH, North Carolina, United States

L. Rosenberger. Department of Surgery, Duke University Medical Center, Durham, NC, USA, Durham, North Carolina, United States

H. Worlax. Duke University School of Medicine, United States

E. Hwang. Duke University, Durham, North Carolina, United States

J. Plichta. Duke University School of Medicine, Durham, North Carolina, United States

A. Chiba. Duke University Medical Center, Durham, North Carolina, United States

Radiation Therapy Toxicities and Survival Outcomes in Monoallelic ATM Variant Carriers with Non-Metastatic Breast Cancer: A Retrospective Analysis Rayan Bensenane¹ MD, Arnaud Beddok^{1,2,3} MD, Nadine Andrieu⁴ PhD, Fabienne Lesueur⁴ PhD, Eve Cavaciuti⁴ MSc, Dorothee Le Gal⁴ MSc, Eon-Marchais Severine⁴ PhD, Dominique Stoppa Lyonnet⁵ MD PhD, Youlia Kirova¹ MD 1. Institut Curie, PSL Research University, Radiation Oncology Department, Paris/Saint-Cloud/Orsay, France. 2. Gordon Center for Medical Imaging, Massachusetts General Hospital, Harvard Medical School, 125 Nashua St., Boston, MA, 02114, USA 3. Institut Curie, PSL Research University, University Paris Saclay, Inserm LITO U1288 Orsay, France 4. Inserm, U900, Institut Curie, PSL Research University, Mines ParisTech, Paris, France 5. Department of Genetics, Institut Curie; Inserm U830, Institut Curie; Paris-Cité University Abstract (characters: 2952; max 3400 characters, not include spaces) Background: The Ataxia-Telangiectasia Mutated (ATM) gene, involved in the repair of DNA double-strand breaks, can contribute to radiosensitivity when a bi-allelic variant is present and lead to Ataxia-Telangiectasia syndrome. Moreover, monoallelic ATM pathologic variant (PV) carriers, especially women, has an estimated occurrence rate of 0.5-1% globally and face a 2 to 3-fold increased risk of developing breast cancer. Despite evidence of in vitro radiosensitivity in cells derived from monoallelic variant carriers, there is a dearth of patient studies examining the risk of radiation-induced toxicity. This study aims to explore radiation therapy (RT) toxicities in non-metastatic breast cancer women carrying a germline monoallelic ATM variant, compared to non-carriers. Methods: A retrospective study was conducted on patients treated at Institut Curie, Paris from 1999 to 2014 and participating to CoF-AT (a French national study) and GENESIS database. ATM variant screenings encompassed both PV and non-PV, with toxicities evaluated using CTCAE v.5. Variants were classified as pathogenic, variant of unknown significance (VUS), or benign. Follow-up started from age/date at breast cancer to acute, late toxicities, disease recurrence or last news. Survival and toxicity comparisons were made using Kaplan-Meier survival analysis and Chi-square tests, respectively, with a significance level of α set at 0.05. Results: Among 50 patients, nine were ATM variant carriers (3 PV/5 VUS/1 benign),

and 41 were non-carriers. Most patients had no smoking history (68%), and invasive ductal carcinoma was the predominant diagnosis (82%). The majority underwent breast-conservative surgery (80%), and the dominant RT techniques were 3D-Conformational Radiation Therapy (70%) and Isocentric Lateral Decubitus (30%). The median RT dose was 50 Gy over an average period of 36.5 days. With a median follow-up of 12 years post-diagnosis, no significant difference in acute dermatitis, esophagitis, lymphedema, cutaneous fibrosis, telangiectasia, or heart disease was observed between the groups. Analysis of overall survival (OS) showed a 5-year OS of 98%, decreasing to 89% at 10 years. For ATM variant carriers, the OS at 5, 10, and 15 years was 100%, 89%, and 89%, respectively, similar to non-carriers. Kaplan-Meier analysis revealed no significant differences in 5, 10, and 15-year overall survival, progression-free survival, local failure-specific survival, and contralateral breast cancer rates between the groups. Conclusion: In non-metastatic breast cancer patients, monoallelic ATM variant carrier status does not significantly influence acute or late RT toxicities and survival outcomes. These findings, derived from a small cohort, highlight the need for prospective studies for further validation.

Table: Acute and Late Toxicities Post-Radiation Therapy in Monoallelic ATM Variant Carriers vs Non-Carriers

Table: Acute and Late Toxicities Post-Radiation Therapy in Monoallelic ATM Variant Carriers vs Non-Carriers

		Number of patients with toxicities (%)				P value*
		Grade 0	Grade 1	Grade 2	Grade 3	
Acute toxicities						
Dermatitis	ATM +/+	7 (14%)	21 (42%)	9 (18%)	4 (8%)	NS
	ATM +/-	1 (2%)	5 (10%)	2 (4%)	1 (2%)	
Esophagitis	ATM +/+	37 (74%)	4 (8%)	0	0	NS
	ATM +/-	9 (18%)	0	0	0	
Lymphoedema	ATM +/+	39 (78%)	2 (4%)	0	0	NS
	ATM +/-	9 (18%)	0	0	0	
Late toxicities						
Fibrosis	ATM +/+	23 (46%)	16 (32%)	2 (4%)	0	NS
	ATM +/-	7 (14%)	2 (4%)	0	0	
Telangiectasia	ATM +/+	37 (74%)	4 (8%)	0	0	NS
	ATM +/-	9 (18%)	0	0	0	
Lymphoedema	ATM +/+	38 (76%)	0	3 (6%)	0	0.07
	ATM +/-	8 (16%)	1 (2%)	0	0	
Heart disease	ATM +/+	40 (80%)	1 (2%)	0	0	NS
	ATM +/-	9 (18%)	0	0	0	

* Pearson/Chi² test; NS: non significant at $\alpha=0.05$; ATM +/+ : wild type for ATM; ATM +/- : ATM monoallelic germline variant carrier

* Pearson/Chi² test ; NS: non significant at $\alpha=0.05$; ATM +/+ : wild type for ATM; ATM +/- : ATM monoallelic germline variant carrier

PO1-10-02

Breast cancer among transgender and non-binary patients on gender affirming hormone therapy: a single institution experience

Presenting Author(s) and Co-Author(s):

N. Krishnamurthy. Icahn School of Medicine at Mount Sinai, United States

E. Ravetch. Mount Sinai Health System, United States

C. Weltz. Dubin Breast Center at Mount Sinai, New York, New York, United States

Background: Estrogen exposure is a known risk factor for the development of breast cancer in women. Less clear is the risk posed by gender affirming hormone therapy (GAHT) in both transgender men and transgender women. We aimed to characterize the breast cancers that have arisen in our institution's transgender patient population including biomarker profile, method of diagnosis, and stage at diagnosis. Methods: For this retrospective cohort study, patients from the Mount Sinai Health System were identified using the electronic medical record from 2016-2023. A cohort of transgender or non-binary patients with breast cancer was established by using ICD-10 codes for carcinoma in situ of breast (D-05) and malignant neoplasm of breast (C-50) and a diagnosis or medical history encompassing gender identity disorders (ICD-10-CM: F64) or a chief complaint related to transgender health. Chart review enabled selection of patients who have a history of GAHT. Patients with incomplete medical records were excluded from analysis. Results: 14 patients met criteria and were included for final analysis. Mean age at diagnosis was 51.7 (31-65) years and 86% (12/14) were at or above 40 years of age at diagnosis and eligible for routine screening mammography. The cohort encompassed six trans men (assigned female at birth), seven trans women (assigned male at birth), and one genderqueer person (assigned female at birth). Family history was not significant for most of the cohort. Two patients had a first-degree relative with a history of breast cancer; both were BRCA negative. Four patients (29%) were diagnosed via screening mammography; six patients (43%) were diagnosed after palpating a breast or axillary mass; and four patients (29%) had not undergone screening but were diagnosed via breast imaging mandated prior to planned chest masculinization surgery. At time of initial presentation, the diagnostic stage was DCIS in five patients (36%); LCIS in one patient (7%); stage 1 cancer in four patients (29%); stage 2 cancer in three patients (21%); and breast implant-associated anaplastic large cell lymphoma in one patient (7%). 50% (7/14) of patients had an active or past prescription for testosterone-based GAHT, and 50% (7/14) patients had an active or past prescription for estrogen-based GAHT. Mean duration of all GAHT prior to diagnosis was 16.6 years (mean duration of estrogen-based GAHT was 27.6 years and mean duration for testosterone-based GAHT was 5.7 years). Biomarker profiles were available for twelve patients; 8/12 (67%) patients were diagnosed with estrogen receptor (ER) positive cancer, four (33%) with ER negative cancers. Of patients on estrogen-based GAHT, three presented with ER+ and four presented with ER- cancers. 10/14 patients had bilateral mastectomies and 4/14 had lumpectomies. Discussion/Conclusion: The mode of cancer detection suggests that screening mammography is under-utilized among transgender and non-binary patients who use GAHT. This represents a health care disparity involving a vulnerable patient population. The biomarker profile among this population demonstrates that both estrogen-responsive and estrogen-nonresponsive cancers can arise in the setting of prior or ongoing gender affirming estrogen or testosterone.

PO1-10-03

Prevalence of and Factors Associated with Food Insecurity and Other Adverse Social Determinants of Health Among Breast Oncology Patients

Presenting Author(s) and Co-Author(s):

C. Sathe. Columbia University Medical Center, United States

D. DeStefano. Columbia University Irving Medical Center, United States

A. Gul. New York Medical College/Metropolitan Hospital, United States

M. Beauchemin. Columbia University Medical Center, United States

J. Kahn. Columbia University Medical Center, United States

M. Accordino. Columbia University Medical Center, United States

K. Crew. Columbia University Irving Medical Center, United States

N. Emezienna. University of Maryland, United States

D. Hershman. Columbia University, New York, New York, United States

Background: Social determinants of health (SDOH), the non-medical factors that influence health status, have a profound impact on breast cancer (BC) outcomes and contribute to survival disparities. Food insecurity (FI), defined as a lack of consistent access to adequate food resources, is a modifiable SDOH associated with treatment disruptions, medication nonadherence, and decreased quality of life. To identify at-risk patients and inform future interventions, we implemented SDOH screening of patients seen in breast oncology clinic at our urban academic medical center. Methods: Screening was conducted through an 8-item questionnaire on the electronic patient portal. The questions covered FI, housing and transportation challenges, and emergency department (ED) visits. We conducted a retrospective analysis of SDOH data collected among patients scheduled for a breast oncology appointment between 11/1/22 and 5/25/23. Any level of food hardship or concern constituted a positive FI screen. Descriptive statistics were used to determine the prevalence of FI and other SDOH, to assess differences in FI rates by age, race/ethnicity, and clinical stage, and to compare characteristics of food-insecure vs food-secure patients. We also conducted a multivariable logistic regression analysis to estimate the odds ratio (OR) and 95% confidence interval (CI) associated with sociodemographic/clinical factors and FI. Results: A total of 2,585 patients were seen in our breast oncology practice, of which 1,189 (46.0%) were screened for SDOH, including 41.2% non-Hispanic White (NHW), 9.6% non-Hispanic Black (NHB) and 21.0% Hispanic patients. Among patients who responded to each SDOH question, 15.5% (146/940) reported some level of FI; 8.7% (84/962) were unable to pay their rent or mortgage on time; for 5.8% (57/989), lack of transportation interfered with their treatment. The FI rate differed significantly by race and ethnicity: 4.5% of NHW, 15.2% of NHB, and 41.8% of Hispanic patients reported FI ($p < 0.001$). In multivariable analysis, NHB and Hispanic patients also had significantly higher odds of FI compared to NHW patients (OR=3.68, 95% CI=1.7-7.7, $p < 0.001$ for NHB and OR=15.0, 95% CI=8.8-27.1, $p < 0.001$ for Hispanic patients). Patients with metastatic disease had higher rates of FI compared to other breast oncology patients (23.6% vs 14.8%, $p=0.048$), and a metastatic BC diagnosis was associated with over twice the odds of FI (OR=2.18, 95% CI=1.1-4.2, $p=0.02$). Among food-insecure patients, 41.1% were unable to pay their rent or mortgage on time and 22.6% reported transportation difficulties interfering with treatment (vs 2.6% and 2.4%, respectively, for food-secure patients ($p < 0.001$)). Compared to food-secure patients, those who were food-insecure had significantly higher rates of self-reported ED visits in the past 12 months: 18.8% vs. 33.6% reported at least 1 ED visit,

respectively, and 5.2% vs. 16.4% reported multiple ED visits, respectively ($p < 0.001$).
 Conclusions: In this analysis of SDOH data among patients seen in breast oncology clinic, FI was the most common social health risk reported, with nearly a quarter of patients with metastatic BC reporting FI. Racial/ethnic minorities were also at considerably higher risk for FI. ED utilization was significantly higher among food-insecure patients. Targeted interventions to reduce FI in at-risk populations are warranted to improve clinical and healthcare utilization outcomes.

Sociodemographic and Clinical Characteristics and Other Reported Social Determinants of Health Among Food-Secure vs Food-Insecure Patients

	Total N=940 (100%)	No FI Reported N=794 (84.5%)	FI Reported N=146 (15.5%)	p-value
Race/Ethnicity				<0.001
NHW	400	382 (95.5%)	18 (4.5%)	
NHB	92	78 (84.8%)	14 (15.2%)	
Hispanic	201	117 (58.2%)	84 (41.8%)	
Other/Unspecified	247	217 (87.9%)	30 (12.1%)	
Age				0.008
<40	82	71 (86.6%)	11 (13.4%)	
40-49	174	135 (77.6%)	39 (22.4%)	
50-59	244	202 (82.8%)	42 (17.2%)	
60-69	230	195 (84.8%)	35 (15.2%)	
>70	210	191 (91.0%)	19 (9.0%)	
Clinical Stage				0.048
High-risk or locoregional BC	837	713 (85.2%)	124 (14.8%)	
Metastatic BC	72	55 (76.4%)	17 (23.6%)	
Unknown/unspecified	31	26 (83.9%)	5 (16.1%)	
	Total N=940	No FI Reported N=794	FI Reported N=146	p-value
Rent/mortgage delays				<0.001
Yes	81	21 (2.6%)	60 (41.1%)	
No	822	755 (95.1%)	67 (45.9%)	
Unknown/declined	37	18 (2.3%)	19 (13.0%)	
Challenges with transport to med appts				<0.001
Yes	52	19 (2.4%)	33 (22.6%)	
No	866	762 (96.0%)	104 (71.2%)	
Unknown/declined	22	13 (1.6%)	9 (6.2%)	
Number of ED visits in past 12 months				<0.001
0	742	645 (81.2%)	97 (66.4%)	
1	133	108 (13.6%)	25 (17.1%)	
2+	65	41 (5.2%)	24 (16.4%)	

PO1-10-04

Racial and Ethnic Disparities in Anthracycline and HER2-targeted Cardiotoxicity in Patients With Breast Cancer Using Global Longitudinal Strain Imaging Techniques

Presenting Author(s) and Co-Author(s):

A. Wang. New York Presbyterian, United States

J. Raikhelkar. Columbia University Medical Center, United States

R. Raghunathan. Columbia University Medical Center, United States

J. McGuinness. Columbia University Irving Medical Center, United States

N. Vasan. Columbia University Irving Medical Center, New York, New York, United States

M. Trivedi. Columbia University Irving Medical Center, United States

K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

K. Crew. Columbia University Irving Medical Center, United States

M. Beauchemin. Columbia University Medical Center, United States

J. Wright. Columbia University Irving Medical Center, United States

D. Hershman. Columbia University, New York, New York, United States

M. Accordino. Columbia University Medical Center, United States

Purpose: Studies of global longitudinal strain (GLS) as a predictor of cancer treatment-related cardiac dysfunction (CTRCD) have been limited in racial/ethnic minority populations who are more likely to have risk factors associated with CTRCD. Our aim was to assess the utilization of GLS and development of CTRCD in a racially and ethnically diverse population of patients at an academic center in New York City. **Methods:** Patients were included if they had a breast cancer diagnosis and began treatment with anthracycline or HER2-directed therapies at Columbia University Irving Medical Center (CUIMC) from February 1, 2020-July 31, 2022. All patients and variables were identified via the electronic health record. Cardiovascular comorbidities including obesity, hypertension, diabetes, hyperlipidemia, coronary artery disease, congestive heart failure, and other cardiac disease, were recorded. Receipt of transthoracic echocardiogram(s) (TTE) with/without GLS were recorded, along with GLS and left ventricular ejection fraction (LVEF) values. CTRCD was defined as LVEF decrease of $\geq 10\%$ to a LVEF value $< 53\%$ or GLS decrease of $\geq 15\%$ from baseline or GLS $< -18\%$. Analyses included descriptive statistics and univariable and multivariable logistic regression models to evaluate predictors of CTRCD by either LVEF or GLS definition. **Results:** We identified 270 eligible patients. Mean age was 51.8 years (standard deviation 13.0), 85 (31.5%) identified as White, 47 (17.4%) as Black/African, and 16 (5.9%) as Asian; 135 (50.0%) identified as Non-Hispanic/Latino, and 79 (29.2%) as Hispanic/Latino. Approximately half of the patient cohort, $n=137$ (50.7%) had a TTE with GLS during the study period. Of the TTEs done at CUIMC ($n=658$), 270 (41%) were ordered with GLS assessment, of which 184 (68%) reported a GLS value and 86 (32%) were not assessable due to image quality. Forty-three (16%) patients developed CTRCD: 20 (7%) by GLS criteria, 13 (5%) by LVEF criteria, and 10 (4%) by both GLS and LVEF criteria. In univariable analyses, race (OR 5.78, 95%CI 1.62-20.4 Asian compared to White), treatment with HER2 therapy without anthracycline versus anthracycline (OR 2.78, 95%CI 1.34-6.23), and prescription for cardiac medication prior to systemic therapy (OR 2.27, 95%CI 1.08-4.63) were predictors of CTRCD by any definition. In multivariable analysis, race (OR 7.86, 95%CI 1.71-38.50 Asian compared to White), and receipt of HER2 therapy without anthracycline compared to anthracycline (OR 5.13, 95%CI 1.42-25.00) were predictors of CTRCD. In multivariable analysis of CTRCD by GLS criteria only, race (OR 78.47, 95%CI 1.47-53.96 Asian compared to

White), and treatment (OR 11.23, 95%CI 1.85-219 HER2 therapy compared to anthracycline; OR 58.7, 95%CI 1.05-60.59 HER2 therapy and anthracycline compared to anthracycline).
 Conclusions: In this retrospective analysis of a racially and ethnically diverse patient population, more than a third of Asian patients developed CTRCD, although the study is limited by small sample sizes. Asian race and receipt of anti-HER2 therapy were independent risk factors for CTRCD. Asian race was especially a predictor of CTRCD by GLS definition. Detection bias may explain the differences in CTRCD by drug class, as patients complete serial TTEs while receiving HER2-directed therapy, while patients who receive an anthracycline without HER2-directed therapy typically only receive a baseline TTE. Future research to better characterize racial differences in CTRCD incidence and develop interventions to reduce this disparity is an area warranting further investigation.

Demographic and Tumor Related Factors Associated with CTRCD (n=270)

Variable	n (%)	Unadjusted OR	Unadjusted 95% CI	Unadjusted P-value	Adjusted OR	Adjusted 95% CI	Adjusted P-value
Age at Diagnosis (continuous)		1.01	98.6-1.04	0.37	1.00	0.95-1.07	0.80
<i>Race</i>							
White	85 (31.5)	Reference			Reference		
Black or African	47 (17.4)	1.68	0.55-5.02	0.35	2.32	0.62-8.90	0.21
Asian	16 (5.9)	5.78	1.62-20.37	0.01*	7.63	1.63-38.4	0.01*
Unknown	122 (45.2)						
<i>Ethnicity</i>							
Non-Hispanic or Latino	135 (50.0)	Reference			Reference		
Hispanic or Latino	79 (29.2)	1.13	0.52-2.40	0.75	1.25	0.15-7.36	0.81
Unknown	56 (20.7)						
<i>Insurance</i>							
Private	89 (33.0)	Reference			Reference		
Medicare	65 (24.1)	1.32	0.55-3.14	0.52	1.55	0.27-9.22	0.62
Medicaid	114 (42.2)	1.02	0.47-2.27	0.95	1.04	0.25-4.52	0.95
Unknown	2 (0.7)						
<i>Metastatic</i>							
No	222 (82.2)	Reference			Reference		
Yes	46 (17.0)	1.16	0.47-2.61	0.72	1.33	0.30-5.41	0.69
Unknown	2 (0.7)						
<i>Chemotherapy</i>							
Anthracycline Only	116 (43.0)	Reference			Reference		
HER2 and Anthracycline	4 (1.5)	3.53	0.17-30.70	0.29	11.9	0.30-606.0	0.16
HER2 Only	149 (55.2)	2.78	1.34-6.23	0.01*	5.11	1.36-25.80	0.03*
Unknown	1 (0.4)						
<i># of baseline cardiovascular comorbidities</i>							
0	108 (40.0)	Reference			Reference		
1	111 (41.1)	0.78	0.37-1.64	0.51	1.33	0.34-5.25	0.68
2+	49 (18.1)	1.13	0.45-2.67	0.79	1.10	0.10-10.10	0.93
Unknown	2 (0.74)						
<i>Cardiac prescription prior to chemotherapy</i>							
No	214 (79.3)	Reference					
Yes	55 (20.4)	2.27	1.08-4.63	0.03*	1.55	0.35-6.49	0.55
Unknown	1 (0.4)						
Baseline BMI (continuous)		0.95	0.90-1.00	0.08	0.92	0.81-1.03	0.16

Univariable and multivariable analysis of CTRCD by LVEF or GLS definition. Multivariable analysis was adjusted for all variables listed.

PO1-10-06

Understanding clinical meaningfulness in metastatic breast cancer treatment decision-making: experiences and perspectives of patients, caregivers, and clinicians

Presenting Author(s) and Co-Author(s):

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

E. Freeman. Gilead Sciences Inc, United States

M. Roach. PRECISIONheor, United States

R. Wilson. PRECISIONheor, United States

R. Fairley. TOUCH, the Black Breast Cancer Alliance, United States

M. Gullatte. Emory Healthcare, United States

J. Stemland. Gilead Sciences Inc, United States

B. Chan. Gilead Sciences, Inc., United States

P. Wochal. Gilead Sciences, Inc., United States

J. Katz. Gilead Sciences, Inc., United States

S. May-Slater. PRECISIONheor, United States

Background: While many clinical and non-clinical factors inform metastatic breast cancer (mBC) treatment recommendations; patient preferences, values, and care goals also influence how treatment options are weighed, deliberated, and decided upon. Additionally, in the mBC care setting, clinical meaningfulness and clinically meaningful outcomes (e.g., survival, quality-of-life) are important factors to consider along the care continuum. However, the extent to which patients and their oncology care team align on the interpretation and use of these concepts during treatment decision-making has not been well elucidated. This study examined perspectives on the concepts of (i) clinical meaningfulness and (ii) clinically meaningful outcomes associated with mBC treatment among five key stakeholder groups: patients, caregivers, oncologists, advanced practice providers (APPs), and oncology nurses. Methods: Qualitative semi-structured in-person and web-based focus groups were conducted between March and June 2023 among: (i) people living with mBC; (ii) unpaid or informal caregivers to people with mBC; and providers involved in the care of patients with mBC, including (iii) oncologists, (iv) APPs (i.e., physician assistants and nurse practitioners), and (v) oncology nurses. Discussion guides were developed to elicit stakeholder perspectives on clinical meaningfulness and clinically meaningful outcomes to help identify areas of convergence and divergence between and within stakeholder groups. All discussions were audio recorded and transcribed. The constant comparative approach was used to identify key themes. Results: Twenty-two focus groups were conducted with 50 patients, 24 caregivers, 8 oncologists, 13 APPs, and 17 oncology nurses. Overall, patients and caregivers were unfamiliar with the concepts of clinical meaningfulness and clinically meaningful outcomes, underscoring the critical need for using accessible and patient-friendly terminology in treatment decision-making discussions. While some providers were familiar with these concepts, they reported not using these terms when discussing treatment recommendations with patients. Although some provider participants thought clinical meaningfulness described quantitative endpoints (e.g., additional months of survival), participants across all stakeholder groups described patients' abilities to achieve life goals (e.g., participation in milestone events and social activities, ability to travel) as paramount. Recommendations for improving treatment decision-making discussions included taking a patient-centered approach, with inclusive,

dynamic patient-provider discussions and continuous evaluation of patient priorities across the care continuum, not just at diagnosis. Meaningful outcomes beyond overall survival need to be considered, including quality of life, progression-free survival, minimal or manageable side effects, and improvement in symptom burden and functioning. Across all stakeholders, participants stressed that outcomes considered meaningful are highly individualized and dynamic, evolving over time as patients move through the treatment journey and life stages. Conclusions: Clinical meaningfulness is poorly understood and not often considered in the clinical setting when making mBC treatment decisions, highlighting a need for accessible and patient-friendly terminology in mBC treatment decision-making conversations. While participants valued overall survival, the importance of meaningful outcomes that support patients' quality of life was emphasized. Study findings can be used to inform both practice and clinical research to better capture meaningful outcomes for patients.

PO1-10-07

A Video Intervention to Improve Patient Understanding of Tumor Genomic Testing in Patients with Metastatic Breast Cancer: Primary Results of a Prospective Intervention Trial

Presenting Author(s) and Co-Author(s):

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

D. Veney. Ohio State University Comprehensive Cancer Center, United States

L. Wei. Ohio State University Comprehensive Cancer Center, United States

A. Toland. Ohio State University, Columbus, Ohio, United States

C. Presley. Ohio State University Comprehensive Cancer Center, United States

T. Padamsee. Ohio State University, United States

C. Lee. Ohio State University Comprehensive Cancer Center, United States

H. Hampel. City of Hope National Medical Center, Lewis Center, Ohio, United States

W. Irvin. Bon Secours Saint Francis Medical Center Cancer Institute/Southeast Clinical Oncology Research (SCOR), Midlothian, Virginia, United States

J. Francis. Bon Secours Cancer Institute, United States

M. Bishop. Bon Secours Cancer Institute, United States

S. Hovick. Ohio State University, United States

L. Senter. Ohio State University Comprehensive Cancer Center, United States

Background: Tumor genomic testing (TGT) has become standard-of-care for all patients with metastatic breast cancer (MBC). American Society of Clinical Oncology (ASCO) and American College of Medical Genetics (ACMG) guidelines for patient education prior to TGT are not widely followed. We have previously demonstrated disparities in general genomic knowledge across race and income. The purpose of this study was to develop a concise (3-4 minute) video for patient education prior to TGT and evaluate the video's impact in a prospective interventional trial. We report the results of the primary endpoint of the MBC cohort (ClinicalTrials.gov NCT05215769).

Methods: We previously published our internal quality improvement cycle involving provider surveys, patient focus groups, and adult learning theory-based content development for TGT educational videos. An animated video incorporating culturally diverse images available in English and Spanish was created to be applicable to any cancer type, with MBC-specific content included for patients with breast cancer. A total of 150 participants were enrolled at a single tertiary academic institution, of whom 53 were diagnosed with MBC. Participants completed validated survey instruments immediately prior to video viewing (T1), immediately post-viewing (T2) and 60-90 days later, after TGT results were documented (T3). Instruments included: 1) 10-question objective genomic knowledge/understanding (GKU); 2) 10-question video message-specific knowledge/recall (VMSK); 3) 11-question Trust in Physician/Provider (TIPP); 4) attitudes regarding TGT. The primary objective was to assess change in VMSK between T1 and T2 and a cohort of 50 participants provided 90% power to detect an effect size of 0.47 from pre- to post-video using two-sided Wilcoxon signed-rank test with alpha of 0.05. Associations of VMSK, GKU, and TIPP with categorical demographic variables were explored with Kruskal-Wallis test.

Results: From April 2022 to May2023, a total of 150 participants were enrolled (MBC n=53, lung cancer n=38, metastatic cancer of any type n=59). The MBC cohort analysis is presented. The MBC cohort had a median age of 59; all were female; majority Caucasian (48/53, 91%); most were married/in domestic partnership (35/53, 66%). For the primary endpoint, there was a significant increase in video message-specific knowledge (Wilcoxon signed rank $p < 0.0001$) but there was no significant change in general genomic knowledge ($p=0.89$) or trust in provider ($p=0.59$). Improvement of video message-specific knowledge was consistent across demographic groups, including age, income, and education. Of the 10-questions in the VMSK survey, results for four questions significantly improved after viewing the video, including questions informing the likelihood of TGT impact on treatment decision, incidental germline findings, and cost of testing (Table 1). Baseline genomic knowledge was significantly associated with income (nominal $p=0.028$), with higher income associated with higher baseline knowledge.

Conclusions: A concise, 3-4 minute, broadly applicable video incorporating culturally diverse images administered prior to TGT significantly improved video message-specific knowledge across all demographic groups. Ongoing work includes analysis of additional cohorts (lung, any type) and evaluation in community oncology setting with a goal to provide a paradigm to efficiently educate and empower patients while addressing ASCO/ACMG guidelines within the flow of clinical practice.

Table 1. Response to video message-specific questions before versus after tumor genomic testing educational video intervention

Video message-specific question (True or False)	Addresses ASCO/ACMG guidelines	MBC Cohort: # (%) correct T1 n=53	MBC Cohort: # (%) correct T2 n=53	Change # Correct T1→T2	p-value
We have genes in every cell of our bodies.	N	49 (92%)	53 (100%)	+2	0.046
Tumor genomic testing might help your doctor make decisions about your cancer treatment.	Y	52 (98%)	53 (100%)	+1	0.32
Tumor genomic testing always determines what treatment a person will have.	Y	43 (81%)	52 (98%)	+9	0.007
I must have tumor genomic testing to continue with cancer treatment.	Y	51 (96%)	51 (96%)	0	1
My doctor has other tools besides tumor genomic testing to use to choose treatments for me.	Y	51 (96%)	52 (98%)	+1	0.56
Tumor tissue genomic results sometimes raise more questions that require more genetic testing.	Y	44 (83%)	52 (98%)	+8	0.01
The information that I get from tumor tissue genomic testing could be valuable to my children and other family members.	Y	52 (98%)	53 (100%)	+1	0.32
When my doctor has my results, they might recommend for me to see a genetics specialist.	Y	47 (89%)	52 (98%)	+5	0.059
The expense of tumor genomic testing is not typically covered by health insurance.	N	32 (60%)	44 (83%)	+12	0.005
If you do not have health insurance, you cannot have tumor genomic tissue testing performed	N	51 (96%)	50 (94%)	-1	0.66

PO1-10-08

Building awareness of triple negative breast cancer: Results from the Canadian Breast Cancer Network national survey

Presenting Author(s) and Co-Author(s):

K. D. Swiger. Canadian Breast Cancer Network, North Carolina, United States

S. Richter. University of North Carolina Greensboro, Statistical Consulting Group, North Carolina, United States

B. Adegbembo. Canadian Breast Cancer Network, Ottawa, Ontario, Canada

C. Ammendolea. Canadian Breast Cancer Network, Ottawa, Ontario, Canada

Background: Assessing the education, information and support needs of Canadians diagnosed with breast cancer involves categorizing and tailoring topics and methods of delivery but, most importantly, it must be rooted in an understating of the patient. In 2022, the Canadian Breast Cancer Network (CBCN) initiated a project to identify the needs of the Canadian breast cancer population, determine differences between those diagnosed with triple negative breast cancer (TNBC) compared to non-TNBC patients and develop tailored, focused programs and materials as a result of the findings. Methods: CBCN conducted a series of 45-minute key informant interviews (7) with patients and oncologists to determine needs, gaps, programs, and materials for triple negative breast cancer patients in Canada. Five 90-minute patient focus groups (32 participants) were conducted to enhance the interviews. One group was specifically for metastatic patients. Findings from the interviews and focus groups were used to inform the questions for an online survey open to all Canadians diagnosed with breast cancer which was fielded May 1 to June 10, 2022. The data analysis began in September 2022 and is on-going. Results: While 47.9% of TNBC respondents (versus 51.3% of non-TNBC patients) said that they were aware of different types and subtypes of breast cancer, 70.6% of patients reported they were not aware of the term “triple-negative breast cancer” and only learned about at diagnosis. 69.9% of TNBC patients said that the person giving them their diagnosis used the term – triple-negative breast cancer. 54.5% reported being provided with specific details about their TNBC diagnosis. This included details about: the aggressive nature of TNBC (76.8%), treatments (67.6%), treatment goals (56.3%), and the urgency of beginning treatment (66.2%). TNBC patients reported that in retrospect, more information on clinical trials (41.7%), the long-term side effects of treatment (38.6%) and post-treatment follow-up (32.5%) should have been included in the discussion at diagnosis. Conclusions: Breast cancer is not a monolithic disease. TNBC impacts 10-20% of the breast cancer population. A majority of those diagnosed with TNBC in the survey were not even aware of this subtype. Building awareness of TNBC, its risk factors and different treatment needs in the public at large and among the breast cancer community could facilitate discussions with healthcare providers and assist researchers seeking new treatments and, most importantly, provide an informed voice for those with TNBC. Making the most current, evidence-based TNBC information and resources available to both patients and providers at diagnosis could build trust and understanding of the differences in treatment and follow up and instill confidence in the overall patient experience.

PO1-10-09

The Performance Of Mobile Units Versus Hospital Units In National Breast Cancer Screening Program In Taiwan, 2010-2020

Presenting Author(s) and Co-Author(s):

V. Vu. International PhD Program in Medicine, Taipei Medical University, Taipei, Taipei, Taiwan (Republic of China)

A. Ming-Fang Yen. Taipei Medical University, United States

M. Min-Szu Yao. Department of Radiology, Koo Foundation Sun Yat-Sen Cancer Center, United States

W. P. Chan. Department of Radiology, Taipei Medical University, United States

Purpose

After the implementation of mobile units, the screened population increased from 3.9% to 40% of all women from 2004 to 2019 in Taiwan's Breast Cancer Screening Program. There are limited studies comparing mobile units to hospital units. This study evaluated and compared the performance of the biennial mammography breast cancer screening in mobile units to hospital units in Taiwan over the past decade.

Methods

A cohort of 3 062 190 women aged 40 to 69 years who underwent biennial breast cancer mammography screenings from 2010 to 2020 was conducted, and data were obtained from the Health Promotion Administration, Ministry of Health and Welfare of Taiwan. Comparing participation of screened women mobile units and hospital units across national screening. Performance measures were determined as percentages and 95% confidence intervals (CIs) using the Wald asymptotic method.

Results

Among 3 062 190 women who underwent 7 444 450 examinations in the study population, the screened population by mobile units accounted for approximately 45.45 % of total examinations. The volume of screening mammograms performed in the mobile unit increased the number of people reached by this program. Since 2015, screenings performed in the mobile units have outnumbered those performed at brick-and-mortar hospitals: they comprised 480 456 of the 859 221 examinations (55.9%) performed in 2019. During the 10-year periods, the screen-detected cancers were 12 000 and 18 370 for mobile units and hospital units, respectively. Young women preferred screening in hospitals, resulting in a greater proportion of screen-detected cancers among those attending hospitals (49.4%) compared to the mobile unit (34.3%). The mean recall rate was higher in the hospitals at 8.95% (95% CI, 8.93%-8.99%) than in the mobile units at 7.27% (95% CI, 7.25%-7.32%).

Conclusion

Implementing mobile units increased the coverage of the screening program across the population. Hospital units had a younger patient population and higher recall rate than those mobile units. We can enhance mammography screening rates and follow-up among these groups by identifying these features, which can use to develop programs and materials fitting populations' specific requirements.

Summary statement

In Taiwan, the development of breast cancer screening has shown beneficial outcomes, especially with the deployment of mobile unit services to increase screened women. Our results could serve as an informative reference for other nations.

Keywords: Breast cancer; screening; mobile units; hospital units.

Table 1. Clinical Demographics for Mammographic Screening Examinations

Characteristic	2010-2020			
	No.	%	No. with SDC	%
No. of women screened	3 062 190		30 370	
Age at screening[†]/diagnosis, y				
40-49	1 548 557	20.8	6192	24.4
50-59	3 333 763	44.8	13117	43.2
60-69	2 562 130	34.4	11 065	36.4
No. of screenings	7 444 450		30 370	
Screening service				
Prevalence screenings	2 477 060	33.3	13 184	43.4
Subsequent screenings	4 967 390	66.7	17 190	56.6
Menopausal status				
Premenopausal	2 164 080	29.1	9216	30.3
Postmenopausal	5 280 370	70.9	21 158	69.7
Breast density				
Fatty breast	310 750	4.2	749	2.5
Scattered fibroglandular density	1 655 443	22.2	6019	19.8
Heterogeneously dense	4 169 444	56.0	19 118	62.9
Extremely dense	1 308 813	17.6	4486	14.8

*SDC denotes screen-detected cancer.

[†]Age at first screening.

Table 2. Performance Measures of Digital Mammographic Screenings for Breast Cancer

Measure	2010-2020		
	Hospital	Mobile	Subtotal
Recall rate, %	8.95	7.27	8.14
	(8.93, 8.99)	(7.25, 7.32)	(8.13, 8.16)
Total no. of examinations	3 762 880	3 681 570	7 444 450
No. of abnormal interpretation	338 100	268 680	606 780
CDR per 1000 examinations, No.	4.88	3.26	4.08
	(4.80, 4.89)	(3.20, 3.30)	(4.03, 4.13)
No. detecting cancer	18 370	12 000	30 370
Total no. of examinations	3 762 880	3 681 570	7 444 450

*Numbers in parentheses are 95% CIs; CDR, cancer detection rate;

PO1-10-10

Leveraging technology to optimize symptom management and patient empowerment in routine breast cancer care: implementation of a remote patient monitoring (RPM) pathway across 24 hospitals in Europe

Presenting Author(s) and Co-Author(s):

M. Franzoi. Gustave Roussy, Villejuif, France, France

A. R Ferreira. Resilience Care, Paris, France, United States

J. d'Andon. Resilience Care, Paris, France, United States

T. Grellety. Centre hospitalier de la Côte Basque, Bayonne, France

E. Ithurbide-Dachary. Centre hospitalier de la Côte Basque, Bayonne, France, United States

L. Polastro. Institut Jules Bordet, Brussels, Belgium, United States

L. Caravella. Institut Jules Bordet, Brussels, Belgium, United States

J. Rodriguez. Centre Hospitalier de Valenciennes, Valenciennes, France, United States

N. Leprevier. Centre Hospitalier de Valenciennes, Valenciennes, France, United States

E. Blanchard. l'Institut de Cancérologie et Radiothérapie Brétilien, France, United States

S. Remy. Centre d'oncologie du Pays Basque, France, United States

B. d' Ythurbide. Ramsay Santé Clinique Belharra, France, United States

R. Rivoirard. Hôpital Privé de la Loire, Saint-Etienne, France, United States

R. Boughzala. Hôpital Privé Arras Les Bonnettes, Arras, France, United States

J. M Ribeiro. Gustave Roussy, Villejuif, France, United States

I. Vaz Luis. Gustave Roussy, Villejuif, France

Background: In clinical trials, RPM has been proven to improve the quality of life and toxicity management for patients receiving systemic treatment and is recommended by international guidelines for routine clinical practice (Di Maio et al., Ann Oncol 2022). Resilience is an oncology-specific RPM system (CE marked, class IIa medical device - mobile application [app] or web interface) which prompts patients to complete a weekly survey including core symptoms from NCI's PRO-CTCAE questionnaire. Severe or worsening symptoms trigger an alert notification sent to the patient's care team. In addition to the RPM system, the mobile app offers a large pool of breast cancer-specific educational, self-management, and patient empowerment resources that are personalized according to symptoms reported, disease stage, and treatments received. Here we present the implementation of the Resilience RPM pathway in routine breast cancer care across 24 highly diverse cancer centers.

Methods: The implementation process followed a phasic process of Exploration, Preparation, Implementation, and Sustainability that involved close collaboration with technology providers, hospital managers, and care teams at participating cancer centers to coordinate, train, provide technical assistance, and respond to site-specific needs. In addition, monthly webinars offered participating centers an opportunity to share best practices and ways to overcome implementation barriers. A dedicated platform with educational RPM resources for healthcare providers was also available.

A process evaluation according to the RE-AIM framework was performed assessing the reach, adoption, implementation, and maintenance of the RPM pathway in routine care. The effectiveness of the pathway was assessed as the ability of the care team to timely respond to

alerts. Aggregated system level metric of RPM was collected covering patients with breast cancer under active systemic treatment followed by Resilience from 01-11-2021 to 29-06-2023. Usage data of mobile app resources was tracked from 01-01-2023 to 29-06-2023. Qualitative assessments with focus groups complemented this evaluation.

Results: 985 patients, 1% male, 99% female, with a median age of 57y (range: 21-95y; P25-75 38.5-64.5y), were registered across 24 cancer centers. In the last 6 months, the predominant RPM interface chosen by patients was the mobile app (64.1 vs 35.9% for the web platform). Adherence to weekly ePRO reporting was 89.4% in the mobile app and 86.6% in the web platform. The median time from prompt receipt to survey completion was 5.6 hours. The median time for the nurse navigator (NN) to process an alert was 3h50min. Most alerts (91%) were handled directly by NN with 9% requiring the support of a physician. The mean number of individual content consumed per patient was 13 (6744 resources/523 pts, 100% of app users accessed resources). Preferred formats of content delivery were written articles (66.5%), followed by videos (23.1%) and podcasts (10.4%). Most assessed contents referred to: symptom management advice (16%), followed by information about breast cancer disease characteristics (12.5%), supportive care strategies (11.5%), self-guided exercises of mindfulness-based stress reduction (9.4%), and breast cancer treatment journey (8.3%). Qualitative assessments of the app interface, educational content, and self-management programs revealed high levels of satisfaction. The RPM pathway is sustained in the 24 cancer centers and implementation is expanding to additional centers.

Conclusion: The Resilience RPM pathway was successfully implemented in routine care across a diverse group of cancer centers with elevated levels of patient engagement and responsiveness from NN. In addition, patients accessed evidence-based educational and empowerment resources, adapted to their medical profile according to their preferences and learning style.

PO1-10-11

Illuminating Breast Cancer Clinical Trials: Unpublication Rates, Causes , and Recommendations

Presenting Author(s) and Co-Author(s):

A. Alhajjeh. king hussien cancer center, United States

G. Bader. university of jordan, United States

S. Aweidah. jordan university of science and technology/ school of medicine, United States

T. Bader. university of jordan, United States

B. Abdin. university of jordan, United States

L. El-Amayreh. university of jordan/ school of medicine, United States

H. Abdel-Razeq. King Hussein Cancer Center, Amman, Jordan

Introduction: Breast cancer stands as the most prevalent cancer among women worldwide. Recent years have witnessed remarkable improvements in patient's outcome, primarily attributed to advancements in management strategies. However, the introduction of novel management approaches necessitates rigorous evaluation through clinical trials, ensuring both their safety and effectiveness. Conducting these trials entails significant financial investments and time commitments, making them susceptible to termination for various reasons. This study aims to investigate the factors that contribute to an increased likelihood of breast cancer clinical trial termination. **Methodology:** A thorough and extensive exploration of ClinicalTrials.gov was undertaken in order to discover completed clinical trials focused on treating breast cancer from 2000 to 2020. By employing the distinctive National Clinical Trial number (NCT) identifier, trial's status; whether completed or terminated, was determined. Subsequently, a meticulous evaluation was carried out on these trials to ascertain the factors that contributed to their termination. In order to unveil the noteworthy factors linked to publication, a comprehensive analysis encompassing both univariate and multivariate approaches was conducted. **Results:** During the specified period, a noteworthy number of oncology clinical trials, totaling 9,145, were conducted. Among them, 12.3% (n=1,127) were focused on breast cancer. These breast cancer trials managed to recruit an impressive 2,669,749 patients. However, it is concerning to note that a significant portion, 38.1% (n=429), of the breast cancer trials did not result in published findings, despite enrolling a considerable number of patients (n= 2,397,179). Our comprehensive univariate analysis revealed several significant associations between the characteristics of clinical trials and their likelihood of going unpublished ($P < 0.001$). Factors such as funding, phase, masking, center type (single vs multi), and country of conduct were all found to have a statistically significant impact on the publication status. Furthermore, our meticulous multivariate analysis demonstrated that certain criteria were associated with higher odds of publication. These included trials that recruited >50 patients, multicenter trials, studies implemented masking, phase-3 trials and those that included low- and middle-income countries (LMIC), Table. **Conclusion:** Our findings indicate that the unpublication rate of clinical trials was alarmingly high. We identified that the sample size, masking, multicenter involvement and phase of the trial impact significantly on publication rate . This knowledge can be valuable for researchers, funding agencies, and other stakeholders who can prioritize resource allocations and improve patients care.

Table: Multivariate analysis, factors that impact publication rate

Criteria	Odds Ratio	95% Confidence Interval	P-value
Recruited more than 50 patients	1.98	1.41-2.77	<0.05
Multicenter trials	1.64	1.18-2.32	<0.05
Studies implementing masking	3.94	1.65-9.44	<0.05
Phase 3 trials	2.18	1.06-4.50	<0.05
Including low- and middle-income countries (LMICS)	1.88	1.00-3.54	<0.05

PO1-10-12

Advancing Gender Equity: A Closer Look at Women's Representation in Leading Breast Cancer Clinical Trials

Presenting Author(s) and Co-Author(s):

A. Alhajajeh. king hussien cancer center, United States

G. Bader. university of jordan, United States

B. Abdin. university of jordan, United States

T. Bader. university of jordan, United States

S. Aweidah. jordan university of science and technology/ school of medicine, United States

L. El-Amayreh. university of jordan/ school of medicine, United States

H. Abdel-Razeq. King Hussein Cancer Center, Amman, Jordan

Introduction: Clinical trials serve as pivotal sources for evidence-based medicine, wielding substantial influence within the medical and scientific community. In recent years, heightened attention has been directed towards encouraging greater female involvement and advancing their representation across various domains of the medical field. Female oncologists tend to focus more over breast cancer as a subspeciality and focused practice. Consequently, this observational study seeks to assess the present status of gender equity in leading breast cancer clinical trials, with the aim of identifying potential concerns and mitigating future risks of bias. By delving into this analysis, we can shed light on the current landscape and pave the way for improved inclusivity and fairness in breast cancer research.

Methodology: To examine the portrayal of female principal investigators (PIs) in breast cancer clinical trials over the past two decades, we conducted a thorough search of breast cancer clinical trials listed on ClinicalTrials.gov. Furthermore, we employed <https://gender-api.com> to assess the gender of each PI and calculate the experience in the medical field of the PI by subtracting the PI graduation year from the year of conducting the clinical trial. In addition, we gathered pertinent details concerning the PIs and the clinical trials, and subsequently subjected the data to univariate analyses to detect any noteworthy distinctions between male and female PIs.

Results: Over the span of the past twenty years, a total of 9,145 cancer clinical trials were conducted, with 1,127 (12.32%) focusing specifically on breast cancer. Through our rigorous efforts, we managed to gather comprehensive information about the principal investigators (PIs) in 788 (69.92%) of these clinical trials. Notably, we discovered that 419 (53.17%) of these trials were led by female investigators.

Upon scrutinizing the characteristics of the PIs, we observed several significant distinctions between male and female PIs. Female PIs exhibited a lower median age (57.0 vs. 60.0) and possessed less medical experience (17 vs. 22 years) compared to their male counterparts ($P < 0.001$). Furthermore, we found a substantial divergence in the funding sources for the clinical trials between the genders. Female-led trials received a lower percentage of industrial funding (13.1% vs. 24.2% for males, $P < 0.001$) but showcased a significantly higher percentage of university funding (38.7% vs. 28.0% for males, $P < 0.001$).

Most of the clinical trials led by female PIs were categorized as phase 2 trials (82.8% vs. 66.8% for males) and were conducted in single centers (61.2% vs. 52.6% for males), demonstrating a

noteworthy statistical difference ($P < 0.001$) in both cases. However, no statistically significant disparities were found between male and female PIs in terms of termination rates, publication rates, or the type of intervention utilized in the clinical trials. Furthermore, the ratio of females PI wasn't different throughout the time as the linear regression model estimated effect was -0.009 with $P = 0.065$.

Conclusions: The study shows the great effort done by female researchers, even though they have lower age, experience, and support from the industrial companies and lower opportunity to have bigger multicenter clinical trials, they still manage to have equivalent rate of termination and publication of the clinical trials showing their capability to lead clinical trials and the need to be supported to maintain the gender equity in leading the breast cancer clinical trials. However, female involvement in other cancer sites might be different and needs to be looked at.

PO1-11-01

Effectiveness of Susan G. Komen's national telehealth patient navigation model in reaching underserved populations and reducing cancer-related distress

Presenting Author(s) and Co-Author(s):

J. McMahon. Susan G. Komen, United States

S. Lautner. Susan G. Komen, United States

M. Spadine. Susan G. Komen, United States

T. Lee. Susan G. Komen, United States

J. Okamoto. Susan G. Komen, United States

Title: Effectiveness of Susan G. Komen's national telehealth patient navigation model in reaching underserved populations and reducing cancer-related distress **Background:** Despite its effectiveness in reducing breast cancer inequities, patient navigation (PN) is not accessible to all patients across the United States. To improve access, Susan G. Komen established a telehealth PN model, scaled to deliver PN services equitably across the country. **Methods:** Patients are referred to Komen patient navigators through Komen's Helpline. Navigators conduct an initial distress screening and barrier assessment and create an individualized care plan. This information, recommended interventions, and other health data are documented, 62 days. Navigators communicate via the patient's preferred method: phone, email, text, or video. A patient satisfaction survey is administered 30 days after the start of navigation. **Results:** From April 1, 2022, to March 31, 2023, 1,092 individuals were navigated. Navigation was provided throughout the continuum of care, including screening and diagnosis through treatment. Of the 3,064 barriers identified by patients, 63% were economic, 20% related to emotional health, 11% indicated lack of access to care and 6% related to care management. Eleven percent of individuals selected Spanish as their preferred language, 84% had a household income at or below 200% of the Federal Poverty Level and 24% were uninsured. Navigated individuals identified as: 46% Black or African American, 37% white or Caucasian, 20% Hispanic or Latino, 2% Asian, and 14% preferred not to answer. The average patient age was 54 years old, ranging from 20 to 101 years old. 588 patients identified as being diagnosed with breast cancer, with 69% diagnosed as early stage (Stage 0-III), 22% as metastatic (Stage IV), and 8% undesignated. Distress screening is administered, within the domains established by the National Comprehensive Cancer Network, at intake, major transitions in care and end of navigation. Average distress across all domains was 6.1 on an 11-point scale at first observation (a score of 10 indicating the highest level of distress). Financial distress was the highest average (7.5) followed by emotional distress (6.6). During navigation enrollment, financial distress decreased 14% and emotional distress decreased 14%. Survey respondents reported: the Komen navigation program helped them: follow their treatment plan (91%), will help them continue their care (92%), feel more prepared to talk with their care team (91%), to be able to get care faster (88%), and improve their quality of life (91%). **Conclusion:** Distress screening was developed for a clinical setting with in-network medical and mental health providers. This program's demonstrates distress screening can be adapted for use in a non-clinical, virtual setting. Socioeconomic, survey, and distress data indicate Komen's model succeeded in reaching people that research shows have numerous barriers to breast health services and cancer care, and overcome the most common barriers, thus improving access to timely, high-quality care. Opportunities for program improvement include: -To improve support for those experiencing high emotional distress, additional training in emotional support is being incorporated into onboarding and Komen's Navigation Training Program. - Research shows that navigation is most effective when delivered by someone who shares a lived experience, so

the diversity of navigators is important. More bilingual navigators have been added to the program to better serve the Spanish-speaking population. - To improve support of those living with metastatic breast cancer seeking navigation support, Komen has launched a research study to identify the unique needs of patients living with MBC, and use this information to enhance navigation services.

PO1-11-02

Reporting of Post-protocol Therapies in Metastatic Breast Cancer Registration Clinical Trials: A Systematic Review

Presenting Author(s) and Co-Author(s):

S. Shachar. Tel Aviv University, Tel Aviv, Israel

Y. Korzets. Tel Aviv Sourasky Medical Center, United States

D. Shepshelovich. Tel Aviv Sourasky Medical Center, United States

N. Zlotchover. Tel Aviv Sourasky Medical Center, United States

E. Amir. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

A. Tibau. Hospital de la Santa Creu i Sant Pau. GEICAM Spanish Breast Cancer Group, Spain

H. Goldvaser. Shaare Zedek Medical Center, United States

BACKGROUND As the treatment for metastatic breast cancer (MBC) often includes sequential lines of therapy, data on post-protocol treatment in clinical trials are valuable in the assessment of long-term outcome. The objective of this study was to assess the reported data on post-protocol therapy in clinical trials supporting US Food and Drug Administration (FDA) approval of drugs for MBC.

METHODS We identified all initial and subsequent published trials supporting FDA approved indications for MBC between 1/2000-2/2023.

Collected data included study design, patient characteristics and whether reporting on post-protocol therapy was available. Differences in study design and population between studies with and without data on post-protocol therapy were evaluated.

FINDINGS A total of 41 indications for MBC were identified. Supporting studies comprised 20,152 patients. Data were evaluated from 241 publications or abstracts. Reporting of post progression therapy was available for 21 (51%) indications. Of these, post-progression therapy data were often partial and the appropriateness of the therapy could not be evaluated. At the time of FDA approval, data on overall survival (OS) were reported only in 17 (41%) studies. Of these, in 8 studies OS was significantly improved, in 7 studies OS was not improved and 2 studies were single arm. Differences between studies with and without data on post progression therapy are presented in the Table. Studies with OS as their primary endpoints were associated with significantly higher reporting of post-protocol therapy, while studies with both OS and progression free survival (PFS) as their primary endpoint had low reporting rate. There were no other statistically significant differences. Reporting post-protocol therapy has not changed over time with reported data in 50% and 52% studies between 2000-2010 and 2011-2023, respectively.

CONCLUSIONS Data on post progression therapy in trials supporting FDA approval of drugs for MBC are available in fewer than half of indications. Reported data are often partial and may not include sequential therapies consistent with standard of care. As subsequent lines of therapy may have a crucial role in patients' outcome, post protocol reporting should be included in the regulatory submission and be made available publicly.

Differences between studies with and without data on post progression therapy

Variable, number of indications	Not reported (%)	Reported (%)	p
Design			
Randomized, 37	45	54	0.34
Single arm, 4	75	25	
Primary endpoint			
PFS, 31	45	55	0.02
PFS and OS, 7	86	14	
OS, 3	0	100	
Line of therapy			
1st line, 13	46	54	0.71
Post 1st line, 19	58	42	
Any line, 8	38	62	
Type of therapy			
Endocrine, 5	80	20	0.14
Chemo, 6	33	67	
Antibody, 12	67	33	
Small molecules, 18	33	67	
Crossover			
Yes, 2	0	100	0.49
No, 35	49	51	

PO1-11-03

Women with Metastatic Disease: Modeling a Clear and Well-Defined Announcement Pathway

Presenting Author(s) and Co-Author(s):

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

S. Guiu. Institut du Cancer de Montpellier (ICM) Val d'Aurelle, Montpellier University, INSERM U1194, Montpellier, France, United States

M. Mouret-Reynier. Centre Jean Perrin, United States

N. Quenel-Tueux. Department of Medical Oncology, Institute Bergonié, Bordeaux, France, United States

Introduction: The announcement of the diagnosis of metastatic breast cancer is a key step in enabling the patient to fully understand her disease and the various treatment options, and thus to be more involved in her management and follow-up. However, according to the « Croyances et réalités 2 » survey conducted in 2021 among 269 French patients with metastatic breast cancer, 38% of them felt that they "did not fully understand" the information given by their doctor during the announcement consultation. **Objective:** The objective of this work is to model an optimal pathway for the announcement of metastatic breast cancer based on precise guidelines and good coordination between the different actors, in order to ensure that all patients have the necessary information and support. **Method:** A scientific committee composed of 4 French oncologists from 4 different centers initiated a collaborative process to propose, after discussions, precise guidelines for the announcement of metastatic breast cancer. **Results:** A set of 13 concrete guidelines were suggested by the expert group (Table 1). The central aspect is to build a specialized and flexible support, adapted to the needs of the patient, without ever hiding the truth about her disease. The announcement process must be adapted to the patient's history (recurrent or immediately metastatic), but also to the organization and resources available in the health care institution. The experts recommend a model of announcement process in two stages, separated by a few days.

First, the oncologist announces what the entry into metastatic disease represents, followed by a repeat of the announcement by a nurse trained in the specificities of metastatic breast cancer, in order to have the patient reformulate her understanding of the disease and treatment.

In a second phase, a new consultation allows to present the next therapeutic steps and ensure a coordinated intervention of the different health care professionals involved: doctors, nurses, pharmacists and supportive care specialists as needed. The offer of supportive care should be flexible and it is recommended that questionnaires should be made available to the patient to help identify her precise needs. The experts recommend that this second consultation be conducted jointly by an oncologist and a nurse.

Subsequently, the town physician and pharmacist must be contacted to ensure the relay in the accompaniment of the patients in partnership with the cancer care center, and thus to ensure a good sharing of information on the patient's follow-up.

To help the establishment of this dynamic announcement model, the experts gave advice on implementation: training the professionals involved in the process through theoretical training and role-playing, increasing the amount of time spent on the announcement consultation, and setting up a library of online or physical information materials to share with the patient.

Finally, it is recommended that the financing of this process be prepared at the institutional level before its effective implementation in order to ensure its sustainability. **Conclusion:** Organizing a consultation for the announcement of metastatic breast cancer is essential to optimize the

experience of the announcement and support. It must be a structured, funded and coordinated process between different health professionals specially trained for this approach.

Table 1: Summary of guidelines for a metastatic breast cancer notification pathway.

Recommendations	
1	Build a specialized, flexible and honest support according to the patient's needs
2	Adapt the announcement process according to the patient's type (recurrent or immediately metastatic)
3	Build a dynamic two-step announcement process
4	Ensure that the announcement is made by a nurse trained in the specificities of metastatic breast cancer
5	Propose a multidisciplinary pathway for the patients during the 2 nd phase of the announcement
6	Develop a flexible supportive care offer, according to the patient's needs
7	Complete a questionnaire at the initial consultation to identify supportive care needs
8	Ensure the consultations of announcement jointly by an oncologist and a nurse
9	Contact the town physician and pharmacy to ensure that the announcement is repeated and followed up
10	Train the professionals involved in the process (nurses, oncologists, surgeons, etc.)
11	Increase oncologist consultation time during announcement consultations
12	Provide patient education materials on metastatic disease
13	Prepare the financing of the process before its effective implementation

PO1-11-04

Breast cancer patient perspectives on the need for psychotherapy and the roll of physician referrals for improved quality of life during and post treatment

Presenting Author(s) and Co-Author(s):

J. Williams. Keepers of the Flame Foundation, Inc, United States

B. Counselman-Carpenter. Adelphi University, United States

W. Burak. Memorial Health University Medical Center, United States

Objective: The purpose of this mixed methods study was to examine what factors may influence emotional suppression and emotional expression in breast cancer patients and how coping styles relate to beliefs about physician-driven referrals to therapy during the cancer treatment process to improve quality of life during and after breast cancer treatment. **Methods:** A mixed method research design consisting of quantitative methods including a demographics survey, the Courtauld Emotional Control Scale and treatment preference questionnaires followed by optional participation in a semi-structured interview. Sixty-nine participants who met the inclusion criteria were selected as the quantitative study sample and 27 participated in interviews to further discuss their personal views on therapy during breast cancer treatment, beliefs about physician-driven referrals and experiences of coping throughout and post-cancer treatment. **Results:** Demographic variables including age, marital status, income, and experience of psychotherapy prior to breast cancer diagnosis are statically significant factors that influence CECS scores and coping styles. Thematic narrative analysis of interviews revealed both Expressers and Suppressors recounted experiencing the 'Elsa effect', a term coined to describe emotional concealment as a form of emotionally protecting self and others and reported that a physician driven referral to therapy would have been helpful in terms with coping and improving quality of life. Participants universally believed that there should be some level of psychotherapy referrals for supportive mental health care during and after the treatment process. Types of supports to which they wanted to be referred, how referrals are made, why referrals are needed, language used when making referrals, what medium through which therapeutic support should be offered, and whether or not therapy referrals should be mandated were all discussed. Physician stigma related to psychotherapy was also suggested as a possible barrier. **Conclusions:** Overwhelmingly, participants who fell into either category of emotional suppressor or emotional expresser believed that there should be physician driven referrals to therapy during the breast cancer treatment process as part of best practices for improved quality of life. Both those identified as suppressors and expressers indicated high rates of concealing one's true emotional experience. This highlights the need for psychological therapy referrals to be integrated as a best practice, regardless of patient's identified coping style or demographic identities. Referral sources should be mindful of language used, patient ability to access to services and other factors as part of the referral process.

PO1-11-05

Diet quality and cardiovascular disease risk among breast cancer survivors in the Pathways Study

Presenting Author(s) and Co-Author(s):

I. Ergas. Division of Research, Kaiser Permanente Northern California, United States
J. Roh. Division of Research, Kaiser Permanente Northern California, United States
L. Kushi. Division of Research, Kaiser Permanente Northern California, United States
C. Iribarren. Kaiser Permanente Division of Research, United States
M. Nguyen-Huynh. Kaiser Permanente Division of Research, United States
J. Rana. Kaiser Permanente Division of Research, United States
E. Rillamas-Sun. Fred Hutch Cancer Center, United States
C. Laurant. Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States
V. Lee. Kaiser Permanente Division of Research, United States
R. Cheng. University of Washington, United States
H. Greenlee. Fred Hutch Cancer Center, United States
M. Kwan. Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States

Background: While studies have shown that breast cancer survivors with healthier diets have a lower risk of non-breast cancer-specific and all-cause mortality after a breast cancer diagnosis, the relationship between diet quality and cardiovascular disease (CVD) among breast cancer survivors is not well characterized. We examined the association between diet quality at the time of breast cancer diagnosis and CVD-related outcomes in the Pathways Study, a prospective cohort of 3,415 women diagnosed with invasive breast cancer. **Methods:** This analysis included four diet quality indices (DQIs) consistent with healthy eating: 1. Dietary Approaches to Stop Hypertension (DASH), 2. healthy plant-based dietary index (hPDI), 3. 2015 Healthy Eating Index (HEI), 4. American Cancer Society nutrition guidelines (ACS). Each DQI was calculated from food frequency questionnaires (FFQ) at or around the time of breast cancer diagnosis, between 2005 and 2013, with a higher score representing a more healthful dietary pattern. DQI scores were categorized into quartiles with the most concordant diets in the highest quartile and the least concordant diets in the lowest quartile, for each DQI. CVD outcomes were ascertained through December 31, 2021 and included ischemic heart disease, heart failure, cardiomyopathy, stroke/transient ischemic attack, arrhythmia, cardiac arrest, valvular disease, venous thromboembolic disease and CVD-related death. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated from proportional hazards regression accounting for clinical and demographic factors. **Results:** FFQs were completed an average 2.2 (range=0.3-7.6) months after a breast cancer diagnosis, and a total 623 (18.2%) incident CVD events and 340 (10.0%) CVD-related deaths were ascertained over 39,263 person-years of follow-up. Participants in the highest quartile of the DASH DQI had substantially reduced risks of heart failure (HR=0.50, 95% CI 0.31-0.81), arrhythmia (HR=0.76, 95% CI 0.62-0.93), cardiac arrest (HR=0.75, 95% CI 0.60-0.93), valvular disease (HR=0.77, 95% CI 0.62-0.96), venous thromboembolic disease (HR=0.74, 95% CI 0.59-0.92), and a 33% reduced risk of CVD-related death (HR=0.67, 95% CI 0.48-0.95) relative to those in the lowest quartile. Tests for trend across quartiles of the DASH DQI were also statistically significant at a p-value < 0.03. The only notable association found in the other three DQIs was between hPDI and lower risk of heart

failure (HR=0.61, 95% CI 0.39-0.95) in women in the highest quartile compared to the lowest quartile (Table 1). Summary: These findings suggest that diets concordant with DASH and hPDI dietary patterns, may be beneficial for preventing CVD and CVD-related death after a breast cancer diagnosis.

Table 1. Cox proportional hazard ratios and 95% confidence intervals for quartiles of diet quality indices and CVD events and CVD-related death

Index	Range	heart failure (n=3,327)		arrhythmia (n=3,149)		cardiac arrest (n=3,401)		valvular disease (n=3,344)		venous thromboembolic (n=3,318)		CVD-related death (n=3,402)	
		E(n)	HR (95% CI)	E(n)	HR (95% CI)	E(n)	HR (95% CI)	E(n)	HR (95% CI)	E(n)	HR (95% CI)	E(n)	HR (95% CI)
DASH (max=40)													
Q1	10-20	52	ref*	80	ref*	20	ref*	18	ref*	44	ref*	91	ref*
Q2	21-24	65	0.84 (0.58, 1.24)	110	0.90 (0.75, 1.07)	22	0.90 (0.75, 1.09)	26	0.90 (0.75, 1.08)	57	0.89 (0.74, 1.06)	105	0.84 (0.62, 1.13)
Q3	25-27	45	0.78 (0.51, 1.20)	78	0.84 (0.69, 1.02)	5	0.88 (0.71, 1.08)	21	0.88 (0.72, 1.08)	36	0.87 (0.71, 1.06)	69	0.67 (0.47, 0.94)
Q4	28-37	33	0.50 (0.31, 0.81)	86	0.76 (0.62, 0.93)	3	0.75 (0.60, 0.93)	25	0.77 (0.62, 0.96)	39	0.74 (0.59, 0.92)	74	0.67 (0.48, 0.95)
hPDI (max=95)													
Q1	27-45	59	ref*	90	ref	19	ref	19	ref	44	ref	84	ref
Q2	46-51	48	0.75 (0.49, 1.13)	91	1.03 (0.86, 1.23)	13	1.09 (0.90, 1.32)	17	1.07 (0.89, 1.30)	48	1.03 (0.85, 1.24)	101	1.06 (0.77, 1.45)
Q3	52-56	48	0.82 (0.55, 1.24)	86	1.12 (0.93, 1.36)	11	1.04 (0.85, 1.29)	30	1.11 (0.91, 1.36)	42	1.01 (0.82, 1.23)	76	0.98 (0.70, 1.38)
Q4	57-77	40	0.61 (0.39, 0.95)	87	0.90 (0.74, 1.10)	7	0.94 (0.76, 1.17)	24	0.91 (0.74, 1.13)	42	0.93 (0.76, 1.14)	78	0.90 (0.64, 1.27)
HEI (max=100)													
Q1	34-65	46	ref	91	ref	20	ref	20	ref	35	ref	97	ref
Q2	66-72	63	1.34 (0.90, 2.00)	83	0.85 (0.71, 1.02)	17	0.90 (0.74, 1.09)	21	0.94 (0.78, 1.14)	52	0.91 (0.76, 1.10)	85	0.82 (0.61, 1.11)
Q3	73-79	45	0.87 (0.57, 1.34)	92	0.89 (0.74, 1.07)	9	0.93 (0.77, 1.14)	19	0.92 (0.76, 1.12)	41	0.96 (0.79, 1.16)	69	0.64 (0.47, 0.89)
Q4	80-98	41	0.80 (0.50, 1.27)	88	0.85 (0.70, 1.03)	4	0.88 (0.72, 1.08)	30	0.93 (0.76, 1.14)	48	0.92 (0.75, 1.13)	88	0.81 (0.59, 1.09)
ACS (max=15)													
Q1	0-5	51	ref	106	ref	23	ref	20	ref	52	ref	94	ref
Q2	6-7	44	0.89 (0.58, 1.37)	61	0.83 (0.68, 1.00)	11	0.91 (0.75, 1.12)	14	0.91 (0.74, 1.11)	36	0.89 (0.73, 1.08)	74	0.82 (0.59, 1.14)
Q3	8-9	45	0.86 (0.55, 1.34)	78	0.89 (0.73, 1.08)	9	0.93 (0.76, 1.15)	20	0.95 (0.77, 1.16)	37	0.95 (0.77, 1.16)	77	0.77 (0.55, 1.08)
Q4	10-15	55	0.78 (0.51, 1.21)	109	0.89 (0.73, 1.08)	7	0.90 (0.73, 1.11)	36	0.91 (0.74, 1.12)	51	0.87 (0.71, 1.07)	94	0.71 (0.51, 1.00)

Abbreviations: CVD (cardiovascular disease), TIA (transient ischemic attack), E (events), Q (quartile), DASH (dietary approaches to stop hypertension score), hPDI (healthy plant-based index score), aHEI (alternative healthy eating index score), HEI (healthy eating index score), ACS (American Cancer Society nutrition guidelines score), HR (hazard ratio), CI (confidence interval), ref (referent), ER (estrogen receptor), PR (progesterone receptor), HER2 (human epidermal growth factor receptor 2).

*Test for trend p-value < .05

^aAdjusted for age at diagnosis, race/ethnicity, education level, menopausal status, physical activity, smoking status, energy intake, alcohol intake, health plan utilization, comorbidities, cancer stage, ER status, PR status, HER2 status, and any CVD event or any cardiometabolic condition prior to BC diagnosis.

PO1-11-06

Evaluating Symptom Clusters in Patients with Breast Cancer Experiencing Aromatase Inhibitor-Associated Musculoskeletal Symptoms

Presenting Author(s) and Co-Author(s):

F. Nicole. University of Iowa Hospitals and Clinics, Iowa City, Iowa, United States

N. Henry. University of Michigan Medical School, United States

Background: Although treatment with an aromatase inhibitor (AI) for 5-10 years decreases 10-year breast cancer mortality by about 40%, up to 25% of patients will stop treatment early because of treatment-related, intolerable joint and muscular pain and stiffness, called aromatase inhibitor-associated musculoskeletal symptoms (AIMSS). We previously identified that nociplastic pain, or chronic pain in the absence of tissue damage or inflammation, is associated with increased likelihood of developing AIMSS. Other studies have found that symptom clusters, such as the SPPADE symptoms (sleep disturbance, pain, physical function impairment, anxiety, depression, and low energy/fatigue) are prevalent and co-occur in patients with cancer. Here we examine the prevalence of SPPADE symptoms for patients experiencing AIMSS and willing to enroll on a clinical trial examining use of cannabidiol (CBD) to treat their symptoms. Methods: Patients with stage 0-3 hormone receptor-positive breast cancer experiencing AIMSS (defined as worst joint pain $\geq 4/10$ during prior 7 days that developed or worsened since starting AI therapy) were eligible for enrollment in this single arm, single center phase 2 open label clinical trial (NCT04754399). Enrolled patients completed validated questionnaires at baseline and then received CBD (Epidiolex) for 15 weeks. Patient-reported outcomes (PRO) data was collected serially, including the following questionnaires which addressed SPPADE symptoms: Brief Pain Inventory (BPI) to assess pain, PROMIS Profile 29+2 v2.1 to assess multiple symptoms, and Fibromyalgia Survey (FMS) to assess nociplastic pain. Results: 39 patients enrolled on this clinical trial. The median age at enrollment was 57 (range 37-59) and 21% of patients were over age 70. The majority of patients were white (92%) and average BMI was 31 (SD 6.6). Anastrozole was the most used aromatase inhibitor (74%), followed by exemestane (18%), and letrozole (8%). 5 patients (13%) required concomitant GnRHa therapy. Baseline PRO data was obtained from 37 patients. BPI average pain score over the week prior to enrollment was 5.1 (SD 1.5) and worst pain score was 7.2 (SD 1.3). Pain interference reported on the BPI was 4.1 (SD 2.1). Compared to the general population, enrolled patients reported better physical function (T-score 60.2, SE 3.7), less depression (T-score 45.5, SE 4.7) and fatigue (T-score 46.7, SE 5.1), and similar levels of anxiety (T-score 51, SE 7.1) and sleep disturbance (T-score 49.5, SE 5.9) on the PROMIS Profile. On the FMS, 62% of patients had evidence of nociplastic pain, with average score 13.3 (SD 5.7). The median number of sites of pain in the body reported by patients was 8 (range 1-16). Conclusions: While patients enrolling on an AIMSS clinical trial reported a high degree of daily pain that regularly interferes with their activities, for most patients these symptoms did not appear to have a negative impact on mood, affect, or other symptoms that typically cluster with pain. Though it is difficult to extrapolate results from a small population, the unexpected absence of co-occurring symptoms in this population raises additional questions about the interplay of AIMSS and other symptoms commonly reported in interventional AIMSS studies. Follow-up PRO data will be obtained in this clinical trial, allowing us to examine the impact of CBD use on pain, pain interference, and other patient-reported symptoms, as well as to explore which patients are more likely to obtain benefit from CBD treatment. Funding support provided by Conquer Cancer, the ASCO Foundation and the Rising Tide Foundation for Clinical Cancer Research.

PO1-11-07

Do factors other than type of surgery performed for breast cancer affect quality of life and sexual functioning in breast cancer survivors? An observational study from Northern India.

Presenting Author(s) and Co-Author(s):

S. KHARE. PGIMER, Chandigarh, Chandigarh, Chandigarh, India

D. Dhamor. PGIMER, Chandigarh, Chandigarh, India

R. IRRINKI. Postgraduate Institute of Medical Education and Research, Chandigarh, Chandigarh, India

B. Padhi. PGIMER, Chandigarh, Chandigarh, India

INTRODUCTION There is an increasing focus of the treating clinicians on issues related to quality of life and sexual functioning in breast cancer survivors. This is even more important in developing countries like India as the incidence of breast cancer in young is also significant here. However, despite this, there is little data from India on the factors affecting quality of life and sexual functioning on breast cancer survivors. Hence, we decided to perform this study.

METHODS Patients who had undergone surgery for breast cancer within the last 2-5 years were included. Patients having significant psychiatric illness were excluded and so were patients who developed metastasis or local recurrence during the follow up. Questions on demographics, clinical history, standard of living index, quality of life (SF-36 questionnaire) and sexual function (CSFQ questionnaire) were asked. Data was analyzed using SPSS v22. Normality of continuous data was tested by Kolmogorov–Smirnov and Shapiro–Wilk tests. As a test of significance, chi square was used for qualitative data and t-test, Mann-Whitney U, and Kruskal-Wallis were used (as applicable) for quantitative data. Bonferroni adjustment was made wherever significance was found, if more than 1 group were involved. Multiple linear regression was carried out for quantitative dependent variables where significant risk factors were found. Independent variables with significant collinearity were excluded from linear regression.

RESULTS A total of 120 patients were enrolled. In QOL scores, both physical health ($B = -13.76$, $p = 0.007$) and emotional problems ($B = -10.65$, $p = 0.035$) were affected adversely by endocrine therapy. Patients who had received radiotherapy had worse emotional well-being scores ($B = -14.61$, $p < 0.001$). Patients who received chemotherapy or were married had significantly better social functioning score ($B = 15.27$, $p = 0.020$, $B = 17.38$, $p = 0.041$ respectively), whereas it was worse in patients who received trastuzumab ($B = -18.32$, $p = 0.024$). Pain scores were higher in premenopausal patients ($B = 11.95$, $p = 0.021$) and lower in patients having co-morbidities ($B = -10.95$, $p = 0.039$). None of the factors affected physical functioning, energy/fatigue, general health or health change scores. In sexual functioning scores, pleasure score ($B = 1.27$, $p = 0.011$) frequency scores ($B = 1.97$, $p = 0.012$), orgasm score ($B = 3.43$, $p = 0.019$) and total score ($B = 12.30$, $p = 0.006$) were higher in married women. Pleasure score was found to be lower in patients with co-morbidities ($B = -0.82$, $p = 0.003$). None of the factors affected desire or arousal.

CONCLUSION Even though sexual functioning depended a lot on having a long-term partner, most of the factors affecting quality of life scores were treatment related. Actively addressing these concerns may help in improving quality of life and in turn, may improve compliance to treatment and follow-up.

PO1-11-08

Late effects of breast cancer treatment among long term breast cancer survivors in the Carolina Breast Cancer Study

Presenting Author(s) and Co-Author(s):

R. Yarosh. University of North Carolina at Chapel Hill, United States

H. Nichols. University of North Carolina at Chapel Hill, United States

R. Hirschey. University of North Carolina at Chapel Hill, United States

E. Kent. University of North Carolina at Chapel Hill, United States

L. Carey. UNC-Lindberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

M. Troester. UNC-Chapel Hill, United States

E. Butler. University of North Carolina at Chapel Hill, United States

Background: Improved precision in breast cancer treatment has contributed to better overall survival. Intensive breast cancer treatments may have long-term impacts on survivor quality of life. Survivors may experience late effects including lymphedema, peripheral neuropathy, and cardiotoxicity from surgery, radiation, or chemotherapy. Estimates of the long-term burden of chronic breast cancer related conditions are important for managing the care of survivors.

Methods: The Carolina Breast Cancer Study 3 is a population-based study of female breast cancer survivors diagnosed from 2008 to 2013 in North Carolina. Black and younger (< 50 years at diagnosis) women were oversampled. We calculated the cumulative prevalence of self-reporting of ever being diagnosed with lymphedema, peripheral neuropathy, or cardiac/heart problems as a result of breast cancer treatment over a 10-year follow-up period. Prevalence differences (PD) and 95% confidence intervals (CI), adjusted for age and race, were calculated to describe the differences in late effects in relation to patient characteristics (including latent class SES and access to care barriers). Additionally, we assessed racial disparities in the prevalence of late effects.

Results: We included 1133 women who completed follow-up assessments at a mean of 11.2 years (SD=0.5) post diagnosis. The sample was predominately diagnosed with early stage (89.2%) and ER+ disease (75.2%). Treatments included lymph node removal (>5 lymph nodes 57.9%), anthracycline chemotherapy (34.1%), taxane chemotherapy (60.3%), breast conserving surgery (58.7%), and mastectomy (41.0%). The prevalence of self-reporting lymphedema was 39.9% and was more common among younger (< 50 vs ≥50 PD: 10.2%, CI 4.7-15.7) and Black women (vs. White PD: 19.1%, CI 13.5-24.7), and those with fewer access to care barriers (vs more PD: -19.5%, CI -31.1- -8). The prevalence of peripheral neuropathy was 64.9% and was more common among younger (< 50 vs ≥50 PD: 5.6%, CI 0.2-11.0) and Black women (vs. White PD: 16.5%, CI 11.1-21.9), and those of lower SES (high vs low PD: -11.7%, CI -17.6- -5.7). Rural survivors were less likely to report peripheral neuropathy (PD: -9.7%, CI: -17.5- -2.0). Cardiac problems were reported in 16.7% of the sample and were more common among those of high SES (vs. low PD: -7.7%, CI -12.5, -3.0).

All three late effects were associated with higher stage disease, ER+ disease, number of lymph nodes removed, anthracycline chemotherapy, and taxane chemotherapy. Both lymphedema and peripheral neuropathy were associated with mastectomy. Lymphedema was associated with trastuzumab use. Peripheral neuropathy was associated with recurrence.

In stratified analyses by ER status, Black women were 13.7-28.8% more likely to have lymphedema in both ER+ and ER- disease (ER+ PD Black vs. White: 13.7%, CI 7.9-20.3; ER- PD Black vs. White: 28.8%, CI 18.3-39.3). Similar patterns were seen in analyses stratified by number of lymph nodes removed and by taxane chemotherapy. Other associations were not suggestive of racial disparities; with one exception. Black women were more likely to have cardiac problems at both high and low levels of SES (High Black vs White PD: 2.8%, CI -3.0, 8.6; low Black vs White PD: -7.0%, CI -15.2, 1.2).

Conclusions: This study identified patient characteristics associated with an increased burden of late effects. Black and younger women experience a higher burden of lymphedema and peripheral neuropathy. Disease stage, ER status, lymph nodes removed, and chemotherapy received were associated with a higher prevalence of all three late effects and this is consistent with the observation that the burden of late effects increases with factors associated with more advanced stage of disease. Improved surveillance and prevention measures for breast cancer late effects can help improve survivorship care.

PO1-11-09

Body composition correlates with BMI and menopausal status in patients with breast cancer

Presenting Author(s) and Co-Author(s):

T. Tsou. The Johns Hopkins University School of Medicine, United States

T. Wang. Johns Hopkins University School of Medicine, United States

A. Blackford. Johns Hopkins University, Baltimore, Maryland, United States

R. Summers. National Institutes of Health Clinical Center, United States

V. Stearns. Johns Hopkins University, Baltimore, Maryland, United States

J. Sheng. Johns Hopkins University, United States

Background: Obesity is associated with higher risk of breast cancer (BC)-related death, all-cause mortality, and recurrence. While used to estimate body fat, body mass index (BMI) is insensitive to body fat distribution and lean muscle mass. We hypothesized that BMI categories (BMI 18.5-24.9 [healthy], 25-29.9 [overweight], and ≥ 30 kg/m² [obesity]) would not correlate with CT-derived body composition. Methods: We retrospectively identified 180 patients diagnosed with new or recurrent Stage I-IV BC who presented to Johns Hopkins from 2015-2018 and were part of an institutional database. We extracted demographics, diagnosis date, cancer characteristics, BMI, and CT abdomen pelvis scans from the medical record. Baseline BMI was defined as the closest measurement to diagnosis between 1 year prior and 1 month after diagnosis. Baseline CT was within 6 months of and closest to the baseline BMI date. Fully automated deep-learning algorithms identified L1 and performed muscle and adipose tissue segmentation and quantification. Body composition data included: cross-sectional areas (CSA) of subcutaneous, visceral, and total adipose tissue; the mean, median, and standard deviation of the average of the muscle attenuation (density); and the body wall musculature CSA. ANOVA tests assessed associations between body composition, BMI, and menopausal status. Results: Among 180 patients, 136 (76%) had early-stage BC, and 44 (24%) had metastatic BC. Most patients were women (98%) and non-Hispanic (94%). Patients identified as White (57%), Black (29%), Asian (6%), and Other Race (8%). Sixty percent were post-menopausal. Hormone receptor-positive, HER2-positive, and triple negative subtypes were 56%, 19% and 22%, respectively. At diagnosis, 24% had a healthy BMI while 36% and 41% had overweight and obesity, respectively. All body composition measures were significantly associated with BMI (Table 1). As BMI increased, the average body wall musculature and subcutaneous, visceral, and total adipose tissue CSAs increased while the average muscle attenuation decreased. Specifically, the average visceral adipose tissue CSAs were 2.7 and 4.0-fold larger for overweight and obesity compared to that of the healthy BMI group, respectively, while their average muscle attenuations were 62.4% and 40.6% of the healthy BMI group. Postmenopausal women had 1.5-fold higher visceral adipose tissue CSA and 44.7% less average muscle attenuation compared to premenopausal women. Conclusion: Body composition correlates with all BMI categories in primarily white, non-Hispanic women with breast cancer. As BMI increases, body composition changes reliably, with increased subcutaneous and visceral adipose tissue, increased muscle area, and decreased muscle density. Muscle density, not size/area, is more associated with muscle performance, which can relate to functional status and outcomes. Despite validity concerns, BMI is an accessible and economical surrogate for body adiposity in patients with breast cancer. Postmenopausal status was also associated with greater visceral and total adiposity and lower muscle density. Further investigation is needed to confirm these findings.

Table 1: Correlation between body composition, BMI, and menopausal status in patients with breast cancer

		BMI Categories			P-value	Menopausal Status			P-value
		Healthy (N=43)	Overweight (N=64)	Obesity (N=73)		Pre-menopausal (N=64)	Post-menopausal (N=108)	Unknown (N=8)	
Cross Sectional Area (cm ²)	Subcutaneous Adipose Tissue								
	Mean [SD]	86.2 [48.7]	154 [52.4]	279 [125]	<0.001	169 [117]	196 [112]	243 [199]	0.154
	Visceral Adipose Tissue								
	Mean [SD]	33.4 [30.8]	89.6 [49.0]	135 [85.0]	<0.001	67.7 [61.7]	103 [64.3]	201 [155]	<0.001
Total Adipose Tissue									
	Mean [SD]	120 [72.8]	244 [85.1]	414 [181]	<0.001	237 [169]	298 [158]	444 [318]	0.002
Body Wall Muscle									
	Mean [SD]	77.6 [15.4]	93.8 [17.7]	120 [34.2]	<0.001	97.2 [28.6]	98.6 [25.1]	152 [59.8]	<0.001
Average Muscle Attenuation (HU)	Mean								
	Mean [SD]	33.0 [14.3]	20.6 [16.8]	13.4 [16.7]	<0.001	29.1 [17.9]	16.1 [16.0]	13.4 [16.7]	<0.001
	Median								
	Mean [SD]	40.3 [15.0]	28.2 [18.9]	21.0 [18.8]	<0.001	37.1 [18.9]	23.3 [18.0]	22.2 [18.2]	<0.001
Standard Deviation									
	Mean [SD]	37.8 [6.65]	39.8 [6.07]	40.7 [5.01]	0.0354	39.1 [6.86]	40.0 [5.24]	39.6 [6.41]	0.687

All measures of body composition were significantly associated with BMI. Visceral adipose tissue increased and muscle density decreased as BMI increased and with post-menopausal status.

PO1-11-10

Use of a standardized tool for the evaluation and treatment of cancer related cognitive impairment (chemo-brain) among breast cancer patients.

Presenting Author(s) and Co-Author(s):

J. Librett. Survivor Healthcare, Salt Lake City, Utah, United States

M. Kosinski. QualityMetric, United States

G. Litton. Survivor Healthcare, United States

There is a steep linear increase in patients surviving a cancer diagnosis. Clinical solutions that address the high prevalence of cancer-related treatment effects (CRTE) are urgently needed. A stark example of this need is the dearth of screening and treatment programs for cancer related cognitive impairment (CRCI) (colloquially called "chemo-brain"). Up to 75% of cancer patients report neurocognitive changes that leave patients unable to cope with the expectations of employers, colleagues, families, and friends. The prevalence of neurological disorders is 275% higher among adult cancer patients, when compared to an adult cancer-free population. For many adolescent and young adult cancer patients, the onset of CRCI occurs during "cognitive prime time"; a time when individuals are pursuing education, careers, and raising families. To address a gap in CRTE we have implemented a virtual multi-disciplinary intervention to measure and treat CRCI. Our CRCI intervention follows National Comprehensive Cancer Network and American Society of Clinical Oncology (ASCO) guidelines for CRCI. These guidelines indicate a multi-disciplinary approach with emphasis on increasing physical activity levels, cognitive-behavioral therapy, memory adaptive training, mood management, and sleep optimization. Our approach also follows recent ASCO guidelines for nutrition counseling. Our CRCI program utilizes medical oncologists, physician assistants, mental health therapists, registered dietitians, and occupational therapists. A nationally validated patient reported outcome (PRO) measurement, analysis, and reporting platform informs clinical treatment pathways, monitors patient progress, guides clinical decision making, and improves patient/provider communication. Using health status measures for CRCI, and following American Cancer Society and ASCO guidelines, patients are risk-stratified into three personalized cancer survivor care pathways: 1) low-complexity patients; 2) medium-complexity patients; and 3) high-complexity patients. Low-complexity patients baseline PROs score in the normal range, medium-complexity patients are those who score below the norm (moderate to large effect size difference from normal), and high-complexity patients are those who score well below the norm (greater than larger effect size difference from normal). Low-complexity patients are enrolled into a self-management and continuation of care program. Medium-complexity patients are enrolled into a shared care program. High-complexity patients are enrolled into an acute care program. All three clinical pathways include continued risk-factor vital-sign surveillance. Nearly 100% (99%) of patients who enroll in our primary cancer survivor care program complete our PRO baseline (N=80). From a convenient sample of breast cancer patients (N=42), provisional results of patient-specific segmentation analyses reveal a nearly perfect bell-shaped curve, with 51% of the population classified within the definition of medium-complexity and even split of outliers (high-complexity 24% and low-complexity 24%). Additionally, of all patients in our primary cancer survivor care program who completed at least three measurement time points for health status measures of cognitive impairment (N=38), 92% had a positive experience, 71% had a clinically significant improvement in cognitive health, 21% had a no change in cognitive status, and only 8% had a decline in cognitive health. If these data, and PRO implementation approach hold true, this program could be scaled to

national and international cancer survivor population suffering from CRCI.

PO1-11-11

A Novel Body Composition Risk Score (B-Score) and Overall Survival among Patients with Early-Stage Breast Cancer

Presenting Author(s) and Co-Author(s):

E. Cheng. Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York, United States

B. Caan. Kaiser Permanente Northern California Division of Research, United States

W. Chen. Dana-Farber Cancer Institute, United States

C. Prado. Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada

E. Cespedes Feliciano. Kaiser Permanente Northern California Division of Research, California, United States

Background: Measurements (amount, distribution, and radiodensity) of muscle and adipose tissue were reported to be individually associated with overall survival in breast cancer survivors, but they were not typically combined to develop an overall risk score. Such a score can identify patients at high risk of death and prioritize patients in need of lifestyle interventions. **Objectives:** We developed a novel body composition risk score (B-Score) by combining multiple tissue measurements. **Methods:** We included 3105 patients with stage II or III breast cancer (diagnosed from 2000 to 2013) at Kaiser Permanente Northern California and Dana Farber Cancer Institute. From CT scans at diagnosis, we used the third lumbar vertebrae as the landmark to assess areas (cm²) and radiodensity (HU) of muscle and adipose tissue. We divided the area by height² (m²) to derive the index and measured the average HU of the tissue area as the radiodensity, which acts as a marker of tissue 'quality' to be indicative of lipid content, inflammation, and angiogenesis. Out of all tissue measurements, we considered skeletal muscle index (SMI), subcutaneous adipose tissue index (SATI) and SAT radiodensity as they were independent predictors for overall survival. Each measurement was dichotomized using optimal stratification, with low SMI (< 40.1cm²/m²), high SATI (≥75.7cm²/m²), and high SAT radiodensity (≥ -97.2HU) considered risk factors. We calculated B-Score as the sum of these factors and estimated its association with overall survival using Cox proportional hazards regression with adjustment for clinicopathologic factors. **Results:** Mean (standard deviation) age at diagnosis was 53.9 (11.8) years, 2161 (70.1%) were Non-Hispanic White, 1880 (60.5%) were stage II, and 919 (29.6%) died over a median follow-up of 10.7 years. Most patients (60.6%) had only one body composition risk factor (B-Score = 1). Compared to those with no body composition risk factors (B-Score = 0), the risk of death increased with more body composition risk factors: the adjusted hazard ratios were 1.10 (95% CI: 0.85, 1.42), 1.47 (95% CI: 1.12, 1.92), and 2.11 (95% CI: 1.26, 3.53) for B-Scores of 1, 2, and 3, respectively (Ptrend < 0.001). **Conclusions:** More unfavorable body composition characteristics were associated with increased risks of overall mortality in a dose-response manner. Considering body composition measurements together as a composite score (B-Score) may prove a useful tool to identify patients at high risk of death following breast cancer diagnosis.

Table. Adjusted Associations of the Body Composition Risk Score (B-Score) with Overall Mortality Among Patients with Early-Stage Breast Cancer

B-Score ^a	No. of Death/at Risk	Adjusted HR ^b
0	70/322	1.00
1	501/1881	1.10 (0.85, 1.42)
2	329/865	1.47 (1.12, 1.92)
3	19/37	2.11 (1.26, 3.53)
<i>P</i> _{trend}	-	<0.001

Abbreviations: HR, hazard ratio.

a Areas (cm²) and radiodensity (HU) of skeletal muscle and subcutaneous adipose tissue (SAT) were extracted from the single axial CT slice at the third lumbar vertebra. The body composition risk score was defined as the sum of three risk factors: low skeletal muscle index (SMI; <40.1cm²/m²), high SAT index (SATI; ≥75.7cm²/m²), and high SAT radiodensity (≥ 97.2HU).

b Adjusted for age (years), race and ethnicity (Asian, Black, Hispanic, Non-Hispanic White, and Others), stage (II, III), ER (ER+, ER-), PR (PR+, PR-), HER2 (HER2+, HER2-, unknown), smoking (current, former, never), Charlson comorbidity index (0, 1-2, ≥3), and BMI (<18.5, 18.5-24.9, 25-29.9, and ≥30 kg/m²). For the trend test, B-Score was considered as a continuous variable with adjustment for the above covariates.

PO1-11-12

Factors associated with treatment failure for chemotherapy-induced nausea and vomiting (CINV) among breast cancer patients receiving adjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

W. Yeo. Chinese University of Hong Kong, Hong Kong

N. Ngai. Chinese University of Hong Kong, Hong Kong

H. Yeo. Chinese University of Hong Kong, Hong Kong

D. Lai. Chinese University of Hong Kong, Hong Kong

E. Pang. Chinese University of Hong Kong, Hong Kong

C. Kwok. Princess Margaret Hospital, Hong Kong

T. Lau. Chinese University of Hong Kong, Hong Kong

F. Mo. Chinese University of Hong Kong, Hong Kong

Background Cancer patients often consider CINV as one of the most disturbing side effects of cytotoxic chemotherapy. Adriamycin and cyclophosphamide (AC), considered by many to be part of the standard adjuvant regimen for breast cancer patients, is highly emetogenic. Despite adopting optimal antiemetic prophylaxis, the control of CINV remains modest for some patients. Among Chinese breast cancer patients receiving adjuvant AC chemotherapy, the present analysis aims to determine the association of the number of risk factors for CINV with (i) likelihood of antiemetic treatment failure; (ii) time to first vomiting in 1st AC cycle. **Methods:** We retrieved data from three previously reported prospective antiemetic studies on patients who received AC, in whom different antiemetic regimens were administered. Treatment failure was defined as (i) not achieving CR (CR= no vomiting and no use of rescue medication over 120 hours after start of AC), or (ii) experiencing nausea (nausea VAS \geq 5mm during the 120 hours). Multivariate logistic regression models were applied to identify potential factors associated with the development of CINV. The Cochran–Armitage trend test was utilized to assess possible trends in the relationship between treatment failure and number of identified risk factors. The time-to-treatment failure curves, as classified by the number of identified factors in each subgroup, were evaluated using the Kaplan–Meier method. **Results:** Based on multivariate analysis of 303 breast cancer patients, not achieving CR was more likely among non-obese patients, not receiving guideline recommended prophylactic antiemetic regimens, history of motion sickness and history of vomiting in pregnancy. Experience of nausea was more likely in non-obese patients, not receiving guideline recommended prophylactic antiemetic regimens, and history of motion sickness. Treatment failure in terms of ‘no CR’ was associated with increased number of risk factors that an individual patient displayed; the figures increased from 18.8% for those with 0 risk factor to 94.1% for those with 4 risk factors ($p < 0.0001$). Treatment failure in terms of nausea was associated also with increased number of risk factors; the figures increased from 25.9% for those with 0 risk factor to 83.3% for patients with 3 risk factors ($p < 0.0001$).

Time to first vomiting was significantly related to number of identified factors ($p < 0.0001$). Among patients who had 0, 1, 2 and 3 risk factors, the 24-hour rate of ‘no vomiting’ were 81.3%, 80.3%, 66.7%, 53.7% and 17.7%, respectively; similar trends were observed for analyses on 48-hour and 72-hour rates. **Conclusions:** The present study confirmed that reported risk factors for CINV in the literature were important in Chinese breast cancer patients receiving AC chemotherapy. Furthermore, patients who had more risk factors had increased likelihood of treatment failure and shorter time to first vomiting. **Funding:** Madam Diana Hon

Fun Kong Donation for Cancer Research

PO1-12-01

'Not even my husband knows that I have this [breast cancer]': Survivors' Experiences in Accessing, Navigating and Coping with Treatment.

Presenting Author(s) and Co-Author(s):

R. Chidebe,. Miami University, Ohio, USA, Project PINK BLUE - Health & Psychological Trust Centre, United States

T. Orjiakor,. Department of Psychology, University of Nigeria, Nsukka, United States

G. Okwu. Project PINK BLUE- Health & Psychological Trust Centre, United States

M. Orji. Network of People Impacted by Cancer in Nigeria, United States

T. Nwosu-Zita. NETWORK OF PEOPLE IMPACTED BY CANCER IN NIGERIA (NEPICIN), UTAKO, Federal Capital Territory, Nigeria

A. Agha. Department of Social Work, University of Nigeria Nsukka, United States

S. Aruah. National Hospital Abuja & College of Medicine, University of Abuja, United States

C. Okem-Akwivu. Breast Health Angels Foundation, USA, United States

C. Nwakasi. Department of Human Development and Family Sciences, University of Connecticut, Storrs, CT, USA., United States

A. Adjei Gyimah. Department of Sociology & Gerontology, Miami University, Ohio, USA, United States

Z. Shinkafi-Bagudu. Medicaid Cancer Foundation, Nigeria, United States

I. Okoye. College of Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria; University of Nigeria Centre of Excellence for Clinical Trials, Enugu Campus, Nigeria, United States

D. Esiaka. Department of Family Medicine and Community Health, Rutgers University, New Brunswick, NJ, USA, United States

Purpose: Nigeria has the highest breast cancer (BC) burden in Africa. While the survival rates for BC are over 90% in many high-income countries; low-and middle-income countries like Nigeria have 40% BC survival rates. Prior studies show that the burden and poor BC survival rates are exacerbated by both health system and individual level factors, yet there is a paucity of literature on the experiences of BC survivors in Nigeria. Hence, this study explored BC survivors' divergent and convergent experiences in accessing, navigating, and coping with treatment.

Methods: Participants (N=24, aged 35 to 73 years) were recruited and engaged in focus group discussions (Group 1, n = 11; Group 2, n = 13 participants). Transcripts were transcribed verbatim and analyzed with inductive thematic analysis.

Results: Four themes were identified: "I am carrying this [breast cancer] alone", "Living my life", "God' helped me", and "A very painful journey". Participants described how they concealed their BC diagnosis from family and significant others while accessing and navigating BC treatment. Also, they adopted spiritual beliefs as a coping mechanism while sticking to their treatment and acknowledging the burden of BC on their wellbeing.

Conclusions: Our findings point to the urgent need for improved BC treatment facilities in Nigeria.

Implications for Breast Cancer Survivors: Nigeria BC survivors are navigating both limited treatment facilities and coping with the personal challenges of BC diagnosis. There is a need for the government and clinicians to explore innovative technologies in improving BC treatment experiences in Nigeria.

PO1-12-02

Impact of Discontinuation of Denosumab on Bone Health in Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

S. Tannenbaum. Uconn Health, West Hartford, Connecticut, United States

A. Alvarez Soto. University of Connecticut Hospital, United States

P. Taxel. UCONN Health, United States

Denosumab (Dmab), an inhibitor of osteoclast activity and proliferation is approved for treatment of women on aromatase inhibitor (AI) therapy for early breast cancer (60 mg Q 6-months) and metastatic disease (120 mg Q 4-weeks) to protect against bone loss and prevention of skeletal-related events (SREs). 60 mg given twice a year has shown fracture reduction, especially in women on aromatase inhibitor therapy, and recent data supports benefits in disease free survival, bone-metastasis free-survival and overall survival with Dmab in early breast cancer. It appears superior in reduction of SREs versus zoledronic acid (ZA) in established skeletal metastatic disease; thus, a preferred choice in the oncology setting. In the osteoporosis setting, withdrawal of Dmab therapy leads to a “rebound” increase of bone resorption, rapid bone loss and potential vertebral fractures. Increased risk of spontaneous and multiple vertebral fractures has been seen in this patient population. To prevent this, after discontinuation of Dmab, the addition of another anti-resorptive such as ZA is initiated. Dmab withdrawal events are uncommonly reported in patients with metastatic skeletal disease due to generally poor prognosis. Dmab given as 120 mg/month in this setting may need to be curtailed for a variety of indications including hypocalcemia, major dental procedures, osteonecrosis of the jaw or atypical femoral fracture. In the oncologic setting, it is unclear if discontinuation of Dmab will lead to rebound bone resorption or increased incidence of fractures.

We describe the case is of a 32-year-old woman with a history of T2N3M1, oligometastatic breast cancer (solitary bone metastases at L1, biopsy-proven) that was ER/PR/HER2 positive. She was treated with neoadjuvant trastuzumab, pertuzumab, taxotere and carboplatin followed by bilateral mastectomy, and radiation to chest wall and L1. She received total estrogen blockade initially with GnRH-agonist and exemestane and ultimately bilateral salpingo-oophorectomy plus exemestane. She continues pertuzumab and trastuzumab (80 treatments to date) for the past 5 years and denosumab 120 mg/month for 14 treatments and then every 3 months, 20 total treatments. Development of hip pain (regular runner) and concern for atypical fracture vs metastatic disease led to bone scan and PET/CT. Metastatic disease was ruled out and stress reaction was diagnosed. Dmab therapy was discontinued with monitoring of her metabolic bone turnover. 1 year after her last Dmab injection, bone turnover markers began to increase and ultimately demonstrated a very significant “rebound phenomenon.” Subsequently, a single dose of 120 mg denosumab decreased bone markers to previously low levels which remain low on routine monitoring, table below. In future, ZA will be initiated and continued on a yearly basis.

Dmab has replaced ZA in managing bone health in breast cancer patients. Many oncologists use this without the assistance of bone health endocrinologists, who are an integral part of our cancer center. Bone modifying agents are often discontinued without consideration of the negative impact this may have. As this is a major survivorship issue, we document this case

with literature review, to raise awareness for oncologists prescribing these medications.

Labs	Prior to Dmab D/C	14 months post last Dmab	4-weeks post 1 - dose Dmab	5 Mo post 1 dose- Dmab
Total /Bone-alk phos (U/L) premenopausal	36/9.2 (4-14 U/L)	135 /54.3	67/17.8	40/9.3
U Ntx (nmol BCE/mmol Cr) premenopausal	15 (17-29)	143, repeat 147	12	14
sCTX (pg/ml) premenopausal	N/A (136-689)	3345, repeat 3294	64	75

PO1-12-03

Quality of Life in Patients Diagnosed and Treated for Breast Cancer in Uruguay

Presenting Author(s) and Co-Author(s):

N. Camejo. Servicio de Oncología Clínica, Hospital de Clínicas, Montevideo, Uruguay, United States

D. Amarillo. Hospital de Clínicas, United States

C. Castillo. Servicio de Oncología Clínica, Hospital de Clínicas, Montevideo, Uruguay, United States

M. guerrina. Hospital de Clínicas, United States

F. Savio. Hospital de Clínicas, United States

M. Carrasco. Hospital de Clínicas, United States

N. Strazzarino. Hospital de Clínicas, United States

A. Hernandez. Hospital de Clínicas, United States

G. Herrera. Hospital de Clínicas, United States

G. Krygier. Servicio de Oncología Clínica, Hospital de Clínicas, Montevideo, Uruguay, Uruguay

Introduction: Breast cancer (BC) and its treatment can impair patient quality of life (QOL), and those undergoing more aggressive treatments may be more severely impacted. Objective: Assess the level of perception of the QOL of patients treated for BC at the Hospital de Clínicas and the Hospital Departamental de Soriano. Materials and Methods: A questionnaire for cancer patients (EORTC, QLQ-C30) and one specific for BC (EORTC QLQ-BR23) were used. Results: A total of 158 patients who had completed chemotherapy treatment at least one year prior to the evaluation were enrolled. The average age was 61 years old. QLQ-C30 questionnaire: the global QOL score (GQOL) was high: 70.9. Patients undergoing conservative surgery (CS) had better scores in physical and emotional functioning ($p < 0.005$) and presented less frequently with: pain, constipation and financial difficulties ($p < 0.005$). Those undergoing sentinel lymph node biopsy (SLNB) had higher scores for GQOL and for physical, role and social functioning scales ($p < 0.001$) and had less fatigue, pain, insomnia and financial difficulties ($p < 0.005$). Questionnaire QLQ-BR23: sexual functioning and sexual enjoyment scales were relatively low. Patients undergoing CS had better scores on the functional scales: body image and future outlook; and fewer breast symptoms ($p < 0.005$). Those undergoing SLNB also had better scores on the functional scales for body image and future outlook future and presented less frequently with symptoms ($p < 0.005$). Conclusion: Patients had high values on the GQOL scale, those undergoing CS and SLNB had better scores on most functional and problem/symptom scales. The implementation of intervention strategies aimed at improving the quality of life and the physical and emotional care of patients is recommended.

PO1-12-04

Exploring Factors Associated with Sexual Well-being and Breast Satisfaction Among Women with Early-stage Breast Cancer

Presenting Author(s) and Co-Author(s):

K. Aldecoa. Trinity Health Oakland/Wayne State University Program, Pontiac, Michigan, United States

Y. Lee. Department of Hematology and Medical Oncology/Dartmouth-Hitchcock Medical Center, United States

L. Deptula. Ross University School of Medicine, United States

C. Mbionwu. Ross University School of Medicine, United States

E. Eto. Ross University School of Medicine, United States

E. Salamatov. Ross University School of Medicine, United States

M. Frame. Ross University School of Medicine, United States

A. Ferris. Department of Hematology and Oncology, Trinity Health Oakland Hospital, United States

G. Krishnamoorthy. Trinity Health Oakland/Wayne State University Program, United States

A. Kirby. Department of Surgery, Trinity Health Oakland Hospital, United States

J. Goodman. Department of Hematology and Oncology, Trinity Health Oakland Hospital, United States

BACKGROUND: Breast cancer affects not only physical health but also psychological and emotional well-being. Among the various aspects that impact the quality of life of breast cancer patients, sexual well-being and body image in terms of breast satisfaction play a crucial role. Unfortunately, these aspects are often overlooked and undervalued in healthcare, leading to inadequate care and support for breast cancer patients. This study delved into the factors that influence breast satisfaction and sexual well-being in early-stage breast cancer patients who have recently received a cancer diagnosis. We aim to offer providers a more patient-centered and comprehensive approach to breast cancer care. **METHODS:** This prospective questionnaire-based study screened 175 early-stage breast cancer patients recently diagnosed at a university-affiliated community hospital in Michigan from October 2022 to June 2023. Participants with a previous history of chemoradiation and advanced-stage breast cancer were excluded. Structured telephone interviews were conducted to obtain informed consent and assess patients' breast satisfaction and sexual well-being. Participants were interviewed after their recent breast cancer diagnosis and before undergoing surgical intervention. A validated BREAST-Q questionnaire was used, and their scores were converted to equivalent Rasch scores for interpretation (0=worst, 100=best). Pre-existing medical conditions, social history, and other variables were collected through electronic medical records review and confirmed by interview. Statistical analyses were performed using SPSS version 28.0, and a p-value less than 0.05 was considered statistically significant. **RESULTS:** Of 175 patients initially screened, 56 met the selection criteria. 75% (N=42) participated, while 25% (N=14) were excluded as they declined to participate or were unreachable via telephone. 81% were White, 14% were Black, and 5% were Hispanics. The cancer stages of the patients were Stage 0 (29.3%), I (48.8%), II (12.2%), and III (9.8%). The mean breast satisfaction score of participants was 67.1 (N=42), and the mean sexual well-being score was 44.6 (N=36). The study found that only the type of surgery was observed to be significantly related to the breast satisfaction of patients. Interestingly, patients who chose mastectomy had higher breast satisfaction scores (75.6 vs.

62.9, $p < 0.05$) and were relatively younger (59 years vs. 67 years, $p < 0.05$) than those undergoing lumpectomy. No other demographic factors (race, education, marital status, BMI), social history (smoking), bra size, or pre-existing medical conditions (hypertension, diabetes) were found to affect breast satisfaction among these patients. On the other hand, age had a negative correlation with sexual well-being (mean age=64 years, $p < 0.05$), while income had a positive correlation (mean income=\$ 76,170 annually, $p < 0.05$). No other variables were significantly associated with patients' sexual well-being. **CONCLUSION:** The study revealed that the patient's sexual well-being was significantly associated with age and income, while breast satisfaction was only related to the type of surgery. These findings underscore the importance of considering multiple aspects of a patient's life when designing a comprehensive treatment plan following a cancer diagnosis. By providing additional support and resources tailored to these specific needs, healthcare providers can enhance patients' overall quality of life and promote greater satisfaction with their treatment outcomes.

PO1-12-06

Is it appropriate to select patients for primary prophylactic use of pegfilgrastim based on the risk of febrile neutropenia?

Presenting Author(s) and Co-Author(s):

K. Narui. Yokohama City University Medical Center, United States

T. Ishikawa. Tokyo Medical University, United States

I. Takashima. University of Tokyo Hospital, United States

K. Kashiwabara. Tokyo Medical University, United States

Y. Uemura. National Center for Global Health and Medicine, United States

Y. Kikawa. Kansai Medical University Hospital, Hirakata city, Osaka, Japan

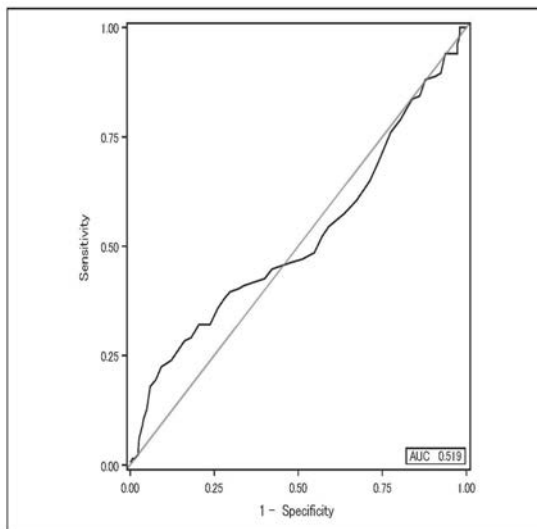
N. Taira. Kawasaki Medical University, United States

H. Mukai. Department of Medical Oncology, National Cancer Center Hospital East, Chiba, Japan

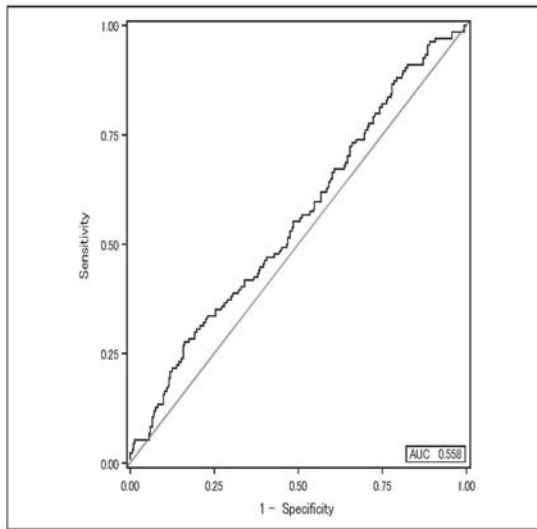
Background: Febrile neutropenia (FN), a major hematologic adverse event in perioperative chemotherapy for breast cancer, is more prevalent among Asians than in Caucasian populations. Four main guidelines, i.e., ASCO, EORTC, NCCN, and ESMO, provide recommendations regarding the appropriate use of hematopoietic growth factors. These guidelines recommend primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) based on the estimated incidence of FN, primarily defined by the chemotherapy regimen. G-CSF administration is recommended when the incidence of FN is $\geq 20\%$ or 10–20% with risk(s). However, the incidence of FN varies depending on the trial and design, and patient-specific risk factors for FN remain unclear. We previously performed a multicenter prospective cohort study in Japan, the CSPOR-BC FN study, evaluating the incidence of FN during perioperative chemotherapy for breast cancer. Herein, we conducted an additional analysis to explore thresholds of patient-specific risk factors for FN that could be evaluated before chemotherapy. We analyzed the risk factors for FN and verified the appropriateness of patient selection for prophylactic G-CSF administration. Methods: The previously reported CSPOR-BC FN study (PubMed ID=33631458) consecutively enrolled 1005 patients with stage I–III breast cancer between August 2015 and July 2017. In the current additional analysis, we intended to have 477 patients in the visiting group that evaluated true-FN, defined as $\geq 37.5^\circ\text{C}$ and grade 4 neutropenia. Multivariate analysis of risk factors for FN was performed, followed by the determination of cutoff values for age and pretreatment absolute neutrophil count (ANC) as risk factors. Results: Chemotherapy regimens administered were FEC (fluorouracil, epirubicin, and cyclophosphamide) in 170 patients (36%), E(A)C (epirubicin (doxorubicin) + cyclophosphamide) in 165 patients (35%), and TC (docetaxel + cyclophosphamide) in 142 patients (30%). The incidence of FN was 28.7% (N = 137). To evaluate the risk factors for FN, we predefined regimens, age, performance status (PS), stage, chemotherapy or radiotherapy history, infectious wounds, open wounds, ANC, and renal and liver dysfunction as potential risk factors. Multivariate analysis of risk factors for FN identified regimen (TC), age (≥ 65), low pretreatment ANC, treatment setting, and no primary pegfilgrastim prophylaxis as significant risk factors. Two patient-specific risk factors (age and pretreatment ANC) were analyzed. Logistic regression analysis revealed that age ≥ 65 years was a significant risk factor (odds ratio=2.24, 95% confidence interval: 1.34–3.75). Applying a cutoff of 65 years (age) to predict FN, the sensitivity and specificity were 28.4 and 83.8%, respectively, which were inaccurate. Despite applying a cutoff of 67 years optimized from the receiver operating characteristic (ROC) curve, the sensitivity (22.4%), specificity (90.7%), and area under the curve (0.519) indicated low

discrimination for predicting FN. The incidence of FN by age group was as follows: < 45 years, 30.8%; 45–55 years, 26.4%; 55–64 years, 20.9%; ≥65 years, 39.6%. Additionally, applying a cutoff of 2436/ μL (pretreatment ANC) optimized from the ROC curve, the observed sensitivity (27.6%) and specificity (83.8%), and area under the curve (0.558) also indicated low discrimination for predicting FN. The incidence of FN by stratum of pretreatment ANC was as follows: < 2000, 33.3%; 2000–3000, 30.7%; 3000–4000, 29.9%; and >4000, 24.6. Accordingly, setting a cutoff value to predict FN incidence using age and/or pretreatment ANC was deemed inappropriate. Conclusion: Selecting patients for primary prophylactic G-CSF based on the existing FN risk can be challenging. Primary prophylactic G-CSF would be considered for every patient undergoing perioperative chemotherapy for breast cancer, especially Asians.

ROC curve for FN and age. The AUC was 0.519.



ROC curve for FN and neutrophil count. The AUC was 0.558.



PO1-12-07

Denosumab vs. Pamidronate in the Management of Osteolytic Bone Metastases Secondary to Breast Cancer, a Multi-Institutional Analysis.

Presenting Author(s) and Co-Author(s):

M. Bradley. University of Texas Medical Branch at Galveston, United States

M. Nichols. University of Texas Medical Branch at Galveston, United States

B. Miles. Baylor University Medical Center Dallas, Department of Radiology, United States

Breast cancer is one of the most common cancers in women and is associated with poor outcomes due to the metastatic potential of high-grade tumors. One common site of breast cancer metastasis is to the bone, leading to serious adverse effects such as bone pain, bone fracture, and spinal cord compression. Denosumab, a monoclonal antibody against the receptor activator of nuclear factor kappa-b (RANK) ligand (RANKL), and Pamidronate, a bisphosphonate, are two pharmacologic agents offered for the treatment of these adverse complications. The goal of this study was to conduct a retrospective cohort analysis across multiple institutions to compare the efficacy of Denosumab vs. Pamidronate in the management of osteolytic bone metastases secondary to breast cancer by evaluating the risk of adverse events. TriNetX, an online network that provides access to anonymized medical records for more than 108 million patients in 72 large healthcare organizations, was used in this study. Two cohorts, consisting of 847 patients with a diagnosis of bone metastases and breast cancer, were created and subsequently matched for age, race, gender, and ethnicity. One cohort was given Denosumab while the other was given Pamidronate, and each cohort was excluded from receiving the other medication. The occurrence of pathologic fracture in each arm, spinal cord compression, and overall five-year survival rate was measured and analyzed. The results of this study showed that Denosumab had a statistically insignificant risk reduction in both pathological fracture (2.7% vs. 2.8%, $p = 0.88$) and spinal cord compression (2.6% vs. 2.7%, $p = 0.88$) and a statistically insignificant difference in the overall five-year survival rate (45.5% vs. 52.4%, $p = 0.78$) when compared to Pamidronate. As a result, additional factors such as financial cost, route of administration, dosing schedule, and potential adverse side effects should be discussed with each individual who requires pharmacological therapy for bone metastases secondary to breast cancer.

PO1-12-09

Doublet or triplet antiemetic prophylaxis for trastuzumab deruxtecan-induced nausea and vomiting: An open-label, randomized, multicenter, exploratory phase 2 study

Presenting Author(s) and Co-Author(s):

M. Futamura. Department of Breast Surgery, Gifu University Hospital, Japan

H. Iihara. Department of Pharmacy, Gifu University Hospital, United States

H. Bando. University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan

Y. Kawaguchi. Department of Breast Surgery, Asahi University Hospital, United States

Y. Mizuno. Department of Breast Surgery, Yokkaichi Municipal Hospital, United States

A. Murakami. Department of Breast Center, Ehime University Hospital, United States

M. Kawai. masaaki-kawai@med.id.yamagata-u.ac.jp, United States

T. Iyoda. Department of Pharmacy, Fukushima Medical University Hospital, United States

K. Ishida. Department of Surgery, Iwate Medical University, United States

K. Ishihara. Department of Surgery, Gihoku Kosei Hospital, United States

T. Nakada. Department of Breast Surgery, Central Japan International Medical Hospital, United States

M. Takeuchi. m-takeuchi@cjimc-hp.jp, United States

M. Kitahora. Department of Pharmacy, Gifu University Hospital, United States

Y. Tokumaru. Breast Surgery, Gifu University Hospital, United States

M. Shimokawa. Department of Biostatistics, Yamaguchi University Graduate School of Medicine, United States

N. Matsuhashi. Department. of Gastroenterology, Gifu University Hospital, Japan

Background: Trastuzumab deruxtecan (T-DXd) is classified as an anticancer agent that poses a moderate emetic risk according to international guidelines for antiemetic therapy, which recommend emesis prophylaxis using a two-drug combination therapy comprising 5-hydroxytryptamine-3 receptor antagonist (5-HT₃RA) and dexamethasone (DEX). The incidence rates of nausea and vomiting in patients in DESTINY BREAST01 and DESTINY BREAST03 were 77.7%, 45.7%, 72.8%, and 44%, respectively. However, no effective antiemetic therapy was observed. The high nausea and vomiting incidence associated with T-DXd is problematic. Hence, this exploratory phase 2 study aimed to assess the efficacy and safety of treatment with 5-HT₃RA and DEX, with or without a neurokinin-1 receptor antagonist (NK1RA), in preventing T-DXd-induced nausea and vomiting. Methods: We conducted an open-label, randomized exploratory phase 2 study at 14 centers in Japan. Patients with breast cancer scheduled to receive T-DXd were enrolled in this study. Patients were randomly assigned to receive granisetron and dexamethasone (arm GD) or granisetron, dexamethasone, and aprepitant (fosaprepitant; arm GDA). Patients in both treatment arms were administered granisetron (1 mg i.v. 30 min before T-DXd on day 1). Those in the GD arm were administered DEX (6.6 mg i.v. 30 min before T-DXd on day 1 and 8 mg p.o. on days 2–3). The patients in the GDA arm were administered DEX (9.9 mg i.v. 30 min before T-DXd on day 1) and NK1-RA (125 mg of aprepitant p.o. 60 min before chemotherapy on day 1 and 80 mg p.o. on days 2 and 3, or 150 mg fosaprepitant i.v. 60 min before T-DXd on day 1). The primary endpoint was complete response (CR; no emesis or rescue therapy) during the overall phase (0–120 h after the start of T-DXd). The primary endpoint was estimated using the CR rate and 95% confidence intervals

(CIs) following the Pearson–Clopper method. The Cochran–Mantel–Haenszel test was used to compare the exploratory results between the two treatment arms with age strata and previous experience with chemotherapy-induced nausea and vomiting. Logistic regression analyses were performed to determine the risk factors associated with the non-achievement of CR, non-achievement of complete control (CC), and non-achievement of total control (TC) in the overall and long-overall phases. Results: Between September 2020 and March 2023, 40 patients were enrolled and randomly assigned to either the GD (n = 19) or GDA (n = 21) arm. In the GDA group, one patient who did not complete the rescue medication listed in the diary was excluded from the efficacy analysis, including rescue medication use. The CR rates during the overall phase were 36.8% and 70.0% in the GD and GDA groups, respectively (odds ratio [OR], 0.1334; 95% confidence interval [CI], 0.0232–0.7672; P = 0.0190), with a difference of 33.2%. The CR rates during the long-overall phase were 31.6% in the GD arm and 70.0% in the GDA arm (OR, 0.1073; 95% CI, 0.0185–0.6239; P = 0.0087), a difference of 38.4%. NK1RA use was associated with a significant decrease in the non-achievement of CR, CC, and TC in the overall and long-overall phases. Only patients in the GDA arm (33.3%) reported being “very satisfied” with the treatment. No grade 3 or 4 toxicities related to antiemetic therapy were observed. Conclusions: Breast cancer patients receiving T-DXd require triple therapy, including mandatory NK1RA administration, for antiemetic prophylaxis. Further investigation is needed to explore the development of more appropriate combination therapies for T-DXd-induced nausea and vomiting.

PO1-12-10

Zoledronic acid to prevent rebound fractures after stopping adjuvant denosumab: a randomized controlled sub-study of the ABCSG-18 trial

Presenting Author(s) and Co-Author(s):

G. Pfeiler. Medical University of Vienna, Austria, Vienna, Austria

C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria

D. Hlauschek. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria

M. Diether. Doctor's office Manfreda, Klagenfurt, Austria, United States

F. Haslbauer. Department of Internal Medicine, Salzkammergutklinikum Hospital Vöcklabruck, Vöcklabruck, Austria, Austria

P. Sevelda. Department of Gynecology, Karl Landsteiner Institute for Gynecologic Oncology and Senology, Hospital Hietzing, Vienna, Austria, United States

K. Köck. Department of Gynecology and Obstetrics, Hospital Klagenfurt, Klagenfurt, Austria, United States

K. Tamussino. Department of Gynecology and Obstetrics, Medical University of Graz, Graz, Austria, United States

A. Reichenauer. Department of Surgery, Hospital BHB St. Veit, St. Veit/Glan, Austria, United States

F. Fitzal. Division of General Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria, Austria

D. Heck. Department of Hematology and Oncology, Ordensklinikum Linz – Barmherzige Schwestern, Linz, Austria, United States

R. Greil. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

C. Pasterk. Department of Gynecology, LKH Villach, Villach, Austria, United States

S. Heibl. Department of Internal Medicine IV, Klinikum Wels-Grieskirchen GmbH, Wels, Austria, United States

W. Herz. Department of Surgery, LKH Hochsteiermark, Leoben, Austria, United States

M. Balic. Division of Oncology, Department of Internal Medicine, Medical University Graz, Austria

D. Egle. Breast Cancer Center Tirol, Department of Gynecology, Medical University Innsbruck, Austria, United States

L. Sölkner. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria, United States

M. Gnant. Medical University of Vienna, Wien, Austria

Introduction ABCSG-18 trial showed that 60mg denosumab subcutaneously every 6 months halves fracture risk in postmenopausal patients with early breast cancer, who are treated with adjuvant aromatase inhibitors. However, it has been reported that stopping denosumab may lead to overactivation of osteoclasts resulting in so called rebound vertebral fractures. As

shown previously, zoledronic acid (ZA), when given to patients of the ABCSG-18 trial after stopping denosumab prevents a high bone turnover state that can occur in some patients. Here we report the impact of a single ZA dose on bone mineral density (BMD) and fractures after stopping denosumab. Methods ABCSG-18 trial patients, who had received adjuvant denosumab were re-randomized to receive a single dose of ZA 5mg i.v. or not, 8 months +/- 4 weeks after their last denosumab dose. DXA scans, lateral spine X-rays and bone turnover markers (CTX and osteocalcin) were assessed at baseline and at 6, 12 and 18 months thereafter. New clinical fractures were assessed until 18 months after randomization. Results 50 patients were randomized to either ZA (24pts) or control (26pts). All patients of the ZA arm and 25 out of 26 patients of the control arm had received 7 doses of denosumab within the ABCSG 18 trial before re-randomization. Baseline bone health factors were well balanced between the 2 arms: Baseline BMD did not differ between the two arms with regard to femoral neck (ZA: 0.817 g/cm²; SOC: 0.816g/cm²), total hip (ZA: 0.918g/cm²; SOC: 0.921g/cm²) and lumbar spine (ZA: 1.128 g/cm²; SOC 1.142 g/cm²), respectively. Relative changes in BMD differed significantly between both arms for femoral neck after 12 months (ZA: 0.5%; control: -4.98%, p 0.004) and for total hip after 6 months (ZA: -0.73%; control: -4.61%, p< 0.001) and after 12 months (ZA: -0.13%; control: -5.62%; p< 0.001). There was a trend towards a greater decline in BMD at lumbar spine after 6 months in the control arm versus the ZA arm (-3.35% vs 0.67%, p=0.052). After randomization, 3 asymptomatic fractures (lumbar vertebral and thoracic vertebral in one patient and thoracic vertebral in a second patient) occurred in the ZA arm, whereas 2 clinical fractures (one radius fracture and one lumbar vertebral fracture) occurred in the SOC arm. Conclusion A single dose of Zoledronic acid prevents high bone turnover state resulting in loss of BMD in some patients after stopping denosumab. ZA may therefore be offered to breast cancer patients with aromatase inhibitor after stopping denosumab.

PO1-12-11

How do chemotherapy and age affect physical performance in breast cancer patients over 12 months of treatment? Results from the UPBEAT Study (UPBEAT WF-97415)

Presenting Author(s) and Co-Author(s):

S. Bluethmann. Wake Forest University, Winston-Salem, North Carolina, United States

B. Levine. Wake Forest School of Medicine, United States

B. Leitzelar. Wake Forest University School of Medicine, United States

K. Ansley. Atrium Health Wake Forest Baptist Health, United States

A. Thomas. Wake Forest Baptist Health, Winston-Salem, North Carolina, United States

N. Avis. Wake Forest University School of Medicine, United States

G. Hundley. Pauley Heart Center, Virginia Commonwealth University, United States

H. Klepin. Wake Forest School of Medicine, Winston-Salem, NC, Winston-Salem, North Carolina, United States

K. Weaver. Wake Forest University School of Medicine, United States

G. Lesser. Wake Forest University School of Medicine, United States

Introduction: Chemotherapy-associated functional decline is a concern for women with breast cancer. **Objective:** To assess effects of chemotherapy and age on objectively measured physical performance among women with breast cancer over time. **Methods:** Analyses utilized the multicenter, longitudinal Understanding and Predicting fatigue, cardiovascular decline, and events after BrEast cAncer sTudy (UPBEAT), a study conducted through the Wake Forest NCORP Research Base (5UG1CA189824). We examined physical performance at baseline and at 3 and 12 months and compared means across time by age group (< 65 years v. 65+ years at baseline) and by cancer/control group. For the latter variable, we had 3 groups of participants: 1) newly diagnosed breast cancer patients with Stage 1-3 breast cancer who received chemotherapy (CC; n= 201); 2) newly diagnosed breast cancer patients receiving no chemotherapy (CNC; n=57); and age-matched healthy controls (HC; n=145). The primary outcome was the Short Physical Performance Battery (SPPB) score (range 0-12, worst to best performance, including chair stands, gait speed, and balance testing). Effects of cancer/control group, age group, and time (treated categorically rather than ordinally) were estimated in a mixed model with a random subject effect and fixed effects of time (baseline, 3 month, 12 month) and cancer/control group. In the model we included all first-order interactions as well as the one second-order interaction between all three predictors. We also used linear contrasts to compare estimated means within groups. Analyses were conducted in SAS 9.4. A two-tailed alpha of 0.05 was used throughout to denote statistical significance. **Results:** Among 403 patients accrued through the Wake Forest Research Base of NCORP, 201 were in the CC group, and 18.9% of these were aged 65 and older; 57 were in the CNC group, and 33.3% were older; and 145 were in the HC group, and 15.9% were 65 or older. We observed a significant ($p < 0.0001$) main effect of older age group in our model: across all 3 groups, and all 3 time points, those who were 65 years of age or older had worse SPPB scores than those who were younger. Healthy controls tended to have better mean scores than the other 2 cancer/control groups, though the main effect of group did not achieve statistical significance ($p=0.06$). We observed no significant interaction terms; in other words, the effect of being older (in terms of association with worse SPPB scores) did not vary by time or group. Within the CC group, both the older and the younger groups declined significantly ($p=0.04$) in mean SPPB at 3 months compared to baseline, but by 12 months, the means had returned to their starting

points. No other groups showed significant changes over time. Conclusions: Chemotherapy was associated with decline in SPPB score over the 12-month time period regardless of age. Older adults, regardless of chemotherapy status and time point, had lower SPPB scores.

PO1-13-01

Safety profiles of Chinese breast cancer patients who received abemaciclib in MONARCH plus and monarchE study

Presenting Author(s) and Co-Author(s):

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China (People's Republic)

Q. Zhang. Harbin Medical University Cancer Hospital, Harbin, United States

Q. Ouyang. Department of Medical Oncology, Hunan Cancer Hospital, United States

Q. Liu. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

J. Feng. Department of Medical Oncology, Jiangsu Province Cancer Hospital, Nanjing, China (People's Republic)

H. Li. Department of Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, Beijing, China (People's Republic)

X. Wang. Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, United States

N. Liao. Department of Breast Cancer, Guangdong General Hospital, Guangzhou, China (People's Republic)

L. Yang. Eli Lilly and Company, Shanghai, China (People's Republic)

Q. Zhu. Eli Lilly and Company, Shanghai, China (People's Republic)

C. Qian. Eli Lilly and Company, Shanghai, China (People's Republic)

Z. Jiang. Medicine–Oncology, The Affiliated Hospital of Military Medical Sciences (The 307th Hospital of Chinese People's Liberation Army), Beijing, China, United States

Aim:

Abemaciclib demonstrated efficacy with tolerable safety profile in Chinese patients (CN pts) with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (ABC) and high-risk early breast cancer (EBC). The overall safety profile of abemaciclib in Chinese ABC and EBC pts was consistent with overall population in the MONARCH plus and monarchE studies. To better understand the safety of abemaciclib in CN pts, beyond the previously reported most frequent adverse events (AEs), we report a comprehensive summary of other selected AEs in CN pts in the two trials.

Methods:

Study designs of MONARCH plus (NCT02763566) and monarchE (NCT03155997) studies were reported previously. To report detailed characteristics of a selected AE profile, including alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, fatigue, nausea, and vomiting, data were pooled across all CN pts from these two phase 3 studies. The safety population was defined as all randomized patients receiving at least 1 dose of Abemaciclib or endocrine therapy. Data cutoff time is May 18, 2020 and July 1, 2022, respectively.

Results:

Among 6052 participants in the overall safety population, 875 CN pts (14.5%) were included

(512/3100 abemaciclib, 363/2952 placebo). CN pts treated with abemaciclib indicated consistent AE profiles in combination with different endocrine therapies (aromatase inhibitors or Fulvestrant). Detailed characteristics of selected AEs are summarized in table. No deaths due to the selected AEs were reported in CN pts.

Conclusion:

The selected AEs of abemaciclib group were in low severity with limited grade 3-4 events. Those AEs were tolerable and generally manageable in CN pts in the MONARCH plus and monarchE trials.

Table: Selected AEs in Chinese patients Pooled from MONARCH plus and monarchE study

Characteristics	Abemaciclib + ET N=512	ET N=363
Fatigue		
Any Grade, n (%)	114 (22.3)	48 (13.2)
Grade 3	2 (0.4)	1 (0.3)
Time to onset, median, days	70.0	116.5
Duration of grade 3, median, days	27.0	15.0
Dose reduction, n (%)	1 (0.2)	0
Dose omission, n (%)	2 (0.4)	0
Treatment discontinuation, n (%)	0	0
Nausea		
Any Grade, n (%)	89 (17.4)	32 (8.8)
Grade 3	2 (0.4)	0
Time to onset, median, days	29.0	71.0
Duration of grade 3, median, days	4.0	-
Dose reduction, n (%)	1 (0.2)	0
Dose omission, n (%)	1 (0.2)	0
Treatment discontinuation, n (%)	0	0
Vomiting		
Any Grade, n (%)	75 (14.6)	20 (5.5)
Grade 3	4 (0.8)	0
Time to onset, median, days	30.0	53.5
Duration of grade 3, median, days	4.5	-
Dose reduction, n (%)	1 (0.2)	0
Dose omission, n (%)	3 (0.6)	0
Treatment discontinuation, n (%)	1 (0.2)	0
	Abemaciclib + ET n1 (%)	ET n1 (%)
Aspartate aminotransferase increased, by laboratory assessment		
	N1=506	N1=353
Any Grade	251 (49.6)	95 (26.9)
Grade 1	208 (41.1)	82 (23.2)
Grade 2	25 (4.9)	9 (2.5)
Grade 3	16 (3.2)	4 (1.1)
Grade 4	2 (0.4)	0
Dose reduction	5 (1.0)	1 (0.3)
Dose omission	8 (1.6)	1 (0.3)
Treatment discontinuation	0	0
Alanine aminotransferase increased, by laboratory assessment		
	N1=507	N1=354
Any Grade	273 (53.8)	110 (31.1)
Grade 1	206 (40.6)	95 (26.8)
Grade 2	36 (7.1)	10 (2.8)
Grade 3	27 (5.3)	5 (1.4)
Grade 4	4 (0.8)	0
Dose reduction	22 (4.3)	1 (0.3)
Dose omission	32 (6.3)	2 (0.6)
Treatment discontinuation	5 (1.0)	0
Blood creatinine increased, by laboratory assessment		
	N1=508	N1=354
Any Grade	506 (99.6)	321 (90.7)
Grade 1	175 (34.4)	306 (86.4)
Grade 2	327 (64.4)	14 (4.0)
Grade 3	4 (0.8)	0
Grade 4	0	1 (0.3)
Dose reduction	0	0
Dose omission	0	1 (0.3)
Treatment discontinuation	0	0

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; MedDRA = Medical Dictionary for Regulatory Activities; N = number of Chinese patient in safety population; N1 = number of Chinese patients with at least a baseline result and 1 postbaseline result, used as denominators for the percentages; n = number of Chinese patients in the specified category; n1 = number of Chinese patients with graded laboratory value; - = not evaluable.
1. ET arm in pooled population represents patient on ET with or without placebo.
2. All AEs were summarized by maximum grade.
3. AEs were coded by MedDRA Version 25.0 and graded based on CTCAE Version 4.0.
4. No Chinese patients reported grade ≥4 fatigue, nausea, or vomiting.

PO1-13-02

Circulating tumor DNA mutation landscape in HR+/HER2- patients with mBC treated with cyclin-dependent kinase 4/6 inhibitors in the SCRUM-Japan MONSTAR-SCREEN study

Presenting Author(s) and Co-Author(s):

M. Hattori. Aichi Cancer Center, United States

V. Serelli-Lee. Eli Lilly Japan K.K., Japan

Y. Naito. National Cancer Center Hospital East, Kashiwa, Chiba, Japan, United States

T. Yamanaka. Department of Breast Surgery and Oncology Kanagawa Cancer Center, Japan

H. Yasojima. Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

R. Nakamura. Division of Breast Surgery, Chiba Cancer Center, Chiba, Chiba, Japan

T. Fujisawa. National Cancer Center Hospital East, Japan

M. Imai. National Cancer Center Hospital East, Japan

Y. Nakamura. National Cancer Center Hospital East, Japan

H. Bando. National Cancer Center Hospital East, Japan

T. Kawaguchi. Eli Lilly Japan, K.K., Kobe, Hyogo, Japan

T. Yoshino. National Cancer Center Hospital East, Japan

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Introduction: Combination of cyclin-dependent kinase 4 and 6 inhibitors (CDK 4/6i) + endocrine therapy (ET) is recommended as first- or second-line treatment (1L or 2L Tx) for hormone receptor-positive, human epidermal growth factor receptor-2-negative metastatic breast cancer (HR+/HER2- mBC). In this study, we assessed cancer-specific genetic alterations in circulating tumor DNA (ctDNA) and tissues in abemaciclib-treated patients with HR+/HER2- mBC in Japan.

Methods: MONSTAR-SCREEN is a multicenter study and part of a nation-wide cancer genome screening project for patients with advanced solid tumors (SCRUM Japan). Regardless of the Tx line, the current analysis included abemaciclib-treated patients with HR+/HER2- mBC (N=97). Data were collected between Jan 2020 and Dec 2021. Blood samples collected at ≤ 21 days before abemaciclib initiation (baseline; n=77) and at disease progression or Tx discontinuation (paired post-Tx; n=33) were tested with the FoundationOne[®] Liquid Companion Diagnostic panel. Additionally, archival or fresh tissue biopsy samples (n=79) were tested with the FoundationOne[®] Companion Diagnostic panel. Patient characteristics, baseline genetic alterations, neoplastic burden (measured by shedding rate and maximum variant allele frequency [VAF]), and alterations at clinical progression were reported.

Results: The total population (N=97) included patients with next generation sequencing ctDNA and/or tissue data. All were female with median age of 57 years (interquartile range 50, 67). Bone, either alone or with other sites, was the most common metastatic site (61%). 78% of patients received abemaciclib in the first or second line of Tx (LoT). Fulvestrant with or without gonadotropin-releasing hormone (55%), letrozole (24%), and anastrozole (11%) were the most common concomitant drugs. Among patients with baseline ctDNA data (n=77), 30% and 21% had received prior ET and prior chemotherapy, respectively. In baseline ctDNA samples,

PIK3CA (37%) and TP53 (28%) alterations were detected most frequently across all LoT; while ESR1 (16%), GATA3 (11%), and FGF3/4/19 (9%) were more frequently detected in samples from later LoT. The frequency of ESR1 alterations ($p < 0.01$), shedding rate, and maximum VAF (both $p < 0.05$) were significantly higher in prior ET recipients than those who did not receive prior ET. Frequency of post-Tx ESR1 alterations numerically decreased from baseline in patients on fulvestrant (23% to 18%) and numerically increased in patients on aromatase inhibitors (27% to 45%). Other genes showed either a numeric increase or similar alteration frequency between the baseline and post-tx. Newly acquired post-Tx alterations were detected in FGF3/4/19 (18%); PIK3CA, TP53, and RB1 (all 15%) and ESR1 (12%). The table shows PIK3CA and ESR1 alterations detected at baseline and post-Tx. In the tissue samples ($n=79$), TP53 (32% vs 20%) and ESR1 (14% vs 7%) alterations were numerically more frequent in metastatic versus primary lesions. Other gene alteration frequencies were similar.

Conclusion: PIK3CA alterations were the most frequently detected genetic alterations in both pre- and post- abemaciclib Tx patients with HR+/HER2- mBC. Patients with prior ET had more frequent ESR1 alterations and higher neoplastic burden. Evidence from this study provides insight into the ctDNA dynamics and potential resistance mechanisms in patients with HR+/HER2- mBC.

PIK3CA and ESR1 alterations detected in circulating tumor DNA at baseline and post abemaciclib treatment

Table: PIK3CA and ESR1 alterations detected in circulating tumor DNA at baseline and post abemaciclib treatment

PIK3CA variants	Detected at baseline (n = 75)*, n (%)	Detected post treatment (n = 33), n (%)
H1047R	10 (13.3)	6 (18.2)
E545K	9 (12.0)	5 (15.2)
E542K	5 (6.7)	3 (9.1)
N345K	2 (2.7)	1 (3.0)
C420R	1 (1.3)	1 (3.0)
K111N	1 (1.3)	1 (3.0)
Q546P	1 (1.3)	Not detected
R88Q	1 (1.3)	1 (3.0)
R108H	1 (1.3)	Not detected
L452_G460del	1 (1.3)	Not detected
G914A	Not detected	1 (3.0)
Amplification	Not detected	1 (3.0)

ESR1 variants	Detected at baseline (n = 75)*, n (%)	Detected post treatment (n = 33), n (%)
D538G	6 (8.0)	5 (15.2)
Y537N	4 (5.3)	1 (3.0)
Y537S	3 (4.0)	4 (12.1)
Y537C	2 (2.7)	Not detected
L536H	2 (2.7)	1 (3.0)
L536R	2 (2.7)	Not detected
S463P	1 (1.3)	Not detected
E380Q	1 (1.3)	1 (3.0)

*From the 77 patients with baseline circulating tumor DNA samples, 2 patients were excluded because their samples failed during assay quality control.

*From the 77 patients with baseline circulating tumor DNA samples, 2 patients were excluded because their samples failed during assay quality control.

PO1-13-03

Tumour infiltrating double negative (CD20+CD27- IgD-) B cells in high-risk early breast cancers. Friend or Foe??

Presenting Author(s) and Co-Author(s):

E. Carpenter. King's College London, United States

P. Buckley. King's College London, United States

T. Alaguthurai. King's College London, United States

R. Graham. King's College London, United States

H. Kakkassery. King's College London, United States

G. Alhity. King's College London, United States

F. Hossain. King's College London, United States

S. Mukhtar. King's College London, United States

S. Irshad. King's College London, United States

Background: B cells exhibit diverse phenotypes and function and the complex interplay between different B cell subsets in the context of chemotherapy treated breast cancers remains unclear. Here, we investigate the dynamic changes in the B cell immune landscape before and after NACT treatment across different breast cancer subtypes. Methods: Treatment naïve, mid-treatment and post-NACT breast tumour, matched lymph node, blood and serum samples were profiled for B cell subsets and cytokines by flow cytometry, cytometry by time-of-flight (CyTOF) and Luminex technologies. Ex vivo autologous tumour organoid and immune cells cocultures to functionally assess the B-cell interactions across breast cancer subtypes were performed. Multiplex spatial analysis method was used to explore the dynamics of double negative B cell cellular crosstalk within the tumour and axillary lymph nodes. The results are being associated with treatment outcomes. Expression and activity of purinergic ectoenzymes within B cell subsets were also assessed by flow cytometry and high-performance liquid chromatography. Current work focusses on how these findings may relate to immunotherapy response, a new paradigm shift in the treatment of triple negative breast cancer patients. Results: We observed a significant expansion in the CD20+CD27-IgD- cells, also termed as double-negative (DN) B cells, within the TME of treatment naïve and post-neoadjuvant residual tumours compared to the periphery. Specifically, DN1 (CD20+ CD27-IgD- CD21+CXCR5+) cells represented the majority of DN B cells within the treatment naïve TME and in circulation. However, NACT promotes an expansion of the DN2 (CD20+CD27-IgD-CD21-CXCR5-) subset as well as a relatively uncharacterised DN3 (CD19+IgD-CD27-CXCR5-CD11c-) cell population. Preliminary analyses on how these changes (especially the enrichment of DN2 cells) relate to treatment response show significant expansion of DN2 cells in the periphery of poor responders to NACT, coupled with significantly reduced infiltration of DN2 into resistant residual tumours. Among circulating B, T and NK cells, B cells showed the highest CD73 and CD39 surface expression at baseline, but their expression significantly drops following NACT especially within the DN2 B cell subset. These ecto-5'-nucleotidases are known to play a critical role in B and T cell interactions. Spatial analyses between these cell types is ongoing. Conclusion: We report for the first time an enrichment of DN cells in breast cancer tumour tissue, specifically the expansion of DN2 cells following neoadjuvant chemotherapy. Functional analyses of tumour-infiltrated B-cells suggest that mechanistically, these B-cell subgroups may contribute to immunosurveillance and point to an important role of purinergic signalling in early breast cancers. Our study highlights the requirement for further investigation into the role of DN B cells

in the context of chemo/immunotherapy resistance in breast cancers.

PO1-13-04

Distinct immune signatures discriminate between patients defined as exceptional survivors of metastatic breast cancer compared to those with rapidly progressing treatment resistant breast cancers.

Presenting Author(s) and Co-Author(s):

H. Kakkassery. King's College London, United States

T. Alaguthurai. King's College London, United States

Z. Kozik. The Institute of Cancer Research, United States

P. Buckley. King's College London, United States

R. Lu. King's College London, United States

E. Carpenter. King's College London, United States

R. Graham. King's College London, United States

G. Alhity. King's College London, United States

F. Hossain. King's College London, United States

S. Mukhtar. King's College London, United States

S. Haider. Breast Cancer Now Toby Robinsons Research Centre, The Institute of Cancer Research, London, United States

J. Choudhary. The Institute of Cancer Research, London, UK, United Kingdom

S. Irshad. King's College London, United States

Background: "Atypical responders" can encompass three sub- categories of patients: "exceptional responders" (those with an unusually favourable treatment response), "rapid progressors" (unusually poor or no response), and "exceptional/long-term survivors" (outlived initial prognosis). Here, we aim to investigate the drivers of immune surveillance mechanisms (local, lymphoid and peripheral) and the nature of immunological tumour recognition in exceptional survivors of stage 4 metastatic disease following standard-of-care chemo- and targeted therapies. Methods: We conducted a complementary multi-platform immune profiling study to define differences in the phenotypic immune landscape including mass-spectrometry-based proteomics on peripheral blood mononuclear cells (PBMCs), multiplex cytokine profiling of patient serum, and high-dimensional flow cytometry on whole blood samples. By staining 500µl of whole blood using 2 panels, 353 immune-cell-related parameters were obtained for comparisons among the following groups: "exceptional survivors," "exceptional responders," "rapid progressors," "non-exceptional metastatic patients," "early breast cancer patients," and "healthy volunteers". Patients were matched for age, breast cancer receptor status, and sites of metastases where possible. Results: Preliminary analysis of serum biomarkers and proteome of the PBMCs of the exceptional survivors showed elevated levels of NK-cell-related proteins such as KCTD10 and RBBP7. Flow cytometry analysis revealed the presence of increased activated CD56^{dim} NK cells, CD56^{bright} NK cells, and central memory (CM) (CD45RA-CD27+) CD8 T cells in both the exceptional survivors and the rapid progressors. However, expression of CD25 appears to be the main mode of activation in rapid progressors compared with increased NKG2D expression in exceptional survivors. Additionally, activation of the unconventional gd T cells was evident in both groups with terminally differentiated effector memory cells re-expressing CD45RA (TEMRA) Vd1 cell predominating in the exceptional survivors. In the rapid progressors, the increased CD25⁺ TEMRA Vd2 cells coupled with elevated serum IL-17A and IL-1b suggest their ability to generate IL-17. Th2 cytokines, IL-5 and

IL-13 were also enriched in rapid progressors and concomitant increase in CD25⁺ Th2 cells reveals a strong Th2-driven immune signature in these patients. Finally increased CD86⁺ atypical double negative (DN) B cells, mostly comprised of the DN2 subset were also significantly enriched in the rapid progressors compared to the exceptional survivors where DN1 B cells were prevalent. Conclusion: The multi-platform approach to investigating immune responses present in atypical responders has identified several distinct immunophenotypes in which the extreme outliers differ in their potential immune surveillance mechanisms. Functional validation of these findings through activation and cytotoxicity assays is currently underway and future work aims to understand the spatial biology of these circulating immune cells within the context of their primary tumours, metastases, and lymph nodes.

PO1-13-05

Genomic characteristics and its therapeutic implications in breast cancer patients with detectable molecular residual disease

Presenting Author(s) and Co-Author(s):

x. yan. Department of Breast and Thyroid Surgery, Daping Hospital, Army Medical University, China (People's Republic)

S. Zhang. Department of Breast and Thyroid Surgery, Daping Hospital, Army Military Medical University, Chongqing, Chongqing, China (People's Republic)

L. zhou. Department of Breast and Thyroid Surgery, Daping Hospital, Army Military Medical University, Chongqing, Chongqing, China (People's Republic)

Y. Jiang. Department of Breast and Thyroid Surgery, Daping Hospital, Army Military Medical University, Chongqing, Chongqing, China (People's Republic)

J. Xu. Department of Breast and Thyroid Surgery, Daping Hospital, Army Military Medical University, Chongqing, Chongqing, China (People's Republic)

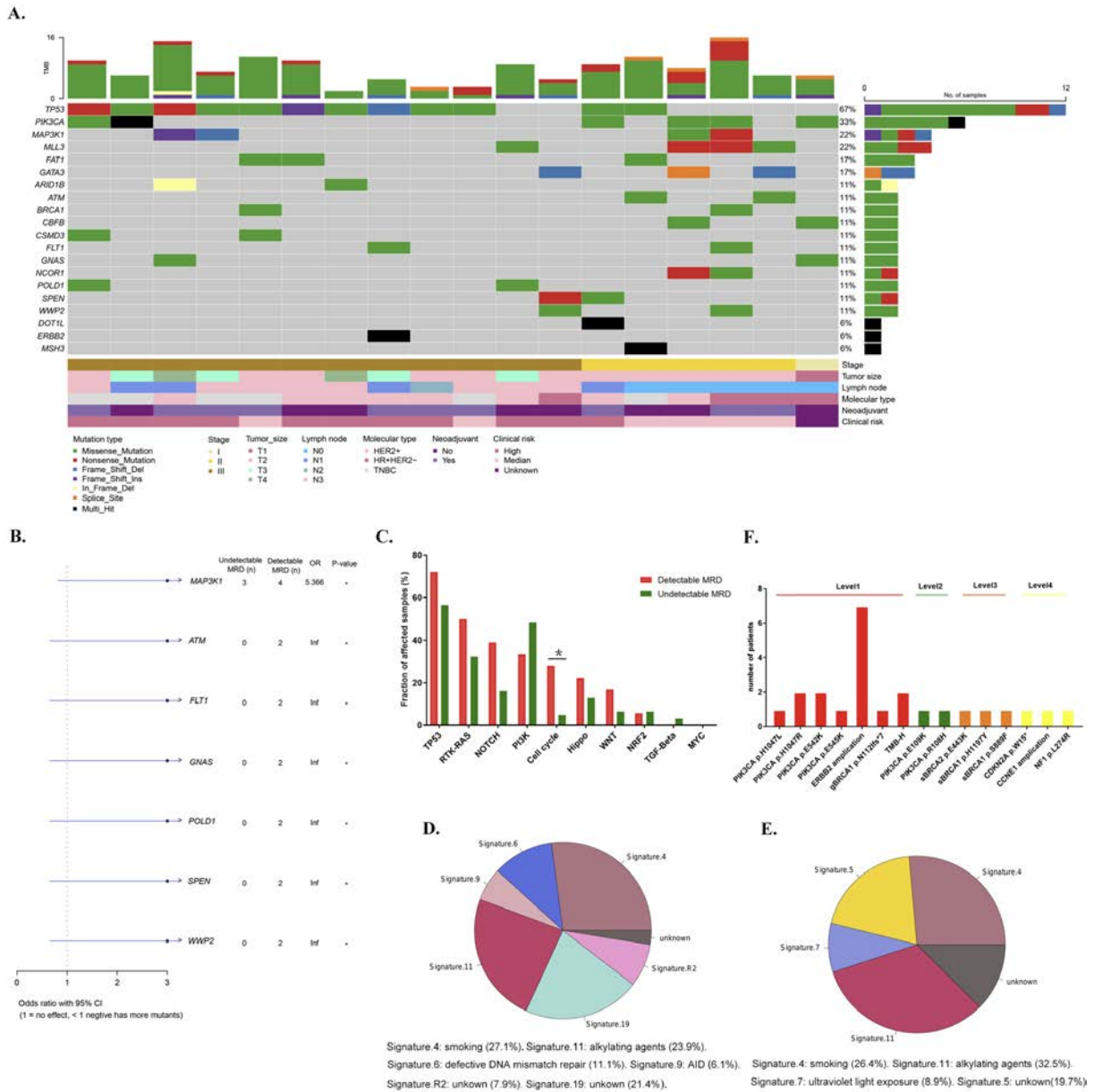
G. Zhang. Department of Breast and Thyroid Surgery, Daping Hospital, Army Military Medical University, Chongqing, Chongqing, China (People's Republic)

L. Shen. Geneplus-Beijing, Chongqing, Chongqing, China (People's Republic)

Background: Breast cancer constitutes approximately 30% of cancers in women, with a mortality-to-incidence ratio of 15%. While early and middle-stage breast cancer patients can undergo radical surgical resection, postoperative recurrence remains a significant challenge for clinicians. Molecular residual disease (MRD) is the main cause of postoperative recurrence of breast cancer. However, the baseline tumor genomic characteristics and therapeutic implications of breast cancer patients with detectable MRD are still unknown. **Methods:** In this study, we enrolled 80 patients with breast cancer who underwent next-generation sequencing (NGS)-based genetic testing of 1,021 cancer-related genes performed on baseline tumor and postoperative plasma from Army Specialty Medical Center between June 2017 and January 2023. The criteria for the patient's enrollment were: (1) pathological diagnosis as breast cancer, (2) no distal metastasis, (3) radical surgery and R0 resection, (4) 1021 cancer-related gene testing of the tumor, (5) plasma MRD testing performed within 3 months after surgery and before adjuvant therapy. **Results:** A total of 18 patients in our cohort had detectable MRD. Baseline clinical characteristics found that patients with higher clinical stages were more likely to have detectable MRD. Analysis of single nucleotide variations and small insertions/deletions in baseline tumors showed that somatic mutations in MAP3K1, ATM, FLT1, GNAS, POLD1, SPEN, and WWP2 were significantly enriched in patients with postoperative MRD. Oncogenic signaling pathway analysis revealed that alteration of the Cell cycle pathway was more likely to occur in patients with detectable MRD ($p=0.0125$). Mutational signature analysis showed that defective DNA mismatch repair and activation-induced cytidine deaminase (AID) mediated somatic hypermutation (SHM) were associated with detectable MRD. Somatic copy number variation analysis found that amplification of CDKN2A, HOXB13, PPM1D, MPL, and VHL was significantly enriched in patients with detectable MRD. According to the OncoKB database, 77.8% (14/18) of patients with detectable MRD had U.S. Food and Drug Administration-approved mutational biomarkers and targeted therapy. **Conclusion:** For the first time, our study reports genomic characteristics of breast cancer patients with detectable MRD. The tumor biology is probably the main driver of detectable MRD. We also found the vast majority of patients with detectable MRD have the opportunity to access targeted therapy. **Keywords:**

Breast cancer, MRD, Genomic character, Cell cycle pathway, Defective DNA mismatch repair, Activation-induced cytidine deaminase

Figure 1. Somatic mutational landscape and clinical actionability of breast cancer patients with detectable MRD



A. Oncoplot of top 20 genes altered in patients with detectable MRD. B. Forest plot of different mutant genes between patients with detectable and undetectable MRD. OR means odds ratio. Inf means infinity. * means P-value < 0.05. C. The ten cancer-related signaling pathways were affected by somatic mutations both in patients with detectable and undetectable MRD. *

means P-value < 0.05 . D&E. The fraction and etiology of each signature in patients with detectable (D) or undetectable (E) MRD. F. The number of patients with detectable MRD in different actionable alterations. gBRCA1 means germline BRCA1 mutation. sBRCA1 means somatic BRCA1 mutation. sBRCA2 means somatic BRCA2 mutation. TMB-H means TMB-High.

PO1-13-06

Androgen Receptor Isoform V7 (AR-V7): A Promising Biomarker for Prognosticating Breast Cancer Aggressiveness

Presenting Author(s) and Co-Author(s):

T. Srivastava. Department of Biochemistry, All India Institute of Medical Sciences, New Delhi, Delhi, India

J. Talukdar. All India Institute of Medical Sciences, New Delhi, United States

R. Verma. Shiv Nadar Institution of Eminence (SNIOE), Greater Noida, India, United States

S. Karmakar. All India Institute of Medical Sciences, New Delhi, United States

Androgen Receptor (AR) is an emerging endocrine therapy target in Breast Cancer (BrCa) with up to 80% expression in clinical cases. AR-V7 is a constitutively activated splice variant of AR having a truncated ligand-binding domain (LBD). This confers ligand-independent transcriptional activity to AR-V7 and makes it susceptible to nonsteroidal antiandrogens such as Bicalutamide or Enzalutamide which target the LBD of AR. Higher levels of AR-V7 in metastatic prostate cancer leads to therapeutic resistance and enhanced metastasis. We assessed AR-full length (AR-FL) and AR-V7 expression in BrCa cell lines of different molecular subtypes. This was extended for a clinical correlation of AR-FL and AR-V7 in validated treatment naïve BrCa patients undergoing surgical intervention at a tertiary care hospital in India. Transcriptomic and proteomic analysis was performed using qRT-PCR and Western Blotting. Immunocytochemistry and immunohistochemistry were used to examine protein expression and localisation in cells and tissues. AR-FL and AR-V7 were variably expressed in cell lines which got elevated with Dihydrotestosterone (DHT) treatment. Cell lines stimulated with Bicalutamide or Enzalutamide showed significant downregulation in AR-FL expression. From a cohort of 82 clinical cases, more than 50% originated from the urban setting, post-menopausal stage, and in the age groups of 61 to 70 years. ER, PR, HER2, and AR were positive in 65%, 55%, 24%, and 67% respectively. We were able to correlate aggressive clinical traits and higher pathological grades with increased expression of AR-V7 in the AR-positive BrCa fraction. This was consistent with the cell line-based preclinical research. This study affiliates AR-V7 as an important prognostic biomarker for predicting breast cancer aggressiveness. It can serve as a screening marker of poor clinical outcomes and aid in appropriate therapeutic intervention. These outcomes, however, seek extensive prospective validation.

PO1-13-07

LIV-1 and Trop2 expression using Immunohistochemistry as prognostic markers in early breast cancer

Presenting Author(s) and Co-Author(s):

Y. Choi. Seoul National University College of Medicine, United States

H. Ryu. Seoul National University Hospital, United States

J. Koh. Seoul National University Hospital, United States

D. Lee. Seoul National University Hospital, United States

K. Lee. Seoul National University Hospital, Seoul National University College of Medicine, United States

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

Backgrounds: Antibody-drug conjugate (ADC) has emerged as treatment option for breast cancer (BC). The ASCENT and TROPiCS-02 trial of Sacituzumab Govitecan, a Trop2 ADC, gained great success in TNBC and HR+ BC. Other targets, such as LIV-1, are being investigated for TNBC and HR+ BC. The clinical trials of Ladiratumumab, an ADC of LIV-1 Ab and MMAE, are ongoing. However, unlike Her2 protein, the predictive and prognostic role of LIV-1 and Trop-2 has not been fully investigated. Therefore, we aimed to analyze the relationship between expression level and clinicopathological features and explore the value of the markers among subtypes of BC. Methods: TMA were selected from 1,349 breast cancer specimen of patients who received curative surgery from 2008 to 2012 at Seoul National University Hospital and IHC staining was performed on the TMA using LIV-1 antibody (HPA042377 manufactured by Sigma-Aldrich, St. Louis, MO, dilution ratio of 1:300) and Trop2 antibody(HPA055067, dilution ratio of 1:75). All IHC slides were carefully evaluated by trained pathologists. IHC expression was assessed as intensity (negative:0, weak:1, moderate:2, and strong:3). A modified histochemical score(H-score) was calculated from the intensity multiplied by the percentage of positive cells. Results: A total of 1119 patients from selected samples were included. The median age was 49 (range 25-90). Most patients had early T stage disease (n=513, 569, 29, 7, for pT1, pT2, pT3, pT4, respectively). The percentage of nodal metastasis (N=687 vs 432 in pN0 vs \geq pN1, 61.4 vs 38.6%) and LVI (N= 678 vs 441 in neg vs pos, 60.6% vs 38.6%). 713 pts (63.7%) were HR+ subtype, 200(17.9%) of Her2+ and 206(18.4%) of TNBC. We divided patients into negative/low/high expression groups according to LIV-1 expression by median expression level (cutoff H-score = 100): 479 of 1119 (42.8%) LIV-1-negative; 270 (42.2%) LIV-1-low expression and 370 (57.8%) LIV-1-high. Patients with LIV-1-low or -high tumors showed better DFS (156.2 vs 158.8 vs 159.95 mo for LIV-1-negative, -low, -high, respectively; P=0.0072) and OS(157.6 vs 163 vs 165.4 mo, P=0.0029) . HR+ subgroup, (N= 193 vs 228 vs 354 for neg vs low vs high), followed overall tendency (153.4vs 158.3 vs 159.9mo, P=0.0571 in DFS, 155.6vs160.2 vs165.4mo, P=0.0627 in OS, respectively) In contrast, for patients with TNBC, LIV-1-high expression showed the worst DFS and OS. (N = 183 vs 18 vs 5 in neg vs low vs high group, 159.7 vs 160.7 vs 93.1mo, P value=0.1854 for DFS, 160.8 vs 160.7 vs 93.1 mo, P=0.0334 for OS, respectively) LIV-1 expression failed to prove a prognostic value in Her2+ BC. We also analyzed Trop2 expression by dividing patients into low/intermediate/high by the method used previously in ASCENT trial. 1009 of 1119 (n=341 in low, 363 in intermediate, 305 in high expression) patients had Trop2 expression. There was no statistically significant difference in DFS and OS among all subtypes. In multivariate analysis, neither LIV-1 or Trop-2 had a prognostic role. Conclusion: The analysis of clinicopathological

findings of LIV-1 protein indicates their values for prognosis markers, especially in HR+ BC and TNBC. Trop2 expression has no prognostic role in line with previous research. Further studies are warranted to explore targetable biomarkers for the development of appropriate ADCs.

PO1-13-08

Comparative analysis of stearoyl-CoA desaturase 1 expression and activity index in model cell lines of breast cancer subclasses

Presenting Author(s) and Co-Author(s):

H. Feizi. Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran., Azarbayjan-e Sharqi, Iran

A. Mehdizadeh. Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran., Azarbayjan-e Sharqi, Iran

Z. Sanaat. Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran., Azarbayjan-e Sharqi, Iran

K. Abbasi. Department of Biochemistry and Clinical Laboratories, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran, Azarbayjan-e Sharqi, Iran

F. Gieseler. Division of Experimental Oncology, Department of Hematology and Oncology, University Medical Center Schleswig-Holstein, Lübeck, Germany, Lübeck, Schleswig-Holstein, Germany

M. Darabi. Division of Experimental Oncology, Department of Hematology and Oncology, University Medical Center Schleswig-Holstein, Lübeck, Germany; Department of Biochemistry and Clinical Laboratories, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran, Lübeck, Schleswig-Holstein, Germany

Introduction

Due to the unique conditions of the tumor microenvironment, such as hypoxia, poor angiogenesis, and mitochondrial dysfunction, cancer cells face challenges in obtaining nutrients and energy supply. However, monounsaturated fatty acids have been identified as preferred substrates for energy generation and maintenance of cellular structures in cancer cells. These fatty acids can be obtained through de novo fatty acid synthesis. Stearoyl-CoA desaturase 1 (SCD1) is the primary enzyme involved in the biosynthesis of monounsaturated fatty acids from saturated fatty acids and is known to be upregulated in various malignancies, including breast cancer. This study aimed to assess the expression and activity index of SCD1 in well-characterized MCF-7, SK-BR3, and MDA-MB231 breast cancer cell lines, representing luminal A/B, HER2-enriched, and triple-negative subtypes, respectively. Methods

The breast cancer cell lines were cultured in RPMI-1640 medium with 10% fetal bovine serum at 37°C, 5% CO₂, and 95% humidity for 72 hours. After harvesting the cells, SCD1 expression was analyzed using real-time quantitative PCR, and the activity index was determined by measuring the ratio of monounsaturated fatty acids to saturated fatty acids using capillary gas-liquid chromatography. Results

MCF-7 cell line showed a significantly higher SCD1 expression compared to MDA-MB231 (250-fold, $p < 0.0001$) and SK-BR3 (83-fold, $p < 0.0001$) cell lines. The activity index of SCD1 was significantly higher in both MCF-7 and MDA-MB231 cell lines with fold changes of 2.6 and 2.5, respectively, compared to SK-BR3 cell line ($p = 0.004$ for both). Conclusion

Cell model assays demonstrated that the luminal A/B and triple-negative subtypes showed a higher capacity to convert saturated fatty acids to monounsaturated fatty acids through SCD1 enzyme activity, indicating a different lipid metabolism profile in the HER2-enriched subtype. These new findings reveal differences in SCD1 expression and activity among breast cancer subclasses. They highlight vulnerabilities in metabolism and identify potential therapeutic targets with clinical implications for managing breast cancer.

PO1-13-09

Programmed cell death ligand 1 (PD-L1) is constitutively expressed on tumorspheres cultured from circulating cancer stem cells in breast cancer patients.

Presenting Author(s) and Co-Author(s):

M. PIZON. Transfusion Center Bayreuth, United States

D. Schott. Transfusion Center Bayreuth, United States

U. Pachmann. Laboratory Dr. Pachmann, United States

K. Pachmann. Laboratory Dr. Pachmann, United States

Background Circulating cancer cells, and in particular their very rare subpopulation, circulating cancer stem cells (cCSCs), are responsible for recurrence and metastasis. The exact role of cCSCs in escape of cancer from immunosurveillance is still unknown, but recent studies revealed that enhanced PDL-1 expression in cancer stem cells is a novel mechanism to promoting cancer cell immune evasion and could crucially contribute to the maintenance of CSC self-renewal. Understanding the mechanisms behind this PDL-1 overexpression in cancer stem cells is critical for developing more effective anti-PD-1/PD-L1 therapy. Therefore the aim of the study was to determine the number of tumorspheres and expression of PD-L1 on tumorspheres cultured from cCSC in breast cancer patients. **Methods:** 110 patients with breast cancer in different stages of disease were included in this study. The determination of circulating cancer stem cells was performed using the sphere-forming assay. Additionally anti-PDL-1 antibody staining was applied to examine PDL-1 expression on breast tumorspheres. **Results:** We have developed an innovative in vitro platform for detection of cCSCs from peripheral blood of cancer patients. The number of tumorspheres increased significantly with tumor progression and aggressiveness of primary tumor. Patients with metastatic disease had statistically more tumorspheres as compared to patients without metastasis (30 vs 10/100 μ l blood, $p < 0.05$). Patients with multiple metastasis had more tumorspheres compared to patients with single metastases (60 vs 30/100 μ l blood, $p < 0.05$). The number of tumorspheres was positively correlated with Ki-67, Her2 status and grade score in primary breast tumors. We observed high PDL-1 expression and their considerable heterogeneity in enriched tumorspheres. **Conclusion:** The number of tumorspheres cultured from peripheral blood directly reflects aggressiveness and proliferation capacity of primary tumor. The presence of tumorspheres with expression of PDL-1 might suggest their immunomodulating potential. Better understanding of the interaction between cCSCs and tumor immunology may help to identify strategies to eradicate the minor subpopulation that escapes conventional therapy attack, thus providing a solution to the problem of drug resistance and metastasis.

PO1-13-11

ZNF689 promotes homologous recombination via NBS1 ubiquitination and its loss confers sensitivity to PARP inhibition in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

L. Ge. Fudan University Shanghai Cancer Center, United States

Z. Wang. Fudan University Shanghai Cancer Center, United States

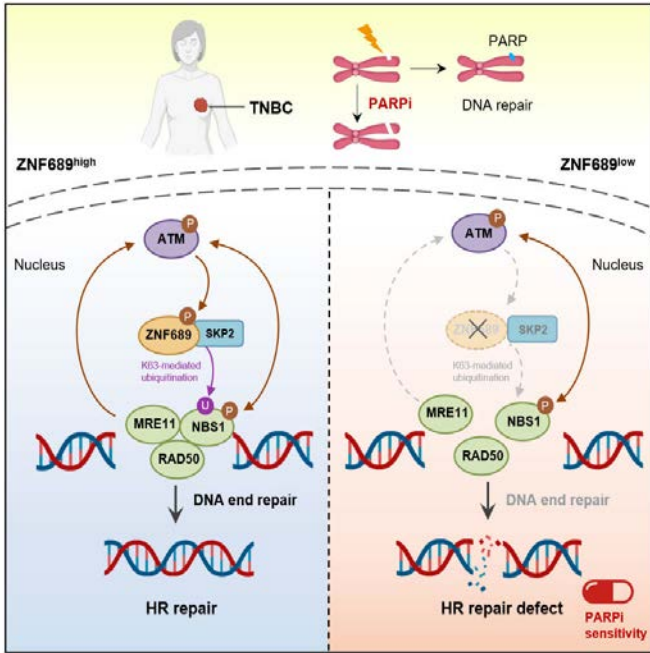
X. Jin. Fudan University Shanghai Cancer Center, United States

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background: Triple-negative breast cancer (TNBC) poses significant clinical challenges due to the lack of targeted therapies and poor prognosis. Homologous recombination (HR) deficiency is a defining characteristic of TNBC and renders tumors susceptible to Poly (ADP-ribose) polymerase (PARP) inhibitors. However, not all TNBC patients respond to PARP inhibitors, highlighting the need to identify novel biomarkers to predict therapeutic response and improve treatment strategies. Methods: In this study, we investigated the role of zinc finger protein 689 (ZNF689) in DNA damage response (DDR) and its impact on PARP inhibitor sensitivity in TNBC. Using a comprehensive set of molecular and cellular techniques, including immunoprecipitation, in vitro and in vivo ubiquitination assays, protein expression analysis, and functional assays using TNBC cell lines, patient-derived organoids (PDOs), patient-derived xenograft (PDX) models, and cell line xenograft models, we elucidated the mechanistic role of ZNF689 in HR and PARP inhibitor response. Results: Our findings revealed ZNF689 as a novel player in DDR. ZNF689 is activated by ATM-mediated phosphorylation and recruited to DNA damage sites in an ATM-dependent manner. At the DNA double-strand break sites, ZNF689 collaborates directly with NBS1 to facilitate K63-linked ubiquitination of NBS1 via the E3 ligase SKP2. Furthermore, ZNF689-mediated NBS1 ubiquitination stabilizes the MRE11-RAD50-NBS1 (MRN) complex and feedbacks activation of ATM, therefore accelerating HR repair. Loss of ZNF689 results in HR deficiency, leading to increased sensitivity of TNBC cells to PARP inhibitors in both in vitro and in vivo models. Additionally, the combination of PARP inhibitors and paclitaxel demonstrated potential for improved efficacy in treating ZNF689-deficient TNBC. In our clinical analysis, we observed a positive correlation between ZNF689 expression and the levels of NBS1 and phosphorylated ATM in TNBC patient samples. Importantly, low ZNF689 expression was associated with a favorable response to PARP inhibitors in TNBC patients. Conclusions: Our study highlights the significant role of ZNF689 in HR and its impact on the response to PARP inhibitors in TNBC. These findings suggest ZNF689 as a promising therapeutic target for enhancing the effectiveness of PARP inhibitors in TNBC patients.

Working Modle



PO1-13-12

Mechanistic Analysis and Potential Therapeutic Implications in Breast Cancer with Fibrotic Focus

Presenting Author(s) and Co-Author(s):

C. Fang. The Chinese University of Hong Kong, United States

J. Tsang. The Chinese University of Hong Kong, United States

G. Tse. The Chinese University of Hong Kong, United States

A fibrotic focus (FF) is a scar-like region that forms in the center of carcinoma due to excessive tumor stroma formation. In our earlier studies, we found FF as an independent poor prognostic factor for breast cancers. However, the underlying mechanisms of how the presence of FF contributed to a poor prognosis are still unknown. To improve our understanding of FF in breast cancer, we have investigated genes associated with FF and their impacts on breast cancer prognosis. Analysis of data from The Cancer Genome Atlas Program (TCGA) indicated that Bone Morphogenetic Protein 8A (BMP8A) was significantly upregulated in breast cancers with FF. To further validate this finding, immunohistochemistry (IHC) on BMP8A was performed on a local cohort of breast cancers (N= 900). Of these samples, 147 (16.3%) were found to be BMP8A positive, and there was a significant association between the presence of FF and high expression of BMP8A (p-value=0.026). We also found that high expression of BMP8A was positively correlated with apocrine phenotype, necrosis, increased Ki67 expression, and triple-negative breast cancer subtype; and most of these are poor prognostic factors for breast cancer. Kaplan-Meier survival estimate analysis revealed that high expression of BMP8A was significantly associated with poor overall survival (p-value=0.035). Gene ontology (GO) analysis showed that "Extracellular matrix organization" was the prominent biological process associated with BMP8A. KEGG pathway analysis suggested that BMP8A was significantly related to "Protein digestion and absorption", "ECM-receptor interaction", and "Focal adhesion" pathways, further validating its correlation with stromal FF. In cellular studies using MCF7 and MDA-MB-231 cell lines, overexpression of BMP8A was found to enhance breast cancer cell proliferation, invasion, and migration. Similar tumor-promoting phenotypes were exhibited when stimulating the cell lines with recombinant human BMP8A. In conclusion, our findings suggested that BMP8A was associated with FF in breast cancer, contributing at least partly to the aggressive features of these cancers. Our findings also provided new insights into the precision treatment and diagnosis of breast cancer. Further exploration of BMP8A as a therapeutic target and prognostic factor may contribute to improved management of breast cancer patients.

PO1-14-01

Clonal Architecture of circulating tumor DNA predicts Early Progression on Tamoxifen With or Without Palbociclib in Hormone Receptor-Positive Advanced Breast Cancer: NCCH1607/PATHWAY trial

Presenting Author(s) and Co-Author(s):

Y. Yap. National Cancer Centre Singapore, Singapore, United States

Y. Kojima. National Cancer Center Hospital, United States

A. Hamada. National Cancer Center Research Institute, United States

H. Mukai. Department of Medical Oncology, National Cancer Center Hospital East, Chiba, Japan

Y. Lu. National Taiwan University Hospital, Taipei, Taiwan.

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

Y. Umeyama. Pfizer R&D Japan, Tokyo, Tokyo, Japan

E. Noguchi. National Cancer Center Hospital, United States

K. Sudo. National Cancer Center Hospital, United States

T. Hata. National Cancer Center Hospital, United States

A. Kuchiba. National Cancer Center Hospital, United States

T. Shibata. Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, tyuouku-tukiji, Tokyo, Japan

S. Yagishita. National Cancer Center Research Institute, United States

M. Yoshida. Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo, Japan, United States

S. Kohsaka. National Cancer Center Research Institute, United States

K. Shiraiishi. National Cancer Center Research Institute, United States

K. Nakamura. National Cancer Center Hospital, United States

K. Tamura. Department of Medical Oncology, Shimane University Hospital, Japan

K. Yonemori. Medical Oncology, National Cancer Center Hospital,, United States

Objective:

Some patients with poor prognosis hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer (ABC) experience early disease progression on the combination of CDK4/6 inhibitors and endocrine therapy. We aimed to determine whether clonal architecture assessed by circulating tumor DNA (ctDNA) could identify patients at higher risk of early progression on tamoxifen therapy with or without palbociclib. Methods:

PATHWAY trial is a randomized, placebo-controlled, Asian international, double-blind, phase 3 study evaluating palbociclib plus tamoxifen (PAL+TAM) versus placebo plus tamoxifen (PLB+TAM) in pre/ perimenopausal and postmenopausal women with HR+/HER2- ABC (NCT03423199). The study was conducted as a Clinical Research Collaboration with the National Cancer Center Hospital as the regulatory study sponsor and Pfizer providing drug and financial support. The primary endpoint was investigator assessed progression-free survival (PFS). Genomic profiling by next-generation sequencing was an exploratory endpoint to characterize molecular alterations in ctDNA and correlate these with clinical outcomes. Plasma

samples were collected at cycle 1-day 1 (pre-treatment) and cycle 2-day 15 and sequenced with the Guardant360 assay (Guardant Health). Patients were included if they had a minimum of 14 days of treatment in the first cycle. The variant allele frequency (VAF) was defined as number of mutant molecules at a specific nucleotide location over the total number of molecules present in the background at a specific given genomic location. We assessed the gene with highest VAF as the dominant clone allele frequency (DCAF). The association of changes in ctDNA alterations with PFS was evaluated to identify biomarkers of early progression. Results:

Pre-treatment plasma was successfully sequenced in 177 of the 184 patients; 88 patients treated with PAL+TAM, and 89 with PLB+TAM. ctDNA was detected in 144 (81.4%) patients; the median number of genetic abnormalities was 2 (range, 0-19). PIK3CA, TP53, ERBB2, ESR1, AKT1, EGFR and PTEN were the genes with highest VAF as the dominant clone (24.3%, 11.9%, 4.5%, 4.5%, 3.4%, 3.4%, 3.4%, respectively). The median DCAF was 1.79 (range, 0.1-81.23); PAL+TAM, 2.53 (range, 0.1-63.5) and PLB+TAM, 1.65 (range, 0.08-81.23). Patients with ≥ 2 detectable genomic alterations and DCAF $\geq 1.8\%$ had worse PFS (hazard ratio (HR) 1.93 [95% confidence interval (CI): 1.375 to 2.721], $p = 0.0003$ and HR 1.95 [95% CI: 1.345 to 2.834], $p < 0.0001$, respectively) compared to all other patients. In addition, we evaluated whether changes of clonal architecture in ctDNA at early treatment time point (ie. Cycle 2 Day 15) are associated with PFS. Patients with increased DCAF had worse PFS on both PAL+TAM (HR 2.80 [95% CI: 0.552 to 14.15], $p = 0.04$) and PLB+TAM (HR 2.02 [95% CI: 1.022 to 3.990], $p = 0.01$). All patients with high pretreatment DCAF ($\geq 1.8\%$) and increase in DCAF progressed within 1 year ($n=5$, 2 patients treated with PAL+TAM, and 3 with PLB+TAM). Conclusion:

Evaluation of clonal architecture in ctDNA could support identification of HR+/HER2- ABC patients with poorer prognosis, who may be at higher risk of early progression, regardless of CDK4/6 inhibitor use.

PO1-14-02

Real world application of a 21-gene recurrence score in a Swiss single center breast cancer population. A comparative analysis of treatment administration before and after TAILORx

Presenting Author(s) and Co-Author(s):

E. Chiru. Basel University Hospital and Cantonal Hospital Baselland, United States

C. Grasic Kuhar. Institute of Oncology Ljubljana, Ljubljana, Slovenia

C. Kurzeder. Breast Center, University Hospital of Basel, Basel, Switzerland, Basel-Stadt, Switzerland

M. Vetter. Cancer Center Baselland, Liestal, Basel-Landschaft, Switzerland

TAILORx was published in July 2018 and showed benefit of chemotherapy (CHT) in premenopausal, HER2 negative breast cancer (BC) patients with a 21-gene intermediate recurrence score (RS). The aim of this study was to determine treatment patterns before and after publication of TAILORx at our Swiss BC center.

This is a retrospective analysis of 326 estrogen receptor positive (ER+)/HER2 negative BC patients, treated at Basel University Hospital and Cantonal Hospital Baselland from 2010-2021. Primary endpoint was to assess change in therapy before (cohort A) and after the publication of TAILORx (cohort B) when adjusted for RS category thresholds as defined by the manufacturer and as modified in the TAILORx study protocol. Secondary endpoint was to determine main therapy decision factors.

There were no significant differences in the two populations. A included 165 and B 161 patients with a mean RS of 17.72 and 17.89 ($p=0.87$) respectively. No differences were noted in terms of demographics or tumor characteristics between the two groups. Mean age in A was 58.8 and in B 57.7 years old. There was a tendency for higher ASA scores in B ($p=0.262$) and higher BMIs in A ($p=0.612$).

There were no differences in RS distribution between A and B when adjusted to manufacturer's thresholds ($p=0.15$ for low RS, 0.833 for intermediate and 0.15 for high RS), and subsequently to TAILORx thresholds for RS categories ($p=0.817$ for low RS, 0.199 for intermediate and 0.795 for high RS). There was no difference in the 2 populations with regards to number of positive nodes ($p=0.366$) and pN status ($p=0.903$).

In the intermediate node negative population, there were 67 patients in A and 55 in B. No significant differences were noted in demographics (median age 58.9 years in A and 57.2 years in B, $p=0.414$, menopausal status, $p=0.806$, relevant comorbidities in 28 patients in A and 21 in B, $p=0.864$). A relevant tendency for higher ASA scores in B was maintained in this subgroup, with a median score of 3 in B vs 2 in A, $p=0.001$). Mean tumor size was 20.73 mm in A and 21.17 mm in B ($p=0.857$) with a mean Ki67 of 20% in both A and B and more cases of higher Ki67 in B (40%) vs A (22%) but not significant ($p=0.624$). Mean RS was 17.43 in A and 17.75 in B ($p=0.674$).

In the intermediate nodal negative subgroup, the majority had conservative breast surgery (64% in A and B), with less reconstruction in A vs B (46% vs 52%, $p=0.031$). Radiotherapy (RT) was administered in 66% of women in A and 69% in B ($p=0.307$) with a mean dose of 53.41 Gy in A and 50.75 Gy in B ($p=0.153$). Only 4 patients had CHT in A and one patient in B ($p=0.775$).

with one case of severe CHT associated complications in A. Seven patients refuse CHT. In A 31% of patients and in B 44% had osteo-oncologic treatment (p=0.005). There are 7 cases of relapse in A and 3 in B (p=0.492) with one BC related death in A. Tumor board seems to weight more post TAILORx (82% of decision implementation in B vs 63% in A, p=0.38).

In the whole population, RS influences decision in the low category, with 91% alignment of RS recommended treatment in A. In B there seem to be a tendency toward more hormonal therapy (138%) but no reduction in CHT application, while in A more patients were administered CHT than recommended by RS guidelines (181%, p< 0.001).

Therapy decision is not influenced by demographic nor tumor characteristics in A nor B, and there are no differences in surgery (68.4% in A and 64% in B, p=0.352), endocrine therapy (65.4% in A vs. 52% in B, p=0.113), RT (78% in A and 76% in B, p=0.223).

At a median follow up of 62.9 months in A and 19.5 in B, relapse was higher in A (19) vs B (5) (p< 0.001) with 5 deaths in A vs none in B. However due to study design which implies different dates of inclusion in the analysis, as well as limited number of events, this data has no power.

Before TAILORx decision was mainly dependent on tumor features. After TAILORx other factors, which are particular to every case weight more.

This data shows that therapy decisions are not particularly shifted after TAILORx, confirming the emergence of personalised medicine.

Demographics, Tumor Characteristics, Therapy and Outcome, RS Categories Thresholds in two Cohorts before and after Publication of TAILORx. What changed?

Demographics				Therapy and Outcomes			
	A	B	p-value		A	B	p-value
Nr. Of Patients	165	161		Therapy according to RS (Chi's test)			<0.001
Age	58.82	57.49	0.937	ET	101	97	
ASA Score (median)	2	3	0.242	ET+CHT	11	27	
BMI	23-30 kg/m ²	18.5-23kg/m ²	0.612	Variaits	49	0	<0.001
Location (median)	left	left	0.142	Therapy administration according to RS (Chi's test)			
Men	2	5	0.799	ET Decision	92	134	
Menopausal	122	119	0.922	ET+CHT Decision	20	27	0.352
Comorbidity	74	62	0.074	Surgery			
Multimorbidity	22	13	0.021	Breast	113	108	
History of cancer	9	16		Conservative			
BC History	14	13		Mastectomy	47	52	
Positive Family History	35	31	0.958	Postoperative	21	16	0.772
Not tested for Germline mutation	108	84	0.868	Complications			
				Reconstruction	78	82	0.253
				No Reconstruction	86	79	0.253
				Adjuvant CHT	29	35	0.865
				RT	128	123	0.223
				ET Complications	9	1	0.84
				Dose RT	54.99	52.35	0.015
				ET	155	152	0.229
				Osteo-oncologic Treatment	67	72	0.895
				TB Decision	121	132	0.048
				Implementation			
				Relapse	19	5	<0.001
				Relapse loco-regional	12	4	
				Relapse distant	7	1	
				Death	5	0	
				Mean Follow Up	62.98	19.52	<0.001
				Disease specific events	5	5	1
				DSS	61.46	26.99	<0.01
Tumor Characteristics				RS Distribution according to RS Category Thresholds before TAILORx			
	A	B	p-value		A	B	p-value
Multicentricity-focality	44	35	0.465	Low RS	99 (60%)	92 (57%)	0.15
Node positive	65	64	0.694	Intermediate RS	52 (31.5%)	51 (22%)	0.893
Size of tumor	25.24	24.78	0.573	High RS	14 (8%)	16 (11%)	0.15
DT (median)	1	1	0.53	RS Distribution according to RS Category Thresholds after TAILORx			
pN (mean)	0.47	0.45	0.835	Low RS	33 (20)	37 (23%)	0.817
Grade 1	11	18	0.811	Intermediate RS	108 (64%)	99 (60%)	0.199
Grade 2	85	90		High RS	26 (16%)	27 (17%)	0.795
Grade 3	61	49					
SNI_Location	20	10	0.787				
Auxiliary Location	22	8					
Nr. Of Nodes	0.85	0.88	0.597				
Histology							
Ductal	125	125					
Lobular	20	26					
Mixed/Other	4	10					
ER+	0.94	0.97	0.971				
PR+	0.68	0.62	0.214				
PR positive	154	147	0.289				
Ki67%	0.19	0.2	0.844				
Mean RS	17.72	17.89	0.533				
Size of tumor	25.24	24.78	0.573				
Ki67_low	109	98	0.343				
Ki67_high	52	63					
Strong	35%	52%	0.402				
IA	3%						
IB	24%	62%					
IIB	20%	34%					
IIIA	4.24%	8%					
IIIB	8%	2%					
IIIC	1.82%	1%					
IV	0%	2%					

PO1-14-03

Discovery of proliferation essential gene signature and ACTL6A as potential biomarker for predicting prognosis and neoadjuvant therapy response in triple-positive breast cancer

Presenting Author(s) and Co-Author(s):

X. Li. Fujian Cancer Hospital, United States

W. Fu. Fujian Medical University Union Hospital, United States

S. Luo. Fujian Cancer Hospital, United States

J. Zhang. Fujian Medical University Union Hospital, United States

Q. Wang. Fujian University of Traditional Chinese Medicine, United States

C. Song. Fujian Provincial Cancer Hospital, United States

Background: Based on the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), a special subtype of breast cancer which expresses all three receptors can be distinguished, namely triple-positive breast cancer (TPBC). TPBC patients has a higher risk of recurrence and lower survival rate compared to other luminal breast cancers. However, there are few studies on predicting molecules of prognosis and treatment response for TPBC. Methods: Proliferation essential genes (PEGs) were identified using CRISPR-Cas9 dataset of DepMap. The expression profiles and clinical data of TPBC were obtained from the TCGA database, GEO datasets and our center cohort. To develop a TPBC-PEG prognostic signature, cox regression and Lasso (Least absolute shrinkage and selection operator) regression analysis were applied. Functional analysis was performed using Gene Set Enrichment analysis. Finally, the relationship between candidate genes and neoadjuvant therapy (NAT) sensitivity was explored using real-time qPCR (RT-qPCR) and immunohistochemistry (IHC) based on clinical samples. Results: Among 900 TPBC-PEGs, 437 genes showed significant differential expression between TPBC and normal tissues. Subsequently, we identified 3 prognostic PEGs (ACTL6A, CCT2, TARS) and used them to construct a PEG signature. Patients with high PEG signature scores exhibited worse overall survival and lower sensitivity to NAT compared to those with low PEG signature scores. RT-qPCR indicated that in patients who lacked sensitivity to NAT, ACTL6A and CCT2 were significantly upregulated. The IHC results showed that ACTL6A protein was highly expressed in the NAT-insensitive group and non-pathological complete response patients. Conclusion: In this study, we developed an efficient PEG prognostic model that can predict the outcome for TPBC. Furthermore, we found that the expression of ACTL6A is associated with neoadjuvant therapy sensitivity in TPBC patients and can serve as an important factor in predicting patient prognosis and drug sensitivity.

Figure 3. Construction and validation of a PEG signature for TPBC patients

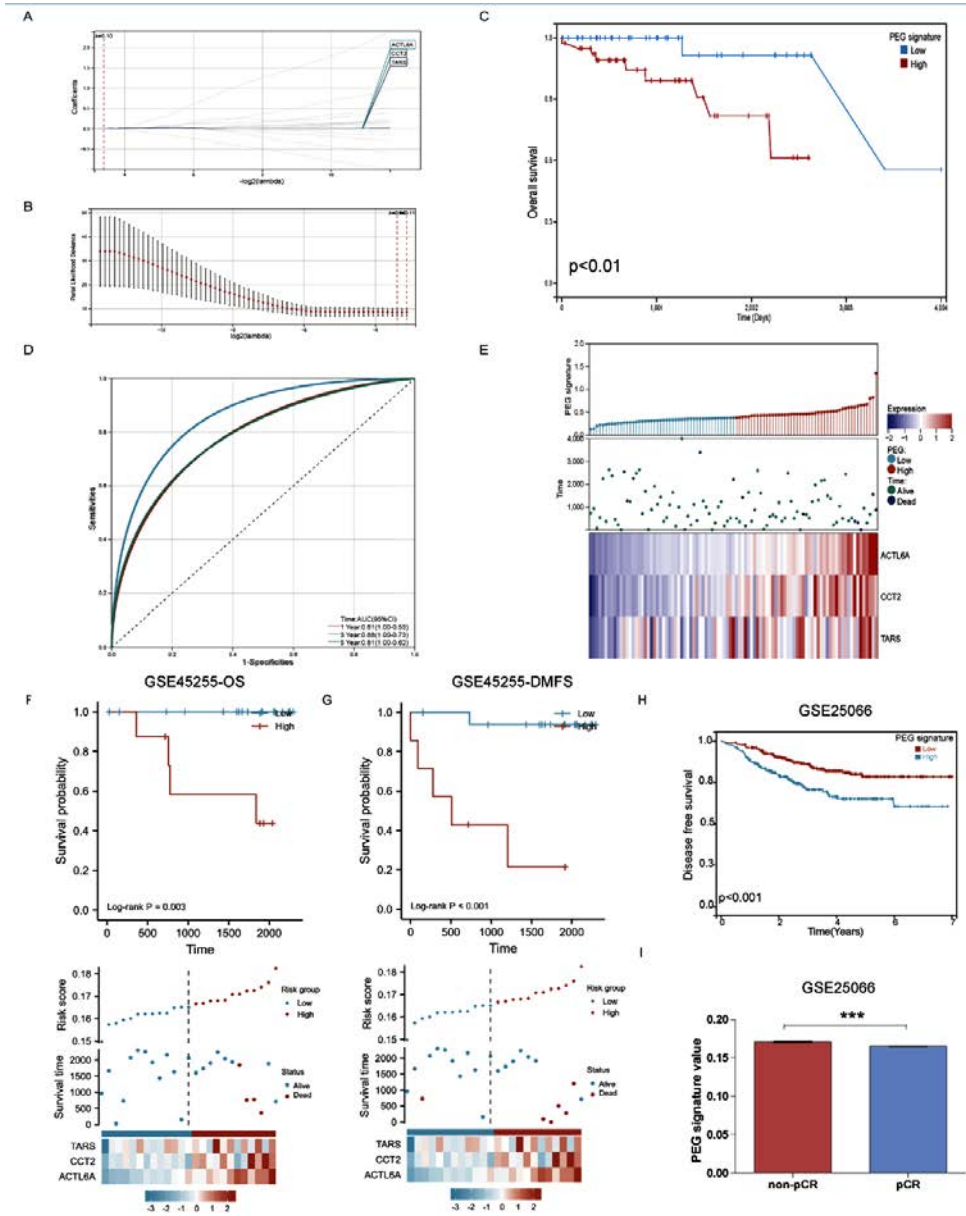
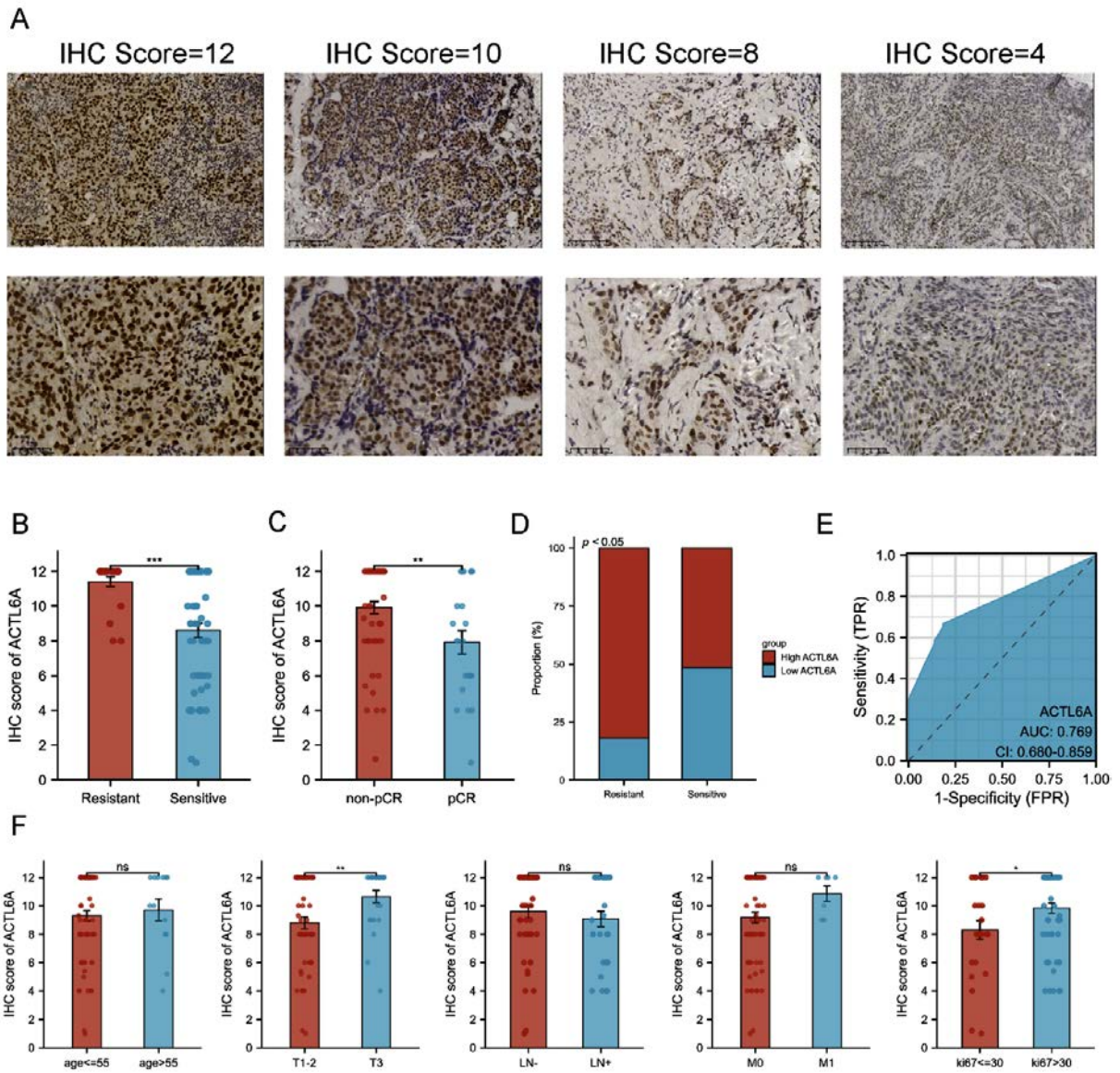


Figure 6. The predictive value of ACTL6A on NAT efficacy and its correlation with clinical characteristics.



PO1-14-04

A multivariate biomarker to guide antibody-drug conjugate selection and provide insight on response differences across breast cancer subtypes

Presenting Author(s) and Co-Author(s):

L. Lamb. Strata Oncology, United States

J. Mowers. Strata Oncology, United States

A. Nasrazadani. Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Burkard. University of Wisconsin Carbone Cancer Center, United States

N. Khazanov. Strata Oncology, United States

D. Hovelson. Strata Oncology, United States

K. Kwiatkowski. Strata Oncology, United States

S. Tomlins. Strata Oncology, United States

D. Johnson. Strata Oncology, United States

D. Rhodes. Strata Oncology, United States

Background: Antibody-drug conjugates (ADCs), including trastuzumab deruxtecan (T-DXd; targeting HER2) and sacituzumab govitecan (SG; targeting TROP2), have transformed the management of metastatic breast cancer, with additional ADCs approved in other solid tumors or in late-stage development. To date, expression of ADC target alone has been poorly predictive of objective response rates (ORRs) in both breast cancer and other tumors. Hence, there is an urgent need to develop better predictive biomarkers to guide ADC vs. other treatments, T-DXd vs. SG treatment, and optimized predictive medicine opportunities involving other ADCs. Additionally, whether ADCs are similarly effective in less common breast cancer subtypes—such as invasive lobular carcinoma (ILC) vs. invasive ductal carcinoma (IDC), is unclear. Given the limited availability of trial tissue samples and cohorts with long-term follow-up, herein we sought to determine whether a tissue based, pan-solid tumor, multivariate biomarker algorithm could predict observed ORRs across ADCs and tumor types, as has been used previously to associate tumor mutation burden with immunotherapy ORRs.

Methods: From 15,032 FFPE tumor tissue samples (from 21 tumor types) tested by clinical comprehensive genomic profiling plus RNA based quantitative transcriptional profiling (qTP) as part of the observational Strata Trial (NCT03061305), the ADC treatment response score (TRS) was discovered and validated to predict published ORRs across tumor types and approved/late-stage ADCs (n=16 observed ORRs [from 7 tumor types and 8 ADCs; SG not included]). The best performing 3-factor algorithm (by Pearson correlation coefficient of observed ORRs vs. tumor type and ADC specific predicted biomarker positivity rates) included only qTP components and combined ADC target expression, cell proliferation, and extracellular matrix adhesion (the latter being negatively associated with ORRs). Importantly, predictive biomarker positivity rates of TRS was more correlated vs. observed ORRs (n=16, $r=0.81$, $p=0.0001$) than target expression alone (n=16, $r=0.54$, $p=0.03$). TRS was then validated using held out SG ORRs from nine tumor types in the IMMU-132-01 basket trial and two ADC ORRs from ASCO 2023 abstracts (enfortumab vedotin [EV; targeting NECTIN-4] in head and neck cancer and patritumab vedotin [targeting HER3] in breast cancer), with TRS predictive biomarker positivity rates again being more significantly correlated vs. observed ORRs than target expression alone (n=11, TRS $r=0.91$, $p=0.0001$; target expression alone $r=0.44$, $p=0.17$). Lastly, the locked TRS model was then applied to the DESTINY-PanTumor02 T-DXd dataset

presented at ASCO 2023 (n=21 tumor type/ HER2 expression groups matched to the trial groups), with TRS predictive biomarker positivity rates again being highly correlated vs. observed ORRs (n=21, TRS $r=0.80$, $p < 0.0001$).

Across the 21 tumor types in the Strata Trial dataset, breast cancer had the highest percentage (76%) of patients predicted positive for at least one ADC, with 23% and 55% positive for the approved ADCs mirvetuximab soravtansine (targeting FOLR1) and EV, respectively. Lastly, patients with ILC vs. IDC had significantly greater TRS positivity rates for T-DXd (61% vs. 47%) and SG (57% vs. 48%) due to significantly decreased extracellular matrix adhesion in ILC vs. IDC. Clinical outcomes data for patients treated with ADCs and available TRS enrolled in the Strata Trial are maturing and will be presented at the meeting.

Conclusion: We have developed and validated TRS, a multivariate RNA based tumor tissue algorithm that predicts observed ORRs across tumor types and approved/late-stage ADCs. More than 75% of all patients with metastatic breast cancer are predicted to be responsive to one or more ADCs, including those approved in other tumor types.

PO1-14-05

A comparison of chemotherapy recommendations by NPI, Predict, and Oncotype DX testing in UK women with early node positive breast cancer.

Presenting Author(s) and Co-Author(s):

S. Holt. Prince Philip Hospital Breast Care Unit, Llanelli, United Kingdom

P. Innis. Exact Sciences Corporation, United States

P. Sai-Giridhar. HYWEL DDA UNIVERSITY HEALTH BOARD, LLANELLI, Wales, United Kingdom

S. Seerapu. Exact Sciences, United States

Introduction: Gene expression testing is expensive and, unless it changes the chemotherapy (CT) decision, unnecessary.

Both Nottingham Prognostic Index (NPI) and Predict Breast Cancer (Predict) are free to use and based on clinico-pathological data. Each gives a guide to the prognosis. Many clinical teams in the UK have used these indices to guide treatment and more recently to help decide who should have access to gene expression testing.

NPI scores of ≤ 2.4 have a cancer-specific ten-year survival of 96%, and >2.4 to ≤ 3.4 , >3.4 to ≤ 5.4 and >5.4 have survivals of 93%, 78% and 44% respectively. UK oncologists use it as a guide in recommending adjuvant treatment. CT is not recommended for patients with $\text{NPI} \leq 3.4$, is discussed as an option for $\text{NPI} >3.4$ to ≤ 5.4 and is recommended for $\text{NPI} >5.4$. Similarly, Predict can be used to guide CT decisions as follows: $< 3\%$ benefit, CT not recommended; 3-5% CT discussed as a possible option; $>5\%$ CT recommended.

The OncotypeDX® Breast Recurrence Score® test has been assessed recently in the RxPONDER trial which concluded that postmenopausal women with a Recurrence Score (RS) result < 26 showed no benefit from the addition of CT.

This study compares the clinical utility of three indices (NPI, Predict, and RS result) by assessing the distribution of NPI and Predict across RS result, evaluates changes in CT recommendations based on risk group, and by estimating the likelihood of CT recommendation. Methods: We recently conducted a prospective UK decision impact, decision conflict and economic analysis of Oncotype DX® test in early node positive, hormone receptor positive and HER2 negative breast cancer involving 664 women. Using these data, we calculated the NPI and the Predict score.

Descriptive statistics, logistic regression and McNemar's tests were used to assess the associations between NPI, Predict, RS result and change in CT decisions for all patients ($n=664$) and in the cohort of post-menopausal patients recruited after RxPONDER reported ($n=176$). Results: Table 1 shows similar stratification for all three indices within the low-risk groups, but not for the high-risk groups. Similar results were observed in the post-menopausal, post-RxPONDER cohort. The results of the CT decision change in the post-menopausal, post-RxPONDER patients by NPI and Predict demonstrate the utility of RS results across all NPI and Predict risk groups (Table 2). There was a stronger association between RS result (26-100 vs 0-25) and CT recommendation (OR 152.8, 95% CI 53.9-433.2, $p < 0.001$) as compared to the association between either NPI or Predict (OR 8.7, 95% CI 3.8-19.8, $p < 0.001$ and OR 7.2, 95% CI 2.8-18.3, $p=0.003$ respectively), suggesting that UK Oncologists are predominantly using RS

to guide their CT decisions. Conclusions: Either basing CT decisions or selecting which patients should undergo OncotypeDX testing by pre-screening with either NPI or Predict risks misclassifying many patients who either need potentially lifesaving CT or who can safely avoid chemotherapy altogether.

Table 1. Predict and NPI risk groups by RS result for all patients and for the post-menopausal, post-RxPONDER cohort.

		Recurrence Score			
All Patients (N=664)					
	Risk Group	0-13	14-25	26-100	Total
Predict	<3%	178 (49.2%)	161 (44.5%)	23 (6.4%)	362
	3-5%	53 (25.5%)	109 (52.4%)	46 (22.1%)	208
	>5%	30 (31.9%)	35 (37.2%)	29 (30.9%)	94
	Total	261 (39.3%)	305 (45.9%)	98 (14.8%)	664
NPI	>2.4 - 3.4	26 (56.5%)	19 (41.3%)	1 (2.2%)	46
	>3.4-5.4	203 (42.1%)	228 (47.3%)	51 (10.6%)	482
	>5.4	32 (23.5%)	58 (42.6%)	46 (33.8%)	136
	Total	261 (39.3%)	305 (45.9%)	98 (14.8%)	664
	Post-menopausal, post-RxPONDER cohort (N=176)				
Predict	<3%	49 (52.1%)	38 (40.4%)	7 (7.4%)	94
	3-5%	15 (25.9%)	30 (51.7%)	13 (22.4%)	58
	>5%	9 (37.5%)	6 (25.0%)	9 (37.5%)	24
	Total	73 (41.5%)	74 (42.0%)	29 (16.5%)	176
NPI	>2.4 to 3.4	5 (55.6%)	4 (44.4%)	0 (0%)	9
	>3.4 to 5.4	58 (45.7%)	56 (44.1%)	13 (10.2%)	127
	>5.4	10 (25.0%)	14 (35.0%)	16 (40.0%)	40
	Total	73 (41.5%)	74 (42.0%)	29 (16.5%)	176

Table 2. CT recommendation pre-and post-assay by risk group for post-menopausal, post-RxPONDER patients

Risk Group	Pre-Assay CT	Post-Assay CT	Change ^a	P-value ^b
Predict				
<3%	64 (36.4%)	12 (6.8%)	-52 (-29.5%)	<.0001
3-5%	49 (27.8%)	13 (7.4%)	-36 (-20.5%)	<.0001
>5%	22 (12.5%)	10 (5.7%)	-12 (-6.8%)	0.0005
NPI				
>2.41-3.4	5 (2.8%)	0 (0.0%)	-5 (-2.8%)	.
3.41-5.4	96 (54.5%)	18 (10.2%)	-78 (-44.3%)	<.0001
>5.41	34 (19.3%)	17 (9.7%)	-17 (-9.7%)	<.0001

CT = Chemotherapy
 Note: percentages are based on post-menopausal, post-RxPONDER cohort (n=176)
 a. absolute percentage point change
 b. P-values derived from McNemar's test

Table 2. CT recommendation pre-and post-assay by risk group for post-menopausal, post-RxPONDER patients.

Risk Group	Pre-Assay CT	Post-Assay CT	Change ^a	P-value ^b
Predict				
<3%	64 (36.4%)	12 (6.8%)	-52 (-29.5%)	<.0001
3-5%	49 (27.8%)	13 (7.4%)	-36 (-20.5%)	<.0001
>5%	22 (12.5%)	10 (5.7%)	-12 (-6.8%)	0.0005
NPI				
>2.41-3.4	5 (2.8%)	0 (0.0%)	-5 (-2.8%)	.
3.41-5.4	96 (54.5%)	18 (10.2%)	-78 (-44.3%)	<.0001
>5.41	34 (19.3%)	17 (9.7%)	-17 (-9.7%)	<.0001

CT = Chemotherapy
 Note: percentages are based on post-menopausal, post-RxPONDER cohort (n=176)
 a. absolute percentage point change
 b. P-values derived from McNemar's test

PO1-14-06

Integrated analysis reveals the impact of obesity on triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

Y. Gong. Fudan University Shanghai Cancer Center, Shanghai, United States

P. Ji. Fudan University Shanghai Cancer Center, United States

H. Wu. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

L. He. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

M. Jin. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

X. Hu. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Oncology, Fudan University, Shanghai Medical College, Shanghai, China., Shanghai, China (People's Republic)

Background: Obesity and overweight status, which has been growing rapidly over the past few decades, is considered as a risk factor for many types of cancers including breast cancer. Despite the multi-omics profile of triple-negative breast cancer (TNBC) has been comprehensively characterized, the impact of obesity on molecular features of TNBC is not fully appreciated. **Methods:** We applied an integrative analysis on clinicopathological data and molecular data (including genomic, transcriptomic, proteomic and metabolomic profiling) using the multi-omics database of TNBC (N = 465) from Fudan University Shanghai Cancer Center (FUSCC) for associations with patient body mass index (BMI). Patients were categorized into overweight/obese (OW/OB, BMI \geq 24 kg/m²) and normal (NL, BMI < 24 kg/m²) group according to the Chinese criteria of BMI. The clinical and molecular differences between OW/OB and NL patients were systematically explored. We also constructed high-fat diet (HFD)-induced obese mouse tumor models and used single-cell RNA sequencing to investigate the impact of obesity on the tumor microenvironment. Furthermore, we analyzed the efficacy of anti-PD-1 immunotherapy on TNBC tumors in both obese and normal mice. **Results:** OW/OB patients exhibited higher proportion of metabolic syndrome, more adipose tissue in the breast and worse survival than NL patients. Among most frequently mutated genes, OBSCN showed statistically significantly less mutated in the OW/OB group (3.2% vs 9.6%), while TP53 (68.3% vs 76.9%) and PIK3CA (21.4% vs 14.1%) had tendency to be different. In terms of copy number alterations, we found OW/OB patients had a higher amplified or gained frequency of 13q14.11 (FOXO1) and a lower frequency of deletion or loss of chromosomal region 7p22.1 (FOXK1). We further dissect the expression profile of TNBC. Differentially expressed gene analysis and pathway enrichment analysis demonstrated that immune and metabolic pathways were the major distinction between OW/OB and NL tumors. OW/OB tumors were characterized with elevated inflammation of tumor microenvironment, as well as higher expression of immune checkpoints. Moreover, analyses focusing on metabolic heterogeneity using transcriptomic, proteomic and metabolomic data revealed upregulation of lipid metabolism and reactive oxygen species pathway in OW/OB group. In addition, our in vivo experiments demonstrated that TNBC in the obese mice displayed faster growth rates. Flow cytometry analysis and single-cell RNA sequencing showed that higher proportion of immunosuppressive myeloid cells and exhausted CD8⁺ T cells and upregulation of lipid metabolism in HFD group. Applying anti-PD-1 immunotherapy in both obese and normal mice displayed that tumors in the obese mice showed more sensitive to anti-PD-1 immunotherapy. **Conclusion:** Our study systematically

revealed that obesity might play a significant role in the molecular heterogeneity of TNBC and showed distinct sensitivities to immunotherapy, which should be taken in account in the field of precision medicine. Keywords: triple-negative breast cancer, obesity, immune, tumor microenvironment, metabolism

PO1-14-07

Programme of mast cell subsets to potentiate breast cancer immunotherapy: from bed to bench to bed (the phase 2 platform RENAISSANCE trial)

Presenting Author(s) and Co-Author(s):

S. Wu. Fudan University Shanghai Cancer Center, China (People's Republic)

X. Jin. Fudan University Shanghai Cancer Center, United States

Y. Liu. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, United States

W. Zuo. Fudan University Shanghai Cancer Center, China (People's Republic)

L. Chen. Fudan University Shanghai Cancer Center, United States

X. Liu. Fudan University Shanghai Cancer Center, United States

L. Fan. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

Z. Wang. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, United States

Y. Liu. Fudan University Shanghai Cancer Center, United States

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background: Immune checkpoint inhibitors (ICIs) have heralded a new era in breast cancer treatment; however, response rates remain limited, making precision immune-oncology a major unmet need. In addition to T cells, effective immune responses to ICIs rely on coordinated interactions between innate and adaptive immune cells. Mast cells are evolutionarily conserved, tissue-resident cells of importance to human health. Specific subsets of mast cells might be endowed with opposite roles in cancer treatment, yet the extent of mast cell heterogeneity and its clinical merit in immunotherapy remain undefined. Objective: We sought to comprehensively characterize mast cells in breast cancer, investigate their association with immunotherapy response with in-depth mechanistic insights, and identify actionable strategies to modulate mast cell functional states, thereby optimizing immunotherapy efficacy. Methods: We employed single-cell profiling on longitudinal breast cancer samples from three independent clinical trials (NCT04613674, NCT03197389 and GSE169246) to delineate mast cell heterogeneity in anti-PD-(L)1 therapy. By integrating multi-omic analyses, tissue characterization, preclinical experiments, transgenic mice, and high-throughput drug screening, we outlined the molecular features, underlying mechanisms, and clinical relevance of distinct mast cells to elicit ICI-responsive microenvironments. Subsequently, we launched RENAISSANCE (NCT05076682), a proof-of-concept, Bayesian adaptive, phase 2 platform trial, to evaluate the efficacy and safety of combining mast cell therapeutics with anti-PD-1 backbone therapy in metastatic triple-negative breast cancer (TNBC) patients who progressed after immunotherapy. The primary endpoint was the objective response rate (ORR) assessed using RECIST v1.1 criteria. Results: We identified a distinct population of mast cells termed antigen-presenting mast cells (APMCs), constituting approximately 30% of intratumoral mast cells and correlating with improved clinical benefit of anti-PD-(L)1 therapy in TNBC. APMCs displayed MHC-II and costimulatory

molecules, and indicated the presence of tumor-reactive T cells and tertiary lymphoid structures. Using three immunocompetent mouse models, we confirmed the immunomodulatory capacity of APMCs in immunotherapy. Mechanistically, by employing Cpa3CreERT2Cd74fl/fl mice, we demonstrated that APMCs potentiate anti-PD-1 efficacy and antitumor T cell immunity through their antigen-presentation machinery. Interestingly, we identified cromolyn, an FDA-approved drug for allergy, as a potential therapeutic agent that elicited APMC-dependent CD8+ T cell cytotoxicity to synergize with anti-PD-1 therapy. Between February 2022 and March 2023, 10 patients with immunotherapy-refractory metastatic TNBC were enrolled to receive cromolyn plus camrelizumab backbone treatment. Given Bayesian predictive probability, this arm was “graduated” due to meeting the pre-specified efficacy boundary, with an ORR of 40.0% (4/10). The treatment was well tolerated with similar safety profiles of relevant drugs. Conclusions: Our findings provide crucial insights into the impact of mast cell heterogeneity on the clinical response to ICIs at a single-cell level, and pave the way for APMC-directed therapeutic interventions in cancer treatment. To our knowledge, this is the first prospective study in breast cancer of cromolyn plus anti-PD-1 backbone regimen after anti-PD-(L)1 immunotherapy failure, demonstrating significant antitumor activity and commendable tolerability. Consequently, we suggest a phase 3 randomized study to consolidate this finding, which might be an effective treatment in patients for whom there are few effective treatment options.

PO1-14-08

Real-world clinical genomics study of HR+/HER2- metastatic breast cancers treated by CDK4/6i plus endocrine therapies revealed a drug resistant tumor segment characterized by ER independence

Presenting Author(s) and Co-Author(s):

Z. Kan. Pfizer Inc., United States

J. Wen. Pfizer Inc., United States

J. Webster. Pfizer Inc., United States

V. Bonato. Pfizer Inc., United States

W. Roh. Pfizer Inc., United States

X. Mu. Pfizer Inc., United States

P. Rejto. Pfizer Inc., United States

J. Bienkowska. Pfizer Inc., United States

Background

CDK4/6 inhibitors (CDK4/6i) plus endocrine therapies (ET) are the standard-of-care for hormone receptor–positive/human epidermal receptor 2–negative metastatic breast cancer (HR+/HER2– mBC). However, drug resistance remains a major unmet need. Investigations of drug resistance mechanisms has been hampered by a dearth of tumor molecular profiling data from the post-treatment setting. To address this challenge, we have conducted a real-world clinical genomics study to better understand the molecular mechanism of CDK4/6i resistance as well as to stratify patients based on integrated multi-omics profiles.

Methods

We retrospectively analyzed a multi-omics dataset of 400 HR+/HER2- mBC patients who had received CDK4/6i plus ET and developed progressive disease (PD) from the de-identified Tempus database. Pre-treatment and post-progression biopsies were taken \square 1 year prior to starting the CDK4/6i treatment or following PD respectively. Tempus xT next-generation sequencing (DNA-seq of 648 genes) and RNA sequencing assays were performed on 427 tumor FFPE samples, including 200 pre-treatment, 227 post-progression and 26 longitudinal pairs.

Results

The median age of the patients was 57 (54.9-57.4) and median progression free survival (PFS) is 379 (341-433) days. Two genes were found to harbor a significant increase in genomic alteration frequencies (GAF) after adjusting for FDR at post-progression vs. pre-treatment – ESR1 (41.9% vs. 15%, $p=5.4e-10$), RB1 (13.2% vs. 3%, $p=8.5e-05$). ESR1 and RB1 also harbored high frequencies of acquired genomic alterations among 26 paired samples at 34.6% and 11.5% respectively. TP53 mutation at baseline was significantly associated with shorter PFS at baseline ($p=4.23e-05$, HR=2.081) and TP53 GAF significantly increased after PD (37% vs. 28.5%, $p=0.039$). BRCA1/2 pathogenic mutations ($p=1.63e-04$, HR=3.066), APOBEC mutation signature S13 ($p=0.0125$, HR=1.55) and CCNE1 gene expression ($p=0.024$, HR=1.46) were significantly associated with shorter PFS. APOBEC signature ($p=0.0035$) and CCNE1 expression ($p=1.33e-06$) also significantly increased post-progression. Among the top molecular features associated with longer PFS were markers of estrogen signaling such as PGR gene expression ($p=6.76e-04$, HR=0.565) and the Hallmark estrogen response signature ($p=0.021$, HR=0.679).

Applying a multi-omics pattern recognition algorithm, we identified a molecularly distinct cluster (IC1) characterized by down-regulation of estrogen signaling. IC1 is significantly associated with shorter PFS ($p=3.72e-05$, HR=0.22) and increased from 4% pre-treatment to 23% post-progression ($p=7.3e-08$). Further, IC1 is strongly enriched in markers previously implicated in CDK4/6i resistance including CCNE1 expression, RB1 mutation and MYC/E2F activation. We then developed machine learning models to predict gene-level dependency trained on cancer cell line expression and CRISPR-KO screen data. These models predicted decreased dependency on ESR1 and CDK4 and increased dependency on CDK2 in IC1, strengthening the association between ER independence and CDK4/6i resistance.

Conclusions

Our real-world clinical genomics study identified a comprehensive list of biomarkers associated with resistance to CDK4/6i plus ET and estimated patient prevalence for these markers in the post-treatment setting. Integrated and machine-learning analyses identified a subset of aggressive tumors with estrogen independence characteristics that are implicated in CDK4/6i resistance and suggested new therapeutic strategies.

PO1-14-09

Age-related remodeling of the systemic and breast microenvironment promotes a tumor-permissive locale for ER+ breast cancer in older women

Presenting Author(s) and Co-Author(s):

N. Carleton. University of Pittsburgh Medical Center, United States

J. Zou. University of Pittsburgh, United States

S. Lee. Women's Cancer Research Center, United States

D. John Mary. Women's Cancer Research Center, United States

R. Li. University of Pittsburgh, United States

J. Atkinson. Institute for Precision Medicine, University of Pittsburgh, United States

Z. Huang. Hillman Cancer Center, United States

H. Osmanbeyoglu. University of Pittsburgh, United States

P. Lucas. UPMC Hillman Cancer Center / NSABP Foundation, Pittsburgh, Pennsylvania, United States

E. Diego. University of Pittsburgh, United States

M. Lotze. University of Pittsburgh, United States

G. Tseng. University of Pittsburgh, United States

J. Hooda. University of Pittsburgh, United States

I. Zervantonakis. University of Pittsburgh, United States

P. McAuliffe. UPMC Hillman Cancer Center, United States

S. Oesterreich. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

A. LEE. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

Introduction: The peak incidence of ER+ breast cancer occurs in women around the age of 70. Compared to younger cohorts, we and others have shown that older patients with ER+ breast cancer have an enrichment of luminal disease and experience fewer recurrences, suggesting overtreatment. Differences in the biological phenotypes of tumors in older women remain poorly understood and treatment remains challenging as older patients are underrepresented in clinical trials. In this study, we hypothesized that aging alters both local and systemic hormones and inflammatory cytokines, creating a permissive environment for tumor formation and growth. To address this hypothesis, we employed a systems biology approach across multiple model systems and tissue samples. Methods: Our study included specimens from two cohorts of patients: (1) n = 90 women without breast cancer obtained from the Komen Tissue Bank, from whom we obtained matched plasma and non-cancerous breast tissue (n = 30 across age groups comprising of young donors (35-45yo), middle-aged donors (55-69yo), and older donors (≥ 70 yo); and (2) n = 115 women with ER+ breast cancer (n = 25 young patients, n = 57 middle-aged patients, and n = 33 older patients) obtained from our institutional biobank, including matched plasma, tumor tissue, and tumor-adjacent tissue. From each of these sets of specimens, we measured estrogen disposition using mass spectrometry, a 22-plex panel of inflammatory markers, and transcriptomic changes using RNA-seq. Using scRNA-seq and multiplexed IHC, we further characterized the immune changes that occur with age. Lastly, we used an aged, carcinogen-induced ER+ tumor model in F344 rats (obtained from the NIA) to model tumor development and growth. Results: In the plasma, estradiol (E2) drastically decreased in post-menopausal women, leaving estrone (E1) as the predominant circulating

estrogen in older women. However, the breast tumor microenvironment (TME) showed comparable levels of E1 and E2 across age groups. Multi-class concordance analysis of breast cancer tissue from RNA revealed significant increases in gene expression of the HSD17B7 enzyme and decreases in HSD17B2 enzyme across age, likely elevating local E1-to-E2 conversion and yielding high local E2 levels despite low circulating levels specifically in older women. In older patients with ER+ breast cancer, there was a significant increase in a chemokine network characterized by CCL2 and CXCL9 within the TME. scRNA-seq revealed enrichment of inflammatory M2-like macrophages in the aged TME. Immune dysfunction and decreased immunosurveillance in older patients manifested with widespread decreases in the presence of cytotoxic lymphocytes and decreased pathway enrichment of key immune pathways, such as JAK/STAT and IFN γ signaling. mIHC analysis revealed decreases in CD4 and CD8 T cells and increases in M2-like macrophages in older patients in both tumor and stromal regions. Lastly, in the carcinogen-induced F344 rat model, aged rats (~ 24mo, human equivalent 60-70yo) had a shorter tumor-free interval than the younger rats (~ 4-6mo, human equivalent 20-30yo), likely due to increases in tumor-promoting inflammation and decreased immune surveillance. Ongoing mechanistic work is focused on macrophage-patient derived organoid co-cultures evaluating the functional relevance of E2, CCL2, and CXCL9 in shaping the aged TME. Conclusions: Our study of systemic and local breast hormones and cytokines in both healthy individuals and breast cancer patients showed that older women with ER+ breast cancer harbor different systemic and local environments compared to younger women. The aged TME is characterized by high E2, cytotoxic lymphocyte depletion, and immune dysfunction, creating a permissive environment for tumor formation. Future translational work should be aimed at chemo-preventative strategies to reduce the age-related chronic inflammation and immune dysfunction.

PO1-14-10

Comprehensive clinicogenomic characterization of inflammatory breast cancer

Presenting Author(s) and Co-Author(s):

N. Priedigkeit. Dana-Farber Cancer Institute / Broad Institute of MIT and Harvard, Boston, Massachusetts, United States

B. Harrison. BWH, United States

M. Hughes. Dana Farber Cancer Institute, United States

R. Shue. Dana-Farber Cancer Institute, United States

Y. Li. Medical Oncology, Dana-Farber Cancer Institute, United States

G. Kirkner. Medical Oncology, Dana-Farber Cancer Institute, United States

C. Remolano. Dana-Farber Cancer Institute, United States

S. Strauss. Dana-Farber Cancer Institute, United States

J. Files. Dana-Farber Cancer Institute, United States

A. Feeney. Dana-Farber Cancer Institute, United States

A. Mohammed-Abreu. Dana Farber Cancer Institute, United States

A. Garrido-Castro. Dana-Farber Cancer Institute, and Harvard Medical School, Brookline, Massachusetts, United States

R. Barroso-Sousa. Dana Oncology, United States

B. Bychkovsky. Comprehensive Breast Health Center, Brigham and Women's Hospital; Breast Oncology Program, Dana-Farber Brigham Cancer Center Division of Cancer Genetics and Prevention; Dana-Farber Cancer Institute; Harvard Medical School, United States

F. Nakhlis. Dana-Farber Cancer Institute, United States

J. Bellon. DFCI/BWH, Boston, Massachusetts, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

B. Johnson. Medical Oncology, Dana-Farber Cancer Institute; Harvard Medical School, United States

L. Sholl. Brigham and Women's Hospital, United States

D. Dillon. Brigham and Women's Hospital, Breast Oncology Program, Susan F. Smith Center for Women's Cancers, Dana-Farber Brigham Cancer Center; Harvard Medical School, United States

B. Overmoyer. DFCI, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Cherniack. Medical Oncology, Dana-Farber Cancer Institute; Broad Institute, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

BACKGROUND: Inflammatory breast cancer (IBC) is a rare type of breast cancer associated with a unique clinical presentation and overall poor outcomes, recognized as a distinct category by the AJCC staging system. The biological mechanisms driving the IBC phenotype are

relatively undefined—partially due to a lack of comprehensive, large-scale genomic studies and limited clinical cohorts. Here, we report one of the largest, subtype-informed clinicogenomic characterizations of IBC to date. **METHODS:** A retrospective analysis of 2457 patients with metastatic breast cancer who underwent targeted tumor-only DNA-sequencing (OncoPanel, up to 447 cancer-associated genes) was performed at Dana-Farber Cancer Institute. Clinicopathologic, single nucleotide variant (SNV), copy number variant (CNV) and tumor mutational burden (TMB) comparisons were made between IBC and non-IBC cases. Median follow-up was 28.1 months. **RESULTS:** Our profiled cohort included 140 patients with IBC specimens (n = 68 primary tumors, 72 metastatic tumors) and 2317 patients with non-IBC specimens (n = 702 primaries, 65 local recurrences, 1550 metastases). Of these, 87.4% of patients were White, 4.7% Black, 3.6% Asian or Pacific Islander, and 4.3% other/unknown. Clinicopathologic differences between IBC and non-IBC cases were consistent with previous reports—including younger age at diagnosis of metastatic disease (51 vs 54 years, $p = 0.04$), and a higher proportion of grade 3, estrogen receptor-negative and HER2-positive tumors ($p < 0.001$). Among the hormone-receptor (HR)-positive subtype, IBC tumors showed a significant enrichment in Luminal B (LumB)-inferred disease (62.5% vs 39.8%, $p < 0.005$), defined as tumors with grade 3 or progesterone receptor staining $< 10\%$. The most recurrent somatic alterations spanning all subtypes in IBC were TP53 (72%), ERBB2 (32%), PIK3CA (24%), CCND1 (12%), MYC (9%), FGFR1 (8%) and GATA3 (8%). A multivariate logistic regression analysis accounting for HR and HER2 status revealed a significant enrichment in TP53 SNVs in IBC vs non-IBC (OR 2.08 [95% CI 1.34-3.24], adjusted p -value 0.04). Frequency of TP53 alterations in IBC vs non-IBC cases was 85.1% vs 64.3% in HER2-positive and 50.0% vs 27.7% in HR-positive disease—with an enrichment of TP53 mutations in IBC LumB-inferred tumors vs non-LumB (64% vs 26%, $p < 0.05$). When comparing HR+ IBC LumB vs HR+ non-IBC LumB cases, TP53 mutations were again enriched ($p < 0.05$)—suggesting LumB-like histopathology is not the only driving feature of TP53 enrichment in HR+ IBC. TMB did not differ substantially between IBC and non-IBC and no other statistically significant enrichments were observed, including when grouping mutations into six canonical cancer pathways (cell cycle, Notch signaling, PI3K pathway, RTK/RAS signaling, TP53 pathway and WNT signaling). **CONCLUSIONS:** Taken together, this study provides a comprehensive landscape of somatic alterations in a large cohort of patients with metastatic IBC and non-IBC. Our data support a lack of major genomic differences other than enrichments in TP53 mutations and an associated LumB-like histopathology. These results both reinforce the importance of TP53 mutations in IBC biology and suggest additional analyses beyond somatic DNA-level changes are warranted. Future efforts with the DFCI IBC cohort will assess germline-somatic interactions, non-genomic or transcriptomic characterizations, and potential environmental influences to better understand the mechanisms driving this unique disease.

PO1-14-11

Different molecular processes are associated with recurrence in the clinical high-genomic low risk (cH/gL) and clinical low- genomic high risk (cL/gH) groups of the MINDACT clinical trial

Presenting Author(s) and Co-Author(s):

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

H. Nguyen. KU Leuven, United States

F. Richard. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, United States

M. Maetens. Laboratory for Translational Breast Cancer Research, KU Leuven, Leuven, Belgium, Belgium

C. Poncet. European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium, Brussels, Belgium

L. De Meulemeester. EORTC, United States

K. Aalders. Diaconessenhuis Utrecht, United States

M. Delorenzi. SIB Swiss Institute Bioinformatics, United States

S. Delaloge. Institut Gustave Roussy, Villejuif, Ile-de-France, France

J. Pierga. Institut Curie & Université Paris Cité, Paris, France

E. Brain. European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium, United States

S. Vrijaldenhoven. Noordwest Ziekenhuisgroep, United States

P. Neijenhuis. Alrijne Ziekenhuis, United States

E. Rutgers. Department of Surgical Oncology, Netherlands Cancer Institute, United States

F. Hilbers. NKI, United States

L. Van 't Veer. The University of California, San Francisco CA, USA, United States

G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy

C. Sotiriou. Institut Jules Bordet, United States

M. Piccart. Institut Jules Bordet, Anderlecht, Brussels Hoofdstedelijk Gewest, Belgium

F. Cardoso. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

Background: Despite the growing understanding of estrogen receptor positive/ HER2-negative (ER+/HER2-) breast cancer (BC) biology, many unknowns remain regarding the mechanisms of disease recurrence. While several multigene prognostic signatures have shown clinical utility in identifying those patients at high or low genomic risk of recurrence, they can present with some limitations. In this retrospective analysis of the MINDACT trial, we interrogated the available transcriptomic data to understand which biological characteristics of the tumor are associated with recurrence in patients from the clinical high- genomic low risk (cH/gL) and clinical low-genomic high risk (cL/gH) groups (where the clinical and genomic risk were defined by a modified version of Adjuvant Online! and the 70-gene signature, respectively). Methods: These analyses focused on the subset of patients with ER+/HER2- tumors of no special type (NST) who received endocrine therapy (which comprised the majority of this NST ER+/HER2- sub-

cohort) and for which central pathology and gene expression data were available (n= 1245). Scores of gene expression modules associated with key biological processes in breast cancer defined in a collection of previous publications were computed from the gene expression matrix using the formula described in Desmedt et al. (Clin. Cancer Res. 2008). Gene Set Variation Analysis method (R package 'GSVA' – version 1.40.1) was used to derive the enrichment scores of fifty hallmark gene sets available in the 'H' collection of the MSigDB database (version 7.5.1). Survival analyses were performed for disease-free survival (DFS) and distant recurrence-free survival (DRFS). Univariable and multivariable regression models, implemented by Cox regression and Fine-Gray subdistribution hazard regression methods, were performed to evaluate the association of enrichment of hallmarks and gene modules with DFS and DRFS, respectively (covariates =age, nodal status, KI67, tumor size, chemotherapy, radiotherapy). Results: DFS event occurred in 150/913 (16.4%) and 51/332 (15.4%) NST ER+/HER2- patients in the cH/gL and cL/gH groups, respectively. DRFS event occurred in 70/913 (7.7%) and 21/332 (6.3%) NST ER+/HER2- patients in the cH/gL and cL/gH groups, respectively. In the cH/gL group, we observed an association of hallmarks related to cell cycle and downregulation of gene modules related to lymphocyte-centric immune activities with worse prognosis (Table). For the cL/gH, we did not observe an association between hallmarks related to cell cycle and worse prognosis but an enrichment of hallmarks related to PI3K/AKT/mTOR signaling as well as several metabolic hallmarks related to insulin activities (Table). Of interest, in this group of patients, higher scores of the HER2-associated gene expression signature were also associated with worse prognosis. Across the two groups effects were more pronounced for DRFS than DFS. Conclusion: Different molecular processes are associated with progression in these two distinct groups of patients. The association of hallmarks related to cell cycle with survival in the cH/gL group supports the observation that adjuvant chemotherapy could benefit a subset of these patients. In the cL/gH group, the association of signatures associated with PI3K pathway and HER2 can have potential clinical relevance given their current targetability in the metastatic setting. This retrospective study is funded by the Breast Cancer Research Foundation.

Table. Representative hallmarks and gene expression modules independently associated with prognosis in NST ER+/HER2- patients in the cH/gL group and in the cL/gH group

cH/gL group				
Gene set	DFS HR (95% CI)	p-value ^a	DRFS HR (95% CI)	p-value ^a
HALLMARK_E2F_TARGETS	2.29 (1.15 - 4.53)	0.018	2.89 (0.99 - 8.38)	0.051
HALLMARK_G2M_CHECKPOINT	2.81 (1.30 - 6.06)	0.009	4.66 (1.40 - 15.52)	0.012
HALLMARK_GLYCOLYSIS	5.87 (1.79 - 19.22)	0.003	20.66 (3.23 - 132.27)	0.001
HALLMARK_MTORC1_SIGNALING	3.79 (1.52 - 9.47)	0.004	8.59 (2.26 - 32.66)	0.002
HALLMARK_PROTEIN_SECRETION	2.50 (1.08 - 5.80)	0.032	6.17 (1.85 - 20.51)	0.003
AKT_MTOR_MG.up	3.41 (1.48 - 7.86)	0.004	12.00 (3.04 - 47.35)	< 0.001
AURKA_proliferation	3.12 (1.42 - 6.89)	0.005	4.15 (1.24 - 13.88)	0.021
CIN25	3.41 (1.54 - 7.52)	0.002	5.38 (1.45 - 20.04)	0.012
CIN70	3.30 (1.49 - 7.32)	0.003	4.93 (1.37 - 17.76)	0.015
GGI_grading	5.01 (2.03 - 12.35)	< 0.001	9.78 (2.23 - 42.79)	0.003
Hypoxia51.up	3.70 (1.63 - 8.39)	0.002	7.35 (2.41 - 22.37)	< 0.001
IRM_immune	0.57 (0.31 - 1.04)	0.069	0.28 (0.11 - 0.72)	0.008
Lymphocyte.down.min	2.83 (1.26 - 6.40)	0.012	16.18 (3.48 - 75.22)	< 0.001
PTEN_loss	2.22 (0.86 - 5.73)	0.098	4.27 (1.09 - 16.76)	0.037
TP53_mut	4.46 (1.70 - 11.70)	0.002	12.97 (2.72 - 61.86)	0.001
cL/gH group				
Gene set	DFS HR (95% CI)	p-value	DRFS HR (95% CI)	p-value
HALLMARK_GLYCOLYSIS	1.20 (0.20 - 7.07)	0.843	16.55 (1.67 - 164.12)	0.016
HALLMARK_PI3K_AKT_MTOR_SIGNALING	4.06 (0.63 - 26.11)	0.140	20.39 (1.72 - 241.36)	0.017
ERBB2	5.07 (0.92 - 27.77)	0.062	23.02 (1.09 - 487.54)	0.044
Hypoxia51.up	2.07 (0.54 - 7.92)	0.290	7.62 (0.97 - 59.86)	0.053
IGF1.up	1.52 (0.37 - 6.31)	0.563	15.71 (1.69 - 145.70)	0.015

#p-values reported were not corrected for multiple testing

PO1-14-12

Quantitative Biomarkers and 21-Gene Assay Results Predict Breast-Conserving Surgery Following Neoadjuvant Therapy in Early-Stage, Hormone Receptor-Positive, HER2-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Freeman. Department of Public Health Sciences, University of Chicago, Chicago, Illinois, United States

S. Shubeck. University of Chicago, Chicago, Illinois, United States

N. Chen. University of Chicago, Chicago, Illinois, United States

R. Nanda. University of Chicago Medicine, Chicago, Illinois, United States

D. Huo. Department of Public Health Sciences, The University of Chicago, Chicago, Illinois, United States

F. Howard. Department of Medicine, Section of Hematology/Oncology, The University of Chicago, Chicago, Illinois, United States

Background: Neoadjuvant chemotherapy (NACT) and neoadjuvant endocrine therapy (NET) are often used to downstage tumors and/or enable breast-conserving surgery (BCS) in patients (pts) with early-stage, hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer. Given the increasing use of neoadjuvant therapy for HR+ breast cancer, studies are needed to better quantify the success of NACT/NET in downstaging tumors as a function of estrogen (ER), progesterone (PR), and Ki-67 expression, and 21-gene recurrence score (RS) in this patient population.

Methods: Data were from pts with stage I-III, HR+/HER2- breast cancer diagnosed from 2010-2020 in the National Cancer Database (NCDB). Quantitative ER, PR, and Ki-67 data became available in 2018. We included pts who received either NACT or NET, with surgical plan categorized as mastectomy or BCS. Pts who received NACT for 12–30 weeks or NET for 4–36 months prior to surgery were eligible. Predicted rates of BCS by quantitative biomarkers (ER, PR, Ki-67 percentage, and RS) were estimated using restricted cubic spline logistic regression. Multivariable logistic regression models were fit to examine the associations between surgical plan and quantitative biomarkers for the two neoadjuvant cohorts. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated per 10% increase in percentages of ER, PR, and Ki-67 expression.

Results: Of 44,589 pts treated with NACT, the mean age was 53 years, the median amount of time they were on NACT before surgery was 21 weeks, and 65% had cT1-2 disease. Of 10,466 pts treated with NET, the mean age was 68 years, the median amount of time they were on NET before surgery was 6 months, and 76% had cT1-2 disease. Overall, 42% of pts underwent BCS after NACT; while 64% did after NET. In the NACT cohort, 13,752 of the pts with available quantitative biomarker data were included in regression analyses; in the NET cohort, 4,003 were included. After adjusting for demographic and clinicopathologic factors, increasing ER% (aOR=0.96, 95% CI: 0.94–0.97) and PR% (aOR=0.98, 95% CI: 0.96–0.99) were associated with lower odds of BCS after NACT. Increasing Ki-67% was associated with greater odds of BCS after NACT (aOR=1.07, 95% CI: 1.04–1.10). Pts with a low (aOR=0.50, 95% CI: 0.29–0.88) or intermediate (aOR=0.58, 95% CI: 0.41–0.81) RS were significantly less likely than pts with a high RS to undergo BCS after NACT. Asian pts were less likely than White pts to have BCS (aOR=0.75, 95% CI: 0.56–0.99), while rates of BCS after NACT were similar to pts from

other racial and ethnic groups. In the NET cohort, increasing ER% was associated with greater odds of BCS (aOR=1.09, 95% CI: 1.01–1.17). There was no significant association between baseline PR% or Ki-67% and BCS after NET. Pts with a low (aOR=0.92, 95% CI: 0.60–1.43) or intermediate (aOR=0.96, 95% CI: 0.65–1.41) RS were numerically less likely than pts with a high RS to have BCS after NET, though not statistically significant. Compared with White pts, Asian pts were less likely to have BCS after NET (aOR=0.60, 95% CI: 0.40–0.91).

Conclusions: In this analysis of pts from the NCDB who received neoadjuvant therapy for early-stage, HR+/HER2- breast cancer, we found that BCS after NACT was higher for patients with a high RS or high Ki-67, suggesting that NACT is unlikely to downstage tumors with a low/intermediate RS or low Ki-67. Most pts receiving NET underwent BCS (likely due to a smaller clinical tumor size); BCT after NET was most dependent on ER expression. Asian pts were less likely to undergo BCS after either NACT or NET, which is consistent with previous reports. These data could facilitate appropriate neoadjuvant treatment selection based on tumor biology and improve patient counseling on the likelihood of successful BCS.

PO1-15-01

Digital pathology models reveal case-specific characteristics of the tumor microenvironment

Presenting Author(s) and Co-Author(s):

Y. Gerardin. PathAI, Boston, Massachusetts, United States

C. Kirkup. PathAI, Boston, Massachusetts, United States

A. Khosla. PathAI, United States

L. Chambre. PathAI, United States

M. Drage. PathAI, Boston, Massachusetts, United States

A. Taylor-Weiner. PathAI, Boston, Massachusetts, United States

Background Phenotypic characteristics and genetic content have been observed to vary within individual tumors. However, translational research and some clinical practices often rely on extrapolating single histopathology slides to be representative of whole-tumor biology, even when the extent of intra-tumor biological heterogeneity is unknown. In addition, technical factors in slide preparation and digitization can also contribute to variability. Here, we use digital pathology models to identify cell and tissue types in whole-slide images of breast cancer tumors, and quantify intra- and inter-case heterogeneity in cell and tissue features of the tumor microenvironment. **Methods** We developed PathExplore, a suite of convolutional neural network models trained on pathologist annotations of cell and tissue types in hematoxylin and eosin-stained slides. The models were deployed on the TCGA breast cancer dataset (n=1083 primary solid tumors). Quantitative human-interpretable features (HIFs) relating to cancer, stromal, and necrotic tissue areas, as well as the abundance and distribution of cancer cells, fibroblasts, and immune cells within these tissues, were extracted for each slide. Similarity between slides on sets of HIFs was assessed using Pearson correlation. Intra- and inter-case variability of individual HIFs was measured using the normalized percent difference (range divided by mean) for each slide pair. Case-specificity was quantified by the AUC of correlation or difference distributions for intra-case vs inter-case slide pairs. Only pairs of slides with matching metadata, including tissue source site, cancer stage, and scanner model, were considered for inter-case analysis. **Results** A total of 55 cases, comprising 114 slides, were identified as having more than one slide per case. Considering all 123 proportional HIFs, intra-case slide pairs showed high correlation compared to inter-case pairs ($r=0.97$ vs $r=0.90$, $AUC=0.88$), with 29% of slides coming from a multi-slide case most closely correlated with another slide from the same case out of the entire TCGA breast dataset. Subsets of these proportional HIFs relating to each identified cell type were also case-specific, with AUC's ranging from 0.79 for macrophage HIFs to 0.87 for cancer cell HIFs. All proportion, density, and ratio HIFs (n=297) individually showed case specificity ($AUC >0.5$), with median intra-case differences ranging from 0.6% to 69%. Area proportion of necrosis was more variable than cancer or stroma tissue, while cancer cell count proportions were less variable than fibroblast or immune cell proportions. Cell count proportions were in general less variable and more specific than their corresponding density HIFs; for instance, the frequency of fibroblasts out of all cells in stroma had a median intra-case difference of 11% compared to 20% for the density of fibroblasts in stroma. **Conclusions** We quantified heterogeneity of key features of the tumor microenvironment both within and across tumors. These results reveal biological and technical variability that can inform selection and interpretation of biomarkers derived from single slides. The ability to uniquely identify slides from the same case additionally demonstrates the technical robustness of digital pathology

models for yielding quantitative insights into tumor biology.

PO1-15-02

Comprehensive characterization of genetic interactions in breast cancer reveals therapeutic vulnerabilities

Presenting Author(s) and Co-Author(s):

C. Lin. Fudan University Shanghai Cancer Center, United States

X. Jin. Fudan University Shanghai Cancer Center, United States

D. Ma. Fudan University Shanghai Cancer Center, China (People's Republic)

C. Chen. Fudan University Shanghai Cancer Center, United States

X. Hu. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background: Genome-informed and genome-targeted precision treatment for breast cancer have achieved remarkable progress in improving clinical outcomes for patients with specific genetic alterations. However, treatment efficacy is compromised by the current practice of basing treatment decision-making solely on single driver alterations, without considering the role of genetic interactions. Consequently, it is of great necessity to conduct systematic investigations to determine the clinical relevance of genetic interactions. **Methods:** We established a large-scale multi-omics cohort (N=873) and a real-world clinical sequencing cohort (N=4,421) representing the Asian breast cancer population. Detailed treatment records were collected. We then investigated the prognostic and predictive effects of genetic interactions based on multivariate Cox proportional hazards model and logistic regression model. To validate our findings, we utilized patient-derived organoids and tumor fragments to confirm the associations observed between genetic interactions and drug response. **Results:** Through integrated analysis of genomics, transcriptomics, proteomics, and metabolomics, we constructed a network comprising 54 co-occurring events and 38 mutually exclusive events, elucidating their association with dysregulated biological processes. External validations were performed in TCGA-BRCA, MSK-IMPACT, METABRIC, and AACR-GENIE datasets, respectively. Furthermore, we systematically revealed the prognostic effects of genetic interactions across distinct clinical subtypes. In triple-negative breast cancer, we found that the co-occurrence of PIK3CAmut-FOXA1mut was associated with unfavorable distant metastasis-free survival while TP53mut-MYBamp and TP53mut-CCNE1amp were associated with decreased overall survival. Additionally, we characterized the genetic interactions that impact the clinical outcomes of patients undergoing specific treatments in the neoadjuvant, adjuvant, and advanced settings. Notably, we identified associations such as TP53mut-AURKAamp with tamoxifen resistance, ERBB2amp-PAK1amp with resistance to trastuzumab-pertuzumab combinations, germline BRCA1mut-MYCamp with sensitivity to PARP1 inhibitors, and TP53mut-MYBamp with immunotherapy resistance. **Conclusion:** Overall, the consideration of genetic interactions may enhance our understanding of the heterogeneity in treatment response and complement ongoing efforts in precision oncology. Our study suggests that decision-making regarding genome-informed and genome-targeted treatment should extend beyond the scope of single driver alterations.

PO1-15-03

Spatially resolved analysis of tumor microenvironment in invasive lobular carcinoma

Presenting Author(s) and Co-Author(s):

M. Serra. Breast Cancer Translational Research Laboratory J-C Heuson, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, Belgium

M. Rediti. 9 Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B), Université Libre de Bruxelles (ULB), Brussels, Belgium., Belgium

L. Collet. Institut Jules Bordet, Belgium

F. Lifrange. Department of Pathology, University Hospital Center of Liege, Liege, Belgium, Belgium

D. Venet. Institut Jules Bordet, Belgium

N. Ocelli. Institut Jules Bordet, Belgium

X. Wang. Institut Jules Bordet, Belgium

D. Vincent. Institut Jules Bordet, Belgium

G. Rouas. Institut Jules Bordet, Belgium

L. Craciun. Institut Jules Bordet, Belgium

D. Larsimont. Institut Jules Bordet, Belgium

L. Buisseret. Institut Jules Bordet, Belgium

M. Vikkula. Human Molecular Genetics, de Duve Institute, Université Catholique de Louvain, Brussels, Belgium, United States

F. Duhoux. Cliniques universitaire Saint-Luc-institut Roi Albert II, United States

F. Rothé. Institut Jules Bordet, Belgium

C. Sotiriou. Institut Jules Bordet, United States

Background: Invasive lobular carcinoma (ILC) is the second most common histological breast cancer subtype; however, little is known about its tumor microenvironment (TME). Here, we aimed to study ILC TME using spatial transcriptomics (ST). Methods: We performed ST (Visium 10x Genomics) on frozen tumor samples from 43 primary hormone receptor positive (HR+), HER2-negative (HER2-) ILCs. Of note, 9 samples were coming from patients who experienced disease relapse. Relative hematoxylin/eosin (H&E) slides were morphologically annotated (QuPath software). xCell was used to perform cell type enrichment analysis on sample pseudo-bulks. After cross-samples integration, ST spots were clustered using hierarchical clustering (STutility R package). intNMF algorithm was used to perform clustering at the patient-level by combining: RNA sequencing information (relative percentage of spot-level clusters in each sample), morphology and level of colocalization between cancer cells and the other cell types of the tumor microenvironment. METABRIC (HR+, HER2- ILC samples, n = 122) was used as external validation cohort. Survival analyses (univariable and multivariable adjusting for clinicopathological features) were performed using Cox proportional hazard models. Results: The patient-level classification revealed four groups showing different biological characteristics. Differences in terms of morphology (annotation) and pathway enrichment analysis based on marker genes (GSEA) were observed between groups. This information allowed us to annotate our groups as: proliferative (P, n = 12, enriched in tumor cells and proliferation-related pathways), normal-stroma enriched (NSE, n = 10, enriched in fibroblasts and carcinoma in situ),

metabolic (M, n = 9, enriched in metabolic-related pathways) and metabolic-immune enriched (MIE, n = 10, enriched in adipose tissue, metabolic and immune-related pathways). Interestingly, a significantly higher presence of macrophages M2 was found in MIE group. Using group-specific gene signatures, we were able to reproduce the same 4 groups in the METABRIC. Of note, we observed significant differences in relapse-free survival (RFS) in METABRIC ($p = 0.03$), with NSE presenting better outcome, while P, M and MIE presented worse prognosis. Analysing the area of contact between adipocytes and cancer cells typical of MIE group, we noticed an enrichment in metabolic and M2 macrophages-related pathways. In doing so, we derived a 28 gene signature relative to the tumor-adipocytes contact area. Importantly, our signature was highly expressed in M and MIE groups, and it was not correlated with proliferation-related signatures. Interestingly, the adipocytes-related signature was significantly associated with shorter RFS in ILC patients in METABRIC (univariable: HR 1.4, $p = 0.023$; multivariable: HR 1.6, $p = 0.005$). Since both proliferation and metabolism showed to be key processes in defining prognosis in ILC, we built a prognostic index by integrating our adipocytes-related signature with genomic grade index (GGI, a proliferation-related signature). Our index outperformed other existing prognostic signatures (e.g., Oncotype DX, MammaPrint, EndoPredict, LobSig) in assessing prognosis (RFS) in ILC in METABRIC (univariable: HR 1.7, $p < 0.001$; multivariable: HR 1.7, $p = 0.002$). Conclusions: We identified 4 biologically driven HR+, HER2- ILC groups describing tumor microenvironment heterogeneity. Of note, two of the three groups associated to worse disease outcome were related to metabolism, highlighting the importance of such process in ILC biology and in the future development of new treatment strategies. Moreover, the prognostic power of our index has the potential to refine the assessment of the risk of relapse in ILC. Further validation is warranted.

PO1-15-04

**Young Black Women With Triple-Negative Breast Cancer Molecular Subtypes:
Population-Specific Patterns and Batch Effect Considerations**

Presenting Author(s) and Co-Author(s):

P. Rajagopal. National Cancer Institute, Washington, District of Columbia, United States

S. Reid. Vanderbilt-Ingram Cancer Center, United States

R. Fan. Vanderbilt University Medical Center, United States

L. Venton. Vanderbilt University Medical Center, United States

A. Weidner. Vanderbilt University Medical Center, United States

M. Roberson. University of North Carolina, United States

S. Vadaparampil. Moffitt Cancer Center, Tampa, Florida, United States

X. Wang. Moffitt Cancer Center, United States

S. Yoder. Moffitt Cancer Center, United States

M. Rosa. Moffitt Cancer Center, United States

J. Hirbo. Vanderbilt University Medical Center, United States

J. Whisenant. Vanderbilt University Medical Center, United States

J. Pietenpol.

F. Ye. Vanderbilt University Medical Center, United States

T. Pal. Vanderbilt University Medical Center, United States

B. Lehmann. Vanderbilt-Ingram Cancer Center, United States

Introduction: While triple-negative breast cancer (TNBC) molecular subtypes have been associated with biological differences and clinical outcomes, studies have overwhelmingly been conducted in populations of European or Asian ancestry. Data collected across diverse populations is required to better leverage clinical directions from translational studies in TNBC. Through females recruited through the Black Women: Etiology and Survival of Triple-Negative Breast Cancers (BEST) study, we sought to characterize subtypes and explore associations.

Methods: Our study included Black women diagnosed with early-stage (I-III) invasive TNBC at \leq age 50 from 2005 to 2016, with recruitment from Florida and Tennessee state cancer registries. Germline DNA, tumor RNA, clinical outcomes, and risk factor data were collected. TNBC status in the BEST study was based on immunohistochemistry from pathology reports, cancer registry data, and self-reported data. Analyses on banked tumor samples, extracted at multiple time points, were conducted through PAM50 (Nanostring) and whole-transcriptome RNA-seq. TNBC subtype was assessed using TNBCtype-4 (Lehmann et al. 2016). Sources of batch effect were evaluated using PCA and corrected via limma. Genetic ancestry based on OncoArray or MEGA genotyping data was inferred using 1000Genomes continental reference samples. Immune cell characterization was performed via CIBERSORT and ESTIMATE. Statistical significance in comparing differences across subtypes was assessed via Chi-square test. Kaplan-Meier estimates and log-rank test were used for survival analysis.

Results: RNA-seq from 114 self-reported Black females with TNBC was analyzed. TNBC subtype distribution in the BEST study cohort included 31.6% basal-like 1 (BL1), 28.9% basal-like 2 (BL2), 16.7% luminal androgen receptor (LAR), and 21.9% mesenchymal (M). While

results were largely consistent with prior studies in patients of European or East Asian ancestry, a higher percentage of BL2 subtype was observed (28.9% vs. 21.0%, $p=0.053$). Based on PAM50 subtyping, 100% of tumors with BL1 and M were basal, whereas 68.8% of LAR and 86.7% of BL2 subtypes were basal. Tumors without subtype decreased from 9.8% to 1.1% after batch correcting for location at which RNA was extracted (Moffitt vs. Vanderbilt) and time between RNA banking and sequencing. All TNBC subtypes in this population demonstrated monocyte/activated dendritic cell predominance, with no significant subtype-specific associations with immune cell patterns. A lower relative proportion of M subtype was found in tumors from BRCA1/2 carriers, but this was not statistically significant due to the small number of carriers (8% vs. 18%; $p=0.22$). With a median follow-up time of 9 years, there was no significant difference in 10-year overall survival by TNBC subtype ($p=0.18$). However, patients with M subtype appeared to have worse survival relative to other subtypes combined ($p=0.036$).

Conclusion: Our study is among the largest to date that interrogates TNBC subtypes and associated molecular/clinical data in self-reported Black females with invasive breast cancer. Our findings suggest that established TNBC subtyping can be applied in patients of African ancestry. Furthermore, data to correct for lab-based confounders remains critical; in this study, it enabled us to use many samples that could not be subtyped initially. Several population-specific patterns were observed, including no difference in 10-year overall survival across TNBC subtypes (consistent with prior data), but worse initial outcomes in M subtype; a preliminary association between BRCA1/2 carriers and non-M subtypes (in contrast to prior data); and no significant difference in immune cell distributions (in contrast to prior data mainly from patients of European ancestry). Studies of associations between TNBC subtypes, additional clinical data, and treatment data (type and response rates) are ongoing.

PO1-15-05

Gene expression signature as a predictor of pathological complete response to neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab treatment in locally advanced HER2-positive breast cancer

Presenting Author(s) and Co-Author(s):

J. Shin. Samsung Medical Center, Seoul-t'ukpyolsi, Republic of Korea

J. Kim. Samsung Medical Center, United States

e. Cho. Samsung Medical Center, United States

S. Kim. Breast Division, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, United States

J. Lee. Samsung Medical Center, United States

H. Lee. Samsung Medical Center, United States

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

J. Ahn. Samsung Medical Center, United States

Y. Im. Samsung Medical Center, Seoul, Republic of Korea

Background: Neoadjuvant pertuzumab and trastuzumab in combination with chemotherapy can achieve pathological complete response (pCR, defined as ypT0/is ypN0) in approximately 40–60% of patients with human epidermal growth factor receptor 2-positive (HER2+) breast cancer (BC). Patients who achieve pCR have significantly improved survival. Therefore, the prediction of pCR is crucial for optimizing neoadjuvant therapy. Methods: To identify a gene expression signature that could predict pCR in patients with HER2+ BC, we used the nCounter Breast Cancer 360TM V2 panel to quantify the expression of 758 genes in 104 HER2+ BC samples from patients who received neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) chemotherapy and subsequent curative breast surgery. Data normalization, differentially expressed gene (DEG) analysis, and gene set enrichment analysis (GSEA) were performed using the NanoTube Bioconductor package. Using the elastic net logistic regression model with optimal hyperparameters determined by 5-fold cross-validation (5-CV), we developed a chemosensitivity score based on the expression of significant DEGs (genes with absolute log₂-fold-change ≥ 0.5 and q-value < 0.1). We tested its predictive value for pCR using multivariable logistic regression analysis. Results: The median age at diagnosis was 49.5 years. The clinical stage was II in 53 (51%) patients and III in 51 (49%) patients at diagnosis. Ninety (86.5%) patients had a HER2 immunohistochemistry (IHC) score of 3+, while the remaining 14 (13.5%) patients had HER2 IHC 2+ but HER2 amplification detected by in situ hybridization. Pathological evaluation of surgical specimens revealed that 55 (52.9%) patients achieved pCR. Menopausal status ($p = 0.01$), PAM50 intrinsic subtype ($p = 0.002$), hormone receptor (HR) status ($p < 0.001$), and HER2 IHC score ($p = 0.019$) were significantly correlated with the pCR rate. DEG analysis using the PAM50 intrinsic subtype, HR status, and HER2 IHC score as covariates revealed 6 downregulated DEGs and 33 upregulated DEGs in patients who achieved pCR compared to patients who did not (Table 1). The 39 DEGs were significantly enriched in nine preselected MSigDB hallmark gene sets representing immunological processes ($p < 0.001$). The optimal elastic net logistic regression model containing 39 DEGs achieved the mean 5-CV area under the receiver operating characteristic curve of 0.81. The chemosensitivity score calculated using the optimal model parameters was significantly correlated with pCR after adjustment for the PAM50 intrinsic subtype, HR status, and HER2 IHC score ($p < 0.001$). GSEA revealed eight hallmark gene sets that were significantly up- or

downregulated in samples with pCR, including epithelial-mesenchymal transition (normalized enrichment score [NES] = -2.16; q < 0.001), late estrogen response (NES = -2.01; q = 0.004), early estrogen response (NES = -1.972; q = 0.005), and inflammatory response (NES = 1.53; q = 0.06). Conclusion: Our findings demonstrate that gene expression patterns can predict the response to neoadjuvant TCHP chemotherapy in HER2+ BC. The functional characterization of 39 DEGs suggests that the tumor microenvironment, including adjacent immune cells, plays a significant role in modulating the response to neoadjuvant chemotherapy in HER2+ BC.

Table 1. Significant DEGs

Table 1. Significant DEGs

Gene	Log ₂ FC	t	P value	Q value
ALDH1A1	0.5	3.8	2.40E-04	0.055
CDH3	-0.72	-3.7	3.40E-04	0.055
HLA-DPA1	0.57	3.7	4.20E-04	0.055
GZMA	0.82	3.6	5.20E-04	0.055
CXCR6	0.66	3.5	6.30E-04	0.055
PIK3CG	0.51	3.5	6.60E-04	0.055
TIGIT	0.6	3.5	6.60E-04	0.055
CCR2	0.7	3.4	0.001	0.059
MYCN	0.79	3.4	0.0011	0.059
CCR5	0.55	3.3	0.0012	0.059
CSF3R	0.51	3.3	0.0013	0.059
GZMH	0.65	3.3	0.0015	0.063
SPN	0.51	3.2	0.0019	0.076
IL2RB	0.65	3.1	0.0027	0.077
CHIT1	0.82	3.1	0.0027	0.077
PLA1A	0.5	3	0.0031	0.077
NKG7	0.68	3	0.0036	0.077
CD19	0.67	3	0.0036	0.077
KLRK1	0.55	3	0.0038	0.077
IL6	0.51	3	0.0039	0.077
RAC2	0.53	2.9	0.004	0.077
IL12RB2	0.51	2.9	0.0041	0.077
FSTL3	-0.54	-2.9	0.0042	0.077
CDSA	0.62	2.9	0.0046	0.078
VIT	0.52	2.8	0.0055	0.084
CDSB	0.59	2.8	0.0057	0.086
PRKCB	0.65	2.8	0.006	0.088
DUSP4	0.65	2.8	0.0064	0.09
NR4A3	0.53	2.8	0.0064	0.09
HLA-DOB	0.64	2.8	0.0065	0.09
IL22RA2	0.5	2.8	0.0067	0.092
CD27	0.63	2.8	0.007	0.094
SFN	-0.59	-2.7	0.0074	0.094
IL1B	0.5	2.7	0.0077	0.094
CCL5	0.59	2.7	0.008	0.094
FGFR4	0.98	2.7	0.0081	0.094
MMP11	-0.7	-2.7	0.0081	0.094
EYA2	-0.55	-2.7	0.0086	0.096
ISG15	-0.59	-2.7	0.0087	0.096

PO1-15-06

Serum thymidine kinase activity as a “real-time” clinical biomarker of tumor response to CDK4/6 inhibition in hormone receptor positive (HR+), HER2 negative (HER2-) metastatic breast cancer

Presenting Author(s) and Co-Author(s):

N. Bagegni. Washington University in St Louis School of Medicine, United States

A. Williams. Biovica International AB, United States

I. Grigsby. Washington University in St Louis School of Medicine, United States

M. Bergqvist. Biovica International AB, United States

K. Clifton. Washington University in St Louis School of Medicine, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

Background: CDK4/6 inhibitors (CDK4/6i) plus endocrine therapy (ET) are standard first-line (1L) treatment for hormone receptor positive (HR+), HER2-negative (HER2-) metastatic breast cancer (MBC). Despite general improvements in long-term outcome, not all patients benefit equally from these drugs. The average duration of 1L CDK4/6i therapy is ~2 years. However, 10-15% of patients will progress within 6 months of therapy initiation, while others will derive durable clinical benefit of years. Differences in treatment efficacy cannot be easily explained by clinical-pathological features. No predictive biomarkers are currently available to determine tumor sensitivity to CDK4/6i. There is an unmet need for a complementary diagnostic to identify patients that will or will not respond to these treatments in order to better inform therapy management.

Thymidine kinase (TK) is an E2F-regulated enzyme that plays a key role in DNA replication during cell division. The expression and activity of TK is strongly linked to the cell cycle. TK is first expressed in late G1, peaks during S-phase, and then is degraded during mitosis. Because of the restricted expression of TK (only during S phase of the cell cycle) combined with the mechanism of action of CDK4/6i, the measurement of TK activity (TKa) may serve as an ideal pharmacodynamic biomarker to assess a tumor's response to CDK4/6i-based therapy.

DiviTum[®] TKa is an FDA cleared assay that can quantitate TKa from human serum (sTKa) and is intended to be used as a disease progression monitoring tool for patients with HR+, HER2-MBC. TK IMPACT is a prospective, single arm trial designed to assess the impact of incorporation of DiviTum[®] TKa on the physician's decision regarding subsequent timing of routine disease monitoring modalities in patients with advanced HR+, HER2- MBC receiving 1L ET plus CDK 4/6i (NCT04968964). As a part of this ongoing study, DiviTum[®] TKa values are serially assessed relative to imaging findings and other circulating tumor biomarkers, such as CA15-3 and ctDNA. The primary endpoint is any physician-reported intended change in imaging testing interval post TKa by study cohort, within the first 48-week period of study participation, assessments for which are ongoing. Here we report real-world data and examples of the clinical utility of sTKa as a companion diagnostic from patients treated at Washington University Siteman Cancer Center, St. Louis, MO. Methods: Patients with HR+, HER2- MBC receiving 1L ET + any FDA-approved CDK 4/6i (palbociclib, ribociclib, or abemaciclib) had blood serum samples collected at baseline, weeks 2, 4, 6, 8, every 4 weeks up to week 24, and then every 12 weeks thereafter until disease progression. Samples were analyzed for TKa levels in real-time using the DiviTum[®] TKa assay. Optional repeat TKa within 2-4 wks (+/- 3

days) is permitted in case of rising TKa. Other standard monitoring assessments were carried out according to institutional guidelines and/or treating clinician discretion. Results: Pre-treatment and early on-therapy TKa levels predicted response to CDK4/6i therapy more accurately than a patient's clinical characteristics. Rising TKa levels also identified patients with clinically occult disease progression ahead of imaging, and in some cases where radiographic interpretation and serum tumor markers such as CA15-3 were ambiguous. Measurement of TKa levels following CDK4/6i dose reduction was able to confirm continued optimal therapy response at the lower dose. A rise in TKa levels aligned with the re-emergence of ESR1 mutation as identified by ctDNA in one patient and may herald molecular progression. Conclusion: sTKa was able to predict tumor sensitivity and resistance (both intrinsic and acquired) to CDK4/6i + ET therapy in patients with HR+, HER2- MBC. We believe these findings help support the role of sTKa as a non-invasive pharmacodynamic biomarker that can assess in real-time a tumor's response to CDK4/6i based therapy.

PO1-15-07

Subtyping-directed precision treatment refines traditional one-size-fits-all therapy in HR+/HER2- breast cancer: a sub-study of the MULAN umbrella trial

Presenting Author(s) and Co-Author(s):

X. Zhu. Fudan University Shanghai Cancer Center, United States

X. Jin. Fudan University Shanghai Cancer Center, United States

H. Zhang. Shanghai Cancer Center, Fudan University, United States

X. Liu. Fudan University Shanghai Cancer Center, United States

Y. Zhou. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

Y. Chen. Fudan University Shanghai Cancer Center, United States

T. Fu. Fudan University, United States

M. Jin. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

Y. Zhao. Fudan University Shanghai Cancer Center, United States

Y. Xie. Fudan University Shanghai Cancer Center, United States

R. Wang. Fudan University Shanghai Cancer Center, United States

Z. Wang. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, United States

L. Fan. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

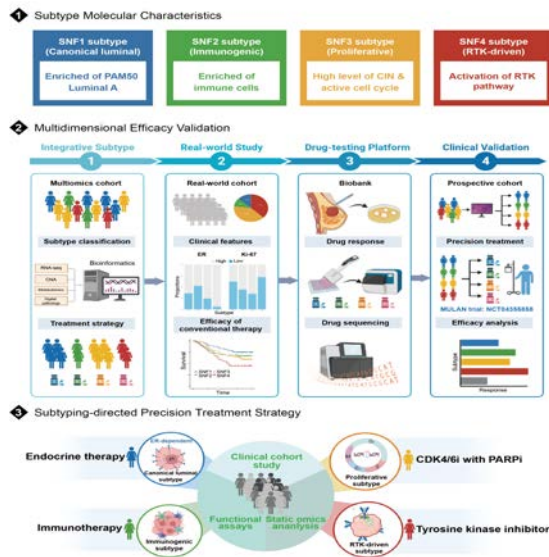
Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background: The standard approach of using one-size-fits-all endocrine therapy for hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancers has faced significant challenges due to variations in treatment response among individuals. Consequently, there is still an urgent need to understand the molecular biology of HR+/HER2- breast cancer and explore precision treatment strategy. **Methods:** We established a multiomics cohort (n = 351), multicenter real-world clinical cohorts (n = 643), a prospective clinical cohort (MULAN trial), and a drug-testing platform containing patient-derived organoids (n = 126) and patient-derived tumor fragments (n = 49) of HR+/HER2- breast cancers. Integrating "bench" and "bedside" data, we conducted comprehensive preclinical and clinical translational research on precision strategies in HR+/HER2- breast cancer. **Results:** We implemented a comprehensive classification system for HR+/HER2- breast cancer, comprising four distinct subtypes. We further demonstrated the efficacy and mechanisms of subtyping-directed precision treatment strategies through clinical cohort studies, omics analysis and functional assays: endocrine therapy alone for the canonical luminal subtype; the addition of CDK4/6 inhibitor and PARP inhibitor for the proliferative subtype; the immunotherapy for the immunogenic subtype; and tyrosine kinase inhibitors for the receptor tyrosine kinase-driven subtype. Using clinically applicable subtyping methods, we validated that matched precision treatment strategies outperformed unmatched approaches in a real-world cohort, almost doubling the median progression-free survival time for patients with refractory advanced HR+/HER2- breast cancer (9.83 months [95% CI, 5.74-13.93] vs 4.77 months [95% CI, 3.35-6.18]; hazard ratio 0.64 [95%

CI, 0.41-0.99]). Importantly, the first-stage analysis of the MULAN phase II umbrella clinical trial (NCT04355858) verified the higher objective response rate (88.9%, 95%CI: 51.7%-99.7%) of the subtyping-directed precision treatment. Conclusion: Our study emphasizes the superiority of subtyping-directed precision treatment strategies for HR+/HER2- breast cancer, refines traditional “one-size-fits-all” therapy, and facilitates the translation of precision treatment strategies from bench to bedside.

Overall study design



Part 1 Subtype Molecular Characteristics: Molecular features of the four subtypes of HR+/HER2- breast cancer.

Part 2 Multidimensional Efficacy Validation: Integrating data from a multiomics cohort, real-world study, drug testing platform and prospective clinical research to validate the subtyping-directed precision treatment strategy in HR+/HER2- breast cancer.

Part 3 Subtyping-directed Precision Treatment Strategy: Integrating clinical cohort studies, omics analysis and functional assays revealed the heterogeneity of treatment response in HR+/HER2- breast cancer, and proposed a subtyping-directed precision treatment strategy. CIN, chromosomal instability; RTK, receptor tyrosine kinase; CNA, copy-number alteration; ER, estrogen receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

PO1-15-08

Genomic characterization of triple-negative breast cancer metastases reveals PKD1 as a novel biomarker for immunotherapy

Presenting Author(s) and Co-Author(s):

X. Zhu. Fudan University Shanghai Cancer Center, United States

Y. Zhou. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

Y. Wang. Fudan University Shanghai Cancer Center, United States

X. Ding. Fudan University Shanghai Cancer Center, United States

X. Jin. Fudan University Shanghai Cancer Center, United States

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Wang. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, United States

Background: While primary triple-negative breast cancer (TNBC) garners significant research attention, the genomic alterations that occur in metastasis remain insufficiently understood, especially within Asian populations. Furthermore, the genomic information obtained from the primary tumor inadequately guides metastatic cancer treatment, highlighting the critical need for in-depth investigations into metastatic TNBC. **Methods:** We constructed the largest cohort of TNBC metastases (n = 296) among advanced TNBC patients treated at Fudan University Shanghai Cancer Center (FUSCC) between October 2018 and December 2020. Comprehensive DNA sequencing was conducted on the collected metastatic samples to analyze genomic alterations associated with treatment response. The underlying mechanisms of specific biomarkers were also explored. **Results:** We presented the genomic landscape of 296 TNBC metastases, encompassing mutant genes, mutation sites and copy number variations. Through multidimensional analysis, significant disparities in TNBC were observed between Western and Asian populations, primary and metastatic tumors, as well as different metastatic sites. Notably, our findings underscore the importance of sequencing TNBC metastases to guide precision therapy, which was associated with longer progression-free survival compared to physician-chosen treatments, shedding light on the pivotal clinical value of genomic studies in metastatic settings. Furthermore, efficacy analysis suggested that PKD1 mutations enriched in metastases mediated resistance to immunotherapy. These findings were further validated through three clinical trials (NCT03805399, NCT04129996, and NCT04395989). Mechanistic studies unveiled the involvement of PKD1 in TNBC immune evasion by upregulating CCL2, thereby facilitating the recruitment of M2-type tumor-associated macrophages. **Conclusion:** Our study emphasizes the critical significance and necessity of genomic profiling of metastases in guiding precision therapy for TNBC. Moreover, our findings reveal PKD1 as a novel and promising biomarker for immunotherapy.

PO1-15-09

Vitamin A Metabolism Induces Ferroptosis to Enhance Immune Therapy Efficacy in HR+/HER2- Breast Cancer

Presenting Author(s) and Co-Author(s):

Y. Zhou. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

H. Zhang. Shanghai Cancer Center, Fudan University, United States

X. Jin. Fudan University Shanghai Cancer Center, United States

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background: Immune checkpoint blockade (ICB) has substantially improved patient overall and progression-free survival in triple-negative breast cancer (TNBC), but its efficacy remains to be elucidated in the hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer, which is characterized by generally impotent lymphocytic infiltration. In the I-SPY2 trial (NCT01042379), pembrolizumab- or durvalumab-containing neoadjuvant therapy increased the pathologic complete response of HR+/HER2- patients. However, pembrolizumab-containing therapy failed to improve the survival of metastatic HR+/HER2- breast cancer patients (NCT03051659). These inconsistent results underscored the necessity of the investigation of predictive biomarkers to pinpoint potential ICB responders in HR+/HER2- breast cancer.

Method: In this study, we collected pretreatment tumor samples from 16 patients in two respective clinical trials (NCT: 04215003 and 04355858) and profiled droplet-based single-cell sequencing, bulk RNA-Seq. Patients were treated with camrelizumab (PD-1 inhibitor)-containing therapy, and five of them achieved partial relief after an 8-week course. We also leveraged the bulk RNA-Seq data from the I-SPY2 trial and Fudan University Shanghai Cancer Center (FUSCC) TNBC ICB trials (NCT04418154 and NCT04613674) for external validation. Another FUSCC transcriptome dataset consisting of 933 treatment-naïve HR+/HER2- or TNBC breast cancer patients was used to detect the abundance of cell types. In vitro and in vivo experiments were used to explore mechanisms of anti-tumor immune response.

Results: Based on the single-cell sequencing results, we comprehensively delineated the microenvironmental landscape of HR+/HER2- breast cancer. We discovered responders of immunotherapy showed a higher presence of CXCL9/10+ M1-like macrophages and exhibited enrichment of tumor cells with ferroptosis. We further identified the upregulation of vitamin A metabolism and the vitamin A metabolic gene CRABP1 in tumor cells with ferroptosis. We verified the vitamin A metabolism could induce ferroptosis in HR+/HER2- breast cancers rather than TNBC by CRABP1-ERK axis, which could further recruit CXCL9/10+ M1-like macrophages and promote anti-tumor immune response in HR+/HER2- breast cancer. Combining anti-PD1 with enhancing vitamin A metabolism via retinoid acid possessed greater therapeutic efficacy than monotherapy in HR+/HER2- breast cancers. Finally, we developed an immune therapy response score and validated its reliability in predicting the immunotherapy efficacy for HR+/HER2-breast cancers through both internal and external cohorts.

Conclusion: Our study represents the earliest efforts to decipher the microenvironmental

landscape and the mechanisms underlying the response to ICB in HR+/HER2- breast cancer at single-cell resolution. We unraveled a HR+/HER2- breast cancer-specific Vitamin A-ferroptosis axis that mediated immunotherapy response and constructed a robust immunotherapy efficacy prediction score based on this Vitamin A-ferroptosis axis.

PO1-15-10

Lower pre-treatment B-cell gene expression signatures correspond with improved overall survival with palbociclib + endocrine therapy in HR+/HER2- metastatic breast cancer: a biomarker analysis from the GEICAM/2013-02 PEARL trial

Presenting Author(s) and Co-Author(s):

Y. Agrawal. Lineberger Comprehensive Cancer Center, University of North Carolina. Division of Hematology-Oncology, Department of Medicine, School of Medicine University of North Carolina at Chapel Hill, Chapel Hill, United States

A. Fernandez-Martinez. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA, United States

M. Gil-Gil. Institut Català d'Oncologia, Insitut d'Investigació Biomèdica Bellvitge. GEICAM Spanish Breast Cancer Group, United States

C. Zielinski. Vienna Cancer Center, Medical University of Vienna and Vienna Hospital Association. CECOG, Austria

M. Ruíz- Borrego. Hospital Universitario Virgen del Rocío. GEICAM Spanish Breast Cancer Group, Sevilla, Spain

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

M. Muñoz. SOLTI Breast Cancer Research Group, Hospital Clínic of Barcelona, Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, Catalonia, Spain

M. Margelí. SOLTI Cancer Research Group. Medical Oncology Department, ICO Badalona, B-ARGO Group. GEICAM Spanish Breast Cancer Group., Catalonia, Spain

B. Bermejo. Hospital Clínico Universitario de Valencia, Valencia, Spain, United States

A. Antón. Miguel Servet University Hospital, Zaragoza, Aragon, Spain

Z. Kahan. Department of Oncotherapy, University of Szeged. CECOG., Hungary

T. Csösz. Department of Oncology, Jasz-Nagykun-Szolnok Megyei Hetenyi Geza Korhaz-Rendelőintezet, Szolnok, Hungary. CECOG, Hungary

J. Alonso-Romero. Hospital Clínico Universitario Virgen de la Arrixaca. GEICAM Spanish Breast Cancer Group., United States

J. García-Sáenz. Instituto de Investigación Sanitaria Hospital Clinico San Carlos (IdISSC), United States

P. Sánchez-Rovira. Hospital Universitario de Jaén, Jaén, Spain, Andalucia, Spain

E. Álvarez. Hospital Universitario Lucus Augusti. GEICAM Spanish Breast Cancer Group, Spain

J. Chacón. Hospital Universitario de Toledo. GEICAM Spanish Breast Cancer Group., Spain

S. González-Santiago. Hospital Universitario San Pedro de Alcántara, Cáceres, Spain

C. Rodríguez. Hospital Universitario de Salamanca-IBSAL. GEICAM Spanish Breast Cancer Group, Salamanca, Spain

S. Servitja. Hospital del Mar, Barcelona, Spain., Spain

A. Pfeifferle. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill. Department of Genetics, University of North Carolina, United States

J. Herranz. GEICAM Spanish Breast Cancer Group, United States

Y. Liu. Pfizer Inc, San Diego, California, United States

L. Carey. Lineberger Comprehensive Cancer Center, University of North Carolina. Division of Hematology-Oncology, Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, United States

I. Romero - Camarero. GEICAM Spanish Breast Cancer Group, United States

R. Caballero. GEICAM Spanish Breast Cancer Group., Spain

C. Perou. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill. 2. Division of Hematology-Oncology, Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, United States

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

Introduction: CDK4/6 inhibitors (CDK4/6i) with endocrine therapy (ET) is standard-of-care for HR+/HER2- metastatic breast cancer (MBC), but little is known about which gene expression and microenvironment features are associated with benefit from CDK4/6i or differentiate response compared to chemotherapy. We examined the relationship of gene expression signatures (GES) to progression-free (PFS) and overall survival (OS) in the GEICAM/2013-02 PEARL phase III randomized study of palbociclib + ET vs. capecitabine in aromatase inhibitor-resistant HR+/HER2- MBC (NCT02028507).

Methods: RNA sequencing (RNAseq) was performed on baseline tumor samples from 328 patients. Intrinsic subtype was derived by the PAM50 predictor after HER2/estrogen receptor subgroup-specific normalization. Correlations to intrinsic subtype signatures, PAM50 proliferation signature, CCNE1 expression, and 10 GES were selected for analysis. After excluding 15 Normal-like samples, Cox models were fitted for PFS and OS endpoints on each selected variable for the combined study population as well as for each treatment arm, adjusted for disease site, prior ET sensitivity, prior chemotherapy for MBC, number of involved sites, treatment arm, and intrinsic subtype. P-values were adjusted based on the Bonferroni method, with an adjusted p-value < 0.05 defined as significant.

Results: PAM50 intrinsic subtype (54.95% Luminal A, 38.98% Luminal B and 6.07% non-luminal (4.79% Her2-enriched and 1.28% Basal-like)) was associated with worse PFS with palbociclib + ET for non-luminal vs. Luminal A tumors (HR 3.19, 95% CI 1.65-6.16) and for Luminal B vs. Luminal A tumors (HR 1.90, 95% CI 1.28-2.82). PAM50 luminal status (Luminal A vs. Luminal B vs. non-luminal) was significantly associated with PFS with palbociclib + ET (p=0.0003) but not capecitabine (p=0.89). In the palbociclib + ET arm, lower expression of two B-cell-associated signatures (BCAS) correlated with improved OS - the Immune1 TCGA BRCA GES (PMID: 32573490) (HR 1.52, 95% CI 1.20-1.92, p=0.009) and the B-cell/T-cell cooperativity GES (PMID: 31730857) (HR 1.42, 95% CI 1.14-1.79, p=0.04). Interaction analysis for OS showed that when stratified by low and high expression using the median, the Immune1 TCGA BRCA GES had a significant interaction with treatment arm (p=0.014). On comparison of outcomes between treatment arms, low Immune1 TCGA BRCA GES expression was significantly associated with improved OS with palbociclib + ET compared to capecitabine (HR 0.44, 95% CI 0.26-0.74, p=0.03), whereas high expression was not associated with a significant OS difference (HR 1.73, 95% CI 1.07-2.79, p=0.40). Further exploratory analysis of 164 immune GES found that, after adjustment for confounders, the top eight GES associated with OS with palbociclib + ET were BCAS (unadjusted p-values < 0.005), including our pre-selected Immune1 TCGA BRCA and B-cell/T-cell cooperativity GES, and all eight negatively correlated with OS. In the capecitabine arm, this exploratory analysis failed to demonstrate a similar association between the immune GES and OS.

Conclusion: PAM50 intrinsic subtype was significantly associated with PFS with second-line palbociclib + ET. Lower expression of BCAS was associated with improved OS outcomes with palbociclib + ET independent of intrinsic subtype, and for the Immune1 TCGA BRCA GES, lower expression corresponded with improved OS with palbociclib + ET compared to capecitabine. This informs recent findings that in HR+/HER2- breast cancer, tumor immune activity may be a negative predictor of CDK4/6i benefit.

PO1-15-11

Molecular and clinical disparities in breast cancer among East Asian populations

Presenting Author(s) and Co-Author(s):

K. Ju Won. Korea university Anam hospital, United States

L. JIWON. Korea university Anam hospital, United States

K. Park. Korea University Anam Hospital, Republic of Korea

S. Jung. Korea University Anam Hospital, United States

J. Sa. Department of Biomedical Sciences, Korea University College of Medicine, Seoul, Korea, United States

S. SANG WON. Korea university Anam hospital, United States

A. Jung seok. Korea university Anam hospital, United States

Background

Breast Cancer (BC) is a complex disease with profound genomic aberrations. However, the underlying molecular disparity influenced by age and ethnicity remains elusive. Method We aimed to investigate the molecular properties of 843 primary and metastatic BC patients enrolled in the K-MASTER program. We explored the unique molecular profiles of breast cancer patients by categorizing them into two distinct age subgroups. The first subgroup comprised young breast cancer (YBC) patients, defined as women under the age of 40, while the second subgroup consisted of older breast cancer (OBC) patients. Our study aimed to characterize the molecular differences between these age-defined groups, providing insights into the underlying mechanisms of breast cancer in different age cohorts. Additionally, we leveraged large-scale genomic data from the TCGA and MSK-IMPACT studies to examine the ethnic-driven molecular and clinical disparities. Results

The K-MASTER patients were mainly comprised of triple-negative breast cancer (TNBC) and HER2-positive tumors, while the TCGA and MSK-IMPACT cohorts exhibited a predominance of hormone receptor-positive (HR+) subtype. We observed a high prevalence of PI3KCA mutations in K-MASTER HER2+ tumors, particularly in older patients. Moreover, we identified increased mutation rates in DNA damage response molecules, including ARID1A, MSH6, and MLH1. Importantly, GATA3 mutations were less frequently observed in East Asian patients, which correlated with poor clinical outcomes. Our analysis also revealed specific associations between genomic aberrations, organotropisms, and metastatic breast cancer. In addition to characterizing the molecular disparities, we developed a gradient-boosting multivariable model to identify a new molecular signature that could predict the therapeutic response to platinum-based chemotherapy. Conclusion

Our findings collectively provide unprecedented insights into the significance of age and ethnicity on the molecular and clinical characteristics of BC patients.

Figure 1. Genomic landscape of KM BRCA. (A) Overall characteristic of KM BRCA sample and clinical data. Clinical features of KM BRCA sample. (B) Genomic landscape of somatic mutations and copy number alterations of BRCA by age group.

Figure 1.

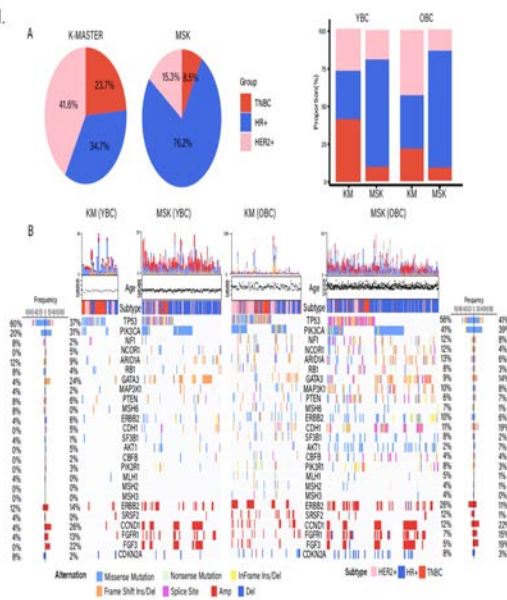


Figure 2. Genomic landscape of KM BRCA: Significantly mutated genes by age group in KM BRCA.

Figure 2.

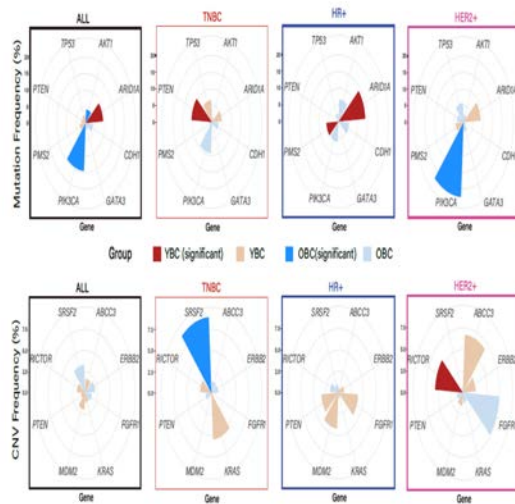
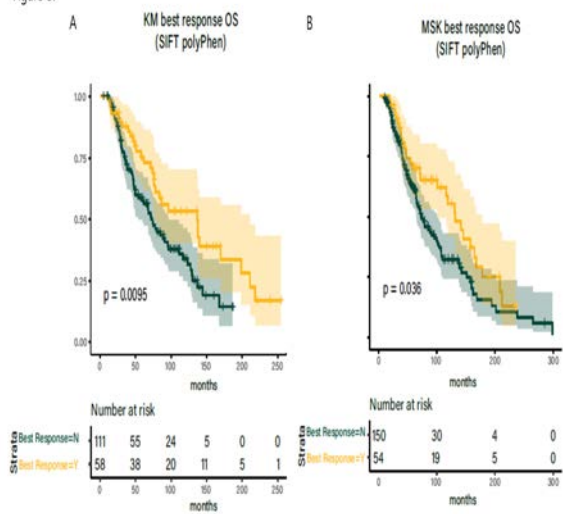


Figure 3. Survival Curve Utilizing a curated Gene Set Developed by a Gradient-Boosting Multivariable Model (A) OS of platinum-based therapy treated KM with curated Gene set. (B) OS of platinum-based therapy treated MSK with curated Gene set.

Figure 3.



PO1-15-12

Circulating tumor DNA (ctDNA) for prediction of pathologic complete response (pCR) after 12 weeks of pembrolizumab + trastuzumab + pertuzumab in HER2-enriched early breast cancer: WSG-Keyriched-1 trial

Presenting Author(s) and Co-Author(s):

M. Graeser. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; Department of Gynecology, University Medical Center Hamburg, Moenchengladbach, Nordrhein-Westfalen, Germany

S. Kuemmel. West German Study Group, Moenchengladbach, Germany; Breast Unit, Kliniken Essen-Mitte, Essen, Germany; Charité - Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany

O. Gluz. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; University Clinics Cologne, Moenchengladbach, Nordrhein-Westfalen, Germany

C. Schroeder. Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany, United States

L. Schuetz. Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany, United States

O. Kelemen. Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany, United States

S. Ossowski. Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany, United States

K. Jozwiak. Institute of Biostatistics and Registry Research, Brandenburg Medical School Theodor Fontane, Neuruppin, Neu-Ruppin, Germany

M. Reinisch. Interdisciplinary Breast Cancer Center/ Breast Unit, Essen, Germany, United States

A. Kostara. Gyn Onco, Medical Center Düsseldorf, Germany, United States

I. Scheffen. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany, United States

K. Lüdtke-Heckenkamp. Zentrum für Onkologie und Hämatologie MVZ II, Franziskus-Hospital Harderberg, Georgsmarienhütte, Germany

F. Hilpert. Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe (AGO) and North-Eastern German Society of Gynecological Oncology (NOGGO), Berlin, Germany; Onkologisches Therapiezentrum, Krankenhaus Jerusalem, Hamburg, Germany, United States

A. Kentsch. Diakovere Henriettenstift, Dept. for Gynecology, Hamburg, Germany

C. Ziske. Praxis Dr. H. Forstbauer, C. Ziske, R. Reihls, E. Rodermann, A. Diel, Troisdorf, Germany, United States

R. Depenbusch. Onkodok GmbH, Guetersloh, Germany, United States

M. Braun. Rotkreuzklinikum München, Germany

J. Blohmer. Charité - Universitätsmedizin Berlin, Germany

M. Christgen. Medizinische Hochschule Hannover, Hannover, Niedersachsen, Germany

S. Bartels. Medical School Hannover, Institute of Pathology, Hannover, Germany; Institute of Neuropathology, University Clinic Freiburg, Freiburg, Germany, United States

H. Kreipe. Medical School Hannover, Institute of Pathology, Hannover, Germany; Institute of Neuropathology, United States

E. Pelz. Institute for Pathology, Viersen, Germany

U. Nitz. West German Study Group and Breast Center Niederrhein, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

N. Harbeck. University of Munich, Munich, Bayern, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

Background

ctDNA testing is emerging as an important biomarker in early breast cancer (eBC). However, its value in prediction of tumor response to de-escalated, chemotherapy-free neoadjuvant therapy (NAT) remains underexplored. In WSG-Keyriched-1 (NCT03988036), a single-arm phase 2 trial, we investigated for the first time a chemotherapy-free NAT with dual HER2 blockade and pembrolizumab in HER2-enriched HER2+ eBC. In this pre-specified translational analysis, we evaluated whether ctDNA measurement could predict pCR.

Methods

48 patients (pts) with HER2 2+ (ISH+) or 3+ eBC (stage I-III) and HER2-enriched subtype by PAM50 were included. Pts received pembrolizumab (200 mg), trastuzumab biosimilar (loading dose (LD) 8 mg/kg bodyweight (BW), maintenance dose (MD) 6 mg/kg BW), and pertuzumab (LD 840 mg/kg BW, MD 420 mg/kg BW) q3w for 12 weeks. Primary objective was pCR (ypT0/is ypN0).

ctDNA was analyzed in 92 plasma samples collected from 31 pts at baseline (BL) and week 3 of NAT and 30 pts at end of treatment (EOT). Sequencing libraries with unique molecular identifiers were constructed from cell-free DNA and hybridization panels with ≤ 50 patient-specific somatic mutations from tumor sequencing were used for enrichment. Libraries were sequenced to an ultra-high depth of 100,000 \times . Sequencing data was analyzed using a combination of public pipelines (megSAP and umiVar2 for mapping and deduplication) and custom in-house scripts (to extract the allele counts for patient-specific variants). To reduce the error rate, only corrected reads with ≥ 4 duplicates were used. p-value for ctDNA detection was calculated using the total variant count, depth and sample-specific error.

Association between ctDNA with pCR and other clinical parameters were assessed with Chi-square or Fisher's exact test and univariable logistic regression. Additionally, bivariable logistic regressions for pCR were performed with ctDNA and either cT, cN, or grade.

Results

ctDNA was detected (ctDNA+) in 58.0% (n=18/31) of pts at BL, 9.7% (n=3/31) at week 3, and 10% (n=3/30) at EOT. ctDNA was cleared by week 3 in 83.3% of pts (n=15/18).

Compared with ctDNA-negative cases (ctDNA-) at BL, those ctDNA+ more often had cT2-3 disease (94.4%, n=17/18, vs 38.5%, n=5/13; p=.001) and lymph node involvement (61.1%, n=11/18, vs 0%, n=0/13; p<.001). 72.2% (n=13/18) of ctDNA+ and 61.5% (n=8/13) of ctDNA-cases at BL were grade 3 (p=.53). Each of the 3 pts who remained ctDNA+ at week 3 was node-positive; all pts remaining ctDNA- at week 3 were node-negative.

pCR rate was 38.9% (n=7/18) in ctDNA+ vs 76.9% (n=10/13) in ctDNA- pts at BL (p=.067), 0% (n=0/3) in ctDNA+ vs 60.7% (n=17/28) in ctDNA- at week 3 (p=.081), and 33.3% (n=1/3) in ctDNA+ vs 59.3% (n=16/27) in ctDNA- at EOT (p=.565). pCR rate was highest in pts who remained ctDNA- throughout week 3 (76.9%, n=10/13), compared to pts with ctDNA cleared by week 3 (46.7%, n=7/15), and pts remaining ctDNA+ (0%, n=0/3, p=.024).

ctDNA at BL was predictive for pCR in univariable analysis (odds ratio, OR 0.22, 95%CI 0.04-

0.93, area under curve, AUC=0.69). Bivariable models including ctDNA and grade yielded the highest accuracy for analyses with ctDNA at BL (AUC=0.77), week 3 (AUC=0.79), and with ctDNA change from BL to week 3 (AUC=0.87).

Conclusions

Absence of ctDNA prior to and during NAT, as well as early clearance of ctDNA associates with a higher pCR rate in eBC pts with HER2-enriched intrinsic subtype treated with chemotherapy-free pembrolizumab plus dual HER2 blockade. These results are in line with prior data with more intensive therapy from I-SPY 2 and NeoALTTO trials in HER2+ eBC and indicate that ctDNA analysis during NAT appears feasible for real-time monitoring of response to treatment and could be used to guide escalation/de-escalation strategies. Further trials with a larger number of pts and pre-designed follow-up are needed to confirm the role of ctDNA for prediction of tumor response and relapse.

PO1-16-01

Clinicopathological and global transcriptional complexity of estrogen receptor low positive breast cancers in a contemporary Swedish prospective population-based cohort.

Presenting Author(s) and Co-Author(s):

S. Kimbung. Lund university, Sweden

S. Veerla. Lund university, Sweden

A. Ehinger. Lund University, Sweden

J. Vallon-Christersson. Lund University, United States

M. Malmberg. Skåne University Hospital, United States

N. Loman. Skåne University Hospital, Sweden

Background: Estrogen receptor (ER) expression is currently the most consequential biomarker for prognostic and therapeutic decision making in clinical management of early breast cancer. Endocrine therapy (ET) is an important part of standard of care in most cases with ER-positive disease, and an effective therapy for patients with endocrine-responsive tumors, decreasing the risk of recurrence and improving the rate of survival. Unfortunately, ET comes with frequently bothersome side-effects and tend to decrease quality of life. The threshold to define ER positivity as a marker of endocrine responsiveness is non-uniform between international and local guidelines. Among ER low positive tumors (ER^{low}, 1-10% expression) endocrine responsiveness is uncertain. Swedish national guidelines recommend a cut-off of $\geq 10\%$ for ER positivity and ET prescriptions, thus patients with ER^{low} tumors are often exempted from adjuvant ET. This study explores the clinicopathological characteristics, global transcriptional complexity and clinical outcome of ER^{low} tumors to better understand their biology and response to therapy. Methods: 9138 patients diagnosed with early breast cancer between 2010 – 2021 in Sweden with available clinicopathological data and RNA sequencing data were included. Patients were classified according to ER expression: ER^{neg} ($< 1\%$; n=897), ER^{low} (1-10%, n=158) and ER^{high} ($> 10\%$, n=8083). Adjuvant ET was provided to 3.6%, 16.8% and 91.5% of patients with ER^{neg}, ER^{low}, and ER^{high} tumors, respectively. Clinicopathological characteristics, overall survival (OS) and global transcriptional profiles of ER^{low} tumors were compared with ER^{neg} and ER^{high} tumors, respectively. Results: Generally, ER^{low} and ER^{neg} tumor pathological characteristics were more similar to each other but were significantly distinct compared to ER^{high} tumors. However, among patients with HER2-negative disease only, significant differences related to tumor biology persisted between ER^{low} compared with ER^{neg} tumors; ER^{low} was enriched with tumors displaying a lobular histology, NHG grades 1&2, PgR^{low/high} expression, low proliferation and Luminal & HER2-enriched molecular subtypes ($p < 0.05$ for all comparisons). Moreover, multivariable survival analyses revealed that the risk of dying was significantly lower for patients with ER^{low} tumors compared to patients with ER^{neg} ($p=0.005$) or ER^{high} tumors ($p=0.011$) in this cohort. The distribution of clinicopathological characteristics and overall survival between ER^{low} compared with ER^{neg} or ER^{high} tumors were similar among patients with HER2-positive tumors only. Global transcriptional comparisons identified only 42 genes to be differentially expressed between ER^{low} vs ER^{neg} tumors (FDR < 0.05); but gene set enrichment analyses failed to identify any significantly enriched cancer-related processes/pathways within the queried databases. Conclusions: Identification of optimal

therapies for all subsets of breast cancer is necessary in the pursuit of personalized medicine. These results confirm that ER^{neg} and ER^{low} tumors are pathologically and transcriptionally distinct from ER^{high} tumors. Although subtle differences exist in the underlying biology of ER^{low} compared to ER^{neg} tumors, similar therapeutic management excluding ET for patients with ER^{low} and ER^{neg} disease is recommended in the Swedish context. Omission of adjuvant ET did not seem to compromise overall survival for ER^{low} relative to ER^{neg} or ER^{high} tumors, urging the need for prospective studies investigating the true benefit of ET for ER^{low} tumors. Our results also raise reasonable clinical thoughts on the benefits of new treatment strategies such as cyclin-dependent kinase 4/6 inhibitors, immunotherapy and antibody-drug conjugates for patients with ER^{low} expressing tumors.

PO1-16-02

Correlation of Circulating Tumor Cells (CTC) with Clinical Characteristics, Pathological Factors, and Treatment Response in Patients with Metastatic Breast Cancer (MBC).

Presenting Author(s) and Co-Author(s):

A. Bayable. Johns Hopkins Hospital, Sidney Kimmel Comprehensive Cancer Center, United States

T. Wang. Johns Hopkins University School of Medicine, United States

A. Blackford. Johns Hopkins University, Baltimore, Maryland, United States

J. Tao. Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

J. Canzoniero. Johns Hopkins Hospital, Sidney Kimmel Comprehensive Cancer Center, United States

s. lee. Johns Hopkins University, United States

F. Too. Johns Hopkins Hospital, Sidney Kimmel Comprehensive Cancer Center, United States

B. Blouw. Biocept, United States

M. wilkinson. Johns Hopkins Hospital, Sidney Kimmel Comprehensive Cancer Center, United States

R. Couzi. Johns Hopkins Hospital, Sidney Kimmel Comprehensive Cancer Center, United States

A. Wolff. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States

C. Hiton. Allegheny Health Network; Pittsburgh, PA, United States

B. Park. Vanderbilt University Medical Center, NASHVILLE, Tennessee, United States

V. Stearns. Johns Hopkins University, Baltimore, Maryland, United States

C. Santa-Maria. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD & Sibley Memorial Hospital, Johns Hopkins, Washington, DC, Baltimore, Maryland, United States

Background: Circulating Tumor Cells (CTC) can be isolated in 40-80% of patients with metastatic breast cancer (MBC). High levels of CTC, defined as $\geq 5/7.5$ ml of blood are associated with shorter progression-free survival and overall survival. CTC can be tested for clinically relevant biomarkers, such as ER, and HER2 status, and have the potential to guide therapy as well as help with disease monitoring. We investigated CTC detection rate, its correlation with clinical characteristics, pathological characteristics, and response to treatment in patients with any type of metastatic breast cancer who progressed on at least one line of therapy. Methods: Eligible patients with MBC were enrolled in the IMAGE-II study (Individualized Molecular Analyses Guide Efforts in Breast Cancer) NCT02965755, in which we obtained archival tissue as part of the standard of care, and prospectively collected serial blood samples for CTC analysis. We compared CTC levels and biomarker status with clinical factors, tissue-based pathology, and molecular biomarkers. We assessed whether changes in CTC count correlated with treatment response. Blood samples were collected at baseline (Day 1), after 1-2 weeks of therapy, after 8-12 weeks, and at subsequent restaging (every 8-12 weeks). Medical records were reviewed every 3 months for ongoing treatment response, and death. Samples were processed at the Biocept CLIA-certified Laboratory. CTC were enumerated by the presence of CD45- and DAPI+ cells. Further CTC characterization was performed by antibody staining of specific protein biomarkers (ER, HER2). Fisher's exact test was used to

evaluate the association between baseline CTC < 5 and $\geq 5/7.5$ ml with patient characteristics. McNemar's test was used to assess discordance between tissue-based and CTC-defined markers. Results: Between 1/26/2018 and 12/31/22 baseline samples were collected from 70 women with a median age of 56 (36-82) who were enrolled at four study sites. CTC was detected in 59 (84%) of participants. Baseline CTC counts were < 5/7.5 ml in 37/59 (63%) and $\geq 5/7.5$ ml in 22/59 (37%) of participants. Differences between breast cancer subtype and CTC-receptor status were observed (Table 1). Among the 41 patients who were ER-positive, 31 (76%) were CTC ER-negative ($p < 0.001$). Among 29 patients who were ER-negative, 4 (14%) were CTC ER-Positive ($P < 0.001$). Among the 7 patients who were HER2 positive, 2(29%) were HER2 positive on CTC. Among 63 patients who were HER2 negative, 7(11%) had HER2 expression on their CTC. The discordance in the classification of HER2 wasn't statistically significant ($p=0.77$). Elevated CTC at baseline was more frequently detected in younger participants (< 50 years old) (55% vs 27%; $P=0.22$), in Black women compared to White (60 % vs 29 %, $P=0.27$), and in participants with visceral vs non-visceral metastasis (52% vs 28 %, $P=0.40$). Patients with CTC ≥ 5 vs < 5/7.5mL at baseline had a shorter duration of anti-HER2-based therapy (61.5 vs 836 days, $p=0.04$). There were no statistically significant differences among participants who received chemotherapy agents (316.5 vs 365.5 days, $P=0.88$), endocrine therapy (376 vs 490 days, $P=0.89$), or overall therapy (272 vs 390 days, $P=0.21$). Conclusions: We observed significant differences in the expression of ER between tumor tissue and CTC, which can be partly due to tumor evolution over time. Additionally, participants who are young, Black, and those who have visceral metastasis may have higher CTC counts. Higher CTC counts were associated with a shorter duration of anti-HER2 therapy. Although it didn't meet statistical significance, a similar trend was observed in patients who received chemotherapy and endocrine therapy.

Table 1: MBC Tissue-Based Subtype and CTC-receptor status at baseline

Breast cancer tissue-based subtype N (%)	ER-positive	41 (58.6%)
	HER-2 Positive	7 (10%)
	TNBC	17 (24.3%)
	Unknown	5 (7.1%)
CTC ER Status N (%)	Detected	14 (20%)
	Not detected	35 (50%)
	Could not be assessed	21 (30%)
CTC HER-2 Status N (%)	Detected	9 (12.9%)
	Not detected	39 (55.9%)
	Could not be assessed	22 (31.4%)

PO1-16-03

GDP-mannose enhances the efficacy of PARP inhibitors and immunotherapy in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

Y. Xiao. Fudan University Shanghai Cancer Center, United States

J. Ding. Fudan University Shanghai Cancer Center, United States

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

G. Di. Fudan University Shanghai Cancer Center, United States

F. Yang. Fudan University Shanghai Cancer Center, United States

X. Song. Fudan University Shanghai Cancer Center, United States

Background: Triple-negative breast cancer (TNBC) patients with high HRD scores benefit from poly (ADP-ribose) polymerase (PARP) inhibitors, while those with low HRD scores still lack therapeutic options. Homologous recombination deficiency (HRD) induction is an effective strategy to broaden the indications of PARP inhibitors. Metabolic reprogramming is a critical feature of TNBC. In this study, we aimed to explore novel metabolic biomarkers for HRD and new strategy for sensitizing PARP inhibitors. **Methods:** We utilized TNBC metabolomics to systematically evaluate metabolites that were correlated with HRD. A crucial metabolite, GDP-mannose (GDP-M), that impedes homologous recombination repair (HR) and sensitizes PARP inhibitors was identified and functionally validated. We further explored the detailed mechanism and proposed a potential treatment strategy utilizing GDP-M for TNBC in preclinical models. **Results:** Systematic metabolomic analysis revealed that GDP-mannose (GDP-M) was significantly enriched in basal-like tumors with HRD. GDP-M promoted cisplatin-induced DNA double-strand breaks by inducing HRD. Mechanistically, the low expression of the upstream enzyme GMPPA led to the endogenous upregulation of GDP-M, which further promoted the ubiquitin-mediated degradation of BRCA2 to inhibit HR. GMPPA expression and GDP-M could serve as predictive biomarkers for HRD and the response to PARP inhibitors. Therapeutically, we validated that the combination of GDP-M and PARP inhibitors synergistically inhibit tumor growth in multiple preclinical models. Moreover, GDP-M supplementation plus PARP inhibition activated STING-dependent antitumor immunity and further augmented the efficacy of anti-PD-1 antibodies. **Conclusions:** GDP-M promotes the degradation of BRCA2 and thus enhances the sensitivity of PARP inhibitors in TNBC. The combination of GDP-M, PARP inhibitors and anti-PD-1 immunotherapy may be a potential treatment strategy for HRD-low TNBC.

PO1-16-04

Targeting PKMYT1 Kinase as a Therapeutic Strategy for Treatment of Triple Negative Breast Cancer with Low Molecular Weight Cyclin E (LMW-E) Expression

Presenting Author(s) and Co-Author(s):

M. Li. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Lulla. The University of Texas MD Anderson Cancer Center, United States

C. Karakas. The University of Texas MD Anderson Cancer Center, United States

S. Tsavaschidis. The University of Texas MD Anderson Cancer Center, United States

Y. Wang. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Nguyun. The University of Texas MD Anderson Cancer Center, United States

T. Bui. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

G. Marshall. Repare Therapeutics, United States

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Keyomarsi. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Purpose: Low molecular weight isoforms of cyclin E (LMW-E) have been implicated in various human cancers, including triple negative breast cancer (TNBC), and are associated with a poor prognosis. However, targeted therapies for TNBC based on biomarkers are currently lacking. This study aims to investigate LMW-E as a potential therapeutic target in TNBC and evaluate the efficacy of RP-6306, a selective inhibitor of the Protein Kinase, Membrane Associated Tyrosine/Threonine 1 (PKMYT1), in LMW-E-positive breast tumors. **Experimental Design:** Immunohistochemical (IHC) analysis was performed on pre-treatment tumor specimens from TNBC patients (n=36) to assess the correlation between LMW-E expression, CDK1 phosphorylation at Threonine 14 (pT14), and pathologic complete response to neoadjuvant chemotherapy. LMW-E inducible human mammary epithelial cells (hMEC) and breast cancer cell lines were used to investigate the regulatory effect of LMW-E on PKMYT1, the kinase responsible for CDK1 phosphorylation at T14, and the response to RP-6306, a first in-class and selective inhibitor of PKMYT1. Patient-derived xenograft (PDX) models and transgenic mouse mammary tumor virus (MMTV) models of TNBC expressing human LMW-E (hLMW-E) were also utilized to assess LMW-E as a biomarker for predicting response to RP-6306. **Results:** Analysis of TNBC tumor biopsies revealed a significant positive correlation between LMW-E expression and CDK1 pT14, and both biomarkers were associated with a lack of pathological complete response to neoadjuvant chemotherapy. In vitro results using LMW-E inducible hMECs and breast cancer cell lines demonstrated that LMW-E up-regulates PKMYT1 and CDK1 pT14, acting as a PKMYT1 binding protein and enhancing PKMYT1 protein stability. High LMW-E protein levels predicted a favorable response to RP-6306, resulting in the accumulation of sub-G1 and polyploid cells, decreased tolerance to replication stress, increased DNA damage, chromosomal breakage, and apoptosis. In vivo treatment of TNBC PDX models and hLMW-E transgenic tumors with RP-6306 resulted in a significant reduction in tumor volume only in mice harboring high LMW-E tumors, while low cyclin E models showed no response. Immunohistochemical analysis confirmed increased γ -H2AX and decreased CDK1-pT14 and Ki67 levels, indicating the efficacy of RP-6306 in both PDX and transgenic models. **Conclusion:** This study highlights the regulatory axis from LMW-E to PKMYT1 and its predictive value for pathological complete response in TNBC patients receiving neoadjuvant

chemotherapy. The selective PKMYT1 kinase inhibitor RP-6306 consistently induced DNA damage and inhibited tumor growth in in vitro and in vivo pre-clinical breast tumor models. Co-expression of LMW-E and CDK1-pT14 in TNBC can be used to stratify patients whose tumors are likely to respond to RP-6306, emphasizing its therapeutic significance.

PO1-16-05

Matched multi-analyte and multi-omic liquid biopsy of cell-free DNA, circulating tumor cells and extracellular vesicles in HER2-positive metastatic breast cancer patients

Presenting Author(s) and Co-Author(s):

S. Kasimir-Bauer. University Hospital Essen, Germany

M. Storbeck. QIAGEN GmbH, Hilden, Germany, United States

I. Andreou. QIAGEN GmbH, Hilden, Germany, United States

S. hauch. QIAGEN GmbH, Hilden, Germany, United States

O. Hoffmann. University Hospital Essen, Germany

R. Kimmig. Department of Gynecology and Obstetrics, University Hospital of Essen, Germany, Germany

C. Keup. Department of Gynecology and Obstetrics, University Hospital of Essen, Germany, Germany

Background: Liquid biopsy, specifically cell-free DNA (cfDNA) mutation analysis, has recently entered clinical practice for treatment decision-making in hormone receptor (HR)-positive (+)/HER2-negative (-) metastatic breast cancer (mBC) patients. However, we showed that the analysis of multiple liquid biopsy analytes in the course of treatment in this BC subgroup has additive value. Since no multi-analyte studies are currently available for the subgroup of HER2+ mBC patients, we here studied multiple analytes [cfDNA, circulating tumor cells (CTCs) and extracellular vesicles (EVs)] and utilized our multi-omics perspective (CpG island methylation, mutations and mRNA expression) to get insight into their utility in therapy management of HER2+ mBC. Methods: 2x 9 ml blood was drawn from 21 HER2+ (HR+ n=16 and HR- n=5) mBC patients at the time of disease progression and at two consecutive staging time points. CTCs and their mRNA were isolated from 2x5 ml blood by positive immunomagnetic selection targeting EpCAM, EGFR and HER2 (AdnaTest EMT2/StemCell Select/Detect). Plasma of CTC-depleted blood was used for cfDNA isolation, while mRNA from EVs was isolated from 4 ml pre-filtered plasma by affinity-based binding to a spin column (exoRNeasy) using the remaining blood. The mRNA purified from CTCs and EVs by Oligo-dT beads was reverse transcribed, pre-amplified and analyzed by a multi-marker (18 genes) qPCR panel. qPCR data was normalized to CD45 (for CTC analysis) and data of 20 healthy female donor controls to identify BC specific overexpression signals with a specificity of >90% for all targets. Variants in the cfDNA were analyzed with a customized QIAseq Targeted DNA Panel with unique molecular indices (UMIs) and high coverage (mean 22.000x), while CpG island methylation in the cfDNA was analyzed with a customized QIAseq Targeted Methyl Panel with UMIs covering 9786 CpG sites (mean 900x). Consumables: QIAGEN, Germany. Results: In general, substantial differences occurred between the CTC and EV mRNA profiles. Transcripts involved in the PI3K pathway (mTOR, AKT2, PIK3CA) as well as ERBB2 signals were significantly more prevalent in CTCs compared to EVs and mTOR, ERCC1, SRC, AKT2 und PIK3CA CTC overexpression signals were found in >50% of these patients. In contrast, PARP1, AURKA, SRC und ERCC1 signals were significantly more prominent in the EVs and detected in >50% of the patients. ERCC1 signals were present in EVs with highest prevalence whereas ERBB2 signals were only present in CTCs. ERBB3+ CTCs were only detected in patients showing disease progression. Currently, cfDNA mutations as well as cfDNA CpG island methylation are under evaluation and the complete multi-analyte and multi-omic data set as well as their relation to clinical outcome will have been finalized to be presented at the meeting. Conclusion: We successfully established a workflow for parallel isolation of multiple liquid biopsy analytes from a minimized

blood volume in HER2+ mBC. Preliminary mRNA profile results for CTCs and EVs show the complementary nature of these two liquid biopsy analytes. Besides the multi-analyte nature of this workflow, the pending results for genomic and epigenomic information will show which one of the analytes, alone or in combination, will help to optimize therapy management in HER2+ mBC patients.

PO1-16-06

LuciA-15 - A real-world prospective study of PARP inhibitors for the treatment of Latin American patients with HER-2 negative metastatic breast cancer with mutation of BRCA1/2 genes or in the Homologous Recombination Repair genes.

Presenting Author(s) and Co-Author(s):

- F. Petracci. Instituto Alexander Fleming, United States
C. Villarreal-Garza. Tecnológico de Monterrey, Nuevo Leon, Mexico
F. Argañaraz. Instituto Médico de Alta Complejidad, Salta, Argentina, United States
G. Gómez Abuin. Hospital Alemán Buenos Aires, Argentina, United States
J. Peñaloza. Centro Oncológico Integral, Neuquén, Argentina, United States
M. Flores. Hospital Privado de Comunidad, Mar del Plata, Argentina, United States
L. Piazzoni. Centro Oncológico Integral, Neuquén, Argentina, United States
C. Riggi. Hospital Italiano, Buenos Aires, Argentina, United States
L. Fabiano. Hospital Municipal de Chivilcoy, Centro Santa María, Chivilcoy, Argentina, United States
L. González. COIR Fundación Centro Oncológico de Integración Regional, Mendoza, Argentina, United States
B. Cieplinski. CENTRO MEDICO ACCORD MONSERRAT, Buenos Aires Argentina, United States
S. Rivero. Instituto Alexander Fleming, Buenos Aires, Argentina, United States
E. Korbenfeld. Hospital Británico, Buenos Aires, Argentina, United States
P. Mandó. CEMIC, Centro de Educación Médica e Investigaciones Clínicas, Buenos Aires, Argentina, United States

Background

PARP inhibitors (PARPi) improves progression free survival among patients with HER2 negative (HER2-ve) advanced breast cancer (ABC) and a BRCA1 or BRCA2 mutation compared to physician choice of chemotherapy (CT). The AIM of this prospective study was to evaluate the clinical benefit of PARPi treatment in terms of response, outcomes and survival by breast cancer type and treatment in a Latin-American population. Methods

We analyzed data of patients with HER2-ve ABC with germline and/or somatic mutation of BRCA 1 or BRCA 2 or in the Homologous Recombination Repair genes, treated with olaparib or talazoparib in daily clinical practice by oncologist from Argentina and México. From September 2019 and April 2023, we collected baseline characteristics, previous systemic treatments, type and pattern of use, treatment beyond PARPi progression, and patient predisposition. Objective responses, best response rate, real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) were analyzed with R software and RStudio version 14.0. Results

After a median follow-up of 18.07 months (CI95% 10.53 - 30.07), 51 patients were treated with PARPi. Mean age at start treatment was 47,08 years. 62.7% had ER+ve/HER2-ve and 35.3% had triple negative breast cancer (TNBC). 62.7% and 37.3% of patients received talalaparib and olaparib, respectively. BRCA 1 and 2 germline mutations were the most common alterations found in 96% of patients. 37.5% of patients received platinum-based CT (PbCT) in the (neo)adjuvant/metastatic setting. 57.5% had visceral metastasis and the median number of metastatic sites were 2 (range 1-4). Median number of lines at the time to start PARPi was 2

(range 0-8), 23.5% and 31.4% received PARPi in the 1st line and 2nd line, respectively. The rwORR was 47.0%, and the median rwPFS1 was 7.77 months (CI95% 5.67-14.7). There was a tendency of better rwPFS1 in patients without previous CT versus previous CT in the advance setting, 14.30 months (CI95% 6.47-NR) versus 6.37 months (CI95% 5.03-8.73), respectively (p 0.084). The median rwOS was 26.97 months (CI95% 13.50-NR) and higher in the subgroup of patients naïve for CT versus previous exposure to CT in the advance setting, the median rwOS was 32.1 months (CI95% 27.0-NR) versus 13.0 (IC95%10.1-NR), respectively (p 0.022). 23.5% of patients progressed on PARPi during the first 6 months of treatment, 32.4% with visceral compromise, 27.8% with visceral crisis, and 26.5% with ≥2 metastatic sites. CT was the treatment of choice in most patients (55.3%). The medium rwPFS2 (next treatment after PARPi failure) was 4.00 months (CI95% 3.43 – 7.13). Treatment was discontinued for adverse events in 4.0 % of patients. Conclusion

This is the first Latin-American evidence that replicate the data already published in randomized clinical trials and other scanty real-world evidence studies in this field, positive results in rwORR and rwPFS, encouraging data in rwOS. Notably, high proportion of patients with visceral progression even with visceral crisis and need for CT. Interestingly, similar rwOS results among subgroups (TNBC versus ER+ve/HER2-ve, talazoparib versus Olaparib, etc).

Outcomes			
Clinical response rate	n: 51 p	%	
rwORR	24	47.0	
Complete response	4	7.8	
Partial response	20	39.2	
Stable disease ≥24 weeks	15	29.4	
Progressive disease <24 weeks	12	23.5	
Clinical benefit rate ≥24 weeks	39	76.4	
Survival Outcomes	Median (months)	CI95%	p
Progression-free survival-1 (rwPFS ₁)	7.77	5.67 - 14.7	-
• 6-months		57.1% (44.7-72.8%)	
• 12-months		34.4% (23.0-51.5%)	
Progression-free survival-2 (rwPFS ₂)	4.00	3.43 – 7.13	-
Overall survival (rwOS)	26.67	13.50 – NR	
• 6 months		68.9% (56.0-84.8%)	
• 12 months		53.4% (38.1-75.0%)	
• naïve for CT	32.1	27.0 - NR	0.022
• previous exposure to CT	13.0	10.1 – NR	

rwORR, real-world Objective response rate, CBR, clinical benefit rate, rwPFS, Real-world Progression-free survival and OS, Overall Survival, IC95%, Interval Confidence 95%.

PO1-16-07

Patient Characteristics and Treatment Sequencing Among HER2-low Metastatic Breast Cancer Patients with Rapid vs. Delayed Progression on First-line Endocrine Therapy

Presenting Author(s) and Co-Author(s):

C. Tan. Pharmacotherapy Outcomes Research Centre, University of Utah, United States

C. Willis. Pharmacotherapy Outcomes Research Centre, University of Utah, United States

T. Au. Pharmacotherapy Outcomes Research Centre, University of Utah, United States

M. Schabath. Moffitt Cancer Center and Research Institute, United States

C. Li. University of Arkansas for Medical Sciences, United States

K. Kelley. Huntsman Cancer Institute, United States

X. Xu. AstraZeneca, United States

L. Park. Oncology Outcomes Research, AstraZeneca, United States

C. Lam. AstraZeneca, Maryland, United States

S. Mehta. Daiichi Sankyo, Inc., New Jersey, United States

J. Kwong. Daiichi Sankyo, United States

D. Brixner. Pharmacotherapy Outcomes Research Centre, University of Utah, United States

D. Stenehjem. Department of Pharmacy Practice and Pharmaceutical Sciences, College of Pharmacy, University of Minnesota, United States

Background Patients with HER2-low (IHC 1+ or 2+ and negative ISH) and hormone-receptor positive (HR+) metastatic breast cancer (mBC) who rapidly progress on first-line (1L) endocrine therapy may experience different treatment pathways than those with delayed progression. The goal of this multisite study is to describe the characteristics, treatment patterns and outcomes of these patients with rapid vs. delayed progression. **Methods** This was a retrospective cohort study of HER2-low, HR+, mBC patients who received 1L endocrine-based treatment regimen at the Huntsman Cancer Institute, Moffitt Cancer Center, and the Winthrop P. Rockefeller Cancer Institute between 2017 and 2021. With no conventional definition, our study defined rapid progression as disease progression within 12 months of 1L treatment initiation vs >12 months/no progression during study follow-up as delayed progression. Demographic and clinical characteristics, and 1L and second-line (2L) treatment patterns were assessed using descriptive statistics. Using Kaplan-Meier analysis, overall survival (OS) was estimated from treatment initiation to death while progression-free survival (PFS) was estimated from treatment initiation to death or disease progression according to physician notes in patients' charts. Censoring was performed at the date of last follow-up or 31 Dec 2021, whichever occurred earlier. **Results** The study included 118 patients who received 1L endocrine therapy (see table), mostly in combination with a CDK4/6 inhibitor (n = 87, 73.7%). Rapid progression was observed for 25 (21.2%) patients with a median 1L PFS and OS of 6.4 months (95% CI: 5.4-8.2) and 20.5 months (95% CI: 14.4-30.5), respectively, compared to delayed progressors (median 1L PFS = 30.5 months, 95% CI: 21.5-54.2 and median OS = 62.1 months, 95% CI: 46.4 -upper bound not reached). Rapid progressors were more likely than delayed progressors to be current smokers (n = 6, 24.0% vs n = 7, 7.5%, p = 0.015) or had liver metastasis at diagnosis of advanced disease (n = 11, 44.4% vs n = 17, 18.3%, p = 0.007) but less likely to have bone as the only metastasis site (n = 6, 24.0% vs n = 46, 49.5%, p = 0.023). A smaller proportion of rapid progressors were on CDK4/6 inhibitors in 1L (n = 17, 68.0%) compared to delayed progressors (n = 70, 75.3%) but the difference was not statistically significant. A substantial proportion of

rapid progressors (68%, n = 17) continued to receive endocrine therapy in 2L, including endocrine therapy alone (n = 6, 24.0%), endocrine therapy with targeted therapy (n = 6, 24.0%) and endocrine therapy with CDK4/6 inhibitors (n = 5, 20.0%). Among patients on 1L endocrine therapy who continued to a 2L treatment, 2L PFS and OS of rapid progressors (n = 24) were 5.7 months (95% CI: 3.2-10.6) and 14.1 months (95% CI: 6.8-24.2), respectively, compared to 9.2 months (95% CI: 3.1-13.7) and 29.2 months (95% CI: 14.4- upper bound not reached) among delayed progressors (n = 39). Conclusion In this study of patients with HER2-low and HR+ mBC, many patients with rapid disease progression on 1L endocrine-based regimens continued to receive endocrine therapy in their next line of therapy and experienced poor clinical outcomes. This preliminary chart review study highlights the unmet need for more effective treatments for patients with rapid progression on 1L endocrine-based regimens. Further research with a larger sample size is warranted to confirm these findings.

Patient characteristics and treatment patterns

Table. Demographic characteristics and treatment patterns of stage IV breast cancer patients with HER2-low disease and received 1L endocrine therapy

Variable	Delayed progressors (n = 39)	Rapid progressors (n = 24)	p-value
Median follow-up - 24.9 months			
Age at diagnosis, median (IQR)	57.8 (47.7, 69.0)	55.8 (49.0, 61.9)	0.43
Race, n (%)			
White	39 (100.0%)	20 (83.3%)	0.59
Black	0 (0.0%)	2 (8.3%)	
Hispanic/Latino	0 (0.0%)	1 (4.2%)	
Asian	0 (0.0%)	1 (4.2%)	
Other	0 (0.0%)	0 (0.0%)	
Education, n (%)			
Less than high school	5 (12.8%)	1 (4.2%)	0.56
High school	26 (66.9%)	13 (54.2%)	
Some college	6 (15.4%)	4 (16.7%)	
College	8 (20.5%)	6 (25.0%)	
Postgraduate	5 (12.8%)	1 (4.2%)	
Insurance status, n (%)			
Medicaid	10 (25.6%)	9 (37.5%)	0.015
Medicare	19 (48.4%)	11 (45.8%)	
Private	9 (23.0%)	6 (25.0%)	
Uninsured	1 (2.6%)	0 (0.0%)	
Income status, n (%)			
Below \$10,000	25 (64.1%)	9 (37.5%)	0.30
\$10,000-\$19,999	10 (25.6%)	10 (41.7%)	
\$20,000-\$29,999	2 (5.1%)	1 (4.2%)	
\$30,000-\$39,999	1 (2.6%)	0 (0.0%)	
\$40,000-\$49,999	0 (0.0%)	0 (0.0%)	
\$50,000-\$59,999	0 (0.0%)	0 (0.0%)	
\$60,000-\$69,999	0 (0.0%)	0 (0.0%)	
\$70,000-\$79,999	0 (0.0%)	0 (0.0%)	
\$80,000-\$89,999	0 (0.0%)	0 (0.0%)	
\$90,000-\$99,999	0 (0.0%)	0 (0.0%)	
\$100,000+	0 (0.0%)	0 (0.0%)	
Marital status, n (%)			
Married	21 (53.8%)	9 (37.5%)	0.80
Single	17 (43.3%)	11 (45.8%)	
Divorced	1 (2.6%)	1 (4.2%)	
Widowed	0 (0.0%)	0 (0.0%)	
Other	0 (0.0%)	0 (0.0%)	
Employment status, n (%)			
Employed	1 (2.6%)	1 (4.2%)	0.30
Unemployed	38 (97.4%)	23 (95.8%)	
Retired	0 (0.0%)	0 (0.0%)	
Other	0 (0.0%)	0 (0.0%)	
Primary site, n (%)			
Breast	39 (100.0%)	24 (100.0%)	0.46
Other	0 (0.0%)	0 (0.0%)	
Primary site with unknown histology, n (%)			
Unknown	0 (0.0%)	0 (0.0%)	0.92
Other	0 (0.0%)	0 (0.0%)	
Site of metastasis, n (%)			
Brain	1 (2.6%)	0 (0.0%)	0.46
Bone	11 (28.2%)	11 (45.8%)	
Liver	1 (2.6%)	1 (4.2%)	
Lung	1 (2.6%)	1 (4.2%)	
Other	25 (63.9%)	10 (41.7%)	
Number of metastatic sites			
One	30 (77.0%)	16 (66.7%)	0.20
Two	8 (20.5%)	6 (25.0%)	
Three or more	1 (2.6%)	2 (8.3%)	
First line treatment, n (%)			
Endocrine therapy alone	11 (28.2%)	9 (37.5%)	0.67
Endocrine therapy + Chemotherapy	18 (45.9%)	10 (41.7%)	
Endocrine therapy + Immunotherapy	1 (2.6%)	1 (4.2%)	
Endocrine therapy + CDK4/6 inhibitor	6 (15.4%)	1 (4.2%)	
Endocrine therapy + Chemotherapy + CDK4/6 inhibitor	10 (25.6%)	10 (41.7%)	
Second line treatment, n (%)			
Chemotherapy alone	3 (7.7%)	3 (12.5%)	0.60
Chemotherapy + Targeted therapy	10 (25.6%)	10 (41.7%)	
Endocrine therapy + Targeted therapy	10 (25.6%)	6 (25.0%)	
Endocrine therapy + CDK4/6 inhibitor	1 (2.6%)	1 (4.2%)	
Chemotherapy + Immunotherapy	0 (0.0%)	0 (0.0%)	
Chemotherapy + Targeted therapy	0 (0.0%)	0 (0.0%)	
Chemotherapy + CDK4/6 inhibitor	0 (0.0%)	0 (0.0%)	
Chemotherapy + Immunotherapy + Targeted therapy	0 (0.0%)	0 (0.0%)	
Chemotherapy + Immunotherapy + CDK4/6 inhibitor	0 (0.0%)	0 (0.0%)	
Chemotherapy + Immunotherapy + Targeted therapy + CDK4/6 inhibitor	0 (0.0%)	0 (0.0%)	
Chemotherapy + Immunotherapy + Targeted therapy + CDK4/6 inhibitor + Immunotherapy	0 (0.0%)	0 (0.0%)	
Chemotherapy + Immunotherapy + Targeted therapy + CDK4/6 inhibitor + Immunotherapy + Targeted therapy	0 (0.0%)	0 (0.0%)	
Chemotherapy + Immunotherapy + Targeted therapy + CDK4/6 inhibitor + Immunotherapy + Targeted therapy + CDK4/6 inhibitor	0 (0.0%)	0 (0.0%)	
Chemotherapy + Immunotherapy + Targeted therapy + CDK4/6 inhibitor + Immunotherapy + Targeted therapy + CDK4/6 inhibitor + Immunotherapy + Targeted therapy + CDK4/6 inhibitor	0 (0.0%)	0 (0.0%)	

Demographic characteristics and treatment patterns of stage IV breast cancer patients with HER2-low disease and received 1L endocrine therapy

PO1-16-08

Real-World Outcomes of Patients Receiving First-line Palbociclib Plus Endocrine Therapy in Spain: Subgroup Analysis Based on Tumor Grade, Progesterone Receptor, Ki-67 and Histological Subtype from PALBOSPAIN Study

Presenting Author(s) and Co-Author(s):

F. moreno. Hospital Clínico San Carlos, Madrid, Spain, United States

M. Bellet- Ezquerro. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain

L. Manso. Hospital Universitario 12 de Octubre, Madrid, Spain

F. Henao. Medical Oncology Hospital Virgen de la Macarena, Sevilla, United States

A. Antón. Miguel Servet University Hospital, Zaragoza, Aragon, Spain

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

P. Tolosa. SOLTI Cancer Research Group, Barcelona, Spain/Medical Oncology Department, Hospital 12 de Octubre, Madrid., Madrid, Madrid, Spain

V. Obadía. 8Breast Cancer Unit, ICO - Institut Català d'Oncologia l'Hospitalet (Hospital Duran i Reynals), L'Hospitalet De Llobregat, Spain,, United States

T. Sampedro. Medical Oncology Department, Hospital Universitario de Cabuenes, Gijón, Spain, United States

R. Andrés. Hospital Clínico Lozano Blesa, Spain

L. Calvo. Oncology Department-University Hospital A Coruña, A Coruña, Galicia, Spain

E. Galve. Hospital Universitario de Basurto, United States

R. López. SOLTI Cancer Research Group; Clinical University Hospital and Health Research Institute of Santiago de Compostela (IDIS)- CIBERONC, United States

F. Ayala de la Peña. Hematology and Oncology Department, Hospital Universitario Morales Meseguer, Murcia, Spain., Murcia, Spain

S. López-Tarruella. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

B. Hernando. Hospital Universitario de Burgos. GEICAM Spanish Breast Cancer Group, Spain

L. Boronat. Medical Oncology Hospital de la Santa Creu i Sant Pau. Barcelona. Spain, United States

J. Chacón. Hospital Universitario de Toledo. GEICAM Spanish Breast Cancer Group., Spain

N. Martínez-Jáñez. Medical Oncology Hospital Universitario Ramón y Cajal. Madrid. Spain. GEICAM Spanish Breast Cancer Group., TRES CANTOS, Madrid, Spain

Background

PALBOSPAIN (NCT04874025) is an observational, multicenter study evaluating real-world patterns and outcomes of first-line treatment with palbociclib plus endocrine therapy (ET) in routine clinical practice in Spain.

Results from real-world progression-free survival (rwPFS) and overall survival (OS) in the total population, as well as subgroup analysis according to endocrine sensitivity, age, menopausal status, location and number of metastatic sites have been previously reported.

Here, we present the prognostic impact of pathological features in metastatic breast cancer patients treated with Palbociclib plus endocrine therapy. Methods
Patients diagnosed with hormone-receptor positive and HER2 negative ABC who started first-line treatment with palbociclib plus ET between November 2017 and November 2019 were included.

We retrospectively collected clinical-pathological and treatment response data from patient medical records. Estrogen receptor (ER), Progesterone receptor (PR), and Ki67 were assessed by immunohistochemistry (IHC). HER2 was assessed by IHC or fluorescence in situ hybridization (FISH). To evaluate the prognostic role of proliferation index, Ki-67 cut-off was set at 20%. If results of several biopsies were available, the most recent one was used for analysis.

Survival analysis (rw-PFS, OS) were estimated using the Kaplan–Meier method with log-rank test. Times for event-free patients at the time of data cutoff in all survival analyses were calculated from the date of treatment start to the date of last follow-up. The association between prognostic factors and survival was examined using Cox proportional hazards regression model. Results

A total of 762 patients from 35 hospitals met inclusion and exclusion criteria and were included in the analysis. The cut-off date for this analysis was July 2022 and the median duration of follow-up was 29 months.

The distribution of the pathological features is shown in Table 1.

Patients with histological grade 1 tumors had a median rwPFS of 33 months, while grade 2 tumors experienced a median rwPFS of 24 months and grade 3 tumors had the poorest outcome with a median rwPFS of 19 months. Median OS was 43, 42 and 40 months for grade 1, 2 and 3 respectively.

Patients with Ki-67 < 20% had better rwPFS (35 vs 20 months; HR 0.60, p=0.004) and OS (not reached [NR] vs 35 months; HR 0.66, p=0.002) than those with Ki-67 ≥20%

Patients with low ki-67 had better outcomes compared with those with high Ki-67. rwPFS (35 vs 20 months; HR 0.60, p=0.004) and OS (not reached [NR] vs 35 months; HR 0.66, p=0.002) for Ki 67 < 20% and ≥20% respectively.

No differences were found according to histological subtype, with similar median rwPFS (23 vs 25 months; HR 0.96, p= 0.77) and OS (42 vs 43 months; HR 0.94, p=0.74) for ductal and lobular carcinomas respectively.

Double hormone receptor positive tumors (ER+/PR+) had significant longer rwPFS (27 vs 18 months; HR 0.72, p=0.001) and OS (44 vs 40 months; HR 0.73, p= 0.01) compared with ER+/PR- tumors. Conclusions

Grade 3 tumors, Ki 67 ≥20% and absence of PR are associated with reduced rw-PFS and OS in patients treated with palbociclib plus ET in clinical practice. Pathologic results have a prognostic role and may be useful to identify patients who derive more benefit with first-line CDK 4/6 inhibitors plus ET treatment.

Table 1

	rwPFS	OS
	Months (CI 95%)	Months (95% CI)
Grade		
G1 (n=78)	33 (27-NR)	43 (43-NR)
G2(n=363)	24 (21-28)	42 (40-NR)
G3 (n=132)	19 (13-27)	40 (31-NR)
KI67		
<20% (n=255)	35 (30-NR)	NR (43-NR)
>=20% (n=398)	20 (18-23)	38 (35-NR)
Histology		
Ductal (n=575)	23 (20-27)	42 (40-NR)
Lobular (n=110)	25 (19-36)	43 (35-NR)
Hormone receptor status		
ER+/PR+ (n=530)	27 (23-31)	44 (40-NR)
ER+/PR- (n=213)	18 (15-24)	40 (35-NR)

Pathological Characteristics in PALBOSPAIN study

PO1-16-09

Does T1c-2N0-1M0 triple negative breast cancer derive a benefit from neoadjuvant chemotherapy?

Presenting Author(s) and Co-Author(s):

J. Zhang. Fujian Medical University Union Hospital, United States

Y. Yu. Fujian Cancer Hospital, United States

W. Chen. The first Hospital of Nanping City affiliated to Fujian Medical University, United States

W. Fu. Fujian Medical University Union Hospital, United States

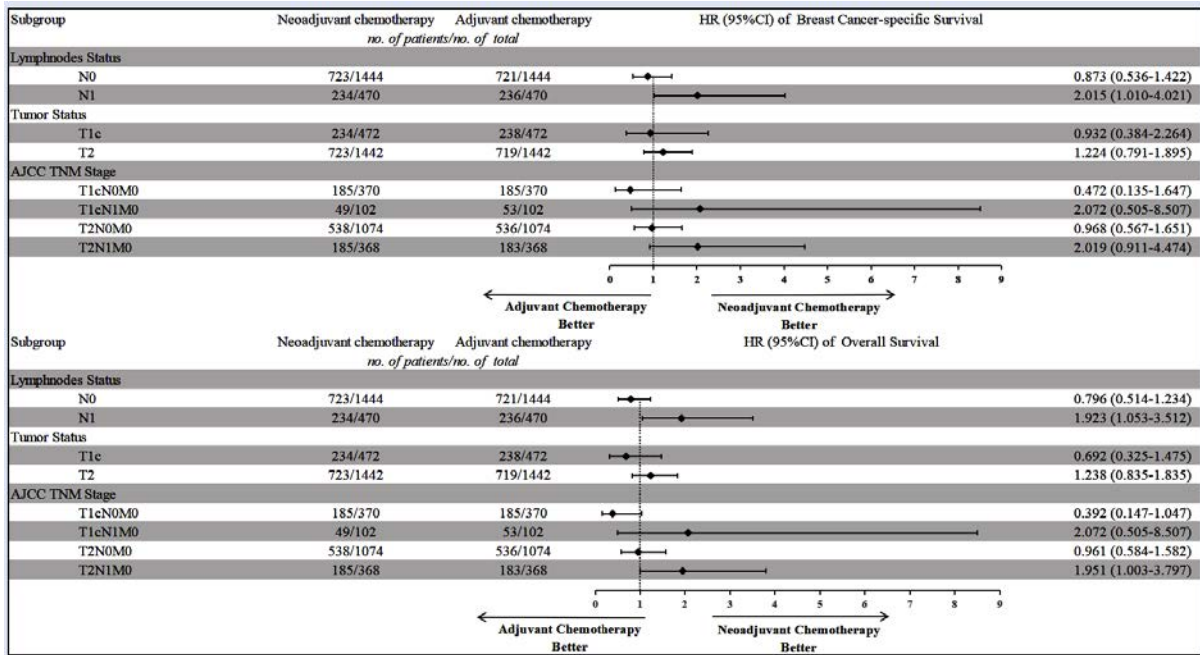
R. Chen. Fujian Medical University Union Hospital, United States

J. Yi. Fujian Medical University Union Hospital, United States

C. Song. Fujian Provincial Cancer Hospital, United States

Objective: Although neoadjuvant chemotherapy (NCT) is a standard approach for operable triple negative breast cancer (TNBC), the potential risks brought by it should also be noticed. Is the expanding indication of NCT to T1cN0M0 population appropriate? We conducted an investigation to compare the long-term survival of small tumor TNBC between NCT and adjuvant chemotherapy (ACT). Methods: For this propensity-matched analysis, we used data from SEER database. We enrolled 1183 cases with NCT and 2550 cases with ACT who are AJCC clinical T1c-T2 N0-N1, diagnosed with TNBC, from 2016 to 2017. The propensity score matching was utilized to minimize baseline characteristics bias. Based on the Cox proportional hazard regression model, we calculated hazard ratios (HR) with 95% confidence intervals (CIs). Results: Multivariate analysis in matched patients showed that NCT had no significant survival benefit compared with ACT in T1c-2N0-1M0 TNBC patients. Stratified analyses by T stage and N stage demonstrated NCT mainly presented a survival advantage in patients with N1 stage. Further investigation found that NCT didn't improve BCSS (HR=0.472; 95% CI: 0.135-1.647; p=0.239) and OS (HR=0.392; 95% CI: 0.147-1.047; p=0.062) for patients with T1cN0M0 TNBC; however, for patients with T2N1M0 TNBC, it was associated with improved OS (HR=1.951; 95% CI: 1.003-3.797; p=0.049). Conclusion: In our study, we did not find any profit brought by NCT in the stage I and stage IIa cohorts, but even more unfavorable outcomes appeared in the T1cN0M0 cohort. Therefore, whether the candidates of NCT should be extended to T1cN0M0 still need to be cautious.

Treatment effect on breast cancer-specific survival (BCSS) and overall survival (OS) by subgroup.



PO1-16-10

BRCA mutated Male Breast Cancer, hallmarks of a distinct disease. Data from the Spanish Male Breast Cancer Registry (GEICAM/2016-04)

Presenting Author(s) and Co-Author(s):

N. Martínez-Jáñez. Medical Oncology Hospital Universitario Ramón y Cajal. Madrid. Spain. GEICAM Spanish Breast Cancer Group., TRES CANTOS, Madrid, Spain

P. Martínez. Hospital Universitario Basurto. GEICAM Spanish Breast Cancer Group., Spain

C. Hernando. Hospital Clínico Universitario de Valencia, Valencia, Spain

S. Recalde. ICO L'Hospitalet- Hospital Duran I Reynalds. GEICAM Spanish Breast Cancer, Barcelona, Spain

A. sánchez. Hospital Regional Universitario de Málaga. GEICAM Spanish Breast Cancer Group, Málaga, Spain

D. Morales. Hospital Universitario Juan Ramon Jimenez. GEICAM Spanish Breast Cancer Group, Huelva, Spain

M. Santisteban. Clínica Universidad de Navarra (CUN), Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Navara, Spain., United States

I. Fernández. Hospital Álvaro Cunqueiro. GEICAM Spanish Breast Cancer Group, Vigo, Spain

S. Del Barco. ICO de Girona-Hospital Josep Trueta. GEICAM Spanish Breast Cancer Group, Girona, Spain

E. Zamora. Hospital Universitario Vall d'Hebron. GEICAM Spanish Breast Cancer Group, Barcelona, Spain

V. Iranzo. Hospital General Universitario de Valencia. GEICAM Spanish Breast Cancer Group, Spain

T. Martos. Hospital del Mar. GEICAM Spanish Breast Cancer Group, Barcelona, Spain

E. Martínez-de Dueñas. Consorcio Hospitalario Provincial de Castellón. GEICAM Spanish Breast Cancer Group, Castellón, Spain

S. Antolin Novoa. Complejo Hospitalario Universitario A Coruña (CHUAC). GEICAM Spanish Breast Cancer Group., Spain

S. Domínguez. Hospital Universitario de Araba. GEICAM Spanish Breast Cancer Group, Alava, Spain

P. Domínguez. Hospital San Agustín de Avilés. GEICAM Spanish Breast Cancer Group, Avilés, Spain

M. Echarri. Hospital Universitario Severo Ochoa. GEICAM Spanish Breast Cancer Group., Spain

A. Santaballa Bertrán. Hospital Universitario y Politécnico La Fe, Valencia, Spain. Instituto de Investigación Sanitaria La Fe, Valencia, Spain. GEICAM Spanish Breast Cancer Group, Valencia, Spain

X. Mira. Hospital General de Granollers. GEICAM Spanish Breast Cancer Group, Spain

A. Blasco. GEICAM Spanish Breast Cancer Group, Spain

S. Bezares. GEICAM Spanish Breast Cancer Group., Spain

A. Urriticoechea. Oncologikoa, United States

Background: Male breast cancer (MBC) accounts for approximately 0.25% of all male cancers and < 1% of all BCs. Its incidence is increasing by 1.1% per year. Most population studies indicate that 10-15% of MBC patients (pts) have a germline BRCA2 mutation (BRCA2 mut). Around 5-10% of BRCA2mut male carriers will develop BC at their lives. Preliminary evidence suggests that BRCA2mut MBC pts tend to have a more aggressive disease. Here we present comparative series of MBC with and without BRCA to gain insight on differences between both groups. Methods: GEICAM/2016-04 (NCT03800355) is a retrospective, observational study which includes data from MBC pts diagnosed between 2000 and 2019 throughout Spain. This analysis includes the 1st unselected 186 pts included in the study, who had BRCA1/2 genes mutational status assessed within clinical practice. BC clinical subtypes are defined: luminal (HR+, HER2-), Triple Negative (TN) (HR-, HER2-), and HER2+ (HR+ or HR-); subtype is unknown in 6% pts. Results: 186 validated pts with BRCA1/2 testing were identified, representing the 24% of pts available in the database at the cut-off date (6-Mar-2023). 36 (19%) pts had germline BRCA1/2 mut (4 pts in BRCA1, 31 pts in BRCA 2 and 1 pt in both BRCA1 and BRCA2), and 150 (81%) pts had BRCA1/2 wild type (wt) or a variant of uncertain significance (VUS)/unknown (UK). Median age at BC diagnosis was 62 (34-87) years, 98% pts were Caucasian, and the median body mass index was 27 (18-46) Kg/m² (overweight). Prior cancer history was reported in 6% BRCA1/2mut BC pts and 11% BRCA1/2wt or vus/uk, and family history included: 56% BC, 8% ovarian cancer, and 14% prostate cancer (PC). PC as part of prior medical history, cancer family history, and 2nd non-breast primary malignancy, was most frequent in BRCA1/2wt or vus/uk pts, with no statistical differences. At first diagnosis, stages III-IV were higher in BRCA1/2mut pts (28% vs. 17%, p=0.0093). Morphologically, invasive carcinoma of no special type (NST) was the most common pattern (92% in BRCA1/2mut vs. 86% in BRCA1/2wt or vus/uk), and lobular invasive carcinoma was not reported up-to-date. Histological grade 2 was the most frequent (54%), but grade 3 was present in 17/36 BRCA1/2mut pts. 88% pts received adjuvant treatment, 7% (neo-)adjuvant, 2% neoadjuvant and 3% did not receive any systemic therapy. Breast conserving surgery was performed in 4% (5/140) BRCA1/2wt or vus/uk EBC pts, and mastectomy was performed in 55% (n=6/11) de novo metastatic pts. In the advanced setting (n=38), visceral lesions were more frequent in BRCA1/2mut pts. Additionally, 92% BRCA1/2mut pts had ≤ 3 organs involved while one third of BRCA1/2wt or vus/uk pts had ≥ 4 metastatic locations. With a median follow-up of 64 months (mo.), median iDFS and DDFS were higher, but not statistically significant, in BRCA1/2wt or vus/uk pts vs. BRCA1/2mut pts. In advanced setting, median PFS to 1L-3L do not show statistically significant differences between both groups. Regarding OS, no differences were also observed, but the median values were not reached. Further detailed information according to BRCA1/2 mutational status and BC subtypes is included in the table below. Conclusions: In this subset analysis of GEICAM/2016-04, BRCA1/2mut pts had some features of worse prognosis, with a more prevalent de novo metastatic disease. No statistically significant differences were observed in outcomes in both early-stage and advanced setting vs. BRCA1/2wt or vus/uk pts

PO1-16-11

Real-world features and outcomes of young advanced breast cancer (ABC) patients (pts) from RegistEM (GEICAM/2014-03) study

Presenting Author(s) and Co-Author(s):

S. López-Tarruella. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

A. Guerrero. Fundación Instituto Valenciano de Oncología (FIVO). GEICAM Spanish Breast Cancer Group., Valencia, Comunidad Valenciana, Spain

I. Álvarez. Hospital Universitario Donostia-BioDonostia. GEICAM Spanish Breast Cancer Group., Spain

S. Antolin Novoa. Complejo Hospitalario Universitario A Coruña (CHUAC). GEICAM Spanish Breast Cancer Group., Spain

A. Tibau. Hospital de la Santa Creu i Sant Pau. GEICAM Spanish Breast Cancer Group, Spain

J. Cruz. Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain, United States

C. Rodríguez. Hospital Universitario de Salamanca-IBSAL. GEICAM Spanish Breast Cancer Group, Salamanca, Spain

P. Martínez. Hospital Universitario Basurto. GEICAM Spanish Breast Cancer Group., Spain

J. Chacón. Hospital Universitario de Toledo. GEICAM Spanish Breast Cancer Group., Spain

M. Hernández. Complejo Hospitalario Universitario de Gran Canaria Dr. Negrín. GEICAM Spanish Breast Cancer Group., Spain

M. Margelí. SOLTI Cancer Research Group. Medical Oncology Department, ICO Badalona, B-ARGO Group. GEICAM Spanish Breast Cancer Group., Catalonia, Spain

E. Adrover. Complejo Hospitalario Universitario de Albacete. GEICAM Spanish Breast Cancer Group., Spain

C. Faló. ICO Hospitalet. GEICAM Spanish Breast Cancer Group., Spain

I. González. Hospital Universitario Son Llàtzer. GEICAM Spanish Breast Cancer Group, Spain

□. Rodríguez-Lescure. Hospital General Universitario de Elche. GEICAM Spanish Breast Cancer Group., Spain

M. Marín. Consorci Sanitari de Terrassa. GEICAM Spanish Breast Cancer Group, Spain

C. Gómez. Hospital Universitario Infanta Sofía. GEICAM Spanish Breast Cancer Group., United States

J. de la Haba-Rodríguez. Instituto Maimonides de Investigación Biomedica, Hospital Reina Sofía, Universidad de Córdoba. GEICAM Spanish Breast Cancer Group., Spain

J. Illaramendi. Hospital Universitario de Navarra-Nafarroako Unibertsitate Ospitalea. GEICAM Spanish Breast Cancer Group., United States

R. Andrés. Hospital Clínico Universitario Lozano Blesa. GEICAM Spanish Breast Cancer Group., Spain

A. Blasco. GEICAM Spanish Breast Cancer Group, Spain

M. Escudero. GEICAM Spanish Breast Cancer Group., Spain

S. Bezares. GEICAM Spanish Breast Cancer Group., Spain

F. Rojo. The Autonomous University of Madrid, Spain

Background: BC is the most incident cancer worldwide in < 40 years old (y) women. Increasing body mass index and changes in reproductive history contribute to the growing incidence of premenopausal BC. A higher proportion of luminal B-like and estrogen receptor negative (ER-) tumors, an increased risk of early relapse, and more unfavorable longer-term outcomes for young women with ER+ tumors when compared to older women, have been reported. In this analysis, we focus on age-specific BC characterization from a real-world population-based perspective.

Methods: Pts were enrolled in the non-interventional and ambispective RegistEM study in ABC diagnosed between 2016 and 2019. We describe the features and outcomes of < 50 y pts at their initial BC diagnosis according to their BC subtype. BC subtypes were based on the most recent tumor tissue sample (distant metastasis, and in its absence, primary BC). Comparisons between < 40 and \geq 50 y groups were performed.

Results: Pts < 50 y represent 39% (n=685) of total pts with available data (n=1739, any age group) in the registry. By age, 12% (n=212) were < 40y, and 27% (n=473) 40-49y. At first BC diagnosis, 75% and 25% pts had early BC (EBC) and de novo metastatic BC (MBC), respectively. In EBC pts, stage II (50%) and III (28%) were the most frequent at diagnosis; invasive non-special type carcinoma was the predominant morphology, and grade 2 was the most common histological grade, but grade 3 was predominant in TN pts and HER2+ < 40y pts. The median time to recurrence was < 2y in TN pts, 3y in HER2+ pts, and 6y in luminal HER2- pts. At ABC diagnosis, the median age was 47y, all pts were female but one, 98% white, and 60% premenopausal (94% were premenopausal at EBC diagnosis). A family history of BC and/or ovarian cancer was reported in 34% pts, and a hereditary-risk genetic test was performed in 39% (254 of 652) pts; 12% (n=30) had BRCA1/2 mutations, with a proportion higher in TN pts (9 of 33, 27%) vs. luminal HER2- (21 of 183, 12%) and HER2+ (0 of 38) pts. Visceral disease was the most frequent in all subgroups, highlighting statistical differences (p=0.022) between age groups (< 40y 55% vs. \geq 50y 71%) only in TN pts. 60% had \leq 2 locations involved, similarly in all subgroups. The presence of >2 metastatic locations was statistically higher in HER2+ pts \geq 50y (54%) vs both < 40y (32%) and 40-49y (48%). Brain disease was more present at ABC diagnosis in TN (9%) and HER2+ (7%) than in luminal HER2- (3%). Median no. of treatment lines (L) was 3 (range 0-11), and median follow-up 44 mo (95% CI: 41-44). 99% pts received 1L, the distribution of treatments by BC subtype within each age subgroup was similar; median duration of 1L was 21 months (mo) in luminal HER2-, 17 mo in HER2+, and 5 mo in TN pts. 68% of pts who received 1L, reached 2L. Duration of 2L dropped dramatically: 8 mo in luminal HER2-, 6 mo in HER2+, and 2 mo in TN pts. No differences between \geq 50y and the rest of pts were observed in PFS for any treatment line. 49% pts had died at the database cut-off date (05-April-23), with no differences between age groups, but TN pts had the highest death rate (80%). Additional data according to BC subtypes and age groups are in the table.

Conclusions: Luminal HER2- was the predominant BC subtype in all age subgroups. Visceral disease was more prevalent in young TN pts compared to older pts. TNBC pts experienced a shorter median time to recurrence and the highest mortality rate regardless of age, compared to

HER2+ and luminal HER2- pts, indicating the need for targeted interventions in this subgroup.

	LUMINAL_LIKE_HER2-neg (n=1216, 61%)						HER2+ (n=327, 16%)						TN (n=198, 11%)															
	<4y		4-4y		≥5y		<4y		4-4y		≥5y		<4y		4-4y		≥5y											
	n=155 (9%) 13% (155/1216)	n=339 (19%) 28% (339/1216)	n=722 (41%) 59% (722/1216)	n=57 (2%) 1% (57/527)	n=34 (9%) 28% (34/127)	n=216 (12%) 63% (216/327)	n=20 (1%) 1% (20/198)	n=50 (9%) 25% (50/198)	n=128 (7%) 64% (128/198)																			
HR	+						+/-neg						-neg															
HER2	-neg						+						-neg															
EBC, n (%)	135 (11%)		238 (20%)		432 (36%)		29 (9%)		54 (17%)		100 (33%)		16 (8%)		39 (20%)		94 (48%)											
Time to ABC (EBC pts), %																												
+>3y and <4y	16		19		17		17		17		27		6		18		17											
+>3y	36		37		29		20		19		16		25		5		9											
Line (L)	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3										
Pts number	155	107	90	339	225	169	722	465	337	57	24	18	84	57	40	208	121	71	20	15	8	50	32	23	128	74	53	
Pts who reached next L, %	69	84	77	66	75	72	67	67	63	65	75	61	68	70	68	59	55	75	53	75	64	72	48	59	72	60		
Pts ongoing on current L, %	25	10	10	28	15	10	18	11	9	24	17	17	24	12	15	23	22	10	10	7	0	14	0	4	6	3	2	
Deaths, %	5	5	12	4	9	9	17	12	20	26	11	8	22	6	16	15	15	15	32	10	40	25	14	28	48	25	24	38
Most frequent therapies*, %																												
ET/ET	51	40	23	58	36	22	43	35	21	-	-	-	-	16	-	-	18	-	-	-	-	-	-	-	-	-	-	-
ET	22	12	-	18	22	-	37	25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CT/ET/ET	-	-	-	-	-	-	-	-	-	46	-	-	40	-	-	33	-	-	-	-	-	-	-	-	-	-	-	-
CT/ET	-	-	-	-	-	-	-	-	-	41	21	50	40	16	55	40	19	46	45	20	25	42	22	17	30	12	-	-
CT	-	-	51	-	27	57	-	27	58	-	-	-	-	-	-	-	35	60	75	46	78	83	58	81	64	-	-	
BT	-	-	-	-	-	-	-	-	58	33	-	81	23	-	54	35	-	-	-	-	-	-	-	-	-	-	-	-
Treatment duration (mo.)	19	8	5	22	7	5	15	6	5	21	6	5	17	6	6	17	8	5	3	2	2	5	3	3	5	3	3	
PFS mo., median	21	8	5	24	8	6	16	7	5	25	8	5	19	8	7	19	9	6	3	2	2	8	3	3	7	4	4	
OS (mo.), median (95% CI)	20 (12, 24)		5 (14, 17)		9 (8, 10)		14 (10, 27)		9 (8, 13)		8 (8, 11)		4 (2, 19)		4 (3, 7)		4 (3, 5)											

*ET: Endocrine therapy; BT: Biological therapy; CT: Chemotherapy; PFS: progression-free survival; CI: confidence interval; OS: overall survival; L: line; mo.: month.

**L: PFS = time from JSC diagnosis to disease progression or death from any cause events. For the rest of therapy lines, PFS is time from the start of the line to disease progression or death from any cause events.

PO1-16-12

The McPeak-Sirois Group Breast Metastases Registry

Presenting Author(s) and Co-Author(s):

J. Lemieux. Centre des maladies du sein du CHU de Québec-Université Laval, Hôpital St-Sacrement, Québec, Quebec, Canada

D. Charpentier. Centre hospitalier de l'Université de Montréal, Montreal, Quebec, Canada

D. Johnson. McPeak-Sirois Group for clinical research in breast cancer, Montreal, Quebec, Canada

N. Bolduc. McPeak-Sirois Group for clinical research in breast cancer, Montreal, Quebec, Canada

C. Blanchette. Centre de recherche du CHU de Québec, Québec, Quebec, Canada

C. Nadon. McPeak-Sirois Group for clinical research in breast cancer, Quebec, Canada

S. Meterissian. McGill University, United States

Background:

In 2020, the McPeak-Sirois Group (MPSG), a Quebec-based breast cancer trials consortium, launched a feasibility pilot project to register prospectively cases of metastatic breast cancer (MBC). This Breast Metastases Registry (BMR) had the following objectives: a) to measure real-world progression-free and overall survival; b) to capture real-world evidence in efficacy of novel therapeutic approaches and c) to facilitate the development of clinical research projects in MBC.

Methods:

The pilot phase was initiated in three major academic hospitals with the intention of testing the feasibility of building a BMR and to assess barriers before extension to other hospitals in the province of Quebec. Funding was obtained through non-profit organizations and the pharmaceutical industry. The project was approved by a research ethics board and informed consent was obtained from each patient. The main inclusion criteria was a MBC diagnosis at the time of enrolment. Metastatic diseases were considered de novo if the metastatic condition was detected at the same time of the primary disease diagnosis or within the following 4 months. The information in the BMR relates to participants' health status, including but not limited to hospitalizations, diagnoses, medications, medical procedures and imaging, pathology, genetic and laboratory results. In addition to the prospective data, the registry also captures information retrospective to the date of enrollment.

Results:

Between July 30, 2021 and April 22, 2023, a total of 427 patients were approached by a research nurse and 423 patients enrolled and 4 refused (99.2% participation rate). Approximately one third of the cohort was diagnosed between 2021-2023 (30.3%) while 69.7% were in 2002-2020 timeframe. The majority was either HR+/HER2- (55.3%) or HER2+ (26.9%). The median age at the time of MBC diagnosis was 57 years (Q1-Q3 range: 47-67 years). We observed that 57.9% of patients had a relapsed MBC while de novo MBC comprised 42.1% of the cohort with the highest percentage in the HER2+ group (59.6%). The median time between primary cancer and metastatic disease in those with relapsed MBC is shorter in triple negative breast cancer (28.9 months) compared to 71.4 months in HR+ disease. Among all lines of treatment for metastatic disease, independently of age at time of MBC diagnosis, 21% of patients participated in a clinical trial.

Discussion:

The pilot project demonstrated the acceptability and feasibility of building a MBC provincial registry as illustrated by the high participation rate (more than 99%). The next step is to expand the registry to other hospital sites in Quebec, however, the main difficulty is having the necessary manpower (oncology registrars) to ensure data entry.

Over one third of the MBC patients presented as de novo disease (and more than half of these with HER2+ disease). This proportion of de novo MBC is unusually high and is likely due to a recruitment bias during the pilot phase as data entry was prioritised for de novo diagnoses over MBC at time of recurrence and patients were recruited at any time in their MBC trajectory and not only at the time of their MBC diagnosis. Clinical trial participation was higher in our cohort compared to the usually reported 5% participation rate. This may be due to recruitment bias but needs to be evaluated further.

Conclusion:

We have found that recruiting patients in a metastatic cancer registry and collecting their real-world data is not only feasible but well received by patients. The limiting factor for expansion to other hospitals is lack of oncology registrars. At maturity, the BMR will be a unique and powerful resource for breast cancer research and will allow researchers and their collaborators to unite their efforts to better understand how stage IV breast cancer is treated and how management of the disease can be improved. The BMR could also have the potential to improve participation in clinical trials and to stimulate clinical research.

PO1-17-01

Surgical Margins and prognosis of borderline and malignant phyllodes tumors of breast

Presenting Author(s) and Co-Author(s):

I. Gan. The First Affiliated Hospital of Chongqing Medical University, Chongqing, China (People's Republic)

J. Su. The First Affiliated Hospital of Chongqing Medical University, China (People's Republic)

Background. To determine the appropriate surgical margin and identify predictive factors for recurrence and prognosis of borderline and malignant phyllodes tumor (PT) of the breast. **Methods.** A retrospective review of patients with borderline and malignant PT treated from March 2011 to December 2022 at the First Affiliated Hospital of Chongqing Medical University were conducted. The main endpoints of this research were local recurrence-free survival (LRFS) and disease-free survival (DFS). Univariate and multivariate Cox proportional hazard models were used to examine the impacts of different variables on LRFS and DFS, and to calculate hazard ratios (HR) and 95% confidence intervals (CI). **Results.** Of 155 patients with phyllodes tumors, 87 (56.1%) were classified as borderline while 68 (43.9%) were malignant. All patients included underwent operation, with a median age of 47 years (range, 12-66 years) and a median tumor size of 60 mm (range, 15-300 mm). Initial surgical margins < 1cm in 72 (46.5%) patients, of which 28 (38.9%) underwent reoperation, resulting in 45 (28.4%) patients with a margin < 1cm and 111 (71.6%) patients with a margin \geq 1cm. At a median follow-up period of 66 months (range 3-146 months), local recurrence was observed in 36 patients (23.2%), and distant metastasis occurred in 10 patients (6.5%). In this cohort, the rates of 5-year LRFS was significantly higher in the surgical margin \geq 1 cm group than in the surgical margin < 1 cm group (83.8% vs 50.4% , log-rank $P < 0.001$), both for the borderline (log-rank $P = 0.010$) and the malignant PT (log-rank $P < 0.001$). Similarly, for both borderline (log-rank $P = 0.019$) and malignant PT (log-rank $P < 0.001$), the rates of 5-year DFS was significantly higher in the surgical margin \geq 1 cm group than in the surgical margin < 1 cm group (80.3% vs 47.5% , log-rank $P = 0.002$). For 72 patients with the initial margin < 1 cm, 5-year DFS for undergoing reoperation to achieve a margin \geq 1 cm and remaining with a margin < 1 cm were 84.1% and 47.5%, respectively ($P = 0.008$). In univariate analysis of the entire cohort, age, fibroadenoma surgery history, surgical methods, and surgical margins emerged as predictive factors for LRFS ($P = 0.003$, 0.019, 0.026, and 0.001, respectively), whereas age, reproductive history, fibroadenoma surgery history, tumor size and surgical margins were predictors of DFS ($P = 0.011$, 0.025, 0.039, 0.022, and 0.002, respectively). In multivariate analysis, age < 45 years (HR=2.186 , 95%CI : 1.105-4.328 , $P = 0.025$) and surgical margins < 1cm (HR=2.181 , 95%CI : 1.021-4.659 , $P = 0.044$) were independent risk factors of LRFS. Independent risk factors for DFS included tumor size > 5cm (HR=2.265 , 95%CI : 1.113-4.606 , $P = 0.024$) and surgical margins < 1cm (HR=2.689 , 95%CI : 1.438-5.027 , $P = 0.002$). **Conclusion.** For borderline and malignant PT, surgical margins of at least 1 cm should be achieved for a better prognosis. Patients aged < 45 years with a high risk of local recurrence and larger tumor patients with poor prognosis, multiple therapy modalities may be required for these high-risk patients.

Survival curves for impact of variables on LRFS and DFS

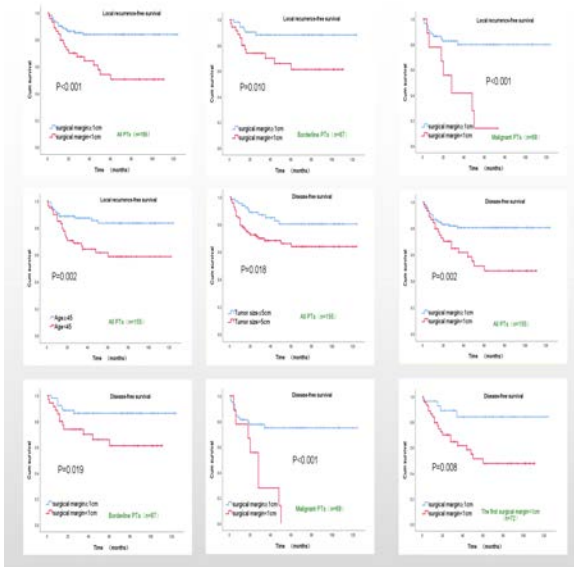


Table 1 Univariate and multivariate analysis of LRFS of PTs of the breast (n=155)

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P
Age, years				
≥45	Reference			
<45	2.736 (1.400-5.348)	0.003	2.186 (1.105-4.328)	0.025
Location				
Left	Reference			
Right	1.063 (0.553-2.043)	0.855	—	—
Reproductive history				
No	Reference			
Yes	0.430 (0.167-1.108)	0.081	—	—
Fibroadenoma surgery history				
No	Reference			
Yes	2.163 (1.095-4.273)	0.026	1.819 (0.912-3.630)	0.089
Histologic grade				
Borderline	Reference			
Malignant	1.402 (0.729-2.696)	0.312	—	—
Tumor size, cm				
≤5	Reference			
>5	1.836 (0.902-3.735)	0.094	—	—
Presenting symptoms				
Breast mass	Reference			
Breast mass with pain	1.222 (0.528-2.826)	0.640	—	—
Skin dimpling or				
Nipple discharge	2.022 (0.703-5.820)	0.192	—	—
Surgery type				
BCS	Reference			
TM	0.390 (0.178-0.856)	0.019	0.610 (0.246-1.514)	0.287
Surgical margin, cm				
≥1	Reference			
<1	3.057 (1.589-5.883)	0.001	2.181 (1.021-4.659)	0.044
Adjuvant radiation therapy				
No	Reference			
Yes	—	—	—	—
Adjuvant chemotherapy				
No	Reference			
Yes	0.970 (0.133-7.081)	0.976	—	—

Table 2 Univariate and multivariate analysis of DFS of PTs of the breast (n=155)

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P
Age, years				
≥45	Reference			
<45	2.232 (1.204-4.136)	0.011	1.400 (0.712-2.749)	0.329
Location				
Left	Reference			
Right	1.010 (0.547-1.863)	0.976	—	—
Reproductive history				
No	Reference			
Yes	0.372 (0.156-0.886)	0.025	0.446 (0.170-1.171)	0.101
Fibroadenoma surgery history				
No	Reference			
Yes	1.971 (1.033-3.761)	0.039	1.916 (0.960-3.824)	0.065
Histologic grade				
Borderline	Reference			
Malignant	1.670 (0.903-3.088)	0.102	—	—
Tumor size, cm				
≤5	Reference			
>5	2.248 (1.126-4.491)	0.022	2.265 (1.113-4.606)	0.024
Presenting symptoms				
Breast mass	Reference			
Breast mass with pain	1.035 (0.453-2.362)	0.935	—	—
Skin dimpling or Nipple discharge	2.194 (0.848-5.675)	0.105	—	—
Surgery type				
BCS	Reference			
TM	0.656 (0.340-1.268)	0.210	—	—
Surgical margin, cm				
≥1	Reference			
<1	2.575 (1.395-4.753)	0.002	2.689 (1.438-5.027)	0.002
Adjuvant radiation therapy				
No	Reference			
Yes	0.941 (0.227-3.899)	0.933	—	—
Adjuvant chemotherapy				
No	Reference			
Yes	1.828 (0.440-7.592)	0.406	—	—

PO1-17-02

Real-world outcomes of systemic therapy for advanced triple-negative breast cancer: a tertiary centre experience

Presenting Author(s) and Co-Author(s):

S. Zhang. Breast Unit—Department of Medicine, The Royal Marsden NHS Foundation Trust, Sutton, London, UK, United States

M. Coriano. Breast Unit—Department of Medicine, The Royal Marsden NHS Foundation Trust, Sutton, London, UK, United States

C. Mac Eochagain. Breast Unit—Department of Medicine, The Royal Marsden NHS Foundation Trust, Sutton, London, UK, United States

D. Yang. Breast Unit—Department of Medicine, The Royal Marsden NHS Foundation Trust, Sutton, London, UK, United States

d. Yiu. Breast Unit—Department of Medicine, The Royal Marsden NHS Foundation Trust, Sutton, London, UK, United States

A. Ring. The Royal Marsden NHS Foundation Trust, Breast Unit - Department of Medicine, The Royal Marsden NHS Foundation Trust, London, UK/ Breast Cancer Research Division – The Institute of Cancer Research, London, England, United Kingdom

N. Battisti. The Royal Marsden NHS Foundation Trust/ Breast Cancer Research Division – The Institute of Cancer Research, London, UK, England, United Kingdom

Background

Despite recent therapeutic developments for advanced triple-negative breast cancer (aTNBC), outcomes are still suboptimal for a significant proportion of patients. Clinical trials focus on a single line of therapy and do not examine outcomes across the whole treatment pathway involving multiple lines of therapy and may not be representative of outcomes in the real world. We evaluated the efficacy of sequential lines of systemic therapies (SACT) in patients with aTNBC treated at our Institution.

Methods

We conducted a retrospective analysis of patients with aTNBC who commenced SACT at our Institution between 1/12/2011 and 31/12/2020. Patients' demographics and tumour characteristics were recorded, along with SACT regime used and treatment outcomes. Median overall survival (mOS) was calculated, as was overall response rate (ORR), median progression survival (mPFS) for each line of therapy.

Results

In total, 239 patients were eligible for inclusion, with a median age of 55 years at diagnosis of aTNBC (range 26-91). Of these, 65 (27.2%) were ≥ 65 . Two hundred and eleven patients (88.3%) had ECOG performance status (PS) 0 or 1 at first-line SACT initiation. Thirty-two (13.4%) had de-novo aTNBC. Of those with recurrent disease (N=207), 110 (53.1%) received neoadjuvant treatment in the early disease setting. Of these, only 8 (7.3%) achieved pathological complete response. In the recurrent disease cohort, 75 (36.2%) had a disease-free interval (DFI) ≤ 12 months.

There was visceral involvement in 144 (60.2%) patients and 10 (4.2%) had bone only disease. The most common histology was invasive ductal (n=142, 59.4%) at metastatic biopsy and 30 (12.6%) were germline BRCA 1/2 mutation carriers. Number of SACT lines ranged from 1 to 8,

with most patients (n=140, 58.6%) receiving 1 to 2 lines of treatment only; with 99 (41.4%) receiving ≥ 3 lines, 60 (25.1%) ≥ 4 lines and 36 (15.1%) ≥ 5 lines.

Fluoropyrimidines was most commonly used drug class in 1st and in 2nd lines (40.6% and 32.7%, respectively). Eribulin was the most common choice in 3rd line and 4th lines (37.4% and 30%, respectively). Check-point inhibitor-based therapy was used in 6.3% of patients in 1st line, 2.5% in 2nd line and 3.0% in 3rd line. Overall, 25.5% (n=61) of patients were enrolled onto clinical trials. Clinical trial enrolment was most common in third-line (12.1%, n=12).

ORR and mPFS were 42.2% (95% CI 35.7-49) and 3.7 months (95% CI 3.0-5.0) respectively in 1st line, 38.5% (95% CI 30.8-46.6) and 3.5 months (95% CI 2.8-4.0) in 2nd line, 30.2% (95% CI 21.3-40.4) and 2.5 months (95% CI 2.1-3.0) in 3rd line, 23.7% (95% CI 13.6-36.6) and 2.1 months (95% CI 2.0-2.8) in 4th line

Patients with a DFI >12 months had a longer mPFS compared to patient with DFI ≤ 12 months at 5.4 (95% CI 3.7– 6.4) and 2.75 (95% CI 2.2– 3.6) months, respectively (P=0.009). At the censor date 18 patients (7.5%) were still alive and mOS was 11.8 months.

Conclusions

Our real-world data shows that over half of patients only receive one or two lines of systemic therapy for aTNBC, emphasising the importance of therapy choice in the early line setting for aTNBC. These data are important to inform decision-making, discussions with patients and considerations of clinical trials.

Table 1.

Table 1. ORR and PFS to First, second, third and fourth-line systemic treatment.

	1 st line	2 nd line	3 rd line	4 th line
ORR (95% CI), %	42.2 (35.7–49.0)	38.5 (30.8–46.6)	30.2 (21.3–40.4)	23.7 (13.6–36.6)
PFS (95% CI), months	3.7 (3.0–5.0)	3.5 (2.8–4.0)	2.5 (2.1–3.0)	2.1 (2.0–2.8)

ORR and PFS to First, second, third and fourth-line systemic treatment.

PO1-17-03

Real-world evidence of Trastuzumab biosimilars in HER2-positive breast cancer: Evaluating utilization, efficacy, and safety in Taiwan

Presenting Author(s) and Co-Author(s):

Y. Lo. Department of General Surgery, Kaohsiung Veterans General Hospital, United States

Y. Tzeng. Kaohsiung Veterans General Hospital, United States

Purpose

Biosimilars have emerged as a promising alternative to reference biologic products for the treatment of cancers and immunological diseases. With regard to breast cancer, trastuzumab, a reference monoclonal antibody biologic, has been the standard of care for early and advanced HER2-positive breast cancer since 1998. Trastuzumab biosimilars, which provide comparable efficacy at a lower cost, have the potential to reduce financial burden on patients and healthcare systems and improve patient access to HER2-targeted therapy. This study aimed to evaluate the utilization, efficacy, and safety of trastuzumab biosimilars in HER2-positive breast cancer patients at Kaohsiung Veterans General Hospital. **Methods**

A total of 113 HER2-positive breast cancer patients were enrolled between February 2020 and December 2022 and treated with trastuzumab biosimilars (OGIVRI®, trastuzumab-dkst). Of these, 44 were in the neoadjuvant group, 27 in the adjuvant group, and 42 in the metastatic group. Clinical outcomes were evaluated, including pathological complete response (pCR) rate in the neoadjuvant group, objective response rate (ORR) and clinical benefit rate (CBR) in the metastatic group, and safety profile in all groups. **Results**

In the neoadjuvant group, 18 out of 44 evaluable patients achieved pathological complete response after surgery, resulting in a pCR rate of 40.90%. In the metastatic group, the ORR was 57.14% and the CBR was 90.47%. Furthermore, in the metastatic group, treatment with dual blockade using biosimilars resulted in a better ORR of 62.96%. No adverse events of cardiac toxicity were reported in any group. In the adjuvant group, longer follow-up is needed to assess efficacy. **Conclusions**

Our real-world experience suggests that trastuzumab biosimilars are a safe and cost-effective alternative to reference trastuzumab in the treatment of HER2-positive breast cancer. Biosimilar trastuzumab demonstrated efficacy in the neoadjuvant setting, while dual blockade with biosimilars resulted in better disease control in the metastatic setting. Further follow-up is necessary to evaluate the efficacy of trastuzumab biosimilars in the adjuvant setting.

PO1-17-04

Influence of regulatory agency approval of trastuzumab-deruxtecan on the diagnosis of HER2-low status at a reference cancer center in Brazil

Presenting Author(s) and Co-Author(s):

P. Vianna. Hospital Alemao OSwald Cruz, United States

V. Alves. Hospital Alemao OSwald Cruz, United States

P. Exman. Hospital Alemao OSwald Cruz, United States

BACKGROUND HER-2 low status is defined by immunohistochemistry (IHC) expression for human epidermal growth factor receptor 2 (HER-2) 1+ or IHC 2+ without gene ERBB2 amplification. HER2-low breast cancers (BC) accounted for approximately 55% of all cases, and among hormone receptor positive (HR+) tumors it represents up to 60% of patients (pts), while 10-20% in triple negative tumors (TNBC). Trastuzumab-deruxtecan (T-dxd) has been FDA approved for HER-2 low breast cancer after Destiny-Breast 04 trial (DB04) demonstrated a robust overall survival benefit either in HR+ or TNBC heavily pre-treated pts. The Brazilian Health Regulatory Agency (ANVISA) has later approved T-dxd for HER-2 low BC. However, due to its dynamic nature and subjectivity, the definition of HER-2 low status still lacks better criteria. This study aims to evaluate whether HER-2 low status diagnosis was impacted according to the time of the diagnosis - before DB04 publication and after ANVISA drug approval - in a reference cancer center in Brazil. **METHODS** This retrospective study was conducted in a single institution in Sao Paulo, Brazil. Pts diagnosed with BC between October 1st 2021 to June 1st 2023 were classified in 2 groups according to the time of diagnosis. Group 1 (g.01) included those who were diagnosed between October 1st 2021 until DB04 publication in July 7th 2022; and Group 2 (g.02) included pts diagnosed after ANVISA T-dxd approval on October 31st, 2022 until June 1st 2023. All pathological analysis of the primary breast tumor was performed by 2 experienced breast pathologists. HER-2 IHQ Score was defined according to ASCO/CAP guideline 2018. The primary endpoint was to evaluate the proportion of patients who were defined as HER-2 low according to the time of diagnosis. Secondary endpoint consists in evaluate change in pathologists practice to distinguish IHC 1+ results from 0 after the definition of HER-2 low. To compare the categorical variables between the groups, the Chi-square test was used. P values below 0.05 were considered statistically significant. Statistical analyses were carried out with the R program (R Foundation, Vienna, Austria). **RESULTS** A total of 713 pts with diagnosis BC were included in the study, 401 (56%) in g.01 and 312 (44%) in g.02. Overall, before DB04 publication, the diagnosis HER "Negative-NOS" without subdivision in score 0 or 1 was found in 127 (31.7%), but only in 27 (8.7%) reports in g.02 ($p=0.007-13$). HER-2 low status was observed in 12.2% in g01 and in 33.3% of the pts in g.02 ($p < 0.00001$). Specifically, negative score 0 was found in 45.6% of pts in g.01 and 44.6% in g.02 ($p= 0.014$). A significant difference was also observed among pts with negative Score 1+ between groups (6.0% vs 21.2%, $p=0.009-3$), as shown in Table 1. No significant difference was seen in the frequency of HER2 score 2+ and score 3+ between g.01 and g.02. **CONCLUSION** The recent impact of a highly effective treatment derived from definition of HER-2 low BC led to a greater relevance in differentiating IHC 1+ from IHC 0, both considered HER negative by ASCO/CAP protocols. Distinguishing between HER2 0 and 1+ is subject to considerable interobserver variability , and the time of regulatory approval demonstrated a direct influence on the HER-low diagnosis.

Table 1

	Group		
HER2 IHQ results	Group 1	Group 2	p-value
Negative (NOS)	127	27	0.007 ⁻¹³
Negative (Score 0)	183	139	0.014
Score 1+	24	66	0.009 ⁻³
Score 2+	25	38	0.101
Positive (Score 3+)	42	42	>0.999
Total	401	312	

Distribution of HER2 IHQ results in Group 1 and Group 2

PO1-17-05

Real-world effectiveness of palbociclib plus aromatase inhibitors (AI) in metastatic breast cancer patients with cardiovascular diseases

Presenting Author(s) and Co-Author(s):

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

X. Liu. Pfizer Inc, United States

B. Li. Pfizer Inc, United States

L. McRoy. Pfizer Inc, United States

C. Chen. Pfizer Inc, United States

D. Makari. Pfizer Inc., New York, New York, United States

R. Layman. The University of Texas MD Anderson Cancer Center, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

Background Breast cancer survivors are at risk for mortality from cardiovascular diseases (CVD). CVD and their treatments can impact breast cancer treatment selection and clinical outcomes. A cyclin dependent kinase 4/6 inhibitor (CDK4/6i) combined with endocrine therapy (ET) is more effective than ET alone for hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2 \square) metastatic breast cancer (MBC). CDK4/6i plus ET is now the standard of care in the first-line setting for HR+/HER2 \square MBC. However, data on the effectiveness of CDK4/6i in MBC patients with CVD are limited. We compared overall survival (OS) and real-world progression-free survival (rwPFS) of palbociclib plus AI (PAL+AI) vs AI alone in HR+/HER2 \square MBC patients with CVD in routine US clinical practices. **Methods** The Flatiron Health longitudinal database contains electronic health records from >280 cancer clinics, representing >3 million actively treated cancer patients in the US. Using the Flatiron database, we conducted a retrospective analysis of 469 patients with HR+/HER2 \square MBC and CVD who started PAL+AI or AI as first-line therapy between February 2015 and March 2020. CVD prior to the initiation of PAL+AI or AI were identified based on their definitions within the National Cancer Institute-Comorbidity Index (NCI-CI), including myocardial infarction, congestive heart failure, peripheral vascular diseases, and cerebrovascular diseases. Patients were assessed from start of PAL+AI or AI to September 30, 2020 (data cutoff date), death, or last visit, whichever came first. OS was defined as months from start of PAL+AI or AI to death. rwPFS was defined as months from start of PAL+AI or AI to death or disease progression, evaluated based on clinical assessment or radiographic scan/tissue biopsy. Stabilized inverse probability treatment weighting (sIPTW) as primary analysis was used to balance baseline demographics and clinical characteristics. Cox proportional-hazards models were used to estimate the relative effectiveness of PAL+AI vs AI alone. **Results** Of the 469 eligible patients, 160 (34.1%) were treated with PAL+AI and 309 (65.9%) were treated with AI alone. Compared with AI-alone patients, those treated with PAL+AI were younger and were more likely to have de novo MBC, ≥ 2 metastatic sites, and lung/liver involvement. After sIPTW, patient characteristics were generally balanced. After sIPTW, median OS (95% confidence interval [CI]) was 40.7 months (30.9 \square 56.0) in PAL+AI patients and 26.5 months (23.3 \square 37.3) in AI patients (hazard ratio [HR]=0.732, 95% CI=0.537 \square 0.997, p=0.0476). Median rwPFS (95% CI) was 20.0 months (11.7–27.5) in PAL+AI patients and 12.5 months (9.7 \square 18.3) in AI patients (HR=0.679, 95% CI=0.512 \square 0.900, p=0.0070). Consistent results were observed with multivariate Cox proportional-hazards models as sensitivity analysis. See Table for baseline

patient characteristics and outcome results. Conclusions First-line PAL in combination with AI is associated with prolonged OS and rwPFS in patients with HR+/HER2- MBC and CVD in a real-world setting compared with AI alone. Further studies with larger cohorts and comprehensive assessments of comorbidities are needed to provide additional evidence of outcomes and safety of CDK4/6i plus AI for MBC patients with various comorbid conditions in routine clinical practice.

Table. Baseline patient characteristics and effectiveness outcomes		
Variable	PAL+AI (n=160)	AI alone (n=309)
Median age, years	72.0	77.0
Female sex, n (%)	157 (98.1)	303 (98.1)
White, n (%)	103 (64.4)	218 (70.6)
African American, n (%)	22 (13.8)	40 (12.9)
Metastatic sites ≥ 2 , n (%)	74 (46.3)	83 (26.9)
Lung/liver involvement, n (%)	50 (31.3)	74 (24.0)
Bone-only disease, n (%)	55 (34.4)	135 (43.7)
De novo MBC, n (%)	62 (38.8)	87 (28.2)
ECOG PS 2-4, n (%)	37 (23.1)	76 (24.6)
Median NCI-CI score	0.94	0.95
Median follow-up, months	19.9	18.9
Outcomes, months (95% CI)		
Unadjusted median OS	52.1 (34.0–58.7)	26.5 (23.3–35.4)
After sIPTW, median OS	40.7 (30.9–56.0)	26.5 (23.3–37.3)
Unadjusted median rwPFS	17.7 (11.7–26.9)	12.8 (9.8–18.5)
After sIPTW, median rwPFS	20.0 (11.7–27.5)	12.5 (9.7–18.3)

AI, aromatase inhibitor; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MBC, metastatic breast cancer; NCI-CI, National Cancer Institute-Comorbidity Index; OS, overall survival; PAL, palbociclib; rwPFS, real-world progression-free survival; sIPTW, stabilized inverse probability treatment weighting.

PO1-17-06

Driving diversity in research participation with ShareForCures™, a patient-centered, nationwide breast cancer research registry to improve outcomes

Presenting Author(s) and Co-Author(s):

J. Jourquin. Susan G. Komen, Dallas, Texas, United States

S. McCoy. Susan G. Komen, Dallas, Texas, United States

B. Segarra. University of Puerto Rico, San Juan, Puerto Rico

E. Marks. Susan G. Komen, Dallas, Texas, United States

C. Proctor McIlwain. Susan G. Komen, Dallas, Texas, United States

B. Kazar. Susan G. Komen, Dallas, Texas, United States

M. Troester. UNC-Chapel Hill, United States

K. Sabelko. Susan G. Komen, Dallas, Texas, United States

M. Bondy. Epidemiology and Population Health, Stanford University School of Medicine, Stanford, California, United States

Background The lack of diversity in research and small and siloed datasets have led to a lack of real-world evidence, limiting our ability to practice precision medicine and optimize treatments and care for all breast cancer patients. Susan G. Komen,® a breast cancer advocacy organization and the largest non-profit breast cancer funder outside the U.S. government, launched ShareForCures™ (SFC), a secure, patient-centered research registry. The registry aims to engage breast cancer survivors from diverse backgrounds as research partners to facilitate sharing of their data to drive innovative breast cancer research and improve outcomes. SFC is IRB-approved and open to any adult living in the U.S. and diagnosed with breast cancer. SFC is designed to be easy to join and accessible online. Participants provide survey information about their diagnosis, quality of life, lifestyle, family history, etc. Some of them will be asked to provide a saliva sample, and their medical records will be retrieved. **Methods** Patient advocates have driven every aspect of the development of SFC, from serving on its governance council to participating in focus groups and beta-testing the platform build. Most important to the success of the registry was to ensure we worked with community partners to conduct breast cancer survivor focus groups and to solicit views and expectations about patient-centered research engagement. Those focus groups were conducted in 2020 and 2021 in-person (N=4) and virtually (N=8) across the U.S., with three conducted in Spanish. The findings that emerged from the focus groups informed the establishment of SFC, from governance and technology implementation to platform features and processes. For feedback on pre-enrollment information, we invited 432 diverse breast cancer survivors to participate in an audience testing of two versions of a SFC landing page, a flyer, and a social media post. One version was designed to be more technical and the other more inspiring/motivational. Finally, we pilot tested SFC with 56 breast cancer survivors. Those who joined provided feedback through individual debriefing sessions about the onboarding process, consent, the questionnaire (“About You”) and the SFC platform. **Results** Four main themes emerged from the focus groups (N=64 participants): tailor communications to specific groups of participants, create an environment of trust and transparency, address concerns about data privacy and security, and share news and results. Audience testing on SFC materials revealed the majority liked positive personal messaging, although technical messaging highlighting the science, research, and data was also favorably reviewed. Participants ranked privacy and data security as priority concerns. Of the 56 breast cancer survivors invited to participate in the pilot testing of

SFC, 31 fully onboarded, three started but did not complete onboarding, and six declined. To fully onboard, participants had to accept the informed consent and medical records release forms and complete the "About You" questionnaire. They indicated the process and online platform were easy, and the dashboard was an important feature for participants to stay engaged. They also confirmed focus group emphasis on clarity regarding SFC research goals and importance of sharing results. Conclusions All individuals who provided feedback expressed interest in sharing their experiences, inspiring others' experiences, and accelerating research. They understood that this research may not benefit them directly but that it could benefit others. The results indicate that people are willing to participate in research if asked. Komen's patient-centered approach of involving patients at all steps of developing SFC fosters trust, transparency and engagement that will enhance SFC's impact.

PO1-17-07

Invasive disease-free survival as a surrogate for overall survival in patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative early breast cancer: a real-world analysis

Presenting Author(s) and Co-Author(s):

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

L. Hart. Atrium Health/Wake Forest Baptist Comprehensive Cancer Center, Fort Myers, Florida, United States

P. Razavi. Memorial Sloan Kettering Cancer Center, New York, New York, United States

W. Janni. Department Gynecology and Obstetrics, University of Ulm, Ulm, Baden-Wuerttemberg, Germany

L. Schwartzberg. William N. Pennington Cancer Institute - Renown Health, United States

A. Danyliv. Novartis Pharma AG, Basel, Switzerland, United States

J. Mora Payan. Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, United States

I. Ferrusi. Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, United States

R. Adhikary. Novartis Healthcare Pvt. Ltd., Hyderabad, Telangana, India, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

Background: Although the goal of treatment is to improve overall survival (OS), in the adjuvant setting, disease-free survival (DFS) is an important endpoint because DFS risk reduction may reduce mortality risk. After introduction of the STEEP criteria, invasive DFS (iDFS) was adopted as an objective, well accepted primary endpoint in early breast cancer (EBC) trials. This analysis evaluated iDFS as a surrogate for OS in the HR+/HER2– EBC adjuvant treatment setting using real-world data. **Methods:** This retrospective analysis of the ConcertAI Patient360 database contains deidentified electronic medical records of patients (pts) treated at US academic and community oncology clinics from Jan 1, 1995 to Apr 30, 2021. The cohort included pts with AJCC (8th ed.) stage II-III (if IIIB or IIIC, confirmation was required on residual tumor status; pathological and/or clinical staging [pathological stage was prioritized if both existed in the record]) HR+/HER2– EBC who had surgery and initiated adjuvant endocrine therapy (ET); ovarian function suppression was permitted. iDFS (disease recurrence, metastasis, second primary tumor, or death) and OS (death due to any cause) were defined as time between ET start and first qualifying event. Pts not experiencing an event were censored at data cutoff or maximum follow-up (whichever was first) for iDFS and maximum follow-up for OS. Correlation analyses between individual iDFS and OS times were performed using Pearson and Spearman correlations and an iterative multiple imputation (IMI) algorithm. Subgroup analyses were conducted by first ET, menopausal status (imputed as 50 years if missing), stage, nodal status, prior (neo)adjuvant chemotherapy, and prior radiation. **Results:** In total, 3133 pts were analyzed. Mean (SD) age (index or ET initiation date) was 58.4 (12.4) years; 98.8% of pts were female, 29.9% were premenopausal, 80.9% had stage II disease, 57.1% had nodal involvement, and 41.6% and 48.8% had received (neo)adjuvant chemotherapy and radiation therapy. Overall, 1854 and 653 pts received nonsteroidal aromatase inhibitors and tamoxifen only. The median follow-up time was 55.1 months for iDFS and 68.2 months for OS. The iDFS (1103 events [35.2%]) rates were 88.9% and 73.9% at 2

and 5 years. The OS (554 events [17.7%]) rates were 97.4% and 90.5% at 2 and 5 years. There was a significant and high correlation (>0.85 based on IQWiG 2011 guidelines) between iDFS and OS in the overall cohort (Pearson 0.91, $P < .001$; Spearman 0.88, $P < .001$) with 82% of OS variation explained by iDFS (least square $R^2=0.82$; Table). Results were confirmed by IMI rho (0.83, $P < .001$), which is interpreted as very strong (>0.8). Results were consistent among all reported subgroups; Pearson and Spearman correlations exceeded 0.85 and IMI exceeded 0.8, except for pts with stage III disease where correlation remained high (Pearson 0.88, $P < .001$) or medium/strong (Spearman 0.84, $P < .001$; IMI 0.79, $P < .001$) and where most censoring was observed (38.2% of pts). Conclusions: This retrospective cohort analysis demonstrates a very strong pt-level surrogacy between iDFS and OS among pts with HR+/HER2- EBC treated in a real-world, US-based, academic and community setting. The findings complement the trial-level surrogacy from prior analyses using data from randomized controlled trials and support iDFS as a surrogate endpoint for OS in HR+/HER2- EBC trials.

Table. Correlation Analysis Results*

Criteria	Sub-criteria	N [†]	Pearson R (95% CI)	Spearman rho (95% CI)	IMI rho (95% CI)	Censoring
Overall cohort		3130	0.91 (0.9-0.91)	0.88 (0.87-0.89)	0.83 (0.79-0.86)	26.4%
Endocrine therapy	NSAI first	2048	0.92 (0.92-0.93)	0.89 (0.88-0.9)	0.83 (0.79-0.87)	27.0%
	Tamoxifen first	1036	0.88 (0.87-0.9)	0.87 (0.85-0.88)	0.81 (0.72-0.87)	25.7%
Menopausal status	Premenopausal	936	0.87 (0.86-0.89)	0.86 (0.84-0.88)	0.80 (0.7-0.87)	22.7%
	Postmenopausal	2194	0.92 (0.92-0.93)	0.89 (0.88-0.9)	0.84 (0.80-0.87)	28.0%
Stage	II	2533	0.91 (0.91-0.92)	0.89 (0.88-0.9)	0.83 (0.79-0.87)	23.6%
	III	597	0.88 (0.86-0.9)	0.84 (0.82-0.86)	0.79 (0.71-0.85)	38.2%
Tumor node involvement	Yes	1766	0.90 (0.89-0.91)	0.88 (0.87-0.89)	0.82 (0.77-0.85)	29.1%
	No	1318	0.92 (0.91-0.92)	0.89 (0.88-0.9)	0.85 (0.79-0.89)	23.1%
(Ne)adjuvant chemotherapy	Yes	1269	0.91 (0.90-0.92)	0.87 (0.86-0.89)	0.84 (0.78-0.88)	26.9%
	No	1861	0.90 (0.89-0.91)	0.88 (0.87-0.89)	0.83 (0.78-0.87)	26.1%
Radiation therapy	Yes	1526	0.91 (0.90-0.91)	0.89 (0.88-0.9)	0.84 (0.79-0.88)	27.0%
	No	1604	0.91 (0.90-0.92)	0.87 (0.86-0.89)	0.82 (0.76-0.86)	25.8%

IMI, iterative multiple imputation; NSAI, nonsteroidal aromatase inhibitor

* $P < .001$ for all estimates. [†]Number analyzed; pts with OS<iDFS were excluded.

PO1-17-08

Post-approval treatment patterns and tolerability of neratinib in HER2+ early-stage breast cancer

Presenting Author(s) and Co-Author(s):

K. McCann. UCLA David Geffen School of Medicine, United States

N. Harbeck. University of Munich, Munich, Bayern, Germany

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

J. Andersen. Compass Oncology/US Oncology, Tigard, Oregon, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

G. Vidal. The West Clinic, Germantown, United States, United States

Background: While the approval status for neratinib in HER2+ early-stage breast cancer (EBC) allows its use following any trastuzumab-based therapy, the phase 3 ExteNET trial (NCT00878709), which yielded an improvement in disease-free survival, was conducted when single-agent adjuvant trastuzumab was standard of care (SOC) and before approvals of adjuvant pertuzumab + trastuzumab (FDA-approved 2017) or trastuzumab emtansine (T-DM1; FDA-approved 2019). Given recent changes in SOC for HER2+ EBC, health care professionals may seek contemporary and real-world information regarding treatment patterns and tolerability of neratinib. **Methods:** A literature review was performed to identify studies that characterized trends in use of extended adjuvant neratinib in HER2+ EBC. Due to differences in study design (interventional, observational, claims data) and populations studied, a descriptive summary of data is presented in lieu of statistical cross-study comparisons. **Results:** Following FDA approval of neratinib in HER2+ EBC in 2017, five studies have reported treatment patterns of extended adjuvant neratinib in a clinical trial or real-world setting; three studies included safety data (Table 1). In the phase 2 CONTROL trial (NCT02400476; N=563; 2015–2021), approx. 82%, 17%, and 1% of neratinib-treated pts received prior adjuvant trastuzumab, pertuzumab, or T-DM1, respectively, and prior neoadjuvant/adjuvant pertuzumab did not affect rates of grade ≥ 3 diarrhea, diarrhea-related discontinuations, or treatment duration.¹ In an interim analysis of the observational ELEANOR study (NCT04388384; N=187; 2020–ongoing), approx. 41%, 33%, and 19% of neratinib-treated pts received prior adjuvant trastuzumab (as their only anti-HER2 treatment), pertuzumab + trastuzumab, or T-DM1, respectively; corresponding rates of grade ≥ 3 diarrhea were 19%, 25%, and 14%, respectively, with no new safety signals reported.² In a chart review from the US Oncology Network (N=166; 2017–2020), approx. 99%, 43%, and 2% of neratinib-treated pts received prior adjuvant trastuzumab (56% as their sole anti-HER2 treatment), pertuzumab, or T-DM1, respectively.³ Diarrhea was mainly moderate (29%; n=43/150) or mild (22%; n=33/150), with few severe cases (1%; n=2/150).³ In a retrospective analysis employing the IQVIA claims database (N=385; 2017–2021), prior use of recently approved adjuvant agents increased over time, with rates of prior pertuzumab + trastuzumab or prior T-DM1 as high as 52% and 14%, respectively, in 2020.⁴ In the Neat-HER virtual registry (N=46; 2018–2021), approx. 41% and 11% of neratinib-treated pts received prior adjuvant pertuzumab or T-DM1, respectively.⁵

Conclusions: Recent studies have observed neratinib use in clinical practice following adjuvant

trastuzumab-based therapy including pertuzumab + trastuzumab or T-DM1. Preliminary data suggest a similar safety profile for pts with/without prior pertuzumab. These datasets are limited by the fact that: (1) some pts were enrolled in the CONTROL trial prior to launch of adjuvant T-DM1 and pertuzumab; (2) the interval between T-DM1 launch in Europe and start of the ELEANOR study was relatively short; and (3) not all toxicity measures were formally graded. A summary of available safety and effectiveness results is forthcoming. Additional interventional and non-interventional studies will continue to evaluate the safety and effectiveness of neratinib following current SOC adjuvant therapy in HER2+ EBC.

Table 1. Treatment patterns of HER2-targeted adjuvant agents preceding neratinib use in HER2+ EBC

Data source	Study type	Study dates	EBC Population	N	Prior HER2 adjuvant therapy ^a			Data available or expected	
					Neoadjuvant therapy, n (%)	Trastuzumab ^b , n (%)	Pertuzumab, n (%)		T-DM1, n (%)
CONTROL ^c	Phase 2 clinical trial	2015-2021	HER2+ (US Label)	563	317 (56.3)	480 (81.7)	95 (16.9)	4 (0.7)	Treatment Patterns, Safety, PROs ^d
ELEANOR ^e	Prospective observational	2020-ongoing	HER2+HR+/≤1 year post trastuzumab-based therapy (EU Label)	187	151 (80.7)	77 (41.2)	61 (32.6)	36 (19.3)	Adherence ^f , Treatment Patterns, Safety, Effectiveness ^g , PROs ^d
US Oncology ^h	Retrospective observational	2017-2020	HER2+HR+/≤1 year post trastuzumab-based therapy (EU Label)	166	106 (63.9)	165 (99.4) ^a	72 (43.4)	3 (1.8)	Treatment Patterns, Safety, Effectiveness
IQVIA ⁱ	Retrospective claims analysis	2017	HER2+ (US Label)	95	NR	87 (91.6)	8 (8.4)	0	Treatment Patterns
		2018	HER2+ (US Label)	234	NR	182 (77.8)	52 (22.2)	0	
		2019	HER2+ (US Label)	178	NR	74 (41.6)	102 (57.3)	2 (1.1)	
		2020	HER2+ (US Label)	125	NR	42 (33.6)	65 (52.0)	18 (14.4)	
Neat-HER ^j	Registry retrospective & prospective	2018-2021	HER2+ (US Label)	46	35 (76.1)	37 (80.4) ^a	19 (41.3)	5 (10.9)	Treatment Patterns

ITT, intent-to-treat; T-DM1, ado-trastuzumab emtansine.

aTherapies were recorded as used for adjuvant therapy in CONTROL, ELEANOR, US Oncology, and Neat-HER. CONTROL includes unpublished data. In the IQVIA claims analysis, HER2-targeted agent(s) used within 12 months prior to neratinib initiation were assumed to be adjuvant therapies. Pertuzumab use was generally taken in combination with trastuzumab as dual HER2 blockade and some pts received more than one anti-HER2 adjuvant treatment, for example T-DM1 in addition to pertuzumab plus trastuzumab.

bAdjuvant trastuzumab monotherapy or in combination with chemotherapy unless noted otherwise.

cThe proportion of patients who took at least one tablet of neratinib for ≥75% of the prescribed treatment days and did not take neratinib on days when neratinib was not prescribed.

dData forthcoming. eIncludes prior trastuzumab monotherapy and trastuzumab used in combination with pertuzumab; 93/166 pts (56%) received trastuzumab as their only anti-HER2 agent (monotherapy or in combination with chemotherapy; unpublished data).

fIncludes prior trastuzumab monotherapy as well as trastuzumab used in combination with pertuzumab.

References

References

1. Chan A, Ruiz-Borrego M, Marx G, et al. Final findings from the CONTROL trial: Strategies to reduce the incidence and severity of neratinib-associated diarrhea in patients with HER2-positive early-stage breast cancer. *Breast* 2023;67:94-101. <https://doi.org/10.1016/j.breast.2022.12.003>.
2. Harbeck N, Wrobel D, Zaiss M, et al. Interim results of the ELEANOR study: a multi-national, prospective, observational study of neratinib use for the extended adjuvant treatment of HER2-positive/HR-positive early breast cancer patients in Germany, Austria and Switzerland. *Breast Care* 2023 (submitted for publication).
3. Liffner D, O'Shaughnessy J, Zirik A, et al. SPP Real-world effectiveness and safety of neratinib in the extended adjuvant treatment of patients with HER2+ early breast cancer (eBC) in the United States community oncology setting. *ESMO Open* 2023;8(1). <https://doi.org/10.1016/j.esmoop.2023.101322>.
4. McCann KE, Cestreich N, Rowan CG, Vidal GA. CL023-051: Real-world use of neratinib in patients with HER2-positive early-stage breast cancer following prior ado-trastuzumab emtansine (T-DM1) or dual HER2 blockade with pertuzumab plus trastuzumab. *J Natl Compr Canc Netw* 2023;21(3.5):CL023-051-CL023-051. <https://doi.org/10.6004/jnccn.2022.7177>.
5. Ruogo H, Vidal G, Cestreich N, et al. 24 Real-world use of neratinib post-pertuzumab (P) and -ado-trastuzumab emtansine (T-DM1). Paper presented at: 39th Annual Miami Breast Cancer Conference 2022, Miami, FL, USA. <https://www.cancernetwork.com/view/real-world-use-of-neratinib-post-pertuzumab-p-and-ado-trastuzumab-emtansine-t-dm1>. Accessed June 13, 2023.

PO1-17-09

Real-world clinical outcomes in US patients with brain metastases secondary to HR+/HER2- metastatic breast cancer treated with abemaciclib

Presenting Author(s) and Co-Author(s):

W. Gathirua-Mwangi. Eli Lilly and Company, United States

H. Martin. Eli Lilly and Company, United States

D. He. Syneos Health, United States

S. Zheng. Eli Lilly and Company, United States

K. Sheffield. Eli Lilly & Company, Indianapolis, Indiana, United States

J. John. Eli Lilly and Company, United States

S. Rybowski. Eli Lilly and Company, United States

P. Brastianos. Harvard Medical School, Massachusetts General Hospital, United States

Background: Abemaciclib has demonstrated pharmacologically relevant intracranial concentrations and antitumor activity in patients with brain metastases secondary to HR+/HER2- metastatic breast cancer (MBC). However, clinical data is limited, and further assessments are warranted. This retrospective study describes real-world outcomes following abemaciclib initiation in patients with brain metastases secondary to HR+/HER2- MBC. **Methods:** Data were accessed from the US nationwide Flatiron Health electronic health records-derived de-identified database from 01/01/2011 to 12/31/2021. This real-world study included adult patients with a diagnosis of HR+/HER2- MBC with brain metastases prior to abemaciclib initiation. Patient and treatment characteristics were summarized using descriptive statistics. Kaplan-Meier methods were used to assess clinical outcomes from abemaciclib initiation: time to treatment discontinuation (TTD), progression-free survival (rwPFS), overall survival (rwOS). Intracranial rw best responses were also reported. **Results:** This study included 82 patients (one male) diagnosed with MBC and brain metastases prior to abemaciclib initiation and the median follow-up was 12.8 months. At data cut-off, 17 (20.7%) patients remained on abemaciclib therapy. Twenty-three (28%) patients received abemaciclib as the first line of therapy for MBC. Of the 82 patients in the study, 68 (82.9%) patients used concomitant endocrine therapy. Prior to abemaciclib initiation, 25 (30.5%) patients received chemotherapy and 33 (40.2%) patients received a CDK4 and 6 inhibitor. Most patients (67.1%) initiated abemaciclib at a dose of 150 mg twice daily. The median time from diagnosis of brain metastasis to abemaciclib initiation was 2.1 months (interquartile range:1.0, 8.0); 16 (19.5%) did not undergo surgical resection or receive radiation to the brain during this time. Sixty-six (80.5%) patients received brain radiation of which 56.1% received stereotactic radiosurgery (SRS) and 47.0% received whole-brain radiation (WBRT) either alone or in combination with craniotomy/metastasectomy, intrathecal chemotherapy, or surgery. The median TTD for abemaciclib was 7.1 months (95% confidence interval [95% CI]: 4.6, 11.3); most common reasons for discontinuation were disease progression (39.0%) or adverse events (29.3%). The median rwPFS was 9.2 months (95% CI: 6.0, 11.6) and median rwOS was 20.8 months (95% CI: 13.9, 26.0). Of the patients where response data were available (n = 51), rw intracranial clinical benefit rate (CBR; complete response [CR]/partial response [PR]/stable disease [SD] \geq 24 weeks of abemaciclib initiation) was 62.7% (Table 1). **Conclusion:** In this real-world study, most patients with brain metastases secondary to HR+/HER2- MBC who initiated abemaciclib treatment received SRS or WBRT prior to or concurrent with abemaciclib initiation. While the clinical outcomes, rwPFS and intracranial CBR were encouraging, these findings should be interpreted with caution due to the nature of the real-world study design.

Table 1. Intracranial Real-World Best Responses

Table 1. Intracranial real-world best responses

Intracranial outcomes	N = 51 n (%)
Complete response	7 (13.7)
Partial response	16 (31.4)
Stable disease \geq 24 weeks of index	9 (17.6)
Stable disease <24 weeks of index	11 (21.6)
Progressive disease	2 (3.9)
Other (radiation necrosis, undocumented, or indeterminate response)	6 (11.8)
nw Intracranial Clinical Benefit Rate	32 (62.7)

Abbreviations: n, patients in the sub-group; N, total number of patients in the population

PO1-17-10

Impact of COVID19 on neoadjuvant endocrine therapy use in breast cancer: A National Cancer Database analysis

Presenting Author(s) and Co-Author(s):

D. Makower. Montefiore Medical Center, United States

J. Choi. Department of Epidemiology and Population Health, Albert Einstein College of Medicine, United States

S. Fineberg. Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, United States

Background: Neoadjuvant endocrine therapy (NET) is associated with similar response rates as neoadjuvant chemotherapy in hormone receptor positive (HR+) breast cancer (BC), with less toxicity. While gene expression assays such as the 21-gene recurrence score (RS) have led to decreased chemotherapy use in early HR+/HER2- BC, NET is often underutilized. In 2020, the COVID19 pandemic led to disruption in oncologic care, including cancellation of surgeries. Guidelines for BC management during the pandemic recommended NET for HR+/HER2- BC patients unable to obtain surgery due to pandemic restrictions. We evaluated NET use in 2020, compared to NET use in prior years.

Methods: Female pts with nonmetastatic HR+/HER2- BC diagnosed between 2016 and 2020 were identified from the 2004-2020 National Cancer Database (NCDB). Annual number of pts receiving NET, and duration of use, were compared between years, and characteristics of pts treated with and without NET were evaluated within and across years, using Chi-squared test for categorical variables and Wilcoxon rank-sum test or Kruskal-Wallis test for continuous variables.

Results: 554,733 pts met inclusion criteria; 84.50% white, 9.19% Black, 4.06% Asian; 5.88% Hispanic. 25,553 (4.61%) pts received NET. Annual NET use increased slightly between 2016 and 2018 [3.25% vs 3.49% ($p=0.021$) vs 3.89% ($p < 0.0001$)], remained stable in 2019 (3.98%), and then increased to 8.67% in 2020 ($p < 0.0001$). Median duration of NET remained relatively stable between 2016 and 2019 [74 days (d), 68d, 73d and 61d, 2016-2019] but declined in 2020 (56d, $p < 0.0001$ for 2020 vs 2016, 2017, 2018, and 2019). Older age and greater comorbidities were associated with NET use in all years ($p < 0.0001$). No racial association with NET use was seen in 2016-2018, but Black race was associated with greater NET use in 2019 ($p=0.0122$) and 2020 ($p < 0.0001$). Lobular histology, moderate grade, larger tumor size, and node involvement were associated with increased NET use in all years ($p < 0.0001$). Progesterone receptor positivity (PR+) and lower Ki67 were associated with NET use in 2020 ($p=0.0007$ and $p < 0.0001$), but not prior. Median tumor size for pts receiving NET was smaller in 2020 (16mm) compared with prior years (22, 23, 22, and 21mm for 2016-2019, $p < 0.0001$). Annual RS use increased for all pts between 2016 (34.59%) and 2020 (43.47%). RS use in NET pts was stable in 2016 (27.79%) and 2017 (27.54%), with modest increase in 2018 (29.56%; $p 0.094$, 2016 vs 2018, $p=0.045$, 2017 vs 2018), and then increased annually in 2019 (33.28%, $p=0.0001$) and 2020 (40.64%, $p < 0.0001$). Median RS was higher in pts receiving NET than in pts who did not in 2016-2019 ($p=0.0078$, 0.0003, 0.0271, and < 0.0001), but was similar in 2020 (RS=16; IQR 11, 22).

Conclusions: Frequency of NET administration more than doubled in 2020, but duration was shorter than in prior years, possibly due to use of NET as “bridging therapy” due to COVID19

restrictions. Black race was associated with receipt of NET in 2020, possibly reflecting disparate impact of COVID19 on Black communities. NET use in 2020 was also associated with smaller tumor size, lower Ki67, and greater likelihood of PR+ disease than in prior years. Use of RS to guide NET increased annually, beginning in 2018. Association of NET with older age, greater comorbidities, higher stage, moderate grade, and lobular histology were seen in all years.

PO1-17-11

Trends in post-mastectomy reconstruction by age in Korea and among Asian-Americans

Presenting Author(s) and Co-Author(s):

S. Lee. Asan Medical Center, United States

M. KC. Yale Cancer Center, United States

H. Han. Asan Medical Center, United States

L. Kim. Yale Cancer Center, United States

M. Golshan. Yale School of medicine, Yale cancer center, United States

E. Schneider. Yale School of medicine, United States

R. Greenup. Yale School of Medicine, New Haven, Connecticut, United States

D. Lannin. Yale School of medicine, United States

H. Kim. Asan Medical Center, United States

B. Son. Asan Medical Center, United States

J. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea., United States

S. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

H. Kim. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

T. Park. Yale School of medicine, Yale cancer center, United States

Background: Post-mastectomy immediate breast reconstruction (PMIBR) has been underutilized in the elderly. This study examines the trends of PMIBR by age in a large Korean medical center and compares them to the Asian-American population in the National Cancer Database (NCDB). **Methods:** We analyzed 5,601 patients who underwent PMIBR out of 13,654 total mastectomy patients between 2001 and 2021 in a Korean Center. Patient characteristics associated with higher likelihood of receiving reconstruction were assessed and compared between patients under 60 years of age and those aged 60 years and older. Complications were investigated in 1,669 patients between 2010 and 2020. In addition, we compared this to 966,354 female patients in the NCDB from 2004-2020 with stage 0-3 breast cancer who underwent mastectomy. **Results:** The number of PMIBR at the Korean center increased almost ten-fold, but there was a discrepancy in the increase between younger and older women. In the younger group, the proportion of PMIBR rose from 13% (53/398) to 77% (508/664), while in the older group, it increased from 0% (0/60) to 26% (49/186). In the NCDB, Asian-Americans had the lowest rate of breast reconstruction (29%) compared to white (35.4%), black (30.1%), and Hispanic Americans (33.5%). As seen in the table, the rates increased in both age groups but plateaued around 2014 and remained stable until 2020. In 2020, the PMIBR rates were 37% for young Asian-Americans, 48% for young non-Asians, 14% for older Asian-Americans, and 24% for older non-Asians.

At the Korean center, patients living in a metropolitan area (42.6% vs. 39.8% $p=0.001$), having higher education (44.7% vs. 10.5% $p<0.001$), being unmarried (63.1% vs. 39.3% $p<0.001$), having no history of childbirth (53.7% vs. 39.9% $p<0.001$), having lower stage and hormone receptor-positive HER2-negative breast cancer were more likely to undergo reconstruction. These factors were all more common in the younger age group. In the NCDB, patients

receiving PMIBR were more likely to be white or non-Asian, have higher income and education, reside in a metropolitan area and in the Northeast, have less comorbidities, be treated in an academic center, and have a luminal subtype, lower stage, and private health insurance.

At the Korean center, autologous reconstruction was more common than implant reconstruction, (68.4% vs. 31.6% for younger women, and 63.3% vs. 36.9% for older women) and the complication rate was similar for both age groups. In contrast, in the NCDB, implant reconstruction was more common in both age groups, tissue-based (29% vs 31%), implant-based (40.7% vs 40%), combined (11% vs 10.8%) and other (18% vs 17.6%) for older and younger women respectively. Conclusion: Both the Korean and American data illustrate remarkably lower utilization of immediate breast reconstruction in older patients. There are notable demographic and clinical differences between age groups but negligible difference in complication rates. Further research and interventions to address barriers in older women are needed. The higher rates of PMIBR in South Korea mirrors that of white women in the northeast USA, suggesting a potential disparity for Asian-Americans.

Percentage of PMIBR over total mastectomy (with or without reconstruction) by age and race

Diagnosis (Year)	Percentage breast reconstruction by age and race					
	Asan Medical Center		NCDB			
	Korean <60 (%)	Korean ≥60 (%)	Asian <60 (%)	Non-Asian<60 (%)	Asian ≥60 (%)	non-Asian ≥60 (%)
2004	29	1	18	29	5	7
2005	29	2	21	31	4	8
2006	34	3	24	33	4	9
2007	37	3	28	36	8	11
2008	34	6	33	40	9	13
2009	38	4	36	44	7	15
2010	39	4	38	47	10	17
2011	45	8	41	49	11	19
2012	48	4	40	52	15	20
2013	49	6	44	53	12	22
2014	54	8	42	53	15	23
2015	55	11	44	53	12	24
2016	60	12	42	53	14	23
2017	67	22	42	52	12	23
2018	68	19	39	50	12	24
2019	68	19	39	49	12	24
2020	72	23	37	48	14	24
2021	77	26				

PMIBR= post-mastectomy immediate breast reconstruction; NCDB= national cancer database

PO1-17-12

The impact of treatment sequence of CDK4/6 inhibitor therapy on Metastatic Breast Cancer treatment outcomes in Real-World practice in U.S.

Presenting Author(s) and Co-Author(s):

G. Kimmick. Duke University Medical Center / Duke Cancer Institute, United States

A. Pillehvari. UNiversity of Virginia, United States

W. You. University of Vlrinia, United States

G. Bonilla. University of Virginia, United States

R. Anderson. University of Virginia, United States

Background A retrospective study to describe the actual benefit of treatment sequence with Endocrine Therapy (ET) plus cyclin D/cyclin-dependent kinases 4 and 6 (CDK4/6) therapy including as 1st-line and 2nd -line treatment for Metastatic breast cancer (MBC) patients with hormone receptor positive (HR+) and HER2 negative. We examined the extent that treatment sequence of CDK4/6 inhibitor therapy is associated with progression-free survival, and overall survival under real-world conditions. **Methods** This study used the nationwide electronic health record-derived-Flatiron Health de-identified database to estimate the real-world progression-free survival (rwPFS) and overall survival (rwOS) of MBC patients under different treatment sequence of CDK4/6 inhibitors. A total of 2,771 patients with ≥ 3 months of follow-up received either CDK4/6 inhibitor plus ET in the first-line setting (n=2,170) or ET alone in the first-line and CDK4/6 inhibitor plus ET in the second-line setting (n=601) between February 3, 2015, and November 02, 2021. We performed inverse probability weighting (IPW) to balance the baseline demographic and clinical characteristics between patients in the two groups. Kaplan-Meier method and Cox proportional hazards were used to test for an association of CDK4/6 treatment line sequence on PFS as the primary outcome and OS as the secondary outcome, adjusting for patient characteristics (e.g., age, race, comorbidities, ECOG value, Tumor site, and health insurance). **Results** Median follow-up was 25.6 months (interquartile range [IQR], 12.7–41.3) for the group with CDK4/6 inhibitor plus ET in first-line treatment and 33.1 months (IQR, 18.1–50.4) in those taking ET alone in first-line and CDK4/6 inhibitor plus ET in the second-line treatment. CDK4/6 inhibitor combination with ET as the first-line treatment was associated with significantly longer median rwPFS compared to receiving ET alone on first line and CDK4/6 inhibitor plus ET in the second line (28.0 vs 13.1 months; hazard ratio [HR], 0.40; 95% CI, 0.35–0.44; $P < 0.0001$). Median rwOS was 52 months for the group with first line CDK4/6 inhibitor plus ET and 48 months for the other group who received CDK4/6 inhibitor in the second line of treatment. However, the difference was not statistically significant (HR=0.91, 95% CI, 0.78–1.09, P-value=0.33). A propensity scores matching analysis showed similar results. **Conclusions** In this “real-world” population of patients with HR+/HER2– MBC, receiving CDK4/6 inhibitor plus ET as first line of treatment was associated with improved progression free survival compared with patients treated with ET alone in the first-line and CDK4/6 inhibitor plus ET on the second line of treatment.

PO1-18-01

Patient Preferences for HR+/HER2- Metastatic Breast Cancer Treatments in Italy: A Qualitative Assessment

Presenting Author(s) and Co-Author(s):

G. Arpino. Federico II University Naples - Italy, United States

C. De Angelis. University of Naples Federico II, United States

L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy

S. Igidbashian. AstraZeneca, Italy

M. Bellini. AstraZeneca, United States

S. Giuntoli. Daiichi-Sankyo, United States

X. Guillaume. Cerner Enviza, France

J. Behillil. Cerner Enviza, United States

C. Graziani-Taugeron. Cerner Enviza, United States

Objectives: Factors that influence treatment preferences of patients with hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (mBC) are being investigated using discrete choice experiment (DCE) methodology. Appropriate attributes for the ongoing quantitative online survey phase were identified by this initial qualitative pilot study. **Methods:** To generate hypotheses and inform variables of the quantitative survey, the pilot phase consisted in online telephone interviews with patients with a diagnosis of Stage IV HR+/HER2- breast cancer at various stages of treatment. Interviews focused on exploring patients' perspectives on their interaction with physicians, preferences, and treatment experiences. Transcripts were coded using NVivo software to identify key themes. The ongoing DCE online survey aims to recruit patients meeting the same selection criteria as in the qualitative phase, also at various stages of treatment. **Results:** Fifteen mBC patients (median age, 43 years [range, 29-64]), including nine chemotherapy-treated and six without chemotherapy exposure, were enrolled in the pilot qualitative study. Eight and four patients reported receiving little information about their treatment plan and their risk status beyond the risk of relapse, respectively. Most participants did not know what to expect from their therapy but expressed trust in their physician's decision in terms of treatment goals. Few patients (n=3) looked for a second opinion before starting treatment. Four out of fifteen patients declared that they were actively involved in their treatment plan decision, although all relied on their physician's knowledge and decision. Reduced symptoms and improved quality of life (QoL) were patients' main treatment goals, and side-effects and efficacy of treatment were their main concerns. When asked about the degree of acceptability of certain side effects, some participants considered hair loss and vomiting as unacceptable side effects, regardless of severity, while others considered them to be the most acceptable. This discrepancy is to be interpreted in the light of participants' own treatment journey. Severity and duration of side-effects were mentioned by three patients as acceptability factors. In a choice task, patients were asked to express preferences between two hypothetical treatments. Efficacy (n=9) and administration mode (n=6) were spontaneously deemed important for treatment selection. While assessing the difference in risk between the two hypothetical treatments, ten patients explained that the main choice feature was extended progression-free survival (PFS) rate. Risk of infection and neutropenia (n=12) were concerns expressed by most patients in the post-COVID-19 period.

Considering their substantial impact on QoL, alopecia (n=9) and vomiting (n=9) were presented by patients as particularly important, regardless of their degree of severity; whereas almost all patients reported that only severe fatigue (n=12), diarrhea (n=13) or nausea (n=13) would be an issue. These results allowed selection of the following attributes for further quantification of their preference weights in a DCE: PFS, risk of neutropenia, risk of alopecia, risk of vomiting, risk of diarrhea, risk of grade 3/4 side effects and mode of administration. Conclusions: This qualitative pilot study allowed for identification of what matters most to patients when selecting a treatment for mBC, which will be further assessed in the DCE. It also highlighted the need of patients with HR+/HER2- mBC for information about their treatment, potential side-effects, and health management. This research suggests that there is a need for patients to be more involved in treatment plans, and that taking patient preferences into account may help improve the treatment selection experiences.

PO1-18-02

Histologic grade is a better predictor of specific survival than Ki67 in localized ER+/HER2- breast cancer: a real-world study

Presenting Author(s) and Co-Author(s):

C. SÁNCHEZ. PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE, United States

C. Alejandro. Universidad tecnologica metropolitana, United States

B. Walbaum. Pontificia Universidad Catolica de Chile, United States

F. ACEVEDO. Pontificia Universidad Catolica de Chile, United States

c. constabel. Pontificia Univesidad Catolica de Chile, United States

A. saure. University of Ottawa, United States

P. Rey. Universidad tecnologica metropolitana, United States

Introduction: Breast cancer (BC) is the most common cancer in women. The determination of prognostic factors is relevant for the decision of systemic therapy. Objective: To determine, in the real world, the prognostic role of Ki67 and histologic grade (HG) in patients with non-metastatic BC in two cancer centers; an academic and a community hospital. Methodology: Retrospective analysis of a longitudinal BC patients registry. Clinicopathological characteristics and disease specific survival (DSS) of women diagnosed in stages I/II/III between the years 2012-2021 were analyzed. Results: We evaluated 3,969 cases that met the inclusion criteria. In the univariate analysis, prognostic factors significantly associated with DSS were: reason for consultation (screening vs symptoms), stage, hormone receptor status, HG and Ki67. On multivariate analysis, stage III, Ki67 $\geq 20\%$, and GH3 were significantly associated with a risk of death of 4.41, 2.52, and 1.92; respectively, regardless of the treatment center and BC subtype. However, in the hormone receptor positive (HR+)/HER2 + group the HG presented greater discriminatory power than Ki67. Hazard ratio 2.0 for both, but not statistically significant for Ki67. The ROC-AUC curves for Ki67 indicated that the best cut-off point for DSS was 20%, for the entire cohort and also for the HR+/HER2- group. Conclusions: The behavior of the prognostic variables was expected and coincided with the literature. HG seems to be a better predictor of specific mortality in HR+ BC. Ki67 showed a cut-off value consistent with that suggested by expert consensus.

PO1-18-03

Chemokine-modulating regimen (rintatolimod, IFN- α 2b, celecoxib): New strategy to drive CD8+T-cells into triple negative breast cancer .

Presenting Author(s) and Co-Author(s):

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

C. Jones. Roswell Park Comprehensive Cancer Center, United States

M. Opyrchal. Indiana University School of Medicine, United States

R. Slomba. Roswell Park Comprehensive Cancer Center, United States

K. Attwood. Roswell Park Comprehensive Cancer Center, United States

J. Wang. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

E. Cortes Gomez. Roswell Park Comprehensive Cancer Center, United States

T. O'Connor. Roswell Park Comprehensive Cancer Center, United States

E. Levine. Roswell Park Comprehensive Cancer Center, United States

P. Kalinski. Roswell Park Comprehensive Cancer Center, United States

BACKGROUND: Pathologic complete response (pCR) is critical for positive long-term outcomes after neoadjuvant chemotherapy (NAC) in triple negative breast cancer (TNBC) but is achieved only in 40-50% of patients. Combination of NAC with pembrolizumab, the new standard of care in TNBC, increases the pCR rate to 65% but is associated with significant and often permanent immune-related toxicities. Higher levels of CD8+ cytotoxic T-lymphocytes (CTLs) and low levels of regulatory T-cells (Treg) and myeloid derived suppressor cells (MDSC) in the tumor microenvironment (TME) predict improved relapse-free survival (RFS), overall survival (OS) and pCR, a surrogate marker for RFS. Locally produced chemokines CCL5, CXCL9, CXCL10 and CXCL11 are critical for CTL infiltration, while CCL22 is responsible for Treg attraction, with high CXCL9 being associated with a 3-fold higher rate of pCR after NAC. Our preclinical data show that Chemokine-modulatory (CKM) regimen, combining rintatolimod (TLR3 agonist), interferon (IFN) α 2b and celecoxib (COX-2 inhibitor), eliminates the suppressive aspects of paclitaxel-induced inflammation and induces CTL-attractants but decreases MDSC- and Treg-attractants in the TME. We hypothesized that the combination of CKM with paclitaxel-based NAC will promote selective CTL infiltration into TNBC, and along with doxorubicin/cyclophosphamide (AC), will result in higher rate of pCR, translating into improved RFS and OS. **METHODS:** In this phase I study NCT04081389, 9 pts with stage I-III TNBC and median age of 47 (37-55) years received 3 weeks of paclitaxel with CKM, followed by 9 weeks of paclitaxel alone, followed by standard dose-dense AC and surgery. Paclitaxel was given weekly IV at 80 mg/m² for 12 weeks, rintatolimod 200 mg IV, IFN- α 2b and celecoxib 200 mg oral twice daily on days 1-3 of each of the initial 3 weeks. IFN- α 2b was administered in an accelerated titration design at doses 0 or 5 million units (MU)/m² [Dose Level (DL) 1 and 2, respectively] in the first 2 pts (no intra-patient dose escalation), then 10 MU/m² [DL3] in 4 pts and then 20 MU/ m² [DL4] in 3 pts. Day 1 pre- and post-treatment blood samples were drawn. Pre- and post-treatment (at 3 weeks) biopsies were obtained from 5 pts at DL3 and DL4. Dose-limiting toxicity (DLT) was defined as grade 3 or higher within the first 3 weeks of treatment. Primary endpoint was safety and tolerability, to determine the recommended phase II dose (RP2D) of CKM for extended efficacy study. Secondary endpoints included efficacy (pCR), along with RFS and OS. Biomarkers were analyzed in exploratory studies. **RESULTS:** Treatment was well-tolerated with mostly grade 1 or 2 treatment-related adverse events (TRAEs) and no DLTs. Grade 3 TRAE were neutropenia (3/9), attributed to CKM (1/9) or

paclitaxel (3/9), pneumonia (1/9) and anemia (1/9) attributed to AC. Paclitaxel- or AC-related toxicities were not higher than expected. There were no delayed or immune-related toxicities beyond treatment. 5/9 (56%) pts attained pCR, and 1 additional pt had ypTmic at the time of surgery. There was consistent ($p=0.07$) selective increase in CD8 α (CTL marker) in post-treatment tumor biopsies with concomitant decrease in CD8 α in the blood ($p=0.04$) measured by RT-PCR. RNA sequencing on the blood samples (7 pre- and post-treatment) showed that higher M2 macrophages and naïve B cells in the pre-treatment samples were associated with higher probability of non pCR (adjusted $p=0.02$ and 0.05 , respectively). CKM treatment decreased CD8 α and CD8 β post-treatment in the blood samples. Higher CD8+ T cells and NK cells in the post-treatment blood samples, were associated with higher likelihood of pCR, although this trend did not reach statistical significance. CONCLUSIONS: We have observed preliminary indications of safety and good tolerability of the combination of CKM regimen with paclitaxel, with promising pCR + ypTmic of 66%. RNA sequencing indicates that CKM may drive CD8+ T cells from the blood into the tumor.

PO1-18-04

Neoadjuvant pembrolizumab + decitabine followed by standard neoadjuvant chemotherapy for locally advanced HER2- breast cancer (NCT02957968)

Presenting Author(s) and Co-Author(s):

H. Bear. Virginia Commonwealth University, Massey Cancer Center, Richmond, Virginia, United States

X. Deng. Virginia Commonwealth University, United States

D. Bandyopadhyay. Virginia Commonwealth University School of Public Health,, Massey Cancer Center, United States

M. Idowu. Virginia Commonwealth University, Massey Cancer Center, United States

M. Kmiecik. Virginia Commonwealth University, Massey Cancer Center, Richmond, Virginia, United States

M. Williams. Virginia Commonwealth University, Massey Cancer Center, United States

G. Archer. Virginia Commonwealth University, Massey Cancer Center, United States

L. Gwaltney. Virginia Commonwealth University, Massey Cancer Center, United States

P. Dillon. University of Virginia Health System, Charlottesville, VA, USA, United States

D. Flora. St, Elizabeth Healthcare, Edgewood, Kentucky, United States

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

A. Poklepovic. Hematology Oncology & Palliative Care Virginia Commonwealth University, Richmond, Washington, United States

M. Hackney. Virginia Commonwealth University, United States

M. Ross. Virginia Commonwealth University, Massey Cancer Center, United States

H. Vachhani. Virginia Commonwealth University, Massey Cancer Center, Richmond, Virginia, United States

R. Louie. Virginia Commonwealth University, Massey Cancer Center, United States

K. McGuire. Virginia Commonwealth University, Massey Cancer Center, United States

A. Grover. Virginia Commonwealth University, Massey Cancer Center, United States

T. Rahman. Dana Farber Cancer Institute, United States

A. Hendrix. Virginia Commonwealth University, Massey Cancer Center, Richmond, Virginia, United States

Background: Higher levels of stromal tumor-infiltrating lymphocytes (sTILs) in breast cancers are associated with increased likelihood of pathologic complete response (pCR) to chemotherapy and improved outcomes. DNA methyltransferase inhibitors (DNMTi) can augment immune responses to cancers by upregulating tumor antigen and MHC expression, decreasing numbers and activity of myeloid derived suppressor cells (MDSC), and increasing responsiveness of T lymphocytes. We have shown that the DNMTi decitabine augments the effectiveness of immunotherapy against murine triple negative breast cancer (TNBC) using murine 4T1 and E0771 mammary carcinoma models.

Methods: In a single-arm phase 2 study, patients with HER2-negative breast cancer who were candidates for neoadjuvant chemotherapy (NCT) received decitabine (15 mg/m² × 4 doses

over 5 days) followed by 2 doses of pembrolizumab (pembro) (200 mg, 2 weeks apart) – collectively, window immunotherapy – prior to starting NCT. Two research biopsies were obtained: 1 prior to the window immunotherapy and 1 afterwards, prior to starting NCT. Biopsies were analyzed using established procedures to quantify sTILs and PD-L1 expression. Patients proceeded to NCT and tumor resection per standard of care and were followed up for immune-related adverse events (irAEs) and response. The primary endpoint was change in sTILs. Key secondary endpoints were occurrence of irAEs and pCR following neoadjuvant treatment. After the study was opened, reported results of a phase 3 trial (KEYNOTE 522) led to allowing patients with TNBC to receive additional pembro (200 mg q3w) concurrently with standard NCT and adjuvantly following resection (Cohort A2).

Results: 46 patients (median age 54.5 yrs, range 28-72; 71.7% White, 28.3% Black; 100% female) were enrolled and treated on study. 21 patients had TNBC and did not receive neoadjuvant pembro concurrently with NCT nor adjuvant pembro (Cohort A), 7 patients had TNBC and did receive neoadjuvant and/or adjuvant pembro (Cohort A2), and 18 patients were ER+ or PR+ and received neither concurrent nor adjuvant pembro (Cohort B). Blood samples collected after decitabine administration before the first pembro dose showed a 59% decrease ($P < 0.01$) in monocytic MDSCs compared to baseline; decrease in granulocytic MDSCs was not statistically significant. 37 patients had paired biopsies adequate for sTIL evaluation with a mean change from 23.4% to 30.3% (absolute change 6.9%, $P < 0.001$). Cohorts A/A2 experienced an absolute sTIL increase of 7.4% ($P < 0.01$); Cohort B experienced absolute sTIL increase of 6.1% ($P = 0.01$). PD-L1 expression in tumors (H-score using MoAb 22C3 clone) increased by 43% ($P < 0.01$) across all cohorts. 16 of the 39 patients (41.0%) who proceeded to resection achieved pCR ($n = 12$ of 27 [44.4%] in Cohorts A/A2 and $n = 4$ of 13 [30.8%] in Cohort B). The most frequently reported irAEs were adrenal insufficiency ($n = 5$, 10.9%), maculopapular rash ($n = 3$, 6.5%), and hypothyroidism ($n = 3$, 6.5%).

Conclusions: Treatment in the pre-neoadjuvant window with decitabine and pembro could potentially sensitize breast cancers to standard NCT by recruitment of TILs to the tumor tissue. The treatment was well -tolerated at the tested doses.

Funding: financial support and drug (pembrolizumab) were provided by Merck

PO1-18-05

Combination treatment with CDK2 inhibitor (BLU-222) and either palbociclib or ribociclib is synergistic in pre-clinical models of CDK4/6 inhibitor-resistant breast cancer

Presenting Author(s) and Co-Author(s):

L. Luo. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Navarro-Yepes. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Y. Wang. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Bui. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

N. Kettner. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Faia. Blueprint Medicines Corporation, Cambridge, MA, Cambridge, Massachusetts, United States

K. Keyomarsi. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background:

Cyclin-dependent-kinase-4/6 inhibitors (CDK4/6 inhibitors) plus endocrine therapy (ET) is the standard of care first-line treatment for patients with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC). However, since most patients progress following long-term treatment, resistance to CDK4/6 inhibitors plus ET remains a clinical problem with limited therapeutic options. Here we show that a potent and selective CDK2 inhibitor, BLU-222, while effective as a single agent, exhibited enhanced, synergistic activity when combined with palbociclib or ribociclib in both in vitro and in vivo (patient-derived xenografts-PDX) models of HR+/HER2- breast cancer resistant to CDK4/6 inhibitors. Methods:

MCF7 and T47D palbociclib-resistant (PR) breast cancer cell lines were generated by culturing cells in media supplemented with increasing concentrations of palbociclib, starting at 1.2 μ M and reaching a final concentration of 4.8 μ M in a stepwise manner over a 6-month period. The single agent activity of BLU-222 and the combination effect of BLU-222 plus palbociclib in vitro were evaluated using the highest single agent model by SynergyFinder. The efficacy of BLU-222 as a single agent or in combination with palbociclib or ribociclib was also assessed in two PDX models (PR 1 and 2) from patients with acquired resistance (i.e. progressed following >6 months of treatment) to palbociclib plus letrozole treatment, and another two PDX models (PR 3 and 4) from patients who were intrinsically resistant (i.e. progressed following < 3 months of treatment) to palbociclib plus fulvestrant or letrozole, respectively. Results:

In palbociclib-resistant MCF7 and T47D cells, protein levels of cyclin E and CDK2 were significantly upregulated, but Rb and p21 levels were downregulated compared to the parental cells. While these PR cells were completely refractory to palbociclib, they were significantly more sensitive to BLU-222. Moreover, combining BLU-222 with palbociclib demonstrated a strong synergistic effect in PR cells accompanied by enhanced apoptosis and cell cycle accumulation in G1 or G2/M phases. Consistent with these in vitro findings, combination

treatment with BLU-222 (60 mg/kg; b.i.d.) and palbociclib (50 mg/kg; q.d.) or ribociclib (50 mg/kg; q.d.) exhibited significant antitumor activity in all four PDX models, as compared to either treatment alone. The combination of BLU-222 plus the CDK4/6 inhibitor induced durable tumor regression and prolonged survival, which continued unabated following drug removal. Mechanistically, treatment of PR cells and palbociclib-resistant PDX models with BLU-222 as a single agent, resulted in the induction of p21, which can sensitize the cells to palbociclib.

Conclusions:

These results show robust activity of BLU-222 in combination with CDK4/6 inhibitors in breast cancer cell lines and PDX models resistant to CDK4/6 inhibitors, providing a strong rationale for advancing BLU-222 plus CDK4/6 inhibitor treatment to clinical development in HR-positive/HER2-negative breast cancer patients who have progressed on CDK4/6 inhibitors.

PO1-18-06

Phase 1/2a Open-label Clinical Trial of BI-1607, an Fc Engineered Monoclonal Antibody to CD32b (FcγRIIB), in Combination with Trastuzumab in Subjects with HER2-positive Advanced Solid Tumors – CONTRAST

Presenting Author(s) and Co-Author(s):

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

A. Priego. IOB Institute of Oncology, Madrid, United States

E. Garralda Cabanas. Vall d'Hebron Instituto de Oncologia, Barcelona, Spain

K. Rojas Lamito. Vall d'Hebron Institute of Oncology, Barcelona, Spain, United States

S. Lord. University of Oxford, Oxford, United Kingdom

T. Goetze. Institut of Clinical Cancer Research, UCT-University Cancer Center Frankfurt, Krankenhaus Nordwest, Frankfurt, Germany, United States

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

S. Crabb. Southampton Experimental Cancer Medicine Centre, University of Southampton, Southampton, UK, United States

M. Borggren. BioInvent, United States

I. Karlsson. BioInvent, United States

L. Mårtensson. BioInvent, United States

A. Ropenga. BioInvent, United States

I. Teige. BioInvent, United States

J. Wallin. BioInvent, Lund, Sweden

B. Frendeus. Bioinvent, United States

A. McAllister. BioInvent, United States

Background

The introduction of trastuzumab has dramatically changed outcomes in patients with human epidermal growth factor receptor 2 positive (HER2+) cancer. However, primary or acquired resistance to trastuzumab has been increasingly recognized as a major obstacle in the clinical management of this disease. Combination of anti-HER2 antibodies with other immunotherapies is likely to improve the quantity and quality of responses.

BI-1607 is a human monoclonal antibody (mAb) targeting FcγRIIB (CD32b) with antagonistic function capable of blocking the inhibitory function of FcγRIIB on immune effector cells. BI-1607 has been engineered to lack a glycan in position N297Q in the constant domain (Fc), and thus cannot interact with FcγRs through its Fc. Given its high specificity and affinity for FcγRIIB, BI-1607 blocks other antibodies' binding to FcγRIIB. As a result, BI-1607 is expected to shift tumor cells coated antibodies (here anti-HER2) to selectively engage activating FcγRs, thus augmenting FcγR-dependent therapeutic activity (ADDC, ADCP).

Tumor-associated macrophages express high levels of FcγRIIB and are a major target of BI-1607 in the tumor microenvironment. This concept was demonstrated in preclinical in vivo models showing increased efficacy of the combination therapy with the murine surrogate of BI-1607 and an anti-HER2, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and an anti-CD20 (rituximab) as compared to monotherapy.

It is important to note that BI-1607 will have no single-agent activity. Instead, its clinical use will be in combination with other immunotherapies and tumor-targeting antibodies such as trastuzumab.

The choice of trastuzumab as the combination agent in this trial was based on promising preclinical studies, a recognized need for additional options for those patients who fail to respond or stop responding to trastuzumab, and promising results from the newly approved Fc-engineered anti-HER2 mAb margetuximab. Ultimately, if shown to be safe and effective in combination with trastuzumab, BI-1607 can also be used in combination with other cytotoxic or immunomodulatory antibodies for cancer treatment.

Methods

This is a Phase 1/2a, first-in-human, open-label, multicenter, dose-escalation, consecutive-cohort study of BI-1607 in combination with trastuzumab in subjects with HER2+ advanced solid tumors. Phase 1 aims to assess safety and tolerability and to determine the RP2D of BI-1607 in combination with trastuzumab. Phase 2a will explore efficacy at RP2D of BI-1607 in combination with trastuzumab in two separate expansion cohorts, a) in subjects with locally advanced or metastatic HER2+ breast cancer and b) in subjects with HER2+ metastatic gastric or gastroesophageal junction adenocarcinoma.

Eligible patients must have a HER2+ locally advanced unresectable or metastatic solid tumor and have received standard of care or be intolerant to standard of care antineoplastic therapy, with progressive disease after the last line of treatment.

Accrual/Planned Accrual

As of June 22nd, 2023 10 patients have been treated into trial and dosed with BI-1607 and trastuzumab at doses from 75-900 mg every 3 weeks (Q3W) in Phase 1. Phase 2a will enroll 15 subjects each in two cohorts of HER2+ advanced/metastatic breast cancer or HER2+ gastric/GEJ adenocarcinoma respectively.

For information regarding the study, please contact: anna.ropenga@bioinvent.com

PO1-18-07

Phase I trial of combination pembrolizumab and ruxolitinib in metastatic triple negative breast cancer

Presenting Author(s) and Co-Author(s):

A. Kassi. Arizona State University / Department of Surgery, Florida Atlantic University, United States

J. Carmona. Arizona State University, United States

S. Green. Arizona State University, United States

H. Kosiorek. Mayo Clinic Arizona, United States

M. Barrett. Mayo Clinic Arizona, United States

B. Pockaj. Department of Surgery, Mayo Clinic Arizona, United States

D. Northfelt. Mayo Clinic, Phoenix, Arizona, United States

K. Anderson. Department of Hematology/Oncology, Mayo Clinic Arizona, United States

BACKGROUND: The amplification of genes PDL-1, PDL-2, and JAK2 on chromosome 9p24, known as the PDJ amplicon, has been identified in 15% of triple negative breast cancer (TNBC) and is associated with tumor infiltrating lymphocytes and elevated JAK2 mRNA, suggesting a coordinated inflammatory response in TNBC. Adding pembrolizumab to chemotherapy in KEYNOTE trials 355 and 522 has validated the use of PD-1 blockade in TNBC and redefined the standard of care. Despite preclinical data suggesting a role for targeting the IL-6/JAK2/STAT3 pathway, the JAK1/JAK2 inhibitor ruxolitinib has not shown efficacy as a single Agent in breast cancer. This is the first phase I clinical trial evaluating the combination of pembrolizumab and ruxolitinib in the treatment of metastatic TNBC. **METHODS:** We conducted a phase I clinical trial with accrual from 2018 to 2023 at Mayo Clinic Arizona. Patients (n=12) received 200 mg of IV pembrolizumab per cycle (every 3 weeks) with 3+3 dose escalation of oral ruxolitinib twice a day (dose level 0: 10 mg PO BID, level 1: 15 mg PO BID, level 2: 20 mg PO BID). The primary endpoint was to determine the maximum tolerated dose (MTD) of ruxolitinib and secondary endpoints were treatment safety and efficacy. Clinical response was assessed by computed tomography of the chest, abdomen, and pelvis every 3 cycles. PD-L1 expression in tumor was measured by immunohistochemistry (IHC). The effect of the combined therapies on T and B cell populations were assessed by flow cytometry and antibody profiling of 695 tumor antigens and 8 viral antigens by nucleic acid protein programmable array.

RESULTS: Twelve female patients with chemotherapy refractory metastatic TNBC were treated on study. All received 200 mg IV pembrolizumab every cycle. Due to rapid disease progression of three patients early after treatment initiation, eligibility was restricted to prohibit patients with extensive pulmonary disease or elevated LDH. Those patients were excluded from efficacy or correlative analysis. The most common toxicities were transaminitis (n=12), anemia/leukopenia (n=12), and fatigue (n=9). The majority of adverse events were grade 1 and occurred at dose level 2. There were 5 adverse events grade 3 or higher: respiratory or thoracic complications (n=3), hypertension (n=1), and abdominal pain (n=1), but MTD was not established. The median number of cycles was 4 for each dose level (range n=2.0-9.0) and the median time to progression was 3 months (range n=1.4-6.3). No patient had tumor response by RECIST v1.1 criteria and there was no association of disease stability with PD-L1 tumor expression by IHC. Circulating antibodies to tumor antigens remained stable, and viral-specific antibodies mildly decreased by month 2 in all patients at dose levels 0 and 1. Of the 7 patients reactive to TRIM21 autoantibodies, 2 patients had a transient increase at 2 months. **CONCLUSIONS:** The combination of pembrolizumab with ruxolitinib was well tolerated at all dose levels, and the

number but not the severity of adverse events increased with higher ruxolitinib dose. Two of six patients in dose level 0 and 1 had stable disease for six months on treatment, suggesting that the lower dose levels of ruxolitinib (i.e. 10 mg PO BID) may have more activity in combination with pembrolizumab.

PO1-18-10

ANNE: A phase II single-arm clinical trial to assess the feasibility and efficacy of neoadjuvant anastrozole in patients with luminal breast cancer and low proliferative index in TNM stages II and III.

Presenting Author(s) and Co-Author(s):

C. Paiva. Barretos Cancer Hospital, Barretos, Brazil
I. Oliveira. Barretos Cancer Hospital, Barretos, Brazil, United States
V. Guimarães. Barretos Cancer Hospital, Barretos, Brazil, United States
A. Faria. Federal University of Uberlândia, UFU, MG, Brazil, United States
D. Lacerda. Barretos Cancer Hospital, Barretos, Brazil, United States
A. Uema. Barretos Cancer Hospital, Barretos, Brazil, United States
N. Onari. Barretos Cancer Hospital, Barretos, Brazil, United States
B. Paiva. Barretos Cancer Hospital, Barretos, Brazil, United States
A. Antoniazzi. Barretos Cancer Hospital, Barretos, Brazil, United States
K. Oikawa. Barretos Cancer Hospital, Barretos, Brazil, United States
M. Machado. Barretos Cancer Hospital, Barretos, Brazil, United States
M. Godinho. Barretos Cancer Hospital, Barretos, Brazil, United States
C. Souza. Hospital de Câncer de Barretos, Barretos, Brazil
c. Amirati. Barretos Cancer Hospital, Barretos, Brazil, United States
G. Teixeira. Barretos Cancer Hospital, Barretos, Brazil, United States
I. de Oliveira Jr. Barretos Cancer Hospital, Barretos, Brazil, United States
M. Marques. Barretos Cancer Hospital, United States
Y. Maia. Federal University of Uberlândia, UFU, MG, Brazil, United States

Background: Neoadjuvant endocrine therapy (NET) is recommended for the treatment of invasive breast cancer (BC), particularly luminal subtypes, in locally advanced stages. Previous randomized studies have demonstrated the benefits of aromatase inhibitors (AIs) in this context. However, in clinical practice, NET is typically reserved for elderly or frail patients who may not tolerate neoadjuvant chemotherapy. Ideally, after identifying suitable candidates for NET, patients undergo tumor re-biopsy after 2 to 4 weeks of treatment, and only those with $Ki67 \leq 10\%$ proceed with NET. Limitations of this strategy include the standardization of re-biopsy and the reliability of Ki67 immunohistochemical analysis, as treatment decisions are based on these results. Objective: To evaluate the feasibility and efficacy of NET in postmenopausal patients with stage II and III luminal BC and to identify predictive biomarkers of therapeutic response. The efficacy will be measured by the rate of patients with $Ki67 \leq 10\%$ after 4 weeks and Preoperative Endocrine Prognostic Index (PEPI) score 0 on the surgical specimen. The feasibility of the study will be assessed by the acceptance rate of participating in the study (recruitment rate $\geq 50\%$) and the inclusion rate of >2 patients per month. Methods: This non-randomized phase II clinical trial includes postmenopausal women with invasive breast carcinoma, Scarf-Bloom-Richardson histological grades 1 or 2, Estrogen Receptor positive (Allred ≥ 6), progesterone receptor positive (any value), HER2 negative, Ki-67 antigen $< 50\%$ on immunohistochemistry, stages TNM II-III, with palpable tumor ≥ 2 cm, and ECOG 0-2. All eligible patients will receive anastrozole (1 mg/day) continuously until the day before the surgical procedure or exclusion from the study (in case of disease progression during endocrine

therapy). After 2 to 4 weeks, a re-biopsy of the breast tumor will be performed. If Ki67 > 10%, endocrine therapy will be suspended, and the patient will be excluded from the study and redirected to neoadjuvant chemotherapy (routine care) or immediate surgery (as per attending clinical oncologist and surgeon). If Ki67 ≤ 10%, the patient will continue to receive NET. Extended NET will be administered for up to 10 months, with monthly physical examinations (using calipers) and bimonthly breast ultrasound. The presence of stable disease on ultrasound at 4, 6, and 8 months indicates scheduling surgery within 2 months thereafter, and disease progression at any time indicates surgery within one month. Patients will complete the EORTC QLQ-C30 and its supplemental module BR45 questionnaires every 2 months. Toxicity will be assessed using CTCAE version 4.0, and patients will respond to 11 specific items extracted from the Brazilian version of PRO-CTCAE. The radiological response will be evaluated by RECIST 1.1. Blood samples for molecular analyses will be collected at baseline and during re-biopsy. MicroRNA profiles will be evaluated using Nanostring, and extracellular vesicles will be examined using ATR-FTIR to identify predictive markers of therapeutic response (Ki67 < 10%) in re-biopsy. All cases will be evaluated using PAM50 at the initial biopsy and at surgery to determine the molecular phenotype (luminal A, B, or other) and molecular response (ROR score difference). Pathologic therapeutic response will be assessed using the PEPI score in all operated cases. The sample size was calculated to be 59 patients. The study was initiated in July 2022, and since then, a total of 26 patients have been enrolled. This study is registered with The Brazilian Registry of Clinical Trials (ReBEC): RBR-5pygzjh.

PO1-18-11

Imaging of tumour microvasculature using high-resolution contrast enhanced ultrasound together with markers of proliferation/ angiogenesis/ vascular mimicry to characterise response to NACT in TNBC

Presenting Author(s) and Co-Author(s):

J. Rait. Maidstone & Tunbridge Wells NHS Trust, United Kingdom

M. Garrett. University of Kent, United States

C. Harper-Wynne. Maidstone Hospital, Kent, UK, United Kingdom

S. Saw. Maidstone & Tunbridge Wells NHS Trust, United States

M. Tang. Imperial College London, United States

P. Palanisamy. Maidstone & Tunbridge Wells NHS Trust, United States

M. TOULEMONDE. Department of Bioengineering, Imperial College London, United States

K. Cox. Maidstone & Tunbridge Wells NHS Trust, United States

Background: In the UK, triple-negative breast cancer (TNBC) comprises 10-15% of breast cancer diagnoses annually. TNBC represents a clinical challenge due to a lack of expression of three treatable drug targets, namely oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER-2). The mainstay of treatment involves the use of neoadjuvant chemotherapy (NACT) followed by surgical excision where up to 50% of patients will achieve a pathological complete response (pCR). The addition of neo-adjuvant immunotherapy may increase the pCR rate to 60%. The presence of lymphatics and blood vessels within/ around malignant tumours plays a role in cancer progression as does the formation of new blood vessels (angiogenesis). The vascular endothelial growth factor (VEGF) family and their receptors (VEGFRs) play an important role in angiogenesis as well as promoting the growth and survival of cancer cells. VEGFR is frequently overexpressed in TNBC and promotes changes in vascular endothelial cells, the basement membrane and the surrounding extracellular matrix. Co-expression of epidermal growth factor receptor (EGFR) and VEGFR enhances tumour growth and angiogenesis in an autocrine and paracrine manner. An alternate mechanism for tumour microcirculation in tumours is vasculogenic mimicry (VM). This is distinct from classical tumour angiogenesis. The presence of VM is associated with poor overall survival in breast cancer patients and anti-angiogenic treatment of TNBC may even promote tumour growth, proliferation and metastasis by stimulating VM. Conventional imaging techniques such as B-mode ultrasound and MRI are commonly used to monitor disease response in the breast but have limited accuracy in predicting pCR or residual disease. High-resolution contrast-enhanced ultrasound (HRCEUS) may offer a more accurate test to monitor TNBC response to NACT. This method utilises intravenously injected microbubbles, which consist of a gas core with an outer shell of lipid/ albumin to image tumour microvasculature as well as gross tumour morphology. Trial Design: Single-centre study to evaluate HRCEUS to image the microvasculature of TNBC tumours in patients undergoing (NACT) and correlate imaging results with established markers of angiogenesis, proliferation and vasculogenic mimicry. Eligibility Criteria: Female, 18 to 60 years, histologically confirmed invasive TNBC with planned NACT, able to consent and in the Investigator's opinion, adhering to the trial recommendations and governance. Aims:

1. To investigate if imaging changes in the tumour microvasculature indicate a response to NACT and are reflected in the expression of proliferative markers.

2. To determine whether changes in the tumour microvasculature and disease response are driven by angiogenesis +/- VM.
3. To investigate whether overall disease response and changes in the microvasculature are influenced by the basal type phenotype or germline mutations in BRCA 1/2.
4. Investigate patient satisfaction with the contrast ultrasound test.

Statistical Methods:

1. Quantify HRCEUS imaging characteristics of microvasculature at 3 treatment points. Compare this with the results of conventional imaging and the histopathological results of surgical excision at the end of NACT.
2. Quantify immunohistochemical markers of angiogenesis, proliferation and VM at three treatment points and compare this with HRCEUS.
3. Determine phenotype of all cases using immunohistochemistry to identify the basal. Perform subtype analysis to assess if the basal phenotype is associated with imaging and immunohistochemical changes in the microvasculature during NACT.
4. Test patients for germline BRCA1/2 gene mutations. Perform subtype analysis to assess if germline BRCA1/2 mutations are associated with imaging and immunohistochemical changes in the microvasculature during NACT.

Present accrual (2 patients) and target accrual (5 patients) Contact details: j.rait@nhs.net

PO1-18-12

Trial in progress: Open-label, randomized, multicenter, phase 3, ELAINE 3 study of the efficacy and safety of lasofoxifene plus abemaciclib for treating locally advanced or ER+/HER2- metastatic breast cancer with an ESR1 mutation

Presenting Author(s) and Co-Author(s):

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

S. Wander. Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

T. Bachelot. Medical Oncology, Centre Léon Bérard, Lyon, France

G. Batist. Segal Cancer Centre and McGill University Centre for Translational Research in Cancer, Jewish General Hospital, United States

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

M. Cristofanilli. Weill Cornell Medicine, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

A. de Nonneville. Institut Paoli-Calmettes, Aix Marseille Université, Centre de Recherche en Cancérologie de Marseille (CRCM), Inserm U1068, CNRS U7258, France

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

H. Parsons. Dana Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

C. Twelves. University of Leeds/Leeds Teaching Hospitals Trust, Leeds, United Kingdom, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

P. Plourde. Sermonix Pharmaceuticals, United States

D. Portman. Sermonix Pharmaceuticals, United States

S. Damodaran. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background: Patients with estrogen receptor-positive (ER+) metastatic breast cancer (BC) may develop resistance to endocrine therapy (ET), particularly following treatment with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i), potentially driven by a mutation in the ER α -coding gene, ESR1. Lasofoxifene, an oral, next-generation ET and ER breast antagonist, had potent activity in mBC xenograft models expressing ESR1 mutations, either as a single agent or

combined with a CDK4/6i. Subsequently, two phase 2 studies evaluated lasofoxifene in women with ER+/HER2- metastatic BC and an ESR1 mutation who had disease progression on previous ET and CDK4/6i. The ELAINE 1 trial showed numerically greater progression-free survival (PFS, median ~6 vs 4 months; P=0.138), objective response rate (ORR, 13% vs 3%; P=0.124), and clinical benefit rate (CBR, 37% vs 22%; P=0.117) with lasofoxifene monotherapy versus the ER degrader fulvestrant, with a favorable safety profile (Goetz MP, et al. *Ann Oncol.* 2022;33:S1387). The single-arm, ELAINE 2 trial demonstrated that lasofoxifene combined with abemaciclib was well tolerated with a median PFS of ~13 months, ORR of 56%, and CBR of 66% (Damodaran S, et al. *J Clin Oncol.* 2023;41:suppl 16; abstr 1057). Based on these data, the phase 3, registrational, ELAINE 3 trial was initiated.

Methods: ELAINE 3 (NCT05696626) is an open-label, phase 3, multicenter study evaluating the efficacy, safety, and tolerability of lasofoxifene plus abemaciclib versus fulvestrant plus abemaciclib. Key inclusion criteria are pre- and postmenopausal women and men aged ≥ 18 years; ER+/HER2-, locally advanced and/or metastatic BC (measurable and/or non-measurable disease); ≥ 1 acquired ESR1 mutation; progression on an aromatase inhibitor plus palbociclib or ribociclib as their first hormonal treatment for advanced/metastatic BC; and ≤ 1 line of chemotherapy in the advanced/metastatic setting. Patients will be randomized 1:1 to receive lasofoxifene 5 mg/day plus abemaciclib 150 mg BID, or fulvestrant 500 mg IM on days 1, 15, and 29, then 4 weekly plus abemaciclib 150 mg BID. Treatment will continue until progression, death, unacceptable toxicity, or withdrawal from the study. The primary endpoint is PFS; key secondary endpoints are ORR, overall survival, CBR, duration of response, and time to response. Time to cytotoxic chemotherapy, quality of life, and safety will also be evaluated. Blood samples for circulating tumor DNA (ctDNA) will be collected at screening, at weeks 4 and 8 and every 8 weeks thereafter, and at the final visit for genomic analyses. Outcomes with lasofoxifene/abemaciclib and fulvestrant/abemaciclib will be compared using a stratified Cox proportional hazards model and stratified logrank test. Expected PFS is ≥ 10.3 months for lasofoxifene/abemaciclib and 7 months for fulvestrant/abemaciclib (PFS hazard ratio of 0.68 at final analysis). The target sample size is 400, to achieve 90% power with a one-sided type I error rate of 0.025 after 285 PFS events. Full recruitment is expected to occur over 18 months at 125 global sites.

PO1-19-01

NRG-BR008: A Phase III Randomized Trial of Radiotherapy Optimization for Low-risk HER2-positive Breast Cancer (HERO)

Presenting Author(s) and Co-Author(s):

L. Braunstein. Memorial Sloan Kettering Cancer Center, United States

M. Mitchell. UT MD Anderson Cancer Center, Houston, Texas, United States

H. Bandos. NRG Oncology Biostatistical Center, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

W. Sikov. Women and Infants Hospital of Rhode Island Breast Health Center, United States

A. Khan. MSKCC, United States

P. Chen. Beaumont Health System, United States

P. Ganz. UCLA Jonsson Comprehensive Cancer Center, and UCLA Fielding School of Public Health, Los Angeles, California, United States

R. Jagsi. Emory University, Ann Arbor, Michigan, United States

J. White. Ohio State University, Columbus, Ohio, United States

R. Cecchini. University of Pittsburgh, Pittsburgh, Pennsylvania, United States

H. Kang. Stritch School of Medicine, Loyola University Chicago, United States

S. Puhalla. UPMC Hillman Cancer Center, United States

K. Bolton. Washington University School of Medicine, United States

E. Connolly. Columbia University Irving Medical Center, New York, New York, United States

E. Stringer-Reasor. University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, Alabama, United States

K. Gergelis. University of Rochester Medical Center, United States

T. Julian. Allegheny Health Network Cancer Institute, Pittsburgh, Pennsylvania, United States

E. Mamounas. NSABP Foundation and Orlando Health Cancer Institute, Orlando, FL, USA, Windermere, Florida, United States

N. Wolmark. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

Background: Breast radiotherapy (RT) is the standard of care for patients with early-stage breast cancer (BC) who undergo breast-conserving surgery (BCS). However, the magnitude of benefit of RT is less clear in BCS patients with low-risk disease who receive effective systemic therapy. Among patients with early-stage HER2-positive (HER2+) BC, 10-year locoregional recurrence has been reported as low as 1.5% following BCS, adjuvant chemotherapy and HER2-targeted therapy, and RT. Given these exceedingly favorable outcomes, with the addition of HER2-directed therapy, we seek to evaluate the feasibility of omitting RT among patients with early-stage HER2+ BC following BCS and appropriate systemic therapy. Methods: This is a phase III randomized trial for patients ≥ 40 years with early-stage, node-negative HER2+ (IHC/FISH) BC treated with BCS with negative margins and sentinel lymph node biopsy or axillary dissection. Patients undergoing primary surgery must have pathologic T1 (< 2 cm) N0 disease, while patients receiving neoadjuvant therapy must have clinical T1-2 (with radiographically T < 3.0 cm) N0 disease and exhibit a pathologic complete response (ypT0N0) at surgery. All patients must receive cytotoxic chemotherapy and HER2-targeted therapy, either

in the adjuvant or neoadjuvant setting. Stratification is by age (< 60; ≥60), tumor size (≤1 cm; >1 cm), estrogen-receptor status (positive; negative), and systemic therapy sequencing (adjuvant vs neoadjuvant). Patients will be randomized to standard breast RT in addition to continuation of trastuzumab to complete a year of treatment (Arm 1), or trastuzumab alone (Arm 2). Endocrine therapy will be recommended for patients with hormone-receptor positive tumors. The primary endpoint is the recurrence-free interval (RFI). Secondary endpoints include the time to ipsilateral breast recurrence, locoregional recurrence, disease-free survival, and overall survival, in addition to the 7-year ipsilateral breast recurrence rate among those not receiving RT. A health-related quality of life sub-study will assess differences in patient-reported breast pain and worry. We estimate a 7-year RFI of 97.5% with RT and allow for a clinically acceptable decrement of 3.63% without RT (7-year RFI of 93.87%; HR 2.5) to establish omission of RT as non-inferior. NRG-BR008 aims to enroll 1,300 patients over 4.5 years, yielding 80% power to detect the non-inferiority of RT omission with a one-sided $\alpha=0.05$. We expect to observe the required 38 RFI events within 6 years of additional follow-up. The NRG-BR008/HERO trial opened to accrual in March, 2023. NCT05705401. Support: U10CA180868, -180822, UG1CA189867, U24CA196067; Susan G. Komen Foundation (JR)

PO1-19-02

A phase III trial evaluating De-escalation of Breast Radiation (DEBRA) following breast-conserving surgery (BCS) of stage 1, HR+, HER2-, RS ≤18 breast cancer: NRG-BR007

Presenting Author(s) and Co-Author(s):

J. White. Ohio State University, Columbus, Ohio, United States

R. Cecchini. University of Pittsburgh, Pittsburgh, Pennsylvania, United States

E. Harris. University Hospitals Case Western Reserve University, Cleveland, Ohio, United States

E. Mamounas. NSABP Foundation and Orlando Health Cancer Institute, Orlando, FL, USA, Windermere, Florida, United States

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

P. Ganz. UCLA Jonsson Comprehensive Cancer Center, and UCLA Fielding School of Public Health, Los Angeles, California, United States

R. Jagsi. Emory University, Ann Arbor, Michigan, United States

S. Anderson. University of Pittsburgh, Pittsburgh, Pennsylvania, United States

C. Bergom. Washington University in St. Louis, St. Louis, Missouri, United States

V. Théberge. CHU de Québec – Université Laval, Québec City, Quebec, Canada

M. El-Tamer. Memorial Sloan Kettering Cancer Center, Weill Cornell Medical School, New York, New York, United States

R. Zellars. Indiana University, Indianapolis, Indiana, United States

D. Shumway. Mayo Clinic, Rochester, Minnesota, United States

G. Chen. Medical College of Wisconsin, Milwaukee, Wisconsin, United States

T. Julian. Allegheny Health Network Cancer Institute, Pittsburgh, Pennsylvania, United States

N. Wolmark. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

Background: Approximately 50% of newly diagnosed invasive breast cancers are stage 1, with the majority being ER/PR-positive, HER2-negative. Genomic assays such as the Oncotype DX® have identified patients (pts) with reduced risk of distant metastasis and without benefit from chemotherapy added to endocrine therapy, freeing them from excess toxicity. Genomic assays are also recognized as prognostic for in-breast recurrence (IBR) after BCS and could similarly allow de-escalation of adjuvant radiotherapy (RT). Reducing overtreatment is of interest to pts, providers, and payers. Methods: We hypothesize that BCS alone is non-inferior to BCS plus RT for in-breast recurrence and breast preservation in women intending endocrine therapy (ET) for stage 1 invasive breast cancer (ER &/or PR positive, HER2-negative with an Oncotype DX Recurrence Score [RS] of ≤18). Stratification is by age (< 60; ≥60), tumor size (≤1 cm; >1-2cm), and RS (< 11, 11-18). Pts are randomized post-BCS to Arm 1 with breast RT using standard methods (hypo- or conventional-fractionated whole breast RT with/without boost, or APBI) with ≥5 yrs of ET (tamoxifen or AI) or Arm 2 with ≥5 yrs of ET (tamoxifen or AI) alone. The specific regimen of ET in both arms is at the treating physician's discretion. Eligible pts are stage 1: pT1 (≤2 cm), pN0, age ≥50 to < 70 yrs, s/p BCS with negative margins (no ink on tumor), s/p axillary nodal staging (SNB or ALND), ER &/or PR positive (ASCO/CAP), HER2-negative (ASCO/CAP), and Oncotype DX RS of ≤18 (diagnostic core biopsy or resected

specimen). Primary endpoint is in-breast recurrence (invasive breast cancer or DCIS). Secondary endpoints are breast conservation rate, invasive in-breast recurrence, relapse-free interval, distant disease-free survival, overall survival, patient-reported breast pain, patient-reported worry about recurrence, and adherence to ET. We assume a clinically acceptable difference in IBR of 4% at 10 yrs to judge omission of RT as non-inferior (10-yr event-free survival for RT group is 95.6% vs 91.6% for the omission of RT group). BR007 is powered to detect non-inferiority with 80% power and a one-sided $\alpha=0.025$, assuming that there would be a ramp-up in accrual in the first two years (leveling off in Yrs 3-5); 1,670 pts (835 per arm) are required for randomization. Conservative loss to follow-up is 1% per yr. Some of the T1a pts screened may have Oncotype DX scores >18, making them ineligible for the study. In the accrual process, 1,714 pts will be required to register to ensure that our final randomized cohort is 1,670 pts. Current accrual (07-07-2023) is 555 screened and 488 randomized (~96% of predicted accrual). Support: U10CA180868, -180822, UG1CA189867, UG1CA189867; Susan G. Komen Foundation (JRW). NCT: 04852887.

PO1-19-03

The T-REX trial: a randomized international non-inferiority trial on Tailored Regional EXternal beam radiotherapy in clinically node-negative breast cancer patients with 1-2 sentinel node macrometastases

Presenting Author(s) and Co-Author(s):

S. Alkner. Lund University, United States

J. de Boniface. Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, and Department of Surgery, Capio St. Göran's Hospital, Stockholm, Stockholms Lan, Sweden

D. Lundstedt. Gothenburg University, Gothenburg, Sweden

I. Mjaaland. Stavanger University Hospital, United States

L. Rydén. Region Skane / Lund University, United States

J. vikström. Stavanger University Hospital, United States

P. Bendahl. Lund University, United States

E. Holmberg. Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, United States

H. Sackey. Karolinska Institute, United States

E. Wieslander. Lund University, United States

P. Karlsson. Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, United States

Background: Modern systemic treatment has reduced the incidence of regional recurrences and improved survival in breast cancer (BC). It is thus questionable whether regional radiotherapy (RT) is still indicated in patients with sentinel lymph node (SLN) macrometastases. Postoperative regional RT is associated with an increased risk of arm morbidity, pneumonitis, cardiac disease, and secondary cancer. Therefore, there is a need to individualize the indication for regional RT in relation to risk of recurrence. **Trial design:** In this multicenter, prospective randomized phase 3 trial, eligible patients have a clinically node-negative, estrogen receptor-positive, HER2-negative BC with 1-2 SLN macrometastases, and have not undergone completion axillary lymph node dissection. Participants are randomly assigned to receive regional RT (standard arm) or not (intervention arm). Regional RT includes the axillary levels I-III and the supraclavicular fossa. Internal mammary nodes are targeted in selected patients. After breast-conserving surgery (BCS), RT to the remaining breast is given in both groups while after mastectomy, chest-wall RT is only given in the standard arm. In the intervention arm, chest wall RT may be indicated in selected cases with extensive multifocality, according to national guidelines. RT quality assurance is an integral part of the trial. In addition, material from the primary tumor, SLN metastases and any recurrences is subjected to gene expression analysis to identify both prognostic markers for locoregional recurrence and predictive markers for the benefit of regional RT.

After confirmation of eligibility and written informed consent, patients are randomized 1:1 between the treatment arms. Allocation is stratified by trial site and breast surgery (BCS vs. mastectomy). Participation in T-REX should not affect decisions on systemic adjuvant treatment. **Eligibility criteria:** Trial inclusion and exclusion criteria are given in Table 1. **Specific aims:** The main aim of the trial is to investigate if the omission of regional RT is non-inferior to routine regional RT in clinically node-negative BC patients with estrogen receptor-positive, HER2-negative T1-2 tumors with 1-2 SLN macrometastases not receiving axillary lymph node

dissection.

Secondary aims are to investigate whether refraining from regional RT reduces arm morbidity and late RT side effects, and improves short- and long-term health-related quality of life. In addition, the use of genomic classifiers for the prognostication of locoregional recurrences and the prediction of a benefit from regional RT will be investigated. Statistical methods: Primary outcome is recurrence free survival (RFS) at five years. Non-inferiority will be declared if the outcome in the intervention arm is not more than 4.5 percentage units below the standard arm, corresponding to a hazard ratio of 1.41 assuming 88% 5-year RFS with standard treatment. Secondary outcomes include locoregional recurrence, overall survival, patient-reported arm morbidity, and health-related quality of life. Accrual: The trial will include 1350 patients in Sweden, Norway and Finland from April 2023 to December 2028. First sites have been opened in April 2023. Contact information: Primary Investigator: Sara Alkner, Skåne University Hospital, Lund University, sara.alkner@med.lu.se. Responsible for the biobank: Per Karlsson, Sahlgrenska University Hospital, Gothenburg University, per.karlsson@oncology.gu.se.

Inclusion and exclusion criteria

<i>Inclusion criteria</i>	<i>Exclusion criteria</i>
<ol style="list-style-type: none">1. Primary unifocal or multifocal invasive breast cancer T1-T2.2. Clinically N0.3. Macrometastasis (>2mm) in 1-2 lymph nodes at sentinel node biopsy.4. Oral and written consent.5. Age \geq 18 years.6. Tumor-free resection margins (no tumor on ink).7. Primary tumor ER-positive, HER2-negative.	<ol style="list-style-type: none">1. Regional or distant metastases outside the ipsilateral axilla.2. Previous RT towards the planned target area, i.e. the ipsilateral chest/lymph nodes.3. Neoadjuvant systemic therapy.4. Axillary lymph node dissection or other previous axillary surgery on the affected side.5. Prior history of invasive breast cancer.6. Pregnancy.7. Bilateral invasive breast cancer.8. Contraindication for radiotherapy or systemic treatment, if indicated. Hence endocrine treatment, chemotherapy and/or targeted therapy should at inclusion be planned to be given according to standard of care, taking age and comorbidity into consideration.9. Inability to absorb or understand the contents of the informed consent form; for example, through disability, insufficient language skills or dementia.10. Other invasive cancer within 5 years prior to breast cancer diagnosis

PO1-19-04

Dalpiciclib and tucidinostat in patients with HR+/HER2- advanced breast cancer and resistance to CDK4/6 inhibitors: A phase Ib trial

Presenting Author(s) and Co-Author(s):

T. Wang. The Fifth Medical Center of PLA General Hospital, United States

J. Zhou. The Fifth Medical Center of PLA General Hospital, United States

X. Wu. Department of Breast Cancer, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China (People's Republic)

Z. Jiang. Medicine–Oncology, The Affiliated Hospital of Military Medical Sciences (The 307th Hospital of Chinese People's Liberation Army), Beijing, China, United States

Background: Hormone receptor (HR)-positive/epidermal growth factor receptor 2 (HER2)-negative breast cancer accounts for approximately 70% of all breast cancers and is associated with a better prognosis. Estrogen plays an important role in the growth of HR-positive breast cancer, thus patients with this type of tumor are sensitive to hormone inhibitors. However, a quarter of patients will inevitably relapse. Several large clinical trials have demonstrated that the combination of CDK4/6 inhibitors and endocrine therapy (ET) as first or second-line therapy could improve the progression-free survival (PFS) and overall survival for patients with breast cancer.

In China, dalpiciclib (a CDK4/6 inhibitor) in combination with fulvestrant has been approved for patients with recurrent or metastatic HR-positive/HER2-negative breast cancer who have failed ET. Moreover, the combination of dalpiciclib and aromatase inhibitors (AI) as an initial treatment for patients with locally advanced or metastatic HR-positive/HER2-negative breast cancer has also been accepted. However, the standard treatment for patients who have failed CDK4/6 inhibitors has not been established. Histone deacetylase (HDAC) inhibitors cause alterations in gene expression in many signaling pathways associated with oncogenesis, leading to the arrest of tumor cell growth and differentiation, as well as promoting tumor apoptosis. Tucidinostat (an HDAC inhibitor) plus AI has been approved for the treatment of locally advanced HR-positive/HER2-negative postmenopausal breast cancer patients who have failed ET. Theoretically, synergistic effects may occur when HDAC inhibitors are combined with CDK4/6 inhibitors.

Currently, the clinical data on combination therapy with CDK4/6 inhibitors and HDAC inhibitors have not been reported. Herein, our study aims to explore the efficacy and safety of dalpiciclib and tucidinostat in patients with late-stage HR+/HER2- breast cancer who have failed CDK4/6 inhibitors. **Trial Design:** The present study is a single-arm, open-label, phase I, dose escalation clinical trial (NCT 05586841). Patients were assigned to four groups to receive either dalpiciclib 125mg/d and tucidinostat 25mg/BIW (group A) or dalpiciclib 125mg/d and tucidinostat 20mg/BIW (group B) or dalpiciclib 100 mg/d and tucidinostat 25mg/BIW (group C) or dalpiciclib 100 mg/d and tucidinostat 20mg/BIW (group D). The Bayesian Optimal Interval (BOIN) design was performed to determine dose-escalation and de-escalation to find the maximum tolerated dose (MTD) of dalpiciclib plus tucidinostat. **Key Eligibility Criteria:** The study is enrolling female patients who are older than 18 years, with HR-positive/HER2-negative locally recurrent or metastatic breast cancer (MBC), with Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2. Before entering this trial, all patients must have received ≤ 1 previous line of chemotherapy for recurrent or MBC, and have failed CDK4/6 inhibitor therapy. **Aims:** The BOIN design is employed to explore the optimal dose combination of dalpiciclib and tucidinostat and determine recommended doses for a phase II dose expansion clinical trial, based on prespecified dose-limiting toxicity (DLT). **Statistical Methods:** Safety will be evaluated in the safety set including all patients who

received at least one dose of study treatment and underwent at least one safety assessment. Efficacy will be assessed in the full analysis set, defined as all patients who received at least one dose of study treatment. Present and Planned Accrual: Up to 30 participants were planned to be enrolled in the present study. The first participant was enrolled on 18 January 2023. The recruitment is ongoing.

PO1-19-05

COGNITION / -GUIDE – Implementation of Precision Oncology in Early High-Risk Breast Cancer

Presenting Author(s) and Co-Author(s):

V. Thewes. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Heidelberg, Baden-Wurttemberg, Germany

L. Strassl. NCT Trial Center, National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Germany

M. Zapatka. Division of Molecular Genetics, German Cancer Research Center (DKFZ), Heidelberg, Germany, Germany

M. Hlevnjak. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Germany

C. Pixberg. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Germany

C. Maurer. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Germany

K. Smetanay. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center; University Hospital Heidelberg, Germany, Germany

C. Fremd. Medical Oncology, National Center for Tumor Diseases Heidelberg, NCT (DKFZ and University Hospital), Heidelberg, Baden-Wurttemberg, Germany

L. Michel. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Germany

S. Heublein. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, United States

C. Wagner. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Germany

J. Suppeln. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Germany

L. Buschhorn. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Germany

A. Stenzinger. Department of General Pathology, University Hospital Heidelberg, Heidelberg, Germany, Germany

R. Haidinger. Brustkrebs Deutschland e.V., Hohenbrunn, Germany, Germany

E. Schumacher-Wulf. Mamma Mia! – The cancer magazines, Cologne, Germany, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

P. Wimberger. Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität and NCT Dresden, Dresden, Germany, Germany

J. Blohmer. Charité - Universitätsmedizin Berlin, Germany

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

W. Janni. Department Gynecology and Obstetrics, University of Ulm, Ulm, Baden-Wuerttemberg, Germany

R. Schlenk. NCT Trial Center, National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Heidelberg, Germany

P. Lichter. Division of Molecular Genetics, German Cancer Research Center (DKFZ), Heidelberg, Germany, Germany

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

Background:

The concept of precision oncology is nowadays increasingly implemented into clinical practice but is predominantly restricted to the metastatic setting limiting the benefits to prolongation of progression-free-survival (PFS). Implementation of precision oncology at an earlier disease stage with less tumor burden, heterogeneity and a higher capacity of tumor lesions to inform on the molecular tumor landscape holds the promise to impact cure rates. Methods:

The prospective COGNITION /-GUIDE precision oncology platform encompasses the COGNITION diagnostic multi-omics biomarker screening platform (NCT05906407) linked to the multi-arm phase II COGNITION-GUIDE umbrella trial (NCT05332561).

Based on a two-step consenting procedure, patients with early breast cancer (eBC) and poor response towards standard-of-care (SOC) neoadjuvant chemotherapy (NACT) are first enrolled into the COGNITION diagnostic platform. Residual bulk tumors are subjected to whole-genome- (WGS) / whole exome- (WES) and RNA-sequencing to enable streamlined detection of a rigorous biomarker-framework for subsequent genomics-guided arm allocation. Pilot analyses revealed that 78% (81/104) of high-risk tumors (TNBC or HER2+ BC with non-pCR or HR+/HER2- BC with non-pCR and CPS-EG score ≥ 3 , or ypN+ and CPS-EG score ≥ 2) can be successfully sequenced and discussed within an interdisciplinary molecular tumor board. In 67% (70/104) eligible biomarker-profiles could be identified for potential biomarker-guided therapeutic intervention.

In a second step, having completed all standard-of-care neoadjuvant and post-neoadjuvant treatments (except endocrine therapy, which can be administered simultaneously to the experimental therapy), patients can be enrolled into one of 6 biomarker-based arms in the COGNITION-GUIDE phase II trial (atezolizumab, inavolisib, ipatasertib, olaparib, sacituzumab govitecan or trastuzumab/pertuzumab).

Primary end point is invasive disease-free survival (IDFS) at 4 years after surgery in the whole study population. Secondary endpoints are overall survival (OS), IDFS in each treatment arm, distant disease-free survival (DDFS) and patient-reported outcomes (PROs). Enrollment in COGNITION-GUIDE started in Q2/2023 and 240 patients will be enrolled in 5 German sites until Q2/2027. A comprehensive biomarker discovery program is integrated on longitudinal tumor tissue and liquid biopsies for exploratory analyses.

Further clinical work and accrual will be reported at the meeting. Conclusion:

The theranostic COGNITION / -GUIDE platform moves the concept of precision oncology to a potentially curative but still high-risk stage of eBC following SOC NACT. Hence, this novel application in the field of precision oncology harbours the prospect to increase cure rates.

PO1-19-06

Physical exercise during neoadjuvant chemotherapy for breast cancer as a mean to increase pathological complete response rates: the randomized Neo-ACT trial

Presenting Author(s) and Co-Author(s):

J. de Boniface. Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, and Department of Surgery, Capio St. Göran's Hospital, Stockholm, Stockholms Lan, Sweden

C. Haddad Ringborg. Karolinska Institutet, Sweden

R. Altena. Karolinska Institutet, Stockholm, Sweden

Y. Wengström. Karolinska Institutet, Stockholm, Sweden

Introduction

In early breast cancer, neoadjuvant chemotherapy (NACT) is increasingly used. The proof of efficacy is pathologically complete response (pCR), i.e. the absence of invasive tumour in breast and lymph nodes at surgery. Today, pCR is a common endpoint in pharmaceutical trials since it is significantly associated with survival especially in triple-negative and HER2-positive subtypes. Apart from the mitigation of treatment-related toxicity and symptoms, physical exercise mediates anti-tumoral systemic effects associated with tumour regression in preclinical and clinical models. The aim of Neo-ACT is to test the hypothesis that physical exercise can improve pCR rates in breast cancer patients receiving NACT.

Method

The Neo-ACT trial is an international prospective clinical trial, randomising T1-3N0-2 breast cancer patients planned for NACT to either a home-based physical exercise intervention supported by a mobile application or routine care. The primary endpoint is pCR; secondary endpoints are patient-reported quality of life, toxicity-related outcomes, and oncological outcomes such as Residual Cancer Burden, objective radiological tumour response, as well as overall, breast cancer-specific and disease-free survival at 2, 5 and 10 years. The intervention consists of a combination of high-intensity interval and resistance training of progressing intensity, and includes two weekly 60-min exercise sessions plus at least 150 min of moderate to vigorous physical activity per week. The Neo-ACT has been registered at clinicaltrials.gov on January 11, 2022 (NCT05184582).

Statistical methods

Patients will be randomized in a 1:1 fashion. It is anticipated that the rate of the primary endpoint pCR will be approximately 30% in the control arm (all subtypes). We aim to increase the rate of pCR in the experimental arm to 40%, i.e. a 10 percentage points increase, which is regarded clinically relevant since it would translate into improved disease-related outcomes. With a power of 80% and an alpha of 5%, a total of 712 patients have to be included; 356 in each arm. Accounting for a drop-out of 10%, we aim to include 790 patients. Stratification at the moment of computerized randomization is based on site of treatment (hospital) and biological tumour subtype (ER+HER2-, ER+HER2+, ER-HER2+, ER-HER2-).

All outcomes will primarily be analysed using an intention-to-treat approach, i.e. all study subjects will belong to the treatment group (exercise intervention or control) they were assigned to, disregarding compliance. As sensitivity analysis, all outcomes will also be analysed using a per-protocol approach, meaning that participants in the intervention group who comply with less than 65% of the prescribed physical exercise program, and participants who complete less than

40% of the planned neoadjuvant systemic therapy (around two 3-weekly courses) will be excluded from analysis.

Present accrual

The Neo-ACT trial has started enrolment at the first site in December 2022 and since then initiated a further five Swedish and one Finnish site. Until June 15, 2023, 26 participants had been randomized in the trial. A feasibility questionnaire is distributed via the EUBREAST network which officially supports this trial and has added the designation EUBREAST12-R. Further participating sites can be accommodated depending on volume, competing trials and language requirements for the mobile application. Contact: jana.de-boniface@ki.se

PO1-19-07

A Phase I Study Accessing Immunotherapy Combination of Balstilimab and Ivermectin in Patients with Metastatic Triple Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

Y. Yuan. Cedars-Sinai Cancer, Los Angeles, California, United States

S. Shiao. Cedars-Sinai, Los Angeles, California, United States

m. Tighiouart. Cedars-Sinai Cancer, United States

M. Mita. Cedars-Sinai, United States

J. Bitar. Cedars-Sinai Cancer, United States

P. McAndrew. Cedars-Sinai Cancer, United States

P. Dorothy. Cedars-Sinai Cancer, United States

M. El-Masry. Cedars-Sinai Cancer, United States

P. Frankel. City of Hope National Medical Center, Duarte, California, United States

P. Lee. City of Hope National Medical Center, United States

Background: Despite recent FDA approval of immune checkpoint inhibitor (ICI) and antibody-drug conjugates (ADCs), therapeutic options for metastatic triple negative breast cancer (mTNBC) remain limited. There is an unmet need to identify novel ICI combinations for improved efficacy. We recently demonstrated that ivermectin induces robust T cell infiltration into breast tumors and turning “cold” tumors “hot” in mouse model of TNBC. Balstilimab is a fully humanized IgG4 anti-PD-1 agent with proven safety and efficacy in metastatic cervical cancer. The current phase I/II trial is designed to test the safety and efficacy of the combination of ivermectin and balstilimab in patients with mTNBC. Methods: Key eligibility criteria include patients with unresectable or metastatic TNBC; progressed on 1-2 prior chemotherapies including an immune checkpoint inhibitor-containing regimen; ECOG 0-1; RECIST 1.1 measurable disease. Eligible patients receive balstilimab 450 mg, IV, on Day 1 and ivermectin (30, 45 or 60 mg po daily), PO, Days 1-3, 8-10, 15-17 of each 21 days cycle till disease progression or intolerance. The primary objective of the phase 1 portion of the study is to determine the recommended phase 2 dose of ivermectin in combination with balstilimab using NCI-CTCAE v5.0. The primary objective of the phase II portion of the study is to determine the efficacy of the combination in mTNBC who are PD-L1 negative using the objective response rate (ORR). Secondary objectives are progression free survival (PFS), overall survival (OS), duration of response (DOR), clinical benefit rate (CBR), and patients' quality of life (QOL) by EORTC QLQ-C30. Peripheral blood, tumor tissue and gut microbiome will be collected for correlative aims include pharmacokinetics, tumor microenvironment ICDs and gut microbiota in association with response to therapy. In the Phase 1 portion, eligible patients will be enrolled to one of three doses using the IQ 3+3 design. In the Phase 2 portion, patients will continue to be accrued to the RP2D (either the MTD or a lower dose depending on clinical judgement considering all the clinical and correlative data available). The Phase 2 portion will be conducted in two stages. In stage 1, a total of 13 PDL1-negative TNBC breast cancer patients will be treated at the RP2D. If there are no responders, the Phase 2 portion will close. With at least one responder, accrual may continue until 25 patients are accrued to the Phase 2 portion. If at least 3 responders are noted in 25 patients, this will be sufficient to consider the combination promising. This rule provides a type I error of 12% for a true response rate of 5%, and a power of 88% for true response rate of 20%. The estimated targeted accrual is 34-41

(Phase 1: 14-16; Phase 2: 20-25). Clinical trial information: NCT05318469

PO1-19-08

Phase I trial of pegylated liposomal doxorubicin chemotherapy in combination with CD40 agonist and Flt3 ligand in metastatic triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

- S. Reddy. UT Southwestern Medical Center, Dallas, Texas, United States
J. O'Shaughnessy. Baylor University Medical Center/ SCRI /Texas Oncology, Dallas, Texas, United States
N. Sadeghi. University of Texas Southwestern Medical Center, Dallas, Texas, United States
S. Syed. University of Texas Southwestern Medical Center, United States
C. Santa-Maria. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD & Sibley Memorial Hospital, Johns Hopkins, Washington, DC, Baltimore, Maryland, United States
V. Kaklamani. UT Health San Antonio, San Antonio, Texas, United States
N. Chen. University of Chicago, Chicago, Illinois, United States
D. Yardley. Sarah Cannon Research Institute, Nashville, Tennessee, United States
Y. Fang. University of Texas Southwestern Medical Center, United States
I. Chan. University of Texas Southwestern Medical Center, United States
N. Unni. University of Texas Southwestern Medical Center, Dallas, Texas, United States
S. Kashanian. University of Texas Southwestern Medical Center, Dallas, Texas, United States
N. Peswani. University of Texas Southwestern Medical Center, United States
S. Shakeel. University of Texas Southwestern Medical Center, United States
M. Carter. University of Texas Southwestern Medical Center, Dallas, Texas, United States
K. Kyle. University of Texas Southwestern Medical Center, United States
F. Fattah. University of Texas Southwestern Medical Center, United States
C. Ahn. University of Texas Southwestern Medical Center, United States
I. Patel. University of Texas Southwestern Medical Center, United States
J. Gruber. University of Texas Southwestern Medical Center, United States
D. Klemow. University of Texas Southwestern Medical Center, United States
G. Delgado. University of Texas Southwestern Medical Center, United States
N. Sinclair. Celldex Therapeutics, New Haven, Connecticut, United States
M. Yellin. Celldex Therapeutics, New Haven, Connecticut, United States
H. McArthur. UT Southwestern, Dallas, Texas, United States
R. Nanda. University of Chicago Medicine, Chicago, Illinois, United States
S. Conzen. University of Texas Southwestern Medical Center, United States
C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

Background: Only a subset of patients with metastatic triple-negative breast cancers (TNBC) demonstrate response to FDA approved PD-1 immune checkpoint blockade (ICB), and few have durable responses. Data suggests that breast cancers have defects in antigen presentation and that antigen presenting cells especially the cDC1 subtype of dendritic cells

(DCs) are required for response to ICB. CD40 agonists activate antigen presenting cells including DCs and B cells and repolarize macrophages to an anti-tumor phenotype. Flt3 ligand is a growth factor that increases differentiation and expansion of DCs. We recently demonstrated in pre-clinical TNBC models that the combination of liposomal doxorubicin chemotherapy, a CD40 agonist, and a Flt3 ligand improves outcomes compared to alternate combinations.

Methods: This is a single arm phase I pilot study of liposomal doxorubicin, CDX-1140 (CD40 agonist monoclonal antibody), and CDX-301 (recombinant Flt3 ligand) combination therapy in patients with metastatic or unresectable locally advanced metastatic TNBC. Patients will be randomized to 3 lead-in arms (triplet therapy, doublet immunotherapy only, or liposomal doxorubicin only) for one cycle prior to receiving triplet therapy with tissue biopsies done before and after the lead-in treatment. CDX-301 will be given for only two cycles; liposomal-doxorubicin and CDX-1140 will be continued until disease progression or clinically limiting toxicities. Primary endpoint is determination of a recommended phase II dose based on treatment-related adverse events and dose-limiting toxicities. Secondary endpoints include anti-tumor immune response after triplet therapy, after immunotherapy alone, and after liposomal doxorubicin alone; median progression-free survival, overall response rate, duration of response, and clinical benefit rate. Key eligibility criteria are unresectable stage III or stage IV TNBC (ER \leq 10%, PR \leq 10%, HER2/neu negative), 1st to 3rd line treatment for metastatic disease (1st line patients need to be PD-L1 negative by 22C3 assay), measurable disease by RECIST 1.1 criteria, consent for pre-treatment and on-treatment biopsies of amenable soft tissue tumor lesions, no prior treatment with an anti-CD40 antibody or a Flt3 ligand, no anthracycline treatment in the metastatic setting, no prior progression while on anthracycline-based therapy or within 6 months of completing neoadjuvant chemotherapy, and no history of non-infectious pneumonitis or current pneumonitis. This trial will enroll up to 45 patients across multiple sites (NCT05029999) and is currently open at University of Texas Southwestern Medical Center, Texas Oncology, University of Chicago, University of Texas San Antonio, Sarah Cannon Research Institute, and Johns Hopkins.

PO1-19-09

Integrating gene signatures to guide HR+ MBC therapy in a diverse cohort (INSIGHT)

Presenting Author(s) and Co-Author(s):

M. Forster. Vanderbilt University Medical Center, United States

J. Whisenant. Vanderbilt University Medical Center, United States

B. Park. Vanderbilt University Medical Center, NASHVILLE, Tennessee, United States

E. Stringer-Reasor. University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, Alabama, United States

W. Audeh. Agendia Inc., United States

A. Menicucci. Agendia Inc, United States

F. Ye. Vanderbilt University Medical Center, United States

H. McArthur. UT Southwestern, Dallas, Texas, United States

S. Reid. Vanderbilt-Ingram Cancer Center, United States

Background: Black women with breast cancer (BC) have a 40% higher mortality rate compared to Non-Hispanic White (NHW) women. Among women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) BC, Black women have worse outcomes than NHW despite comparable systemic therapies. Gene expression profiling assays have been used in early-stage BC to provide prognostic and sometimes predictive information beyond standard immunohistochemical classifications. The 80-gene molecular subtype signature (BluePrint) with the 70-gene risk of distant recurrence signature (MammaPrint®) (Agendia, Irvine, CA) further classify HR+/HER2- BC into luminal A-type, luminal B-type, HER2-type, and basal-type tumors. Luminal B, HER2, and basal-type tumors (non-luminal A) are more aggressive with worse survival outcomes and are overrepresented among Black women. In the metastatic setting, the role of molecular subtype signatures in guiding therapeutic decisions has not yet been determined. We hypothesize that patients with metastatic HR+/HER2- non-luminal A-type BC post-progression on endocrine therapy +/- CDK4/6 inhibition will derive more benefit from chemotherapy than standard-of-care endocrine therapy in the second line setting. We also hypothesize that the impact of the intervention will be more pronounced in Black women compared to NHW women. Methods: This is a randomized phase II study that will evaluate the anti-tumor effect of capecitabine compared to physician's choice endocrine therapy as second line therapy for adult (>18 years) patients with non-Luminal A HR+/HER2- metastatic or unresectable locoregional invasive carcinoma (NCT 05693766). The study plans to enroll up to 62 patients. This trial enriches for racial/ethnic minority patients through collaborations with the University of Texas Southwestern and the University of Alabama at Birmingham, two health systems that serve a large minority population. Eligible patients who have received prior endocrine therapy with a CDK4/6 inhibitor will have their tumor tissue analyzed using the MammaPrint® and BluePrint assays. Patients with Luminal A tumors will receive standard of care and will be followed for survival only. Patients with non-Luminal A tumors will be randomized (1:1) to receive physician's choice endocrine therapy versus capecitabine (dosed at 2000mg twice daily for 7 days on, 7 days off) with stratifications by molecular subtype and race. Patients will be evaluated for response every three cycles using the Response Evaluation Criteria in Solid Tumors. Therapy will be continued until evidence of disease progression or unacceptable major toxicity. The primary endpoint is progression free survival; secondary endpoints are overall response rate, clinical benefit rate, overall survival, and patient reported outcomes. The study will have 80% power to detect a minimal hazard ratio

of 0.5 at one-sided significance level of 0.05. Cell-free DNA will be collected at baseline and at three times post-baseline to investigate potential genetic markers of disease response and resistance. Enrollment opened on June 1, 2023. We anticipate opening the trial at the external sites before the end of 2023.

PO1-19-10

Durvalumab + datopotamab deruxtecan in patients with PD-L1 positive advanced/metastatic triple-negative breast cancer: Arm 8 of the phase 1b/2, open label, platform BEGONIA study

Presenting Author(s) and Co-Author(s):

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

R. Huisden. AstraZeneca, Cambridge, United Kingdom

R. Stewart. AstraZeneca, Cambridge, United Kingdom

K. Heider. AstraZeneca, Cambridge, UK, United States

P. Vuković. AstraZeneca, Cambridge, United Kingdom

N. Denduluri. AstraZeneca, Gaithersburg, Maryland, United States

Background: Patients (pts) with advanced/metastatic triple-negative breast cancer (a/mTNBC) have limited treatment options and poor prognosis. Immune checkpoint inhibitors combined with chemotherapy is the standard of care for pts with PD-L1 positive tumors; still, most pts progress within a year, highlighting a need for new treatments. BEGONIA is an ongoing Simon 2-stage, multicenter, multi-arm platform study evaluating the safety and efficacy of durvalumab (D), an anti-PD-L1 monoclonal antibody, with or without paclitaxel, in combination with novel oncology therapies as first-line treatment for a/mTNBC (NCT03742102). Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate (ADC) consisting of a humanized anti-trophoblast cell surface antigen 2 (TROP2) IgG1 monoclonal antibody linked to a topoisomerase I inhibitor payload via a plasma stable, tumor selective, tetrapeptide-based cleavable linker. TROP2 is broadly expressed on breast and other epithelial tumors and Dato-DXd monotherapy showed antitumor activity in heavily pretreated mTNBC pts (Bardia SABCS 2022 P6-10-03). Pts treated with Dato-DXd+D in Arm 7 of BEGONIA showed a 74% objective response rate (ORR) with median 7.2 months follow-up (Schmid SABCS 2022 PD11-09). Although responses were observed in both PD-L1-high and -low-expressing tumors, most pts (87%) had PD-L1-low-expressing tumors. In Arm 8 of BEGONIA, pts determined to have PD-L1 positive tumors by pre-existing/local testing will be recruited and treated with Dato-DXd+D to evaluate efficacy and safety in a PD-L1-high population.

Methods: Eligible female pts are aged ≥ 18 years with untreated unresectable, locally advanced or mTNBC; ≥ 6 months between completion of treatment for earlier-stage breast cancer and recurrence of distant disease; ≥ 12 months since prior taxane therapy; ECOG PS 0/1; adequate organ function; and ≥ 1 nonirradiated measurable lesion. For inclusion in Arm 8, a PD-L1 positive tumor as determined by local immunohistochemistry (IHC) testing is required (either pre-existing or obtained during prescreening). Exclusion criteria for Arm 8 are clinically significant corneal disease; history or suspicion of interstitial lung disease/pneumonitis; underlying pulmonary disorder; prior exposure to immune-mediated therapy; or prior treatment with an ADC containing a topoisomerase I inhibitor. Arm 8 will evaluate Dato-DXd (6 mg/kg) + D (1120 mg) given intravenously every 3 weeks until disease progression or unacceptable toxicity. Tumors will be assessed per RECIST v1.1 every 6 weeks for 48 weeks, then every 12 weeks thereafter.

A safety run-in will not occur for Arm 8, as Dato-DXd+D was evaluated in Arm 7 and was

tolerable with no DLTs reported. Part 1 of Arm 8 will enroll 30 pts. The primary endpoint of Part 1 is safety and tolerability. A futility analysis will be performed with an option to expand Arm 8 to Part 2, where an additional 27 pts will be enrolled if expansion criteria are met. The primary endpoint for Part 2 is ORR. Secondary endpoints include ORR (Part 1 only), testing for antidrug antibodies and treatment pharmacokinetics (Part 1 only), duration of response (DoR), progression-free survival (PFS), and overall survival (OS). ORR will be summarized with descriptive statistics and 95% Clopper-Pearson confidence intervals. Kaplan-Meier analysis will be used for DoR, PFS, and OS. All tumor response and survival endpoints will be based on investigator assessments. Additional PD-L1 testing with the VENTANA PD-L1 (SP263) Assay will be performed on pretreatment tumor samples; high expression is defined as $\geq 10\%$ of the tumor area populated by PD-L1-expressing tumor or immune cells. TROP2 expression will be assessed by IHC. Enrollment is ongoing.

Funding: AstraZeneca/Daiichi Sankyo

PO1-19-11

Phase 3 Study of Tucatinib or Placebo in Combination With Trastuzumab and Pertuzumab as Maintenance Therapy for HER2+ Metastatic Breast Cancer (HER2CLIMB-05, Trial in Progress)

Presenting Author(s) and Co-Author(s):

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

J. Tsurutani. Advanced Cancer Translational Research Institute at Showa University, Tokyo, Shinagawa, Japan

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

C. O'Sullivan. Mayo Clinic, Rochester, MN, USA, ROCHESTER, Minnesota, United States

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

K. Tryfonidis. Merck & Co., Inc., Rahway, New Jersey, United States

L. Santarpia. Seagen Inc., Bothell, WA, USA, United States

S. Yang. Seagen Inc., Bothell, WA, USA, United States

V. Diéras. Eugene Marquis Centre, Rennes, France, France

Background

The current first-line (1L) standard of care (SOC) for human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC) is trastuzumab (T) plus pertuzumab (P) and a taxane. Despite advances in 1L SOC, most patients progress during maintenance therapy with T+P. Tucatinib is a tyrosine kinase inhibitor (TKI) approved in combination with T and capecitabine for adults with HER2+ MBC, with and without brain metastases (BM). In HER2CLIMB, addition of tucatinib significantly prolonged progression-free survival (PFS) and overall survival (OS) in patients with HER2+ MBC and was well tolerated. Adding tucatinib also reduced the risk of disease progression or death in patients with untreated and/or active BM (Murthy et al. NEJM 2020, Curigliano et al. Ann Oncol 2022). HER2CLIMB-05 investigates whether adding tucatinib to 1L SOC as maintenance therapy will extend PFS while maintaining quality of life (QOL). Methods

HER2CLIMB-05 (NCT05132582) is a phase 3, randomized, double-blind study evaluating tucatinib plus T+P as maintenance therapy for HER2+ MBC. Approximately 650 patients will be enrolled. Eligible patients will have advanced HER2+ disease, no progression on 4–8 cycles of prior 1L SOC, Eastern Cooperative Oncology Group Performance Status of 0 or 1, and no or asymptomatic BM. Exclusion criteria include prior treatment with anti-HER2 and/or anti-epidermal growth factor receptor TKI (prior SOC for early BC is permitted) or inability to undergo contrast magnetic resonance imaging of the brain. Patients will be randomized 1:1 to receive either tucatinib or placebo twice daily, with T+P once every 21 days. Patients with hormone receptor-positive disease may receive endocrine therapy. The primary endpoint is investigator-assessed PFS. Secondary endpoints include OS, time to deterioration of health-related QOL, central nervous system PFS, safety, and pharmacokinetic (PK) parameters. PFS and OS will be compared using a two-sided stratified log-rank test between treatment groups. Time-to-event endpoints will be summarized using the Kaplan–Meier method. PK and safety data will be summarized using descriptive statistics. Enrollment is ongoing in Austria, Chile, Greece, Italy, Japan, Poland, Portugal, Spain, the US, and several other European, APAC, and LATAM countries. This abstract was previously presented at ESMO-BC 2022, FPN (Final

Publication Number): 415, by Veronique Dieras (reused with permission).

PO1-19-12

VERITAC-2: a phase 3 study of vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, vs fulvestrant in ER–positive/human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer

Presenting Author(s) and Co-Author(s):

M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

M. de Laurentiis. Istituto Nazionale Tumori "Fondazione Pascale", Italy

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

S. Hurvitz. Fred Hutchinson Cancer Center/University of Washington, Los Angeles, California, United States

S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States

M. Danso. Virginia Oncology Associates, Norfolk and Virginia Beach, VA, USA, United States

D. Lu. Pfizer, United States

J. Perkins Smith. Pfizer Inc., New York, New York, United States

Y. Liu. Pfizer Inc, San Diego, California, United States

L. Tran. Pfizer Inc., La Jolla, California, United States

S. Anderson. Arvinas Operations, Inc., New Haven, Connecticut, United States

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

Background: Vepdegestrant (ARV-471) is an oral PROTAC ER degrader that binds to and degrades wild-type ER and clinically relevant mutants. Vepdegestrant directly recruits the ubiquitin-proteasome system to degrade ER, whereas selective ER degraders (SERDs) indirectly cause ER degradation. In a first-in-human phase 1/2 study (NCT04072952), vepdegestrant monotherapy was well tolerated and showed clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer. The phase 3 monotherapy dose (200 mg once daily [QD]) was chosen due to comparable efficacy and favorable tolerability relative to 500 mg QD and robust ER degradation in paired tumor biopsies. The global, randomized phase 3 VERITAC-2 study (NCT05654623) will compare efficacy and safety of vepdegestrant vs the SERD fulvestrant in patients with ER+/HER2- advanced breast cancer after prior combination cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy and endocrine therapy (ET). Trial design: Eligible patients (aged ≥ 18 years) have a confirmed diagnosis of ER+/HER2- locoregional recurrent or metastatic breast cancer not amenable to surgical resection or radiation; 1 prior line of combination CDK4/6 inhibitor therapy and ET; ≤ 1 additional line of ET; most recent ET given for ≥ 6 months before disease progression; and radiological disease progression during or after the last line of therapy. Prior chemotherapy in the locally advanced or metastatic setting and prior fulvestrant are not permitted. Patients (N \approx 560) are randomized 1:1 to receive vepdegestrant 200 mg orally QD continuously or fulvestrant intramuscularly on days 1 and 15 in the first 28-day cycle and on day 1 in subsequent cycles; patients are stratified by ESR1 mutation status and presence of visceral disease. The primary endpoint, progression-free survival, will be assessed by blinded independent central review in the intention-to-treat population and the ESR1 mutation subpopulation. Secondary outcome measures include overall survival, antitumor activity (objective response rate, duration of response, and clinical benefit rate), safety, and quality of life assessments.

PO1-20-01

A Prospective Single-Arm Pilot Interventional Trial to Assess Individual Breast Cancer Risk Prior to Gender-Affirming Chest Masculinization Surgery

Presenting Author(s) and Co-Author(s):

C. Cortina. Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin, United States

A. Purdy. Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin, United States

S. Stachowiak. Medical College of Wisconsin, United States

K. Klement. Department of Plastic Surgery, Medical College of Wisconsin, United States

S. Sasor. Department of Plastic Surgery, Medical College of Wisconsin, United States

K. Krucoff. Department of Plastic Surgery, Medical College of Wisconsin, United States

A. Petroll. Inclusion Health Clinic, Froedtert & the Medical College of Wisconsin, United States

K. Robertson. Inclusion Health Clinic, Froedtert & the Medical College of Wisconsin, United States

A. Lakatos. Inclusion Health Clinic, Froedtert & the Medical College of Wisconsin, United States

E. Doren. Department of Plastic Surgery, Medical College of Wisconsin, United States

Background: The number of individuals who identify as transgender and/or gender-diverse (TGD) is steadily increasing and the number of individuals seeking chest masculinization surgery, commonly called “top-surgery,” is also increasing. In persons assigned female at birth, top surgery removes most breast tissue to allow the chest to appear masculine. However, top surgery is not equivalent to oncologic risk-reducing mastectomies (RRM), which aim to remove all breast tissue to reduce future breast cancer (BC) risk. While top surgery has significant psychological and health benefits, its impact on future BC risk is unclear, especially for those individuals who are at high-risk for future BC development (defined as $\geq 17\%$ by international consensus guidelines) and/or have a pathogenic germline mutation for BC. The aims of this study are to 1) determine the percentage of TGD persons assigned female at birth who are considering undergoing top surgery and are at elevated BC risk using validated risk models, 2) determine the percentage of TGD persons at elevated BC risk who choose to undergo RRM as part of top surgery, and 3) assess and compare self-perceived BC risk compared to calculated risk. Methods: A single-institution prospective single-arm pilot study is currently underway from March 2023 through January 2024. Individuals assigned female at birth, who are age ≥ 18 years, and considering undergoing top surgery, but have not yet undergone top surgery, are eligible to enroll (goal accrual N=35). Participants are being actively recruited from our institution’s Comprehensive LGBTQIA+ Inclusion Health Clinic and Plastic Surgery Clinic. Consented participants undergo a personalized BC risk assessment the validated IBIS and Gail (for those ≥ 35 years old) BC risk models. Those with an average lifetime BC risk ($< 17\%$) are recommended to continue top surgery as planned/no intervention, participants with a moderate lifetime BC risk (17-30%) are counseled they may consider RRM as part of their top surgery operation given that sparse data exists in this space, while those with a high lifetime BC risk ($> 30\%$ or pathogenic germline variant) are counseled on the potential benefits of RRM. Participants with a family history suggestive of a hereditary cancer syndrome meet with a certified Genetics counselor for consideration of genetic testing, per NCCN guidelines. Results: We anticipate reporting 1) general demographic description of the cohort, 2) the percentage who have an elevated lifetime BC risk and/or a pathogenic genetic mutation, 3) the percentage

of those with an elevated risk who choose to undergo RRM as part of top surgery, and 4) report the differences between self-perceived vs calculated lifetime BC risk. Conclusion: Our findings will inform TGD persons and surgeons on the utility of a personalized BC risk assessment prior to top surgery to assist in surgical decision-making, report the accuracy of self-perceived BC risk in TGD persons, and potentially change the standard pre-operative evaluation for TGD persons considering top surgery to include a formal BC risk assessment to ensure high-risk individuals have the option to undergo RRM to appropriately reduce their future BC risk.

PO1-20-02

MiRaDor: A proof-of-concept study of treatment efficacy by monitoring Minimal Residual Disease (MRD) using circulating tumor DNA (ctDNA) in hormone receptor-positive/HER2-negative (HR+/HER2-) early breast cancer (EBC)

Presenting Author(s) and Co-Author(s):

A. Llombart-Cussac. 17 Medical Oncology Department, Hospital Arnau de Vilanova, Valencia, Comunidad Valenciana, Spain

J. Pérez-García. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Catalonia, Spain

M. Gion. Hospital Universitario Ramón y Cajal, United States

D. Alcalá-López. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

J. Fazal-Salom. MEDSIR, United States

A. Lazaris. MEDSIR, United States

M. Mancino. MEDSIR, United States

E. Shimizu. MEDSIR, United States

S. Victorino. MEDSIR, United States

R. Zhang. MEDSIR, United States

Z. Machackova. F. Hoffmann-La Roche Ltd., United States

F. Schimmoller. Genentech, Inc., United States

M. Wongchenko. Genentech, Inc., United States

J. Gligorov. Institut Universitaire de Cancérologie AP-HP Sorbonne Université, Paris, Ile-de-France, France

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

Background:

Detection of MRD through ctDNA has been consistently associated with high risk of relapse. Longitudinal evaluation of ctDNA to monitor MRD is a minimally invasive tool that may predict disease recurrence and treatment response. MiRaDor aims to improve the clinical utility of ctDNA and understand its applicability in high-risk, HR+/HER2- EBC patients (pts).

Trial Design:

MiRaDor (NCT05708235) is a multicenter, open-label, non-comparative, phase II trial. Selection criteria include pts: a) with HR+/HER2- EBC at high risk of relapse, b) on adjuvant treatment with endocrine therapy (ET) for at least 2 years with 3 additional years of planned ET, c) no prior treatment with cyclin-dependent kinases 4/6 inhibitors or fulvestrant, and d) had surgery for their primary BC in the last 5 years. The trial has two phases, ctDNA surveillance (n=1260) and treatment (n=40-60). The surveillance phase will analyze ctDNA, with the FoundationOne® Tracker, every 3 months for the 1st year and every 6 months thereafter until ctDNA detection, end of the adjuvant ET, or completion of treatment phase accrual. Pts with positive ctDNA

without radiological disease progression (PD) will be allocated to 1 of the treatment arms (n=10): A) standard ET; B) giredestrant; C) giredestrant + abemaciclib; or D) giredestrant + inavolisib (if PIK3CA mutation). Treatment will continue until evidence of PD, physician's and/or patient's decision, or until the end of study treatment (abemaciclib/inavolisib for up to 2 years, 5 years for ET). Tumor assessments will be periodically performed to rule out radiological PD. The primary objective is to evaluate the rate of pts with at least 90% decrease or clearance in ctDNA after 3 months of treatment. Key secondary objectives include the proportion of pts with 90% decrease in baseline ctDNA at 6, 9, and 12 months, 70%, and 50% decrease in ctDNA at 3, 6, 9, and 12 months, and treatment safety and tolerability. A cohort expansion up to 20 pts in 1 or 2 arms will occur if at 3 months a 90% ctDNA decrease is observed in at least 30% of pts and if, after 3 additional months, a 90% ctDNA decrease is maintained in at least 20% of pts.

PO1-20-03

Acupuncture for Preventing Progression of Taxane-Induced Peripheral Neuropathy (ATP): A Phase II Randomized, Placebo Controlled Trial

Presenting Author(s) and Co-Author(s):

W. Zhi. Memorial Sloan Kettering Cancer Center, United States

L. Taylor. Memorial Sloan Kettering Cancer Center, United States

R. Baser. Memorial Sloan Kettering Cancer Center, United States

M. Weitzman. Memorial Sloan Kettering Cancer Center, United States

Q. Li. Memorial Sloan Kettering Cancer Center, United States

C. Seluzicki. Memorial Sloan Kettering Cancer Center, United States

T. Bao. Memorial Sloan Kettering Cancer Center, United States

J. Mao. Memorial Sloan Kettering Cancer Center, United States

Background: Chemotherapy-induced peripheral neuropathy (CIPN) from chemotherapy drugs such as taxanes can be detrimental to cancer survival, increasing the risk of falls and worsening physical functions. However, there is no effective treatment or preventative measure for CIPN. The current management of worsening and persistent CIPN during chemotherapy is dose reduction or discontinuation of chemotherapy. Our group previously completed a single-arm phase IIA pilot trial of women who developed National Cancer Institution Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 2 CIPN during weekly paclitaxel for stage I-III breast cancer. The result suggested an acupuncture intervention for grade 2 CIPN might slow CIPN progression during chemotherapy. However, the role of acupuncture still needs to be better defined.

Trial design: The ATP trial is a two-arm, parallel, randomized controlled trial comparing weekly real acupuncture (RA) versus sham acupuncture (SA) during preplanned curative intent taxane containing regimens in patients with breast cancer. The study will include two phases: screening and intervention. In the screening phase, eligible patients will consent and receive CIPN screening each week. Patients who develop grade 1 CIPN or higher based on NCI-CTCAE version 5.0 will be consented to the intervention phase and randomized to receive either weekly RA or SA using a standardized, semi-fixed protocol developed in our preliminary studies to improve CIPN pain.

Eligibility criteria for the screening phase: English or Spanish-proficient; aged ≥ 18 years; histological diagnoses of invasive carcinoma of the breast; and plan to receive curative intent chemotherapy regimen containing paclitaxel or nab-paclitaxel weekly or biweekly as standard of care.

Eligibility criteria for the intervention phase: in addition to the screening phase eligibility criteria, developed CIPN grade ≥ 1 based on the NCI-CTCAE version 5.0, while receiving taxane; ≥ 4 weeks of paclitaxel or nab-paclitaxel weekly or biweekly planned, as standard of care and at treating physician's discretion; willing to adhere to requirement that no new pain medication or dose changes be taken throughout the first 12 weeks of the study period; and willing to adhere to all study-related procedures, including randomization to one of the two possible acupuncture treatments.

Specific aims: The primary aim is to evaluate the effectiveness of RA versus SA in preventing

taxane-induced peripheral neuropathy progression as measured by Neuropathic Pain Scale (NPS) in patients with early-stage breast cancer who are receiving curative intent neurotoxic chemotherapy. The secondary aim is to evaluate the effectiveness of RA versus SA on chemotherapy relative dose intensity (RDI) and CIPN-related chemotherapy discontinuation.

Statistical methods: We will randomize 80 patients, 40 to each arm. All randomized patients will be evaluable in the Intent to Treat (ITT) analyses because all will have completed the baseline assessment before randomization. We will use a linear mixed model (LMM) to compare the change in NPS between the arms from baseline to week 4. Based on our pilot data, a difference in CIPN grade from 1 to 2 corresponded to a difference in NPS from 12 to 22, a difference of ten points in 27 patients. The NPS standard deviation (SD) in patients with grade 1 CIPN was 17. With 80 patients we will have 80% power to detect a difference between arms as small as 10 points on the NPS, assuming a one-sided test, type I error of 5%, correlation between baseline and follow-up measurements of 0.5, SD of 17, and 15% attrition at week 4.

Present accrual and target accrual: We accrued 20 participants in the intervention phase by the end of June 2023; the target accrual is 80 participants.

Contact information for people with a specific interest in the trial: W. Iris Zhi, MD, PhD, zhiw@mskcc.org. ClinicalTrials.gov Identifier: NCT05458284.

PO1-20-04

STX-478-101: A phase 1/2, first-in-human study of STX-478 monotherapy or in combination with fulvestrant in patients with breast cancer or other advanced solid tumors (trial in progress)

Presenting Author(s) and Co-Author(s):

A. Montero. UH/Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA, United States

D. Orr. Mary Crowley Cancer Research, Dallas, Texas, United States

P. Munster. University of California San Francisco, San Francisco, California, United States

P. LoRusso. Yale Cancer Center, United States

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

I. Winer. Wayne State University/Karmanos Cancer Center, Detroit, Michigan, United States

M. Streit. Scorpion Therapeutics, Inc., Boston, Massachusetts, United States

M. Patterson. Scorpion Therapeutics, Inc., Boston, Massachusetts, United States

S. Roberts. Scorpion Therapeutics, Inc., Boston, Massachusetts, United States

S. Corsi-Travali. Scorpion Therapeutics, Inc., Boston, Massachusetts, United States

C. Ewert. Scorpion Therapeutics, Inc., Boston, Massachusetts, United States

D. Juric. Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

Background: The phosphoinositide 3-kinase-alpha (PI3K α)/AKT/mTOR pathway is one of the major pathways in oncogenesis. PI3K α alterations are especially prevalent in breast, gynecological, and head and neck squamous cell carcinomas. PI3K α oncogenic mutations are highly enriched for kinase (H1047X) and helical (E542K, E545K) domain hotspots. The therapeutic potential of isoform-selective PI3K α inhibition in PI3K α -mutant cancers was established with alpelisib, which shows equipotent activity against both wild-type (WT) and mutant PI3K α . However, alpelisib use is limited by toxicities induced by WT PI3K α inhibition, e.g. hyperglycemia and mucositis. This suggests that mutant-selective PI3K α inhibitors have the potential to improve efficacy while sparing WT-related toxicity. STX-478 is an investigational allosteric, mutant-selective PI3K α inhibitor. Preclinical testing in human breast cancer xenografts bearing helical- or kinase-domain mutant PI3K α demonstrated that STX-478 monotherapy and combinations with fulvestrant and/or CDK4/6 inhibitors provided robust efficacy without the metabolic dysfunction observed with alpelisib.

Trial Design: This first-in-human, multicenter, phase 1/2 study (NCT05768139) evaluates the optimal dosing, safety, and preliminary efficacy of STX-478 as monotherapy in patients with locally-advanced or metastatic HR+/HER2- breast cancer or other solid tumor types with PI3K α H1047X mutations, other kinase domain mutations, or helical domain mutations (Part 1), and STX-478 in combination with fulvestrant in patients with locally-advanced or metastatic HR+/HER2- breast cancer with PI3K α H1047X or other kinase domain mutations (Part 2). Part 1 comprises 2 subparts (Table 1) to define the optimally biologically active dose (OBD) and maximum tolerated dose (MTD) in Part 1.1, and recommended phase 2 dose (RP2D) of STX-478 monotherapy in Part 1.2. At the conclusion of each dose-level in Part 1.1 (3 + 3 design), a

backfill cohort will be initiated in patients with HR+/HER2- breast cancer with PI3Kα H1047X mutations or other kinase domain mutations, who will receive STX-478 at the determined safe dose. Part 2 comprises two subparts (Table 2) to define RP2D and assess the initial efficacy of STX-478 in combination with fulvestrant in patients with HR+/HER2- breast cancer expressing PI3Kα H1047X or other kinase domain mutations.

Key Eligibility Criteria: Adults with a PI3Kα-mutant advanced or refractory solid tumor malignancy that is metastatic or locally advanced and unresectable, ECOG performance status score of 0–1, and no prior PI3K/AKT/mTOR inhibitor(s) use (except with prior intolerance) are eligible. Individuals with diabetes mellitus type 1 or uncontrolled diabetes mellitus type 2 are excluded. Cohort-specific eligibility criteria are provided in Tables 1 and 2.

Endpoints: Efficacy, safety, pharmacokinetics, pharmacodynamics, patient-reported quality of life, and biomarkers (e.g., glucose metabolism, circulating tumor DNA) will be assessed.

Trial Status: Recruitment opened April 2023 in the US and is ongoing, with potential for ex-US site expansion. Contact clinicaltrials@scorpiontx.com for additional information.

Table 1. Part 1 Dose Escalation, RP2D Selection, and RP2D Expansion (STX-478 Monotherapy)

Dose Escalation Subpart	Cohort(s)	Treatment	Primary Objective/Endpoint(s)
1.1: Dose escalation	Cohort A0: Solid tumors with PI3Kα kinase domain and/or helical domain mutations ^a Cohort A1: (Backfill) HR+/HER2- breast cancer with PI3Kα H1047X mutations or other kinase domain mutations ^b	STX-478 monotherapy, 20 mg PO QD starting dose, escalated per 3 + 3 design (36–60 patients)	<ul style="list-style-type: none"> • MTD based on DLTs • OBD based on PK, PD, preliminary efficacy (ORR), and safety
1.2-DE: Dose expansion at MTD	Cohort A2: Gynecological cancer with PI3Kα H1047X mutations or other kinase domain mutations ^{a,c} Cohort A3: HNSCC with PI3Kα H1047X mutations or other kinase domain mutations ^a Cohort A4: Other solid tumors with PI3Kα H1047X mutations or other kinase domain mutations other than the tumor types permitted in cohorts A1, A2, and A3 ^d Cohort A5: Solid tumors with PI3Kα helical domain mutations ^a	STX-478 monotherapy at MTD determined in Part 1.1 (n=20 per cohort)	<ul style="list-style-type: none"> • Preliminary efficacy (ORR)
1.2-DS: RP2D selection <i>(conducted concurrent to Part 1.2-DE)</i>	Cohort A1: HR+/HER2- breast cancer with PI3Kα H1047X mutations or other kinase domain mutations	STX-478 monotherapy at OBD (n=10) or MTD (n=10) as determined in Part 1.1	<ul style="list-style-type: none"> • RP2D based on PK, PD, preliminary efficacy (ORR), and safety
1.3: RP2D expansion	Cohort A1: HR+/HER2- breast cancer with PI3Kα H1047X mutations or other kinase domain mutations	STX-478 monotherapy at RP2D determined in Part 1.2-DS (up to 20 patients)	<ul style="list-style-type: none"> • Preliminary efficacy (ORR)

Note: "Other" PI3Kα kinase mutations include Y1021, T1025, M1043, N1044, H1048, G1049P; helical PI3Kα mutations include P539, E542, E545, Q546.
DLT, dose-limiting toxicity; HNSCC, head and neck squamous cell carcinoma; MTD, maximum tolerated dose; OBD, optimally biologically active dose; ORR, objective response rate; PD, pharmacodynamics; PI3Kα, phosphatidylinositol 3-kinase alpha; PK, pharmacokinetics; PO, oral; QD, once daily; RP2D, recommended phase 2 dose.
^aPatients received standard therapy option(s) or additional standard therapy option(s) that were either refused by the participant or are contraindicated; or the participant is deemed by the investigator not to be an appropriate candidate for standard therapy option(s).
^bPatients required to receive prior therapy for locally advanced or metastatic disease with at least 1 CDK4/6 inhibitor regimen, at least 1 anti-estrogen therapy, and no more than 2 prior systemic chemotherapy regimens.
^cEndometrial cancer, ovarian cancer, or cervical carcinoma.

Table 2. Part 2 RP2D Selection and Expansion (STX-478 + Fulvestrant Combination Therapy)

Dose Expansion Subpart	Cohort(s)	Treatment	Primary Objective/Endpoint(s)
2.1: Combination RP2D selection	Cohort B: HR+/HER2- breast cancer with PI3Kα H1047X mutations or other kinase domain mutations ³	Combination STX-478 (at OBD or MTD determined in Part 1.1) + fulvestrant (n=10 each)	<ul style="list-style-type: none"> • RP2D for combination therapy based on PK, PD, preliminary efficacy (ORR), and safety
2.2: Combination RP2D expansion	Cohort B: HR+/HER2- breast cancer with PI3Kα H1047X mutations or other kinase domain mutations ³	Combination STX-478 (at RP2D determined in Part 2.1) + fulvestrant (up to 20 patients)	<ul style="list-style-type: none"> • Preliminary efficacy (ORR)

Note: ³Other³ PI3Kα kinase mutations include Y1021, T1025, M1043, N1044, H1048, G1049P.

MTD, maximum tolerated dose; OBD, optimally biologically active dose; ORR, objective response rate; PD, pharmacodynamics; PI3Kα, phosphatidylinositol 3-kinase alpha; PK, pharmacokinetics; RP2D, recommended phase 2 dose.

³Prior systemic treatment for locally advanced or metastatic disease with at least 1 but no more than 2 prior lines of therapy in which the patient progressed or was intolerant to CDK4/6 inhibitor therapy, antiestrogen therapy, and/or approved HER-2 directed therapy.

PO1-20-05

SURVIVE study – a multicenter, randomized, controlled phase 3 superiority trial, evaluating liquid biopsy guided intensified follow-up surveillance in women with intermediate-to high-risk early breast cancer

Presenting Author(s) and Co-Author(s):

F. Mergel. University hospital Ulm, Department for obstetrics and gynecology, Ulm, Baden-Wurttemberg, Germany

S. Huesmann. University hospital Ulm, Department for obstetrics and gynecology, United States

T. Friedl. Department of Obstetrics and Gynecology, University Hospital Ulm, Germany

K. Pfister. University hospital Ulm, Department for obstetrics and gynecology, United States

T. Braun. University hospital Ulm, Department for obstetrics and gynecology, United States

A. Fink. University hospital Ulm, Department for obstetrics and gynecology, United States

F. Mehmeti. University hospital Ulm, Department for obstetrics and gynecology, United States

T. Fehm. University Hospital Düsseldorf, Düsseldorf, Germany

V. Müller. Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

K. Pantel. Department of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

E. Wiesmüller. University hospital Ulm, Department for obstetrics and gynecology, United States

B. Rack. Department of Obstetrics and Gynecology, University Hospital Ulm, Germany

W. Janni. Department Gynecology and Obstetrics, University of Ulm, Ulm, Baden-Wurttemberg, Germany

Background: Current guidelines limit routine breast cancer follow-up to clinical examinations and breast imaging. This is based on the results of two large cohort studies conducted in the 1980s that showed no improvement in overall survival (OS) by an intensified screening for distant metastases. Thus, imaging for distant metastases should currently only be performed in patients with specific symptoms. To detect distant relapse in a pre-symptomatic stage, we suggest the evaluation of a liquid biopsy-guided intensified surveillance, analyzing tumor markers (CA 27.29, CA 125 and CEA), circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA).

Trial design: Funded by the German Federal Ministry of Education and Research, the SURVIVE study is the first large, randomized breast cancer surveillance trial to investigate the potential survival benefit of a liquid biopsy guided follow-up care in intermediate- to high-risk early breast cancer patients. The trial is a German multicenter, controlled phase 3 superiority study, in which 3500 patients are randomized in a 1:1 ratio to standard vs. liquid biopsy guided intensified follow-up care. At the time of writing 150 patients have been enrolled since December 2022. The total study duration is 144 months. Stratification factors are study site as well as HR-, HER2- and nodal status at surgery. Both study arms receive standard follow-up according to national guidelines. Additional blood samples (year 1-3 every 3 months, year 4-5 every 6 months) and standardized Quality of Life (QoL) questionnaires (EORTC-QLQ-C30/PA-F12, every 6 months) will be collected. While the standard surveillance arm samples will only

be stored in a biobank, samples collected in the intensive surveillance arm will be tested for standard tumor markers, CTCs and ctDNA. Pre-specified abnormal findings of any of the liquid biopsy markers indicative of minimal residual disease trigger complete staging. In the event of confirmed disease recurrence, guideline-based treatment follows, otherwise, liquid biopsy testing continues. If applicable, study participants may enter interventional trials.

Eligibility criteria: Eligible patients are adult females or males with histologically confirmed primary invasive intermediate to high-risk early breast cancer, defined as an indication for (neo-)adjuvant chemotherapy, and/or large tumor size (> 50 mm), and/or positive lymph nodes (\geq pN1mi), and/or high grade (\geq G3). Primary anti-tumor therapy (surgery, adjuvant chemo- or radiotherapy) must have been completed ≤ 24 months (≤ 60 months for luminal carcinoma) previously. Patient enrollment during adjuvant endocrine- or antibody-therapy, CDK4/6-/PARP- or PI3K-inhibitors and antibody-drug conjugates is allowed.

Statistical methods: The two primary objectives are to determine whether intensified, liquid biopsy-guided surveillance leads to better OS or an overall lead-time effect, compared to standard surveillance. The primary endpoint OS will be analyzed in the ITT population using Kaplan Meier methods and cox regression models, the overall lead time effect is a purely descriptive composite measure. Secondary objectives include invasive disease-free survival (IDFS), distant disease-free survival (DDFS), distant recurrence free survival (DRFS), breast cancer-specific survival (BCSS) and quality of life (QoL).

Specific aims: To improve OS and the QoL during breast cancer follow-up, we propose a liquid biopsy guided follow-up method, with high sensitivity and specificity for the earlier detection of distant (oligo-)metastases, to enable earlier initiation of therapy.

Conclusion: The SURVIVE-study is a long-awaited trial in early breast cancer follow-up, based on promising liquid biopsy markers. If successful, the results will lead to a paradigm shift in current follow-up care of intermediate to high-risk early breast cancer survivors.

Clinical trial information: NCT05658172

PO1-20-06

Phase 2 study of novel HER2-targeting, TLR7/8 immune-stimulating antibody conjugate (ISAC) BDC-1001 +/- pertuzumab in patients with HER2-positive metastatic breast cancer (MBC) previously treated with trastuzumab deruxtecan

Presenting Author(s) and Co-Author(s):

- M. Pegram. Stanford School of Medicine, United States
- C. Calfa. University of Miami Miller School of Medicine, United States
- C. Chen. Stanford University, United States
- A. Cortes Salgado. Hospital Universitario Ramon y Cajal, United States
- A. Heeke. Levine Cancer Institute, Atrium Health, United States
- I. Kang. City of Hope Orange County, United States
- B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France
- P. Pohlmann. The University of Texas MD Anderson Cancer Center, United States
- H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States
- C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain
- C. Vicier. Institut Paoli-Calmette, United States
- C. Pearson. Bolt Biotherapeutics, United States
- C. Tapia. Bolt Biotherapeutics, Redwood City, California, United States
- M. Yin. Bolt Biotherapeutics, United States
- T. Yu. Bolt Biotherapeutics, United States
- M. Alonso. Bolt Biotherapeutics, United States
- E. Perez. Bolt Biotherapeutics, United States
- J. Drago. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Therapies to effectively manage patients (pts) with metastatic HER2+ breast cancer have significantly improved over the years, but improvement is still needed in both efficacy and tolerability. BDC-1001 is an ISAC consisting of a trastuzumab biosimilar conjugated to a proprietary cell membrane impermeable TLR7/8 agonist via a non-cleavable linker, administered IV every 2 weeks. It is designed to trigger the innate immune system and generate a durable tumor-targeted adaptive immune response. Preclinical studies indicate that HER2-targeted ISACs elicit potent and durable immune-mediated antitumor efficacy, leading to complete tumor regression in a TLR- and Fc receptor-dependent manner [1]. Moreover, preclinical studies with a murine surrogate of BDC-1001 (trastuzumab-T785 ISAC) indicate improved anti-tumor activity with trastuzumab-T785 compared with trastuzumab/pertuzumab.

In these preclinical studies, the combination of trastuzumab-T785 and pertuzumab demonstrated significantly enhanced efficacy in multiple HER2-expressing tumor models, including those with lower HER2 expression [1]. The addition of pertuzumab decreased the quantity of ISAC required for anti-tumor activity in the JIMT-1 HER2 IHC2+ model. Moreover, the combination of pertuzumab with the ISAC significantly increased the cytokine and chemokine concentrations in the tumor xenografts, compared with monotherapy or trastuzumab/pertuzumab, indicating enhanced myeloid activation in the tumor. These

preclinical studies suggest that this combination may enhance the clinical activity of trastuzumab-based ISACs.

The completed part of the BDC-1001 dose escalation trial (NCT04278144) demonstrated safety, PK and pharmacodynamic changes compatible with the ISAC mechanism of action, and a wide range of antitumor activity (incl. cases with breast cancer); resulting in a RP2D of 20 mg/kg q2w [2]. Two trials are underway, including a Phase 2 trial in other HER2+ malignancies, and a randomized Phase 2 trial with BDC-1001 alone and in combination with pertuzumab in patients with HER2-positive MBC previously treated with 2 or more prior anti-HER2 therapies, including trastuzumab deruxtecan.

Methods: The Phase 2 multicenter, open-label, randomized study (BBI-20231001) is enrolling up to 66 pts with HER2-positive (ASCO/CAP guidelines 2018) MBC previously treated with 2 or more prior anti-HER2 therapies, including trastuzumab deruxtecan as one of the prior therapies. Pts must be 18 years or older, have measurable disease (RECIST v1.1), and have Eastern Cooperative Oncology Group performance status of 0 or 1. Pts will be administered BDC-1001 20 mg/kg every 2 weeks (IV q2w) and randomized 1:1 to receive BDC-1001 as a single agent or in combination with pertuzumab. The trial has a Simon 2-stage design within each arm. The primary objective is to determine the overall response rate per RECIST v1.1 of BDC-1001 alone and in combination with pertuzumab. Secondary objectives will evaluate safety, additional efficacy parameters, pharmacokinetics, and immunogenicity of BDC-1001 alone and in combination with pertuzumab. Exploratory objectives will include pharmacodynamic biomarkers in tumor tissue (baseline and on-treatment biopsies if feasible) and in peripheral blood to elucidate the mechanism of action and seek to identify biomarkers associated with BDC-1001 biological activity with or without pertuzumab. This study is expected to initiate accrual in 2H 2023. For additional information, please contact Bolt Biotherapeutics at 1-650-665-9295 or info@boltbio.com.

References

1. S. Ackerman et. al., Nature Cancer, 2021
2. Li, B.T. et. al. J Clin Oncol, 2023 (abstr 2538)

PO1-20-07

Valosin-containing protein (VCP)/p97: A novel breast cancer susceptibility gene?

Presenting Author(s) and Co-Author(s):

A. LeVee. City of Hope Comprehensive Cancer Center, United States

D. Sturgeon. City of Hope National Medical Center, Duarte, CA, United States

J. Mortimer. City of Hope, Duarte, California, United States

K. McDonnell. City of Hope National Medical Center, Duarte, CA, California, United States

Introduction: Mutations in the valosin-containing protein (VCP, also known as p97) gene are associated with autosomal dominant inclusion-body myopathy with early-onset Paget disease and frontotemporal dementia. VCP is an ATPase that subserves a variety of cellular functions, prominently, organelle biogenesis and ubiquitin-dependent protein degradation. Recently, VCP has also been shown to physically interact with BRCA1 and is postulated to orchestrate the response to DNA double-strand breaks, a critical molecular prelude to homologous recombination DNA repair. Moreover, VCP is also involved in the removal of trapped poly [ADP-ribose] polymerase 1 (PARP1) from chromatin and may play a key role in the response of tumor cells to PARP inhibitors. Whether VCP acts as a breast cancer predisposition gene is currently unknown. These observations raise speculation as to whether pathologic variation in VCP may predispose to breast cancer. **Case Description:** A 45-year-old female presented with early-age, locally advanced invasive ductal carcinoma, grade 2, ER < 1%, PR 10%, HER2 IHC 3+, FISH ratio 5.4. The patient completed 6 cycles of neoadjuvant PTH and was surgically downstaged to ypT1bN1a at the time of her left mastectomy. She declined adjuvant radiation. She received 1 dose of trastuzumab emtansine which was discontinued due to intolerance and transitioned to complete 1 year of adjuvant trastuzumab and pertuzumab. Her medical history is significant for inclusion body myopathy with Paget disease of bone and/or frontotemporal dementia, which was diagnosed at age 36 after presenting with proximal muscle weakness. Bone scan was consistent with Paget's disease and neurocognitive testing did not identify any abnormalities. Diagnosis was confirmed via whole genome germline sequencing which identified a pathogenic variant in VCP [c.463C >G (p.Arg155Gly)]. Germline resequencing of 155 known cancer predisposition genes did not identify any pathogenic variants. Whole exome genomic analysis of the patient's breast cancer revealed an elevated homologous recombination score (> 42), consistent with molecularly important role of VCP in homologous recombination breast cancer DNA repair. The patient's family history is significant for muscular dystrophy in multiple family members on her paternal side, each of whom was deceased prior to age 60. Her paternal half-sister has both inclusion body myopathy and breast cancer, and her paternal cousin was diagnosed with breast cancer at age 46 (unknown genetic testing for each). No history of cancer on her maternal side. **Discussion:** This case raises the intriguing question of whether the VCP gene represents a heretofore unrecognized breast cancer predisposition gene. Further investigation into the role of VCP in tumorigenesis is warranted, and additional population studies are necessary to confirm VCP's role in breast cancer predisposition. Given that cancers with homologous recombination deficiencies benefit from PARP inhibitors and VCP is involved in the function of the PARP1 protein, patients with mutations in the VCP gene may benefit from PARP inhibition.

PO1-20-08

Primary breast implant-associated squamous cell carcinoma with subsequent TEMPUS testing and failure of immunotherapy

Presenting Author(s) and Co-Author(s):

E. Podany. Washington University in St. Louis, St. Louis, Missouri, United States

K. Clifton. Washington University in St Louis School of Medicine, United States

Primary squamous cell carcinoma of the breast is a rare entity, and there are a limited number of cases in the literature describing squamous cell carcinoma arising from breast implants. It has been hypothesized that these implant-associated cancers may arise from epithelialization of the implant capsule followed by chronic inflammation. None of the cases in the literature were treated with immunotherapy. We present a case of an aggressive, primary sarcomatoid squamous cell carcinoma of the breast arising from a breast implant that was treated unsuccessfully with simultaneous chemotherapy and immunotherapy following TEMPUS testing.

Introduction: Breast augmentation is the most common plastic surgery procedure performed worldwide, with more than 300,000 done in the United States every year. While breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is extensively discussed in recent literature, other breast implant-associated cancers are rarer and less studied. Breast implant-associated squamous cell carcinoma (BIA-SCC) specifically is an extremely rare complication of breast augmentation and no guidelines for treatment exist. The American Society of Plastic Surgeons (ASPS) released a statement on BIA-SCC on 9/2022 following a safety communication from the FDA, and it is recommended health care providers submit case reports of BIA-SCC to a patient registry.

Case study: We present the case of a female patient who underwent bilateral breast augmentation in 2006 with Mcghan textured, pre-pectoral, areolar saline implants. In 2022, she presented with swelling and a lump in her breast and underwent bilateral breast implant removal with capsulectomy. Pathology showed triple negative sarcomatoid squamous cell carcinoma of the right breast capsule. TEMPUS testing on the breast biopsy revealed a PIK3CA mutation and PD-L1 negative status. Her case was discussed with a multi-disciplinary team including plastic surgery, multiple oncologists, and radiation oncology and her clinical picture was determined to be most consistent with BIA-SCC. Based on the KEYNOTE-522 study, she was determined to be a candidate for neoadjuvant therapy with pembrolizumab and chemotherapy as she was newly diagnosed, previously untreated, nonmetastatic, and had a triple negative tumor. She received two cycles of carboplatin, paclitaxel, and pembrolizumab but unfortunately rapidly progressed with chest wall extension, multiple new pulmonary nodules, worsening lymphadenopathy, right ventricular tumor thrombus, and new malignant pleural effusion and was transitioned to hospice.

Discussion: Seven cases of BIA-SCC, one case of squamous cell carcinoma (SCC) after liquid silicone injection augmentation, one case of squamous metaplasia on the breast implant capsule, and one case of epithelialization of the breast implant capsule have been previously described in the literature (Table 1). None of the available cases of BIA-SCC report TEMPUS testing, and none of the patients were treated with immunotherapy. The origin of BIA-SCC is unclear, but several theories have been described including chronic inflammation leading to conversion of epithelial tissue on the capsule to SCC. It is unknown how the breast implant capsule might become epithelialized to begin with – introduction of epithelium intraoperatively

during augmentation, rupture of epidermal cysts, existence of epithelium in the area from a childhood injury or from birth, or epithelization from chronic shear forces from the augmentation or leakage of the implant are all possibilities. With the ongoing data gathering through the FDA patient registry, we will continue to learn more about these rare cancers and potentially get further insight into their origins.

Table 1

Study	# of patients	Age at diagnosis	Type of implant	Time to diagnosis	Implant rupture?	Tumor location	Pathologic features	Receptor status	Treatment	Outcome
Paletta et al (1992)	1	52	Silicone gel	15	No	Posterior capsule	Invasive SCC, areas of poorly differentiated carcinoma resembling sarcoma	Unknown	Radical mastectomy	Disease free at 12 mos.
Zomerlei et al (2015)	1	58	Smooth silicone implant	15	No	Posterior capsule	Well-differentiated SCC	Triple negative	None	Unknown
Olsen et al (2017)	2	56	Textured saline	18	No	Posterior capsule	Invasive well- to moderately differentiated SCC	Triple negative	Radical mastectomy, chemotherapy, and radiation	Palliative radiation therapy
		81	Silicone implant	42	No	Posterior capsule	Invasive SCC, moderately differentiated with areas of high-grade sarcomatoid/spindle cell differentiation	Triple negative	Radical mastectomy, chemotherapy, and radiation	Died
Buchanan et al (2018)	1	65	Silastic implant	35	Yes	Unknown	Well-differentiated SCC	Unknown	Radical mastectomy and radiation	Disease free at 8 years
Goldberg et al (2020)	2	40	Smooth saline	11	No	Unknown	Moderately differentiated infiltrating, keratinizing SCC	Unknown	Neoadjuvant chemotherapy	Died 3 months after diagnosis
		62	Silicone implant	29	No	Posterior capsule	Well-differentiated, invasive, keratinizing SCC	Unknown	Neoadjuvant chemotherapy and radiation	Palliative care

An overview of cases of BIA-SCC in the literature

PO1-20-09

A rare unilateral expression of hand-foot syndrome: a case report

Presenting Author(s) and Co-Author(s):

D. Urueta Portillo. University of Texas Health and Science at San Antonio, United States

K. Lathrop. UT Health San Antonio, San Antonio, Texas, United States

Introduction: Hand-foot syndrome, also known as palmar-plantar erythrodysesthesia, is a common side effect observed in patients undergoing various chemotherapeutic treatments, including capecitabine. It is characterized by symmetrical palmoplantar numbness, pain, erythema with or without edema, and desquamation. Case Presentation: A 38-year-old woman was diagnosed with multifocal mucinous invasive carcinoma of the left breast, which was ER+, PR+, and HER-2-. She underwent neoadjuvant therapy with docetaxel and trastuzumab, followed by bilateral mastectomy. Postoperatively, radiation therapy was administered to the chest wall, and Tamoxifen and trastuzumab were prescribed. Disease progression occurred after 15 months, involving the sternum, retroperitoneal lymph nodes, and supraclavicular areas. Gemcitabine plus trastuzumab was initiated, along with Zometa for supportive care, resulting in a favorable response for five months. Chemotherapy was discontinued, and the patient received goserelin with anastrozole. One month after discontinuing gemcitabine, she developed recurrent lung disease. Lapatinib plus Capecitabine were administered for 12 months, resulting in further progression to the brain. Brain lesions were managed through whole brain radiation, stereotactic radiosurgery, and a palliative craniectomy. The patient developed a chronic left-sided hemiparesis and a contracture in her left hand. Ado-trastuzumab was initiated but resulted in disease progression. Subsequently, Capecitabine and Neratinib were administered, with a positive response. However, within six months, she developed grade 2 hand-foot syndrome, characterized by erythema and desquamation of the right palm and soles. Supportive care and dose reduction of Capecitabine improved symptoms. Discussion: The pathogenesis of Hand-Foot Syndrome (HFS) remains incompletely understood and may vary depending on the chemotherapeutic agents used. Possible causes include direct toxicity to eccrine coils, activation of enzymes leading to increased metabolite concentration, micro-trauma causing persistent drug extravasation and tissue damage, and activation of inflammatory pathways. Further research is needed to better understand the neurovascular mechanisms involved in HFS. Conclusion: This case report provides insights into the pathophysiological mechanisms of Hand-Foot Syndrome associated with capecitabine use. Preexisting hemiparesis may play a role in protecting against HFS development, suggesting the involvement of mechanical stress. Patients should be advised to avoid activities that subject the palms and soles to excessive friction. Clinicians should be aware of atypical presentations of HFS in patients with neurological disorders and medications that can trigger HFS. Future studies should focus on elucidating the neurovascular mechanisms to enhance patient management.

PO1-20-10

Wernicke Encephalopathy Syndrome in Metastatic Breast Cancer – A Diagnostic Dilemma or An Underdiagnosed Entity

Presenting Author(s) and Co-Author(s):

A. Patel. Roswell Park Comprehensive Cancer Center, United States

A. Roy. Roswell Park Comprehensive Cancer Center, Amherst, New York, United States

R. Alberico. Roswell Park Comprehensive Cancer Center, United States

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

Wernicke encephalopathy (WE) is an acute medical syndrome that manifests as a clinical triad of encephalopathy, gait ataxia, and oculomotor dysfunction, requiring urgent treatment. Early recognition and treatment can prevent severe neurological morbidity and the chronic neurological consequence of WE, known as Korsakoff syndrome. Thiamine (vitamin B1) deficiency is the root cause of WE, which can occur due to several underlying conditions, including chronic alcoholism, hyperemesis of pregnancy, malnutrition, prolonged fasting, and malignancy. In cases of malignancy, WE is often undiagnosed or misdiagnosed because the presenting symptoms can be confused with several other complications of malignancy. We present the case of a 47-year-old woman with no significant medical history who was diagnosed with triple negative metastatic breast cancer and admitted to the hospital with confusion, memory loss, and progressive lower extremity weakness. During her breast cancer treatments, she experienced significant nausea and vomiting, leading to a prolonged state of nutritional imbalance. Patient underwent extensive infectious and neurological workup for encephalopathy including lumbar puncture which was negative for leptomenigeal disease or infection. MRI brain did not show any new metastatic lesions however revealed enhancement of mammillary bodies bilaterally. Mammillary body enhancement can be seen in WE but not always present on imaging. She was treated for WE with high dose of thiamine infusion for five days, resulting in an improvement of her neurological symptoms.

Diagnosing WE in cancer patients is challenging, as there are various factors to consider, such as cerebral metastasis, infection, chemotherapy treatment, and electrolyte imbalances, that can cause neurological symptoms. Cancer patients are at high risk for development of WE due to chemotherapy or whole brain radiation induced nausea and vomiting that can lead to chronic malnutrition. The typical triad of symptoms is not present in many cases and presenting symptoms can be nonspecific which makes the diagnosis challenging. As a result, WE is often underdiagnosed in such patients, making it essential to educate the physician community about this acute neurological manifestation that can be easily treated. A high index of suspicion is necessary for early recognition, and prompt treatment can prevent Korsakoff syndrome, thereby enhancing the overall quality of life of patients with malignancy.

PO1-20-11

Delay in Diagnosis of Locally Advanced Breast Cancer during Lactation “Case Report”

Presenting Author(s) and Co-Author(s):

J. Flores Banda. The University of Texas Health Science Center at Tyler, Tyler, Texas, United States

K. Donthireddy. UT Health Science Center at Tyler, United States

A 38-year-old breastfeeding female with no family history of breast or gynecological cancer presented to her PCP with a 4-month history of galactorrhea and enlarged left-sided breast mass. On physical exam, a 4-inch round complex, nonmobile, non-tender mass in the left breast and bloody-to-pink discharge from the nipple was present on the exam. Diagnostic mammogram and US revealed BIRADS 5, microcalcifications consistent with DCIS, 4-cm mass, with a positive lymph node (LN), and needle core biopsy of both breast and LN, showed DCIS and metastatic carcinoma, respectively. Further workup did not show distant or skeletal metastatic disease. Therefore, a diagnosis was made, and the patient was provided a clinical-stage cT3, cN2, cM0, ER+, PR-, and HER2+. The patient completed neoadjuvant therapy with TCHP and underwent a left lumpectomy with sentinel LN biopsy. Additionally, pathology diagnosis showed scant residual DCIS (10mm) and no metastatic disease in the LN. After that, the patient completed adjuvant radiotherapy and was placed on adjuvant therapy with trastuzumab and pertuzumab. In conclusion, any breast abnormality reported by a pregnant or breastfeeding woman should not be neglected and assumed that it is a regular and physiological change until proven otherwise. Future proposals include guidelines for managing abnormal breast findings during pregnancy.

PO1-20-12

CD8+ Tumor Infiltrating Lymphocytes Turn a Cold Tumor Hot in Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Kuker. University of Miami, United States

F. Valdes-Albini. University of Miami, United States

G. Del Priore. BriaCell Therapeutics, Philadelphia, Pennsylvania, United States

A. Arif. University of Miami, United States

K. Schmiedehausen. ImaginAb, United States

C. Calfa. University of Miami Miller School of Medicine, United States

Introduction: Turning “cold” tumors “hot” is considered essential for immune-oncology therapies to be effective. Bria-IMT is an allogenic human cancer cell line with antigen presenting cell activity (SV-BR-1-GM) designed to overcome the immune-suppressive tumor microenvironment. However, until now there has not been proof that “cold” tumors can become “hot” with this therapy. Using Zr-89 crefmirlimab berdoxam, a zirconium-89 labelled truncated antibody specific to human CD8 α and developed for CD8 ImmunoPET, we image before and after Bria-IMT therapy administration to assess the baseline status as well as changes in CD8 cell presence after initiation of therapy. Here we present the first evidence that cold tumors can become hot on treatment with Bria-IMT combined with an anti-PD-1 checkpoint inhibitor (CPI), showing CD8+ cells increased over baseline using CD8 ImmunoPET. Case: After informed consent, a 61 year-old Hispanic female, enrolled in the ongoing randomized phase 2 Bria-IMT trial in advanced heavily pretreated metastatic breast cancer (MBC) (NCT03328026). Her history included MBC in May 2020, ductal type, grade 3, triple negative breast cancer (TNBC) with 6 prior lines of therapy including a Trop-2-directed antibody-drug conjugate and 6 lines of chemotherapy. Precision medicine testing identified no actionable targets. All prior therapies had progressive disease as their best response. The subject was randomized to start the CPI after 2 cycles of Bria-IMT to “train” the host immune system before proceeding with combination immune-oncology therapy. Baseline testing revealed the subject to be anergic to candida and SV-BR-1-GM inoculation. However, by cycle 3 delayed-type hypersensitivity to SV-BR-1GM developed. Interestingly the subject matched SV-BR-1-GM at 2 HLA loci: DRB3*02:02 and DRB1*11:04 which in previous publications is associated with greater clinical benefit. Tumor markers were stable or decreased slightly including CEA (25% decrease) and CA 15-3 (43% decrease). Circulating Tumor Cells (CTCs) and Cancer Associated Macrophage Like cells (CAMLs) also improved. Standard imaging at baseline showed 3 main sites of disease including a large right breast mass, multiple right axillary lymph nodes and a right lower lobe mass with CD8 ImmunoPET uptake in these areas similar to the blood pool. On the follow-up CT imaging, all of these lesions increased in size with newly appreciated pulmonary nodules. The right lower lobe mass showed increased CD8 ImmunoPET accumulation with an SUV of 5.8 (close to the liver background) as compared to an SUV of 2.2 at baseline. The lesions in the right breast and right axilla remained at blood pool levels. There was an increase in CD8 ImmunoPET uptake in bilateral inguinal lymph nodes reaching an SUV of 4.8 as compared to SUV 2.2 at baseline. In addition, there were non-enlarged lymph nodes in bilateral axillary regions that also showed increased radio-tracer accumulation reaching an SUV of 9.5 as compared to SUV 4.9 at baseline. Conclusion: This subject demonstrated a mixed response of metastatic lesions on CD8 ImmunoPET with encouraging changes in peripheral blood tumor markers and CTCs. The nonspecific nodal localization of CD8 ImmunoPET may indicate a

systemic activation of CD8 positive lymphoid cells. This shows the value of CD8 ImmunoPET in identifying lesions that are progressing on treatment versus pseudo progression. It also provides support that the Bria-IMT + CPI combination immune-based therapy can result in an increase of CD8+ tumor infiltrating lymphocytes in breast cancer metastatic sites as well as an increase in lymphoid organs. This advance may aid in triaging patients, adjudicating pseudo-progression and predicting clinical benefit of immune based therapies.

PO1-20-13

TROPION-Breast04: A phase 3 study of neoadjuvant datopotamab deruxtecan (Dato-DXd) + durvalumab followed by adjuvant durvalumab vs the standard of care in treatment-naive early-stage triple negative or HR-low/HER2- breast cancer

Presenting Author(s) and Co-Author(s):

H. McArthur. UT Southwestern, Dallas, Texas, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

R. Dent. National Cancer Centre Singapore, Singapore

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

J. Asselah. McGill University Health Centre, Montreal, Quebec, Canada

E. Song. Breast Tumour Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

N. Niikura. Tokai University School of Medicine, Isehara-shi, Isehara, Kanagawa, Japan

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

G. Werutsky. Hospital São Lucas, PUCRS University, Porto Alegre, Rio Grande do Sul, Brazil

G. Bianchini. IRCCS Ospedale San Raffaele, Milan, Lombardia, Italy

J. Andersen. Compass Oncology, United States

R. Kozarski, PhD – AstraZeneca

N. Rokutanda, MD, PhD – AstraZeneca

B. Pistilli, MD – Medical Oncologist, Gustave Roussy

Background: The current standard of care for patients (pts) with treatment-naive Stage II–III triple-negative breast cancer (TNBC) is neoadjuvant pembrolizumab + anthracycline/taxane/platinum-based chemotherapy followed by surgery and adjuvant pembrolizumab monotherapy. However, among pts who received the combination of pembrolizumab and chemotherapy in the KEYNOTE-522 trial (NCT03036488), 28% ultimately discontinued therapy due to treatment-related adverse events, and 37% had residual disease at the time of surgery, which was associated with poor outcomes. Consequently, there remains an unmet need to develop a treatment approach that improves pathologic complete response (pCR) rates and long-term survival while reducing chemotherapy-associated toxicity in pts with early-stage TNBC. Dato-DXd is a TROP2-directed antibody-drug conjugate that consists of a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to a potent topoisomerase I (Topo-I) inhibitor via a plasma stable tetrapeptide-based tumor-selective cleavable linker. Dato-DXd monotherapy has demonstrated a manageable safety profile and encouraging preliminary efficacy in pts with metastatic TNBC in the Phase 1 TROPION-PanTumor01 study (NCT03401385), with a confirmed objective response rate (ORR) of 32% in all pts and 44% in Topo-I inhibitor-naive pts with measurable disease at baseline. The combination of Dato-DXd with durvalumab has demonstrated durable responses in unresectable locally advanced or metastatic TNBC in the Phase 1b/2 BEGONIA study (NCT03742102), with an ORR of 79%, median duration of response of 15.5 months and median progression-free survival of 13.8 months. The ongoing Phase 3 TROPION-Breast03 trial (NCT05629585) is evaluating Dato-DXd ± durvalumab versus standard-of-care therapy as adjuvant treatment in pts with Stage I–III TNBC with residual invasive disease at the time of surgery after neoadjuvant treatment. The

TROPION-Breast04 trial aims to determine if improved efficacy and safety can be achieved with neoadjuvant Dato-DXd + durvalumab followed by adjuvant durvalumab, compared with the pembrolizumab-based standard of care regimen in pts with previously untreated TNBC or hormone receptor-low (estrogen and/or progesterone receptor 1% to <10%; neither hormone receptor may be ≥10%)/HER2-negative (HR-low/HER2-) breast cancer.

Trial design: TROPION-Breast04 (NCT06112379) is an ongoing Phase 3, 2-arm, parallel-group, randomized, open-label, multicenter, global trial. Approximately 1728 adults (aged ≥18 years) with previously untreated histologically confirmed Stage II–III unilateral or bilateral primary invasive TNBC or HR-low/HER2- breast cancer per AJCC edition 8 as assessed by the investigator, and an ECOG PS of 0 or 1, will be randomized 1:1 into one of two arms: neoadjuvant Dato-DXd + durvalumab followed by adjuvant durvalumab-based therapy, or neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab-based therapy (full treatment details are provided in the Table). Randomization will be stratified by lymph node status, tumor stage, HR status, and geographic region. Pts with distant disease and any prior surgery, radiotherapy, or systemic anticancer therapy will be excluded from the study. The primary endpoints are pCR and event-free survival. The key secondary endpoint is overall survival; others are distant disease-free survival, patient reported outcomes, pharmacokinetics, immunogenicity, and safety/tolerability. TROPION-Breast04 opened for enrolment in November 2023.

Table. TROPION-Breast04 treatment arms.

	Neoadjuvant therapy	Surgery	Adjuvant therapy
Experimental arm	Dato-DXd ⁽¹⁾ AND durvalumab ⁽²⁾ for 8 cycles.	Indicated	Durvalumab ⁽³⁾ for 9 cycles. Olaparib ⁽⁴⁾ may be given with durvalumab in pts with gBRCA-positive tumors and residual disease, but pts cannot receive chemotherapy and olaparib concurrently. Adjuvant chemotherapy* may be given in combination with durvalumab only if pts <u>have</u> residual disease.
Control arm	Pembrolizumab ⁽⁵⁾ AND carboplatin ⁽⁶⁾ AND paclitaxel ⁽⁷⁾ for 4 cycles, THEN: Pembrolizumab ⁽⁵⁾ AND cyclophosphamide ⁽⁸⁾ AND EITHER doxorubicin ⁽⁹⁾ OR epirubicin ⁽¹⁰⁾ for 4 cycles.	Indicated	Pembrolizumab ⁽⁵⁾ for 9 cycles. Olaparib ⁽⁴⁾ may be given with pembrolizumab in pts with gBRCA-positive tumors and residual disease, but pts cannot receive capecitabine and olaparib concurrently. Adjuvant capecitabine ⁽¹¹⁾ for 8 cycles may be given in combination with pembrolizumab ⁽⁵⁾ only if pts <u>have</u> residual disease.

*Chemotherapy may be one of four regimens:
1) Either doxorubicin⁽⁹⁾ or epirubicin⁽¹⁰⁾ + cyclophosphamide⁽⁸⁾ for 4 cycles followed by paclitaxel⁽⁷⁾ and carboplatin⁽⁶⁾ for 4 cycles;
2) Either doxorubicin⁽⁹⁾ or epirubicin⁽¹⁰⁾ + cyclophosphamide⁽⁸⁾ for 4 cycles followed by paclitaxel⁽⁷⁾ for 4 cycles;
3) Carboplatin⁽⁶⁾ + paclitaxel⁽⁷⁾ for 4 cycles;
4) Capecitabine⁽¹¹⁾ for 8 cycles.
⁽¹⁾6 mg/kg IV Q3W; ⁽²⁾1120 mg IV Q3W; ⁽³⁾300 mg PO BD for 1 year; ⁽⁴⁾200 mg IV Q3W; ⁽⁵⁾AUC 5 mg/mL/min IV Q3W; OR AUC 1.5 mg/mL/min IV QW (based on investigator preference); ⁽⁶⁾90 mg/m² IV QW; ⁽⁷⁾600 mg/m² IV Q3W; ⁽⁸⁾60 mg/m² IV Q3W; ⁽⁹⁾90 mg/m² IV Q3W; ⁽¹⁰⁾1000 or 1250 mg/m² (based in standard institutional practice) PO BD on Days 1 to 14, Q3W.
AUC, area under curve; BD, twice daily; Dato-DXd, datopotamab deruxtecan; gBRCA, germline breast cancer resistance gene; IV, intravenously; PO, orally; QW, weekly; Q3W, every 3 weeks.

PO1-21-01

A Case of High Grade Metastatic Encapsulated Papillary Carcinoma and a Look at Current Treatment Guidelines

Presenting Author(s) and Co-Author(s):

N. Gore. University Hospital, United States

M. Silva. University Hospital, United States

C. Calvo-Strube. University Hospital, United States

Title: A Case of High Grade Metastatic Encapsulated Papillary Carcinoma and a Look at Current Treatment Guidelines. Abstract: Authors: Nicholas Gore MD, Madeline Silva MD, Carissia Calvo-Strube MD Background: Encapsulated papillary carcinoma is a well-documented malignancy in the world of breast surgery. It is often described as a less invasive form of breast cancer, with a more indolent clinical course. Most EPC pathology demonstrates low grade tumors, with rare findings of metastases at time of diagnosis. EPC currently accounts for 1-2% of all breast cancers. It is distinguished by its fibrovascular core, which is covered with epithelium with or without a myoepithelial layer. Despite EPC being well-recognized, current management remains controversial. Most commonly, however, it is treated and managed as an in-situ disease. Case Presentation: We present a case of a 64-year-old female who initially presented with a painless lump in her left breast, which on biopsy demonstrated DCIS involved with a papillary lesion. On excision, the patient was upstaged to IDC in a background of EPC. She then underwent re-excision with confirmed negative margins. Despite this, over the following months, the patient continued to have increased pain, swelling, and an episode of superficial thrombophlebitis. She was taken back to the OR at this time and was found to have a new mass with a large feeding vein. Pathology was significant for high grade multifocal EPC with small and large vessel lympho-vascular invasion. Lesion noted to be metachronous. Additionally, metastases to the axilla were identified, requiring an axillary dissection. Conclusion: High grade encapsulated papillary carcinoma is a rare member of the indolent papillary breast cancer family. This unusually invasive type of cancer should be treated and managed in a more aggressive fashion, like its clinically similar cousin invasive ductal carcinoma. The current management standard of treating EPC as in situ disease is not robust enough and can lead to disease recurrence and need for repeat resection and treatment.

PO1-22-02

Optimal intra-fraction PTV margins for patients receiving stereotactic partial breast radiation (SPBI) using cone beam adaptive radiation therapy

Presenting Author(s) and Co-Author(s):

M. Hsieh. UTSW, United States

J. Visak. UTSW, United States

S. Domal. UTSW, United States

G. Gard. UTSW, United States

S. Montalvo. UTSW, United States

L. Chen. UTSW, United States

X. Zhong. UTSW, United States

Z. Iqbal. UTSW, United States

T. Zhuang. UTSW, United States

B. Cai. UTSW, United States

H. Kim. UTSW, United States

M. Arbab. UTSW, United States

P. Alluri. UTSW, United States

N. Kim. VUMC, United States

M. Lin. Medical Artificial Intelligence and Automation (MAIA) Lab, Department of Radiation Oncology, UT Southwestern Medical Center, United States

D. Parsons. UTSW, United States

A. Rahimi. University of Texas Southwestern Medical Center, Dallas, Texas, United States

Objectives To quantify the intra-fraction tumor bed motion using image guidance and fiducial markers to determine optimal PTV margins in early-stage breast cancer patients receiving adaptive radiation therapy SPBI after partial mastectomy. **Methods** A retrospective cohort of five patients with pT1a-pT2N0, grade 1-2, ER+/PR+ early-stage invasive ductal carcinoma of either the right breast or left breast underwent partial mastectomy and adjuvant five-fraction SPBI using cone beam based online adaptation. A total of 62 CBCTs and 22 total fractions were analyzed after post-processing with an average time span of 39.1 ± 8.9 minutes. Two methods were utilized to determine optimal CTV to PTV margins: one contouring-based and another fiducial-based. Our contouring-based method involved independently contouring on each fraction's CBCTs including pre-treatment CBCT, intra-treatment CBCT, and post-treatment CBCT. After image registration with the original simulation CT image, these contours were propagated to and combined to create a new union CTV. Using the original CTV on the simulation CT, optimal PTV margin was determined to achieve 95% overlap of the union CTV created from fractionated CBCTs. In addition to the contouring-based method, our fiducial-based method utilized an in-house script to calculate the centroid of all fiducials per CBCT. The average and maximum anterior-posterior, medial-lateral, superior-inferior shifts of fiducials between intra-fraction CBCTs were recorded. **Results** Using our contouring-based method, we calculated and determined that a uniform 3.5 mm expansion around the original CT simulation CTV is needed to achieve 95% PTV overlap encompassing the pre-treatment, intra-treatment, and post-treatment union CTV. Furthermore, with our fiducial-based method, we calculated average centroid anterior-posterior, medial-lateral and superior-inferior shifts to be the

following: 1.51 ± 0.79 mm, 1.04 ± 0.55 mm, 1.78 ± 0.94 mm respectively. Average maximum shifts were determined to be 2.13 ± 1.18 mm anterior-posterior, 1.45 ± 0.76 mm medial-lateral and 2.47 ± 1.40 mm superior-inferior shifts. Conclusion With our contouring-based analysis, this preliminarily study suggests CTV to PTV margin of 3.5mm is adequate. On the other hand, our fiducial-based method suggests decreased movement and smaller asymmetric margin. Further CBCT adaptation images will be analyzed. In conjunction with these two methods, we currently recommend utilizing a 3.5mm uniform margin for intrafraction motion and to assess adequate coverage with image guidance during daily adaptation for patients with early-stage breast cancer receiving SPBI.

PO1-22-03

Radiation Toxicity and Treatment Outcomes in Breast Cancer Patients with ATM Pathogenic and VUS Mutations: Implications for Personalized Therapy

Presenting Author(s) and Co-Author(s):

E. Tezcanli. Acibadem MAA University, Research Institute of Senology, United States

S. Eroz. Acibadem MAA University, Research Institute of Senology, United States

U. Ozbek. Acibadem MAA University, Research Institute of Senology, United States

A. Yesilyurt. Acibadem MAA University, Research Institute of Senology, United States

C. URAS. Acibadem MAA University, Research Institute of Senology, Head, United States

N. Bese. Research Institute of Senology Acibadem, Istanbul, Turkey, United States

Introduction: Previous studies have shown that ATM (ataxia-telangiectasia mutated) mutations may be associated with increased radiation sensitivity and altered treatment response. However, there is a limited understanding of the clinical implications and optimal management strategies for breast cancer patients with ATM mutations receiving radiotherapy (RT). The aim of our study is to assess the impact of ATM mutations on radiation response and treatment outcomes in breast cancer patients undergoing RT.

Material and Methods: A total of 79 female patients diagnosed with breast cancer were included in the study, with 31 (39.3%) having pathogenic (P) and likely pathogenic (LP) variants (all of the variants were heterozygous) and 48 (60.8%) having VUS variants detected through whole ATM gene sequencing screening for patients in accordance with NCCN clinical practice guideline. Statistical analysis, including descriptive, graphical, and inferential methods, such as the Kolmogorov-Smirnov test, Mann-Whitney U Test, and Chi-square tests, was conducted using SPSS version 25.0 to evaluate the normal distribution of continuous variable scores and perform quantitative and qualitative comparisons between groups at a 95% confidence level ($p < 0.05$).

Results: The median age of the patients was 44 years (range: 24-74), with 75% of them being 50 years old or younger. The rate of breast cancer in patients with VUS variants was significantly higher in those aged 50 and below compared to those with P/LP variants (83% vs. 61%, $p=0.028$). There was no statistically significant difference in clinical stage, tumour histological type, and molecular subtype classification based on ATM gene variant type (P/LP vs. VUS) among the patients ($p>0.05$), but the rate of high tumour grade was significantly higher in the VUS variant group (65% vs. 40%, $p=0.034$). The rate of patients who received RT was 87%, with 26 patients receiving radiation to the breast or chest wall and 43 patients receiving additional regional lymph node irradiation. There were no statistically significant differences in surgical and systemic treatment types and RT dose based on ATM gene variant type (P/LP vs. VUS) ($p>0.05$). Among the patients who received RT, 33 (48%) experienced early-stage skin reactions, and 15 (22%) experienced late-stage skin reactions according to Common Terminology Criteria for Adverse Events (CTCAE) v5. No Grade 3, 4 and 5 early and late toxicity were observed. The rate of early (83% vs. 23%; $p< 0.001$) and late (35% vs. 13%; $p=0.029$) skin reactions was significantly higher in the P/LP variant group compared to the VUS variant group. Grade I lymphedema was observed in 2 (2.5%) patients, 1 (3.2%) in the P/LP group and 1 (2.1%) in the VUS group ($p>0.05$). Among the 23 patients who underwent breast reconstruction, 1 (4%) had implant revision and 1 (4%) experienced implant loss, both of which were observed in the pathogenic variant group ($p>0.05$).

Conclusion: Limited clinical data exists on RT toxicity in breast cancer patients with ATM gene mutations, and clear guidelines for decision-making are lacking. Our study revealed higher rates of acute and chronic skin reactions in the P/LP variant group, highlighting the need for further investigation into the impact of these variants on treatment outcomes and patient management. However, it is crucial to manage these reactions effectively and not allow them to hinder treatment. Additional research and interventions are warranted to better understand and address these reactions, aiming to enhance the overall treatment experience and outcomes for patients with ATM gene mutations.

PO1-22-04

Cosmetic results of the breast in patients treated with Five Fraction Accelerated Partial Breast Irradiation for early stage breast cancer: retrospective review comparing Daily versus Every Other Day Treatment.

Presenting Author(s) and Co-Author(s):

A. Goss. Christus St Vincent Regional Cancer Center, Santa Fe, New Mexico, United States

E. Haroz. Christus St Vincent Regional Cancer Center, Santa Fe, New Mexico, United States

A. Voltura. X-Ray Associates of New Mexico, Breast Surgery Associates, Santa Fe, New Mexico, United States

J. McGrath. Christus St Vincent Regional Cancer Center, Santa Fe, New Mexico, United States

O. Sloan. Christus St Vincent Regional Medical Center, United States

M. Jackson. Christus St Vincent Regional Cancer Center, United States

S. Morris. Christus St Vincent Regional Cancer Center, Santa Fe, New Mexico, United States

B. Goss. Christus St Vincent Regional Cancer Center, United States

Introduction: Breast cosmesis results using Accelerated Partial Breast Irradiation (APBI) with IMRT external beam in 5 fractions (6Gy x 5 fractions) has been reported as good to excellent in the literature. This retrospective review compares breast cosmesis in patients treated with Daily versus Every Other Day APBI in the community practice setting. Methods: The patient electronic medical records (EMR) were used to identify APBI patients treated at the community cancer center with the 6Gy x 5 fraction regimen. Harvard breast cosmesis four point scale results (poor, fair, good, excellent results) were extracted for each treated APBI patient from clinical notes in the EMR to rate breast cosmesis. For many patients in this review, provider reporting of cosmesis in the EMR overlapped good and excellent categories and so a "good to excellent" score was assigned. Therefore, a three point scale was utilized in statistical analysis (poor-1, fair-2, good to excellent-3). Results: There were 62 patients treated with APBI at a single institution with greater than 6 months follow up (18 patients treated daily and 44 patients treated every other day). Median follow up was 12 months (range 6- 32 months). Of all patients treated there were 0 with poor cosmesis, 3 with fair (1 every other day treatment, 2 every day treatment), 59 with good to excellent cosmesis. Univariate logistical regression analysis revealed no significant difference between daily and every other day treatment (p=0.457) Conclusion: With careful patient selection, quality planning and treatment delivery, good to excellent cosmesis is achievable in the great majority of patients undergoing breast APBI (6Gy x 5 fractions) using IMRT in the community radiation oncology clinic with either daily or every other day treatment. More study is needed, but in this review cosmetic differences seem to be minimal between daily and every other day treatment schedules.

PO1-22-05

Radiation Therapy Toxicities and Survival Outcomes in Monoallelic ATM Variant Carriers with Non-Metastatic Breast Cancer: A Retrospective Analysis

Presenting Author(s) and Co-Author(s):

R. BENSENANE. Institut Curie Paris, Paris, Ile-de-France, France

Y. Kirova. Institut Curie, Paris, Ile-de-France, France

A. BEDDOK. Institut Curie Paris, United States

A. ANDRIEU. Institut Curie Paris, United States

F. Lesueur. INSERM900/Institut Curie, Paris, France, United States

E. CAVACIUTI. Institut Curie Paris, United States

D. Le GAL. Institut Curie Paris, United States

S. EON-MARCHAIS. Institut Curie Paris, United States

D. STOPPA LYONNET. Institut Curie Paris, United States

Radiation Therapy Toxicities and Survival Outcomes in Monoallelic ATM Variant Carriers with Non-Metastatic Breast Cancer: A Retrospective Analysis Rayan Bensenane¹ MD, Arnaud Beddok^{1,2,3} MD, Nadine Andrieu⁴ PhD, Fabienne Lesueur⁴ PhD, Eve Cavaciuti⁴ MSc, Dorothee Le Gal⁴ MSc, Eon-Marchais Severine⁴ PhD, Dominique Stoppa Lyonnet⁵ MD PhD, Youlia Kirova¹ MD 1. Institut Curie, PSL Research University, Radiation Oncology Department, Paris/Saint-Cloud/Orsay, France. 2. Gordon Center for Medical Imaging, Massachusetts General Hospital, Harvard Medical School, 125 Nashua St., Boston, MA, 02114, USA 3. Institut Curie, PSL Research University, University Paris Saclay, Inserm LITO U1288 Orsay, France 4. Inserm, U900, Institut Curie, PSL Research University, Mines ParisTech, Paris, France Abstract (characters: 2952; max 3400 characters, not include spaces) Background: The Ataxia-Telangiectasia Mutated (ATM) gene, involved in the repair of DNA double-strand breaks, can contribute to radiosensitivity when a bi-allelic variant is present and lead to Ataxia-Telangiectasia syndrome. Moreover, monoallelic ATM pathologic variant (PV) carriers, especially women, has an estimated occurrence rate of 0.5-1% globally and face a 2 to 3-fold increased risk of developing breast cancer. Despite evidence of in vitro radiosensitivity in cells derived from monoallelic variant carriers, there is a dearth of patient studies examining the risk of radiation-induced toxicity. This study aims to explore radiation therapy (RT) toxicities in non-metastatic breast cancer women carrying a germline monoallelic ATM variant, compared to non-carriers. Methods: A retrospective study was conducted on patients treated at Institut Curie, Paris from 1999 to 2014 and participating to CoF-AT (a French national study) and GENESIS database. ATM variant screenings encompassed both PV and non-PV, with toxicities evaluated using CTCAE v.5. Variants were classified as pathogenic, variant of unknown significance (VUS), or benign. Follow-up started from age/date at breast cancer to acute, late toxicities, disease recurrence or last news. Survival and toxicity comparisons were made using Kaplan-Meier survival analysis and Chi-square tests, respectively, with a significance level of α set at 0.05. Results: Among 50 patients, nine were ATM variant carriers (3 PV/5 VUS/1 benign), and 41 were non-carriers. Most patients had no smoking history (68%), and invasive ductal carcinoma was the predominant diagnosis (82%). The majority underwent breast-conservative surgery (80%), and the dominant RT techniques were 3D-Conformational Radiation Therapy (70%) and Isocentric Lateral Decubitus (30%). The median RT dose was 50 Gy over an average period of 36.5 days. With a median follow-up of 12 years post-diagnosis, no significant difference in acute dermatitis, esophagitis, lymphedema, cutaneous fibrosis, telangiectasia, or

heart disease was observed between the groups. Analysis of overall survival (OS) showed a 5-year OS of 98%, decreasing to 89% at 10 years. For ATM variant carriers, the OS at 5, 10, and 15 years was 100%, 89%, and 89%, respectively, similar to non-carriers. Kaplan-Meier analysis revealed no significant differences in 5, 10, and 15-year overall survival, progression-free survival, local failure-specific survival, and contralateral breast cancer rates between the groups. Conclusion: In non-metastatic breast cancer patients, monoallelic ATM variant carrier status does not significantly influence acute or late RT toxicities and survival outcomes. These findings, derived from a small cohort, highlight the need for prospective studies for further validation.

Table: Acute and Late Toxicities Post-Radiation Therapy in Monoallelic ATM Variant Carriers vs Non-Carriers

Table: Acute and Late Toxicities Post-Radiation Therapy in Monoallelic ATM Variant Carriers vs Non-Carriers

	Number of patients with toxicities (%)				P value*	
	Grade 0	Grade 1	Grade 2	Grade 3		
Acute toxicities						
Dermatitis	ATM +/+	7 (14%)	21 (42%)	9 (18%)	4 (8%)	NS
	ATM +/-	1 (2%)	5 (10%)	2 (4%)	1 (2%)	
Esophagitis	ATM +/+	37 (74%)	4 (8%)	0	0	NS
	ATM +/-	9 (18%)	0	0	0	
<u>Lymphoedema</u>	ATM +/+	39 (78%)	2 (4%)	0	0	NS
	ATM +/-	9 (18%)	0	0	0	
Late toxicities						
Fibrosis	ATM +/+	23 (46%)	16 (32%)	2 (4%)	0	NS
	ATM +/-	7 (14%)	2 (4%)	0	0	
Telangiectasia	ATM +/+	37 (74%)	4 (8%)	0	0	NS
	ATM +/-	9 (18%)	0	0	0	
<u>Lymphoedema</u>	ATM +/+	38 (76%)	0	3 (6%)	0	0.07
	ATM +/-	8 (16%)	1 (2%)	0	0	
Heart disease	ATM +/+	40 (80%)	1 (2%)	0	0	NS
	ATM +/-	9 (18%)	0	0	0	

* Pearson/Chi² test ; NS: non significant at $\alpha=0.05$; ATM +/+ : wild type for ATM; ATM +/- : ATM monoallelic germline variant carrier

* Pearson/Chi² test ; NS: non significant at $\alpha=0.05$; ATM +/+ : wild type for ATM; ATM +/- : ATM monoallelic germline variant carrier

PO1-22-06

Pre-operative radiotherapy followed by mastectomy and breast reconstruction – a systematic review of oncological and reconstructive outcomes

Presenting Author(s) and Co-Author(s):

K. Ho. Department of Breast Surgery, Imperial College Healthcare NHS Trust, London, UK, United States

J. Ward. Department of Plastic Surgery, The Royal Marsden Hospital NHS Foundation Trust, London, UK, United States

C. Ike. Department of Plastic Surgery, The Royal Marsden Hospital NHS Foundation Trust, London, UK, United States

P. Thiruchelvam. Department of Breast Surgery, Imperial College Healthcare NHS Trust, London, UK, United States

A. Khan. Department of Plastic Surgery, The Royal Marsden Hospital, London, UK, United States

D. Leff. Imperial College London, United States

Background Pre-operative radiotherapy (PRT) followed by mastectomy and autologous breast reconstruction for locally advanced breast cancer has the potential to reduce the deleterious impact of radiotherapy on the reconstructed breast and expedite treatment without impact on oncologic control. The PRADA feasibility study (Lancet Oncol 2022; 23: 682-90) has previously demonstrated the technique is technically feasible and safe in modern breast oncology practice, however, there is a clear necessity for longer term outcome data to precisely determine clinical efficacy. In order to understand and appraise this evidence gap, we performed a systematic review focused on oncologic and reconstructive outcomes of PRT followed by mastectomy and breast reconstruction. Methods A prospectively registered search (PROSPERO ID: CRD42023349524) of Medline (Ovid), EMBASE (Ovid), EMCARE (Ovid) and CINAHL (EBSCO) databases was performed in August 2022 for studies reporting NART prior to mastectomy and breast reconstruction. Oncological and aesthetic outcomes were extracted with risk of bias (ROBINS-I) and methodological quality assessed (STROBE checklist) for each study. Results Twenty one published articles (18 papers and 3 abstracts) were identified reporting the outcomes of 1,126 patients with median follow-up between 19.0-212.4 months. Seventeen studies were non randomised single-centre cohort studies (12 retrospective and 5 prospective). Patients received neoadjuvant chemotherapy in 18 studies. The majority of studies were of low methodological quality and at serious risk of bias. Rates of locoregional recurrence and overall survival ranged between 0-21.7% and 79.8%-98.3% respectively. Rates of flap loss or necrosis ranged from 0-12.0%. Rates of revisional procedures ranged between 0-35.3%. Patient-reported outcomes were reported in 8 studies and were mostly 'good' or 'excellent'. Conclusion The published literature described a heterogeneity of outcome for patients undergoing NART prior to mastectomy and breast reconstruction. This reflects a large number of small retrospective single-centre cohort studies of low methodological quality at risk of bias. There is a clear need for a prospective randomised controlled trial appraising the outcomes of PRT in the context of autologous breast reconstruction.

PO1-22-08

Ductal Lavage versus Oral Corticosteroids in Patients with Idiopathic Granulomatous Mastitis: A Multicenter, Open-label, Randomized, Controlled, Non-inferiority Study

Presenting Author(s) and Co-Author(s):

K. Chen. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

X. Chen. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

S. Li. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

L. Zhu. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

J. Zhang. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, United States

T. Hu. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

H. Huang. Department of Mammary Surgery, Maternity and Child Health Care Hospital of Jiangmen, United States

H. Huang. Department of Mammary Surgery, Lianjiang People's Hospital, United States

L. Chen. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

Q. Xiao. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

L. Su. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

Background: Idiopathic granulomatous mastitis (IGM) is an inflammatory breast disease characterized by the presence of mass, erythema and fistula. Various treatments have been proposed, including steroids, surgery, immunosuppressants, and observation alone. However, most of the reported studies are single-center, retrospective, single-arm with limited sample sizes, leaving the optimal treatment strategy unknown. In a previous single-arm study, we reported the efficacy and safety of ductal lavage as a novel treatment. This presentation presents the results of a multicenter, open-label, randomized controlled, non-inferiority trial that compares the efficacy and safety of ductal lavage with oral corticosteroids as the first-line treatment for IGM patients. Methods: Eligible IGM patients were randomized 1:1 to receive either ductal lavage or oral corticosteroids, stratified by M-score status. The M-score quantitatively evaluates IGM symptom severity as reported in our previous studies. Ductal lavage involved the intraductal infusion of lidocaine, triamcinolone acetonide, and ceftriaxone with saline, a total 5 times within 2 weeks. Oral corticosteroids were administered using prednisone or methylprednisolone at an initial dose of 20-40mg per day, decreased by 5mg every 2 weeks, and then maintained at 20mg per day for at least 1 month. The primary outcome was the rate of complete Clinical Response (cCR), which was defined as achieving M-score \leq 1 during any follow-up visit. Secondary outcomes included median time to first cCR, treatment failure, relapse, adverse events, and protocol compliance rate. If the lower limit of 95%CI of the absolute difference between ductal lavage and oral corticosteroids was greater than -15%, the non-inferiority was met. This trial was approved by the ethical committee of Sun

Yat-sen Memorial Hospital and registered with ClinicalTrials.gov (NCT03724903). Results: Recruitment for this trial began in March 2019 and follow-up ended in May 2023 at 3 hospitals in China. In the intention-to-treat set (N=140), 69 patients were randomly assigned to the ductal lavage group and 71 patients to the oral corticosteroids group. The cCR rates after treatment were 85.51% (95% CI 77.20 ~ 93.81%) and 87.32% (95% CI 79.59 ~ 95.06%) in the ductal lavage and oral corticosteroids groups, respectively. The rate difference was -1.82% (95% CI -13.17 ~ 9.54%), not exceeding the non-inferiority margin (Non-inferiority P=0.011). In the per-protocol set (N=111), the cCR rate difference was -5.32%(ductal lavage: 92.86% vs. oral corticosteroids: 98.18%), with a 95%CI of -12.94% to 2.29%, also not exceeding the non-inferiority margin(Non-inferiority P=0.006). No significant differences were observed between groups in median time to first cCR (34.0 vs. 32.5 days, P= 0.878), treatment failure rate (14.49% vs. 11.27%, P=0.569), or relapse rate (10.14% vs. 4.23%, P=0.302). In the safety analysis set (N=129), the most frequently reported adverse events (>15%) in the ductal lavage group were irregular menstruation (46.27%), while in the oral corticosteroids group, they were Cushingoid (79.03%), epigastric pain (17.74%), and arthralgia (16.13%). Conclusions: Ductal lavage demonstrates non-inferiority to oral corticosteroids in terms of efficacy as a first-line treatment for IGM patients. Furthermore, ductal lavage exhibits a significantly favorable adverse events profile.

Primary endpoint in ITT and PP set

	Ductal lavage(N1)	Oral corticosteroids(N2)	Risk Difference(95%CI)	P value
Primary endpoint				
ITT set: cCR rate % (95%CI) (N1=69, N2=71)	85.51(77.20,93.81)	87.32(79.59,95.06)	-1.82(-13.17,9.54)	0.011
PP set: cCR rate % (95%CI) (N1=56, N2=55)	92.86(86.11,99.60)	98.18(94.65,101.71)	-5.32(-12.94,2.29)	0.006

cCR: complete clinical response

ITT, Intention-to-treat

PP, Per-protocol

*P value for non-inferiority comparison.

Secondary endpoint in PP set

	Ductal lavage (N=69)	Oral corticosteroids (N=71)	Rate Difference (95%CI)	P value§
Median Time to 1st cCR (days)	34.0	32.5		0.878
Treatment failure rate % (95%CI)	14.49(6.19,22.80)	11.27(3.91,18.62)	3.23(-7.87,14.32)	0.751
Relapse rate % (95%CI)	10.14(3.02,17.27)	4.23(0.00,8.90)	5.92(-2.60,14.44)	0.205
Protocol compliance rate % (95%CI)	81.16(71.93,90.39)	77.46(67.75,87.18)	3.69(-9.71,17.10)	0.590

§P value calculated by chi-square test.

Adverse event in safety set

Adverse event	Ductal lavage(N=67)	Oral corticosteroids(N=62)
Cushingoid	2.99% (2)	79.03% (49)
Irregular menstruation	46.27% (31)	12.9% (8)
Urinary tract infection	0.00% (0)	3.23% (2)
Epigastric pain	0.00% (0)	17.74% (11)
Constipation	0.00% (0)	3.23% (2)
Nausea	1.49% (1)	0.00% (0)
Diarrhea	0.00% (0)	1.61% (1)
Blurred vision	0.00% (0)	14.52% (9)
Dry eye	0.00% (0)	1.61% (1)
Glaucoma	0.00% (0)	1.61% (1)
Arthralgia	0.00% (0)	16.13% (10)
Back pain	1.49% (1)	3.23% (2)
Fracture	0.00% (0)	0.00% (0)
Fatigue	0.00% (0)	6.45% (4)
Dizziness	2.99% (2)	1.61% (1)
Depression	0.00% (0)	1.61% (1)
Insomnia	0.00% (0)	4.84% (3)
Headache	0.00% (0)	0.00% (0)
Alopecia	0.00% (0)	4.84% (3)
Rash	1.49% (1)	8.06% (5)
Palpitation	1.49% (1)	3.23% (2)
Flush	0.00% (0)	1.61% (1)

No adverse event exceeding Grade 3 have been recorded.

PO1-22-09

Current margin assessment practice for breast-conserving surgery in China: a single institution audit

Presenting Author(s) and Co-Author(s):

F. Qu. Fudan University Shanghai Cancer Center, United States

C. Shen. Shanghai Cancer Center Fudan University, United States

W. Yang. Department of Oncology, Fudan University Shanghai Cancer Center, United States

J. Li. Fudan University Shanghai Cancer Center, United States

G. Liu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China, United States

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background

The appropriate negative margin width following breast-conserving surgery (BCS) for both ductal carcinoma in situ (DCIS) and invasive carcinoma (IC) has witnessed a shift towards de-escalation in international guidelines. However, there are limited nationwide data regarding margin assessment practice for BCS in China. This study aims to clarify the current real-world status of margin assessment from a single institution audit and secondarily to update the evidence on the association between margin width and local recurrence.

Methods

Eligible cases were derived from an extensive series of consecutive unselected patients with early invasive breast cancer who were treated with BCS at the Department of Breast Surgery in Shanghai Cancer Center Fudan University (FUSCC) between January 2015 and December 2017. Patient demographic and clinicopathological information as well as follow-up data were extracted from the hospital's electronic medical records. Pathological evaluation of negative margins was defined as no ink on tumor for IC in accordance with the SSO/ASTRO consensus guidelines released in 2014. Where applicable, margins were categorized as tumor on ink (involved), close margins (no tumor on ink but ≤ 1 mm), clear margins (1-2 mm), wide margins (2-5 mm), and wider margins (>5 mm). The positive margin rate (PMR), reoperation rate, and ipsilateral breast recurrence (IBR) rate were calculated according to different margin widths. Multivariable analyses of factors associated with re-excision were performed using binary logistic regression. Kaplan–Meier survival curve analysis was performed for local recurrence-free survival (LRFS).

Results

A total of 2707 patients were enrolled in the current study, with a total PMR of 2.7%. The distribution of margin width revealed that wider margins (>5 mm) were optimized by most surgical oncologists (2092/2707, 77.3%) for BCS in our center. Additionally, the reoperation rates were 1.9% in the whole population, accounting for 48.3%, 7.5%, 4.2%, 0.8%, and 0.4% in each margin group. Specifically, among 247 patients with margins ≤ 2 mm, 41 (16.6%) received reoperation either by margin re-excision or mastectomy. Multivariable analyses identified that lobular histology, no selective additional resection and in situ pathology of involved/close margins are independent factors of re-excision recommendation. With a median follow-up of 54.3 months, the incidence of IBR was 1.7% in the whole cohort, representing for 5.2%, 4.2%,

2.8%, 1.9%, and 1.3% in each margin group, respectively. Kaplan–Meier survival curve analysis showed a marginally significant difference in 5-year LRFS between groups with margins >2 mm and margins ≤2 mm (95.9% vs 97.8%, Table 1).

Conclusions

A wider margin width was preferably adopted in the routine practice of BCS. Our audit was aligned with previous evidence that a minimum clear margin of 2 mm is associated with a lower reoperation rate but favorable local control. Patients with margins no more than 2 mm were more likely to have re-excision in cases of lobular histology, no selective additional resection, and in situ pathology of involved/close margins.

Ipsilateral breast recurrence models by margin status

Table 1. Ipsilateral breast recurrence models by margin status

Ipsilateral breast recurrence	Hazard ratio	95% CI	p value
> 1 mm versus ≤1 mm	0.46	0.23-1.01	0.053
> 2 mm versus ≤ 2 mm	0.51	0.26-1.01	0.049

PO1-22-10

Long term outcomes of breast cancer patients with local recurrence after mastectomy undergoing immediate breast reconstruction: A retrospective multi-institutional study of 4153 cases

Presenting Author(s) and Co-Author(s):

A. ogiya. Cancer Institute Hospital, Japanese Foundation for Cancer Research, United States

N. Nagura. St Luke's International Hospital, United States

A. Shimo. St. Marianna University School of Medicine, United States

H. Nogi. Jikei University School of Medicine, United States

K. Narui. Yokohama City University Medical Center, United States

H. Seki. Saitama Medical Center, United States

H. Mori. Tokyo Medical and Dental University, United States

S. Sasada. Hiroshima University, United States

M. Ishitobi. Mie University Hospital, United States

N. Kondo. Nagoya City University Graduate School of Medical Sciences, United States

C. Yamauchi. Shiga General Hospital, United States

K. Akazawa. Niigata University Medical and Dental Hospital, United States

T. Shien. Okayama University Hospital, Okayama-city, Okayama, United States

Background: The number of breast cancer patients in Japan undergoing immediate breast reconstruction (IBR) has increased and the postoperative follow-up period has been extended. This study was conducted to clarify the clinical aspects of and factors associated with local recurrence (LR) after IBR. Methods: This was a multicenter study which included 4153 early breast cancer patients who underwent IBR. Clinicopathological characteristics were examined and factors potentially contributing to LR were analyzed. Risk factors for LR were examined separately for non-invasive and invasive breast cancers. Results: The median follow-up period was 75 months. The 7-year LR rates were 2.1% and 4.3% for non-invasive and invasive cancers, respectively ($p < 0.001$). The proportions of LR detected by palpation, subjective symptoms, and ultrasonography were 40.0%, 27.3%, and 25.9%, respectively. Overall, 75.7% of LR were solitary, and 92.7% of these cases had no further recurrences during the observational period. Multivariate analysis of LR for invasive cancer showed that skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM), the presence of lymphovascular invasion, cancer at the surgical margin, and not receiving radiation therapy were factors related to LR. The 7-year overall survival rates of the patients with LR and non-LR of invasive cancers were 92.5% and 97.3%, respectively, ($p=0.002$). Conclusions: The rate of LR after IBR was acceptably low and IBR can thus be performed safely for early breast cancer patients. Invasive cancer, SSM/NSM, lymphovascular invasion, and/or cancer at the surgical margin should prompt awareness of the possibility of LR.

PO1-22-11

Use of magnetic tracer and magnetic resonance imaging for sentinel lymph node detection after breast cancer recurrence and previous axillary surgery: The SentiRecur feasibility study

Presenting Author(s) and Co-Author(s):

E. VikhePatil. Linkoping University, United States

K. Chin. Dept of Surgery, Sahlgrenska Academy, Gothenburg University, United States

A. SegerbardPlanoudis. gusplanam@student.gu.se, United States

C. Dussan. Linkoping University, United States

H. Leonhardt. Dept of radiology, Sahlgrenska Academy, Gothenburg University, United States

P. Zaar. Dept of radiology, Sahlgrenska Academy, Gothenburg University, United States

P. Gialis. Linkoping University, United States

F. Wärnberg. Gothenburg University, Gothenburg, Sweden

Background: Preoperative imaging increases the chance of finding the sentinel lymph node (SLN) in patients with previous axillary surgery. Current clinical routine for preoperative localization is Technetium (Tc99) and lymphoscintigraphy. An alternative method has been proposed using superparamagnetic iron oxide nanoparticles (SPIO) and non-contrast enhanced magnetic resonance imaging (MRI) of the axillae. In this feasibility study, SPIO+MRI was used in parallel with Tc99+scintigraphy for SLN localization. Methods: Twenty patients with recurrent breast cancer and previous axillary surgery at Sahlgrenska and Linkoping University Hospitals scheduled for SLN-biopsy will be included. All patients received Tc99+scintigraphy as per standard practice. In addition, a SPIO injection and bilateral axillary MRI was performed up to four weeks before surgery. Both preoperative and perioperative SLN-detection rates were studied. Rates and number of concordant SLNs were presented as percentages. Results: So far, ten patients received both SPIO+MRI and Tc99+scintigraphy. The SLN-detection rates per patient were 70% (7/10) for SPIO+MRI and 50% (5/10) for Tc99+scintigraphy, respectively. The perioperative SLN-detection rates per patient were 60% (6/10) for SPIO using the magnetic probe (SentiMagTM) and 30% (3/10) for Tc99 using a gamma-probe. In total, eleven SLNs were detected with SentiMag and four with gamma-probe. Of all SLNs, only four (36%) contained both SPIO and Tc99. Conclusion(s): Although preliminary, the results suggest that Tc99+scintigraphy may be replaced by the magnetic technique for detecting SLNs after earlier axillary surgery. The magnetic technique enables logistic advantages as tracer injection and SLN identification during a wider time frame. Table 1. Sentinel lymph node detection in patients with recurrent breast cancer

Table 1. Sentinel lymph node detection in patients with recurrent breast cancer

Pat ID	SLN-detection SPIO-MRI	SLN-detection Tc99-lympho-scintigraphy	Number of SLNs detected with SentiMag	Number of SLNs detected with Gamma-probe	SLNs containing SPIO and Tc99
1	Yes	No	4	1	1
2	No	No	0	0	0
5	No	No	0	0	0
6	Yes	No	1	0	0
8	Yes	Yes	1	0	0
13	Yes	Yes	1	1	1
15	Yes	Yes	2	0	0
16	Yes	Yes	2	2	2
17	No	No	0	0	0
18	Yes	Yes	0	0	0

Table 1. Sentinel lymph node detection in patients with recurrent breast cancer

PO1-22-12

Predicting Additional Axillary Metastases in Breast Cancer Patients with Positive Targeted Axillary Dissection Lymph Nodes after Neoadjuvant Treatment

Presenting Author(s) and Co-Author(s):

F. Munck. Herlev-Gentofte Hospital, Hovedstaden, Denmark

M. Jensen. Danish Breast Cancer Group, Hovedstaden, Denmark

I. Vejborg. Gentofte Hospital, Denmark

M. Gerlach. Gentofte Hospital, Hovedstaden, Denmark

M. Maraldo. Department of Clinical Oncology, Center of Cancer and Organ Diseases, Copenhagen University Hospital - Rigshospitalet, United States

N. Kroman. Herlev-Gentofte Hospital, Hovedstaden, Denmark

T. Tvedskov. Herlev-Gentofte Hospital, Hovedstaden, Denmark

Background: Neoadjuvant chemotherapy (NACT) is increasingly used for axillary downstaging in clinically node-positive breast cancer patients, and a considerable proportion achieves axillary pathological complete response (ax-pCR). After NACT, axillary staging can be done by targeted axillary dissection (TAD). In case of metastases at TAD, axillary lymph node dissection (ALND) is offered regardless of metastases size. This contrasts primary surgery, where small sentinel node metastases (ypN0(i) and ypN1mi) and ≤ 2 positive sentinel nodes do not confer ALND, although a proportion of patients with small metastases have additional metastatic lymph nodes (LNs) in the axilla. So far, the residual metastatic burden in the axilla when TAD LNs are positive after NACT is unknown. If subgroups of patients with low residual metastatic burden in the axilla (non-TAD LNs) could be identified, these subgroups may be offered de-escalated axillary treatment. Therefore, we investigated the risk of residual metastatic burden in the axilla when the TAD LNs harbored metastases.

Methods: We retrospectively retrieved DBCG data on patients staged by TAD after NACT in Denmark between 1.1.2016-31.8.2021. We registered: age, breast biopsy date, type of surgery, type of axillary surgery, count of LNs, sentinel nodes, and marked lymph nodes with and without metastases, including metastasis size, breast tumor histology and receptor subtype, breast tumor size at diagnosis and in the surgical specimen, malignancy grade and type of neoadjuvant treatment. We excluded patients with inflammatory breast cancer, $< 4/ > 8$ cycles of NACT, or a non-standard NACT regimen.

The primary outcome was risk factors for having high (>3), low (1-3), or no residual metastatic burden in the axilla when the TAD LNs harbored metastases. We modeled risk factors for both high and low residual metastatic burden in the axilla using multivariable logistic regression and constructed risk models based on the regression coefficients.

Results: We identified 1626 patients receiving NACT and TAD in the inclusion period. After excluding ineligible patients and patients who achieved ax-pCR with no subsequent ALND (46%), the study included 383 patients with positive LNs at TAD for further analysis: thereof 188, 127, and 68 with 0, 1-3 and >3 positive non-TAD LNs, respectively.

In the adjusted logistic regression analysis, we found that breast pCR (OR= 0.06, 95% CI $< .01$ -0.41, $p < .001$) and a low proportion of positive TAD LNs (0-66% vs $>66\%$) (OR=0.32, 95% CI 0.17-0.58, $p = < .001$) were associated with low risk of high residual metastatic burden in the

axilla. Patients with one or both low-risk factors present had an 8% (14 of 176 patients) risk of high residual metastatic burden in the axilla. The predictive value of the model for having < 3 non-TAD LN metastases was 92%.

When analyzing the 315 patients with ≤ 3 positive non-TAD LNs, the adjusted logistic regression analysis of 1-3 vs 0 positive non-TAD LNs showed that ypN0(i) in the TAD LN (OR=0.14, 95% CI 0.04-0.53, $p = 0.002$), small tumor size at diagnosis (20-49 mm vs ≥ 50 mm) (OR = 0.29, 95% CI 0.14-0.60, $p = 0.002$), breast pCR (OR= 0.38, 95% CI 0.15-0.98, $p = 0.04$) and low proportion of positive TAD LNs (33-66% vs >66%) (OR= 0.46, 95% CI 0.27-0.77, $p = 0.01$) were associated with no residual metastases in the axilla. Using these risk factors, 19% (11/58) of the patients in the lowest risk quartile had further metastatic spread to the axilla.

Conclusion: Based on an extensive breast cancer registry, we find that breast pCR, low proportion of positive TAD LNs, small metastases, and small tumor size are associated with low risk of residual metastatic LNs in the axilla when the TAD LNs are positive after NACT. With these risk factors, we propose two models to identify patients with low non-TAD residual metastatic burden and patients with a high likelihood of no further metastases. The models can guide breast surgeons in de-escalating axillary treatment in these groups.

PO1-23-01

A novel nomogram for predicting the possibility of omitting axillary lymph node dissection after neoadjuvant chemotherapy for clinical node-positive breast cancer

Presenting Author(s) and Co-Author(s):

H. Seki. Saitama Medical Center, United States

Y. Ishiguro. Department of Thoracic Surgery, Keio University School of Medicine, Tokyo, Japan

K. Shimizu. Saitama Medical Center, United States

A. Makino. Division of Surgery, Saitama Medical Center, United States

Y. Ishizaka. Department of Breast Surgery Kyorin University School of Medicine, Japan

A. Tsuchiya. Department of Breast Surgery Kyorin University School of Medicine, United States

H. Isaka. Department of Breast Surgery Kyorin University School of Medicine, United States

S. Imoto. Kyorin University Hospital, Tokyo, Tokyo, Japan

Purpose: Currently, there is no validated strategy established for omitting axillary lymph node dissection (ALND), when axillary node metastases are expected to disappear with neoadjuvant chemotherapy (NAC) for clinical node-positive (cN+) breast cancers. In contrast, it was reported that the axillary pathological complete response (pCR) rate to NAC for cN+ breast cancer is approximately 40%. Therefore, it is necessary to develop a more accurate method for predicting nodal pCR (ypN0) to select patients who can omit ALND after NAC for cN+ breast cancer. **Methods:** This is a single-centered, retrospective clinical study conducted in 128 patients with cN+ primary breast cancer who underwent ALND after NAC between January 2014 and July 2021 at Saitama Medical Center. Clinical complete response (cCR) was defined as the disappearance of the primary tumor or axillary node metastasis, as confirmed by the findings of imaging. The pCR was defined as the absence of microscopic evidence of residual invasive carcinoma in primary breast tumor or axillary nodes. Clinicopathological variables were compared using Fisher's exact test or logistic regression, as appropriate. Statistical significance was set at $p < 0.05$. **Results:** The median age of the patients was 52 years; 48.4% were premenopausal, 38.3% had cT3 or higher, 22.7% had cN2 or higher, and 50% had stage III disease. Estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) positivity accounted for the patients were 58.6%, 50%, and 31.3%, respectively. NAC included sequential taxanes and anthracyclines in 47.7% of the patients, and anti-HER2 therapy was used in all patients of HER2-positive breast cancer. Breast primary tumor cCR (ypT0) was 29.7% and ypN0 was 44.5%. The ypN0 rate was 19.5% higher than the ypT0 rate in all patients ($p < 0.001$); it was 4.8% higher in the luminal subtype ($p=0.009$), 25.5% higher in the triple-negative subtype ($p < 0.001$), and 29.3% higher in the HER2 subtype ($p=0.015$). Additionally, the ypN0 rate was 3.9% higher than the axillary node cCR (ycN0) rate in all patients ($p < 0.001$), 7.6% lower in luminal type ($p < 0.001$), 13.6% higher in triple-negative type ($p < 0.001$), and 5% higher in the HER2 subtype ($p=0.006$). When ycN0 was predicted to be ypN0, the negative predictive value (NPV) was 77.2% and the false negative rate (FNR) was 19.7% (Table 1). In the association between ypN0 and preoperative clinicopathological factors in cN+ breast cancer treated with NAC, univariate analysis showed significant differences in ER negativity (ER-) [hazard ratio (HR): 0.186, 95% confidence interval (CI): 0.086–0.401, $p < 0.001$], PgR negativity (HR: 0.360, 95% CI: 0.176–0.736, $p=0.005$), HER2 positivity (HER2+) (HR: 4.394, 95% CI: 1.941–9.949, $p < 0.001$), ycT0 (HR: 10.667, 95% CI: 4.020–28.304, $p < 0.001$), and ycN0 (HR: 9.966, 95% CI: 4.399–922.576, $p < 0.001$). The multivariate analysis revealed that ER, ycT0, and ycN0 were independent predictive factors for ypN0 after NAC in the patients with cN+ breast cancer (Table 2). These independent factors in

multivariate analysis were used to create a nomogram for ypN0 prediction. The points added were 82 if the patient was ER-, 56 if the patient was ycT0, and 100 if the patient was ycN0, and the total of these scores was used to predict whether the patient had ypN0. When the Receiver Operating Characteristic curve was used to determine the cut-off value of the total points, 119 or more points were predicted to be ypN0, the NPV was 92.9%, and the FNR was 4.5%, which demonstrated an approximately 15% improvement over the prediction of ypN0 by ycN0 alone (Table 3). Conclusion: ER, ycT0, and ycN0 are independent predictive factors of ypN0 in cN+ breast cancer, suggesting that ypN0 prediction using a nomogram may contribute to individualized axillary treatment.

Table 1. Accuracy of ypN0 prediction with ycN0 after NAC for clinical node-positive breast cancer

		ypN0		
		No	Yes	
ycN0	No	53	18	71
	Yes	13	44	57
P<0.001		66	62	128

Sensitivity 80.3%, Specificity 71.0%, PPV 74.6%, NPV 77.2%, FNR 19.7%, FPR 29.0%, Accuracy 75.8%

Table2. Univariate and multivariate analyses of the relationship between preoperative clinicopathological factors and pathologically axillary node-negative after neoadjuvant chemotherapy in clinical node-positive breast cancer

Factor	Univariate		Multivariate	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Age (years) (≥60<60)	0.535 (0.252-1.137)	0.104		
Menopause (yes/no)	0.781 (0.390-1.565)	0.486		
BMI (≥25<25)	0.992 (0.433-2.270)	0.992		
Clinical tumor size (≤T3>T2)	0.847 (0.666-10.77)	0.847		
Clinical nodal status (≥N2<N1)	0.929 (0.610-1.414)	0.658		
Clinical stage (stage IIII)	0.820 (0.408-1.645)	0.576		
Pathological subtype (IDC/special type)	1.071 (0.326-3.517)	0.909		
Nuclear grade (3/1or2)	0.931 (0.820-1.057)	0.269		
ER (+/-)	0.186 (0.086-0.401)	<0.001	0.031 (0.002-0.429)	0.009
PgR (+/-)	0.360 (0.176-0.736)	0.005	4.736 (0.378-59.310)	0.228
HER2 (+/-)	4.394 (1.941-9.949)	<0.001	2.924 (0.989-8.641)	0.052
Ki-67 (%) (≥30<30)	1.403 (0.498-3.950)	0.521		
ycT0 (yes/no)	10.667 (4.020-28.304)	<0.001	3.552 (1.016-12.413)	0.047
ycN0 (yes/no)	9.966 (4.399-22.576)	<0.001	13.276 (4.257-41.398)	<0.001

Table 3. Accuracy of ypN0 prediction after NAC for clinical node-positive breast cancer using Nomogram

		ypN0		
		No	Yes	
Nomogram	Positive (score < 119)	63	23	86
	Negative (score ≥ 119)	3	39	42
P < 0.001		66	62	128

Sensitivity 95.5%, Specificity 62.9%, PPV 73.3%, NPV 92.9%, FNR 4.5%, FPR 37.1%, Accuracy 79.7%

PO1-23-02

Magnetic seeds used for the detection of target lymph nodes after neoadjuvant therapy for early breast cancer – a subgroup analysis of the prospective AXSANA (EUBREAST-03) trial

Presenting Author(s) and Co-Author(s):

H. Kolberg. Department of Gynecology and Obstetrics, Marienhospital Bottrop, Bottrop, Nordrhein-Westfalen, Germany

S. Hartmann. Department of Gynecology and Obstetrics, University Hospital Rostock, Germany

M. Banys-Paluchowski. Department of Obstetrics and Gynecology, Asklepios Hospital Barmbek, Hamburg, Germany

E. Stickeler. Klinik für Gynäkologie und Geburtsmedizin, Uniklinik RWTH Aachen, Germany, United States

J. de Boniface. Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, and Department of Surgery, Capio St. Göran's Hospital, Stockholm, Stockholms Lan, Sweden

O. Gentilini. Breast Surgery Unit, San Raffaele University Hospital, Milan, Italy

S. Fröhlich. Department of Gynecology and Obstetrics, University Hospital Rostock, Germany

M. Thill. Agaplesion Markus Krankenhaus, 60431 Frankfurt a.M., Hessen, Germany

M. Lux. St. Vincenz-Kliniken Paderborn, Germany

G. Karadeniz Cakmak. Zonguldak Bulent Ecevit University, Department of Surgery, Turkey

I. Rubio. Clínica Universidad de Navarra, Madrid, Spain, United States

M. Kontos. 1st Department of Surgery, Laiko Hospital, National and Kapodistrian University of Athens, Greece

R. Di Micco. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), Italy

D. Murawa. Department of General Surgery and Surgical Oncology, Collegium Medicum, University of Zielona Góra, Poland, Poland

T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany

Background:

Surgical strategies for axillary staging in patients with early breast cancer who convert from clinical lymph node positivity (cN+) to a clinically negative lymph node status (ycN0) after neoadjuvant therapy (NAT) vary between breast cancer centers and countries. The international prospective multicenter-cohort study AXSANA (EUBREAST-03) aims to comparatively evaluate long-term outcomes of different surgical staging procedures such as axillary lymph node dissection, sentinel lymph node biopsy (SLNB), target lymph node biopsy (TLNB) and targeted axillary dissection (TAD). A secondary study aim is the comparison of different localization techniques for the target lymph node (TLN), one of which is the use of magnetic seeds. Here we report on the largest so far studied prospective cohort using this technique.

Methods:

We prospectively examined the retrieval rate of magnetic seeds and the identification rate of a TLN in cN+ patients who underwent NAT and were scheduled for TAD. Magnetic seeds were inserted under ultrasound guidance before the start of NAT. The detection rate of TLN and its

associations with residual axillary tumor burden as well as with techniques used for detection of SLN were analyzed.

Results:

Of the 169 patients with magnetic seed marking of the TLN prior to NAT who were included in the AXSANA study, 135 (79.9%) had undergone final surgery at the time of analysis. 13 patients had 2 magnetic seeds implanted, 122 only 1 seed. In 133 (98.5%) patients the magnetic seeds were successfully identified and removed. No additional procedures or imaging were performed in the two cases with seeds still in situ. In 131 out of 135 patients (97.0%) the TLN was identified and resected, in 4 cases no TLN could be identified although in two of those a dislocated magnetic seed was removed. 85 patients converted from cN+ to ycN0 and a TAD was planned. In 84 of these cases (98.8%) the TLN could be detected during TAD. Eight patients (9.4%) had residual tumor only in the TLN, 15 (17.6%) had residual tumor in TLN and SLN and seven (8.2%) only in the SLN. In 71 (84.2%) cases the TLN was also a SLN. Techniques used for the detection of SLN were Tc99 alone (41.2%), blue dye alone (3.5%), both tracers combined (7.1%), indocyanine green (1.2%) and magnetic tracers (36.5%). Because of the high detection rate of 98.5% for all TLN and 98.8% during TAD a formal analysis of confounding parameters was not performed.

Conclusion:

To our knowledge this is the largest prospective series of patients using magnetic seeds for the marking of involved lymph nodes prior to NAT. The retrieval rate of the seed and the detection rate for the TLN after NAT is excellent. Magnetic seeds are a reliable tool for the marking of involved lymph nodes before NAT.

PO1-23-03

Management and risk of upgrade of Atypical Ductal Hyperplasia in the breast – a population-based retrospective cohort analysis

Presenting Author(s) and Co-Author(s):

C. Wadsten. Dept of Surgery, Sundsvall Hospital, Sundsvall, Sweden

G. Rask. Dept of Pathology, Umeå University Hospital, United States

Introduction International guidelines recommend open surgery for Atypical Ductal Hyperplasia (ADH) in the breast due to risk of underestimating malignant disease. The aim here was to evaluate the management and risk for upgrade of lesions diagnosed as ADH in percutaneous breast biopsies in two Swedish institutions. **Methods** All women with a screen-detected or symptomatic ADH diagnosed on percutaneous biopsy between 2013-2022 at Sundsvall and Umeå University Hospitals were included. Women with lesions classified as Breast imaging-reporting and data system (BI-RADS) 5 (highly suspicious) or 6 (confirmed malignancy) were excluded. Data were retrieved from medical records and histopathology reports. Odds ratio (OR) and 95 % confidence intervals (CI) for upgrade to malignant diagnosis after surgery was calculated by logistic regression analysis. **Results** Altogether, 101 women were included, mean age 56.1 years (range 36-93 years). Most women were selected from the national mammography screening program due to microcalcifications. Biopsies were performed with vacuum-assisted biopsy (VAB)(60.4%) or core-needle biopsy (CNB)(39.6%). Forty-eight women (47.5%) underwent surgery. Presence of a first degree relative with breast cancer ($p < 0.001$), more extensive microcalcifications ($p=0.01$), biopsies with ADH bordering DCIS ($p=0.01$) and CNB as opposed to VAB ($p=0.02$) increased the likelihood of surgical excision. Among the women undergoing surgery, eleven were upgraded to Ductal Carcinoma in Situ and seven to invasive breast cancer (overall upgrade rate 37.5%). In these women, no variable correlating to risk of upgrade in the surgical specimen was identified. After median 74 months of follow-up (range 4-105 months), one out of 53 women managed conservatively (1.9%) developed subsequent ipsilateral DCIS. **Conclusion** The upgrade rate to carcinoma was 37.5% after surgery while the estimated 5-year risk of ipsilateral upgrade in women managed conservatively was 1.9%. Acknowledging the short median follow-up time, these results indicate that the selection for non-surgical management in a subset of women was appropriate.

Summary of histopathological results after surgical excision of ADH

Histopathological results	No. (%)
Ductal Carcinoma In situ	11 (22.9)
- Low grade	- 6 (12.5)
- Intermediate grade	- 3 (6.3)
- High grade	- 2 (4.2)
Invasive ductal carcinoma	5 (10.4)
Invasive lobular carcinoma	2 (4.2)
Atypical Ductal Hyperplasia	19 (39.6)
Benign	11 (22.9)

PO1-23-04

The IBRAnet localisation study; a UK National multi-centre cohort study comparing the safety and effectiveness of guidewire, RFID, and magnetic seed- guided localisation for impalpable breast lesions

Presenting Author(s) and Co-Author(s):

R. Foster. Manchester Foundation Trust, Manchester, United Kingdom

J. Harvey. Manchester Foundation Trust, United States

R. Dave. Manchester University NHS Foundation Trust, Manchester, UK, United States

A. Maxwell. Manchester Foundation Trust, United States

S. Mylvaganam. The Royal Wolverhampton NHS Trust, United States

M. Gardiner. Frimley Health NHS Foundation Trust, United States

S. Down. James Paget University Hospitals, United States

N. Barnes. Manchester Foundation Trust, United States

M. Chandarana. University Hospitals of Leicester NHS Trust, United States

S. Potter. Bristol Medical School, United States

Y. Masannat. Aberdeen Breast Unit, Aberdeen Royal Infirmary, Aberdeen, United Kingdom, United States

C. Holcombe. Royal Liverpool and Broadgreen University Hospitals NHS Trust, United States

T. Masudi. Rotherham NHS Foundation Trust, United States

A. Carmichael. Queens Hospital Burton, United States

R. Milligan. Queen Elizabeth Hospital Gateshead, United States

J. Morgan. University of Sheffield, United States

Background Wire-guided localisations (WGL) of breast cancers have been the gold-standard for pre-operative localisation of non-palpable breast cancers for many years but have significant limitations. Newer localisation techniques have been introduced including Radio Frequency ID tags (RFID) and magnetic seeds which aim to overcome these limitations. The UK iBRA-net group have designed a multi-centre platform study aiming to compare the safety and effectiveness of wire, RFID, magnetic seeds, and radar-based localisation. A second aim was the qualitative assessment of shared learning as users gained experience. Methods A UK national multi-centre prospective observational platform study was designed to compare a control arm of WGL for women undergoing breast conserving surgery with two interventional arms of RFID tags and magnetic seeds. Patient data were collected between August 2018 and July 2022 in UK centres. The primary outcome was accurate excision of the index lesion at the time of surgery. Secondary outcomes were defined as; resection margins, breast reoperation rate (planned and unplanned), complications, cancellation rate on day of surgery, and duration of the surgery. To account for lesion size in the assessment of excision weight, we used size as a denominator over two dimensions, reporting this as weight/size^2 , in g/mm^2 . Data was collected prospectively on a secure REDcap database following approval from local audit departments. To calculate the sample size a power calculation was employed, with $n=950$ patients per group the upper limit of the observed one-sided 95% confidence interval for the difference between identification rates (intervention vs WGL) is expected to be less than 0.9% with 80% power, assuming the two methods both have an expected identification rate of 99.4%. Simple summary statistics were calculated for each outcome and data were tested for

distribution and differences between groups using unpaired t-tests, Mann-Whitney U tests, and Chi squared tests as appropriate. Analyses were conducted using Stata® IC version 14 (StataCorp, College Station, Texas, USA). Results Data were accrued from 3484 patients in 55 units. This included 1293 patients having WGL, 1188 RFID tags, and 1003 magnetic seeds. RFID had a lower rate of identification of the index lesion compared to magnetic seed and wire (97.9% vs. 99.8% vs. 99.1% respectively). When comparing the reasons behind failure of the primary outcome, the majority were not thought to be related to the modality of localisation. Data from 1560 patients with unifocal, unilateral breast lesions were included in subgroup analysis, excluding those having neo-adjuvant chemotherapy and those having therapeutic mammoplasty. Positive margins were lower in RFID excisions compared to wire (11.2% vs. 15% respectively, $p < 0.05$), whereas magnetic seed were equivalent (11.2% vs 13.3%, $P=0.22$). Routine cavity shaves were performed in 64.5% of WGL vs 48.3% of RFID vs 64.3% of magnetic guided excisions. There was no difference in specimen weight/size² (0.138 WGL vs. 0.131 RFID vs. 0.15 magnetic seed). Re-excision (for positive or close margins) was equivalent across the three groups (13.2% of wire vs 15% of RFID vs 12.3% of magnetic seed guided excisions, $p=0.3$). There have been four shared learning educational events focussing on three key themes relating to preoperative, intraoperative, and postoperative learning outcomes in addition to 130 database shared learning entries. This may aid other surgeons as they adopt these techniques. Conclusions All three localisation devices demonstrate high levels of localisation accuracy. There was a higher rate of device dislodgement in the RFID group, which was also identified in the shared learning events. However, re-excision rates were equivalent across the three groups. This study has demonstrated a robust platform for the comparative evaluation of new localisation technologies and of sharing learning and experience.

PO1-23-05

Exploratory clinical trial of preoperative non-invasive localization before surgery in breast cancer patients using augmented reality technology

Presenting Author(s) and Co-Author(s):

M. Lee. Department of Radiology, College of Medicine, Ewha Womans University, Seoul, Seoul-t'ukpyolsi, Republic of Korea

J. Lee. Ewha Womans University, School of Medicine,, Seoul, Seoul-t'ukpyolsi, Republic of Korea

W. Lim. Department of Surgery, Ewha Womans University School of Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

J. Woo. Department of Surgery, College of Medicine, Ewha Womans University, United States

H. Kim. Ewha Womans University Hospital, United States

S. Paek. Department of Surgery, College of Medicine, Ewha Womans University, United States

S. Park. Department of Pathology, College of Medicine, Ewha Womans University, United States

J. Kim. Department of Pathology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, United States

J. Chung. Department of Radiology, College of Medicine, Ewha Womans University,, United States

J. Lee. Department of Radiology, College of Medicine, Ewha Womans University,, United States

J. Kim. Department of Radiology, College of Medicine, Ewha Womans University,, United States

Purpose: A single-center, randomized, prospective exploratory clinical trial to assess the clinical efficacy of augmented reality(AR)-based breast cancer localization medical imaging solution in patients with breast cancer **Methods:** This prospective exploratory clinical trial enrolled 20 women who were diagnosed with invasive breast cancer between the ages of 19 and 70, had a single lesion or multifocal lesion with a lesion size of 5mm or more and 30mm or less, had no metastasis to other organs, and had not received prior chemotherapy. All patients underwent mammography, ultrasound, CT, and MRI for preoperative assessment. Patients were randomly assigned to US-guided skin marking (control) and SKIA-breast (AR localization) groups of 10 each. **Result:** Two surgeons performed breast-conserving surgery on twenty patients. Pathologic evaluation of all patients confirmed negative margins. Two independent pathologists evaluated marginal distance, and neither the two reader's estimates (R1, 6.20±4.37 vs. 5.04±3.47, p=0.519; R2, 5.10±4.31 vs. 4.10±2.38, p= 0.970) nor the two reader's average values (5.65±4.19 vs. 4.57±2.84, p= 0.509) showed any difference between the two groups. In comparing the tumor plane area ratio, there was no statistically significant difference between the two groups for the two readers (R1, 15.90±9.52 vs. 19.38±14.05, p=0.525; R2, 15.32±9.48 vs. 20.83±12.85, p=0.290) and the two reader's mean values (15.56±9.11 vs. 20.09±13.38, p=0.388). Based on the two surgeons' responses, convenience, safety, satisfaction, and reusability were all superior in the AR localization group (p=0.000). **Conclusion:** AR localization is an acceptable alternative to US-guided skin marking with no significant differences in surgical outcomes.

PO1-23-07

The effect of intra-operative margin assessment during breast conserving surgery for breast cancer in a Dutch cohort

Presenting Author(s) and Co-Author(s):

S. Wooldrik. Franciscus Gasthuis&Vlietland, United States

E. van de Voort. Franciscus Gasthuis&Vlietland, United States

T. Klem. Franciscus Gasthuis&Vlietland, United States

T. van Dalen. Erasmus MC, United States

C. Verhoef. Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer Institute, Rotterdam, the Netherlands, United States

G. Struik. Erasmus MC, United States

E. Birnie. Franciscus Gasthuis&Vlietland, United States

Background

Pre-operative tumour localisation and intraoperative specimen radiography are necessary to perform adequate resection of non-palpable breast tumours. Intraoperative digital specimen mammography (IDSM), is an alternative to conventional specimen radiography (CSR) and has the benefit of providing immediate specimen evaluation and the potential of decreasing operation time. IDSM may also reduce positive margins and re-excision rates. IDSM was implemented in our hospital in 2018. The study objective was to evaluate the surgery time, radicality and re-excisions in IDSM and CSR.

Methods

A single centre retrospective cohort study with two cohorts: CSR (n=532) and IDSM (n=475). The primary outcome was duration of surgery. Secondary outcomes were margin status of the primary surgery, the perioperative cavity shave rate and the re-excision rate. Differences between cohorts were compared using univariate statistics and multiple regression to adjust for variables that were statistically significantly associated with duration of surgery.

Results

IDSM use was associated with 8 minutes shorter surgery time (B -8.242, $p < 0.001$). Treatment variables independently associated with the duration of surgery were use of IDSM, type of (axillary) surgery and the performance of cavity shaving. Cavity shaves were more often performed when IDSM was used (24% versus 14% in CSR group, $p < 0.001$), while the proportion of radical first surgeries (93% versus 96% respectively, $p = 0.070$) was comparable.

Conclusion

IDSM was associated with a modest reduction in duration of surgery. Surgeons performed more cavity shaves since IDSM but this was not reflected by a lower proportion of patients with positive margins.

Table 1. Baseline characteristics of the CSR versus the IDSM cohort

	CSR Cohort n = 532	SD%	IDSM Cohort n = 475	SD%	P-value
Age (years), mean±sd	60.74	10.69	62.72	12.29	0.007
Cup Size					< 0.001
A/B	105	20	144	30	
C	143	27	136	29	
D	126	24	120	25	
E	82	15	64	14	
Unknown	76	14	11	2	
Quadrant					0.022
Lateral upper	276	52	243	51	
Medial upper	103	19	75	16	
Lateral lower	62	12	64	14	
Medial lower	68	13	49	10	
Retromamillar	15	3	27	6	
Unknown	8	2	17	4	
Neoadjuvant chemotherapy					< 0.001*
Yes	63	12	108	23	
No	469	88	367	77	
Tumour localisation type					< 0.001
Iodine seed	236	44	429	90	
Wire	276	52	32	7	
Other [†]	20	4	14	3	
Operator					0.122 [‡]
Surgeon	444	84	378	80	
Surgeon in training	88	17	97	20	
Tumour size maximum diameter (mm), mean±sd	14.22	6.90	14.24	12.40	0.974
Tumour type					0.037
NST	451	85	378	80	
Lobular	47	9	42	9	
NST and lobular	2	0	3	1	
No residual tumour in specimen	32	6	52	11	< 0.001
Surgery type					
Lumpectomy without SN	80	15	80	17	
Lumpectomy with SN	380	71	264	56	
Lumpectomy with ALND	37	7	45	10	
Lumpectomy with plastic surgeon	29	6	65	14	
Other [†]	6	1	21	4	
Number of excised tumours					0.320 [‡]
1	477	90	416	88	
> 1	55	10	59	12	

Table 1. Baseline characteristics of the CSR versus the IDSM cohort[†].
Abbreviations: NST: no special type; SN: sentinel node; ALND: axillary lymph node dissection.
[†] Data are expressed as Number, (%) of participants unless otherwise indicated.
[‡] Fisher's exact. ALND/ALND (magnetic markers), no localisation, or both a wire and iodine seed.
[†] Other includes: Surgical procedure at both sides with SN or ALND or a lumpectomy with SN and ALND (Marking Axillary lymph nodes with Radioactive Iodine seeds) procedure.
[‡] Fisher's exact.

Table 2. Results of surgery in the CSR versus the IDSM cohort.

		CSR Cohort n = 532	SD%	IDSM Cohort n = 475	SD%	P-value
Specimen weight (grams), mean ± sd [†]	Missing	81	15	28	6	0.246
Specimen maximum diameter(mm), mean ± sd		62.19	19.47	59.44	21.57	0.038
Cavity shave						< 0.001
	Yes	76	14%	115	24%	
	No	456	86%	360	76%	
Margins						0.074
	Free	450	85%	389	82%	
	Focally irradical	60	11%	56	12%	
	More than focally irradical	22	4%	30	6%	
Margins						0.070
	Free/focally irradical	510	96%	443	93%	
	More than focally irradical	22	4%	32	7%	
Re-excision						0.109 [‡]
	Yes	42	8%	51	11%	
	No	490	92%	424	89%	

Table 2. Results of surgery in the CSR versus the IDSM cohort[†]

[†] Data are expressed as number (%) of participants unless otherwise indicated.

[‡] Missing: n = 81 (15%) in the CSR cohort, and n = 28 (6%) in the IDSM cohort.

[‡] Fisher's exact. Based on the sample size calculation, non-inferiority could not be demonstrated.

PO1-23-08

Exosome-based delivery of microRNAs confers adriamycin-resistance to sensitive cells through modulating the immune and metabolism-related gene PTEN in HER2-negative breast cancer

Presenting Author(s) and Co-Author(s):

S. Yang. The First Affiliated Hospital with Nanjing Medical University, United States

T. Cheng. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, United States

J. Wu. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, United States

W. Chen. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, Changzhou, Jiangsu, China (People's Republic)

Background: Anthracycline-based chemotherapy is widely used to treat breast cancer. However, acquired drug resistance remains a challenge to successful treatment. Recently, increasing evidence has shown that changes in the tumour immune microenvironment (TIME), in addition to increasing drug resistance of tumour cells, consistently contribute to the development of chemoresistance. Methods: TIME scores and tumor-infiltrating immune cells (TICs) scores were used to investigate the prognosis, clinicopathological characteristics and gene transcriptome profiling of HER2-negative breast cancer patients who received anthracycline-based chemotherapy. Exosomes isolated from MCF/7-ADR (ADR-exos) and MCF/7-S (S-exos) cell lines were characterized. We identified dysregulated miRNAs using miRNA microarray analysis on MCF/7-ADR cells and their exosomes compared to MCF/7-S cells and their exosomes. Protein profiling was performed to identify differentially expressed proteins in up- and down-regulated miR-222 cells. The ability of ADR-exos to transfer drug-resistance mediated by miR-222 was assessed by immunofluorescence assay, flow cytometry and qRT-PCR. We optimized the conditions to load miR-222 mimic (or inhibitor) into exosomes produced by HBL-100 cells (H-exos). The influence of miR-222 inhibitor-containing exosomes (inhibitor-exos) on the downstream pathway of miR-222 and the potential therapeutic effects both in vitro and in vivo were evaluated. We also evaluated the relationship between miR-222/PTEN and drug resistance in circulating exosomes from mice after adriamycin-based chemotherapy. Results: Firstly, we discovered the complicated and heterogenous TICs subtypes and their unique biological behaviors in HER2-negative breast cancer. Then, we identified 85 differentially expressed immunologic signature gene sets and 7202 corresponding immune-related genes in three subtypes quantified by gene set variation analysis (GSVA). We identified 12 up-regulated and 13 down-regulated genes using miRNA microarray analysis in adriamycin-resistant cells and their exosomes. The TMT mass spectrometry found 45 differentially expressed proteins affected by the miR-222 level. Moreover, we successfully established miRNA mimic/inhibitor-containing exosomes to explore the solo function of exosomal miR-222 in adriamycin-resistance both in vitro and in vivo. More importantly, for the first time, we detected the levels of miR-222 and its target gene PTEN in circulating exosomes from mice after adriamycin-based chemotherapy and explored the potential clinical implications of miR-222/PTEN-containing exosomes in chemotherapy and immune suppression of breast cancer patients. Conclusions: HER2-negative breast cancer patients own unique TIME subtypes, leading to different outcomes of chemotherapy. We exhibit the potential applications of miR-222-mimic/inhibitor-containing exosomes for reversing chemo-resistance. Adriamycin-resistant cells can transmit drug-resistance to sensitive cells via delivering miR-222 by

modulating the immune- and metabolism-related target gene PTEN both in vitro and in vivo without interference from other relevant drug-resistance factors in exosomes. Therefore, miR-222-containing exosomes as well as their target gene PTEN may be a promising biomarker for predicting the efficacy of chemo-resistance and tumor immunity regulation in breast cancer patients receiving anthracycline-based chemotherapy. Keywords: exosomes, breast cancer, tumor immune microenvironment, chemo-resistance, microRNAs

PO1-23-09

A bedside-to-bench translational analysis demonstrates that NF1 alterations promote CDK4/6 inhibitor (CDK4/6i) resistance in hormone receptor-positive (HR+) metastatic breast cancer (MBC)

Presenting Author(s) and Co-Author(s):

M. Lloyd. Beth Israel Deaconess Medical Center, United States

M. Chica-Parrado. University of Texas Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, United States

T. Knepper. Moffitt Cancer Center, Tampa, Florida, United States

C. Lin. University of Texas Southwestern Simmons Comprehensive Cancer Center, United States

E. Podany. Washington University in St. Louis, St. Louis, Missouri, United States

C. Walko. Moffitt Cancer Center, University of South Florida Morsani College of Medicine, United States

F. Napolitano. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

C. Weipert. Guardant Health, United States

J. Liao. Guardant Health, United States

A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States

L. Ryan. Cancer Center, Massachusetts General Hospital, United States

J. Keenan. Massachusetts General Hospital Cancer Center, United States

N. Zhang. Guardant Health, United States

S. Liu. Washington University in St. Louis, United States

G. Wulf. Harvard Medical School, United States

K. Clifton. Washington University in St Louis School of Medicine, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

H. Han. H. Lee Moffitt Cancer Center, Tampa, Florida, United States

L. Ellisen. Massachusetts General Hospital, Boston, Massachusetts, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

A. Hanker. UT Southwestern Medical Center, Dallas, Texas, United States

S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States

Background: CDK4/6i are part of the standard management of HR+ MBC. The MAPK pathway has been implicated in mediating resistance to CDK4/6 blockade (Wander 2020). A variety of molecular alterations dysregulate MAPK signaling, including NF1 mutations (NF1-MUT) (Wallace 2012), though NF1 has not been implicated in CDK4/6i resistance. To assess this, we analyzed retrospective clinical data from multiple institutions, real-world data (RWD) from the GuardantINFORM database, and preclinical models of HR+ breast tumors. The primary

objective of this study was to characterize clinical outcomes of CDK4/6i in patients (pts) with NF1-MUT MBC, and to validate those findings in laboratory models. Methods: Pts with pathogenic (p)NF1-MUT were identified via sequencing of circulating tumor DNA (ctDNA) or tumor tissue. Pathogenic was defined as nonsense, insertion/deletion, frameshift, or oncogenic missense mutations. Progression free survival (PFS) on CDK4/6i was analyzed, and intrinsic resistance was defined as progression < 6 months on 1st line (1L) CDK4/6i or < 3 mo on 2nd line and beyond (2L+). Acquired resistance was defined as PFS >6 mo (1L) or >3 mo (2L+) with a NF1 alteration detected post-progression. RWD from the GuardantINFORM dataset had Guardant360 (G360) ctDNA testing linked with claims data on >37,000 pts with advanced or MBC tested between June 2014 and March 2023. Pts on CDK4/6i within 90 days pre-G360 were stratified as NF1-MUT (n = 28) vs. NF1-non-mutant (NF1-nonMUT) (n = 1133) and analyzed for real-world time-to-next-treatment (rwTTNT) and real-world overall survival (rwOS). Propensity score weighting for age, sex, line of therapy, and year of G360 were used to create a balanced control group. To determine whether NF1 loss-of-function alterations were causal of CDK4/6i resistance, we used CRISPR/Cas9 to delete NF1 in MCF7 breast cancer cells. MCF7 wild-type (WT) and two NF1-knockout (KO) clones were treated with palbociclib ± estrogen deprivation, followed by cell viability assays. MAPK and PI3K/AKT pathway activation were measured by immunoblot analysis. Results: Across 4 institutions, 40 pts with HR+, HER2- MBC expressing pNF1-MUT and prior CDK4/6i were included. The mean age at MBC diagnosis was 56 years, and the majority of pts received no prior treatment in the metastatic setting before CDK4/6i (range 0 - 5 prior lines). Intrinsic or acquired resistance to CDK4/6i was seen in 29/40 (73%) tumors harboring pNF1-MUT. We analyzed pts with baseline pNF1-MUT who received 1L CDK4/6i plus endocrine therapy (n = 13) and found that the median PFS was 7.7 months (range 2 - 18 mo). We next examined GuardantINFORM RWD and discovered a significant difference in rwTTNT and rwOS on CDK4/6i for NF1-MUT (n = 28) vs. weighted NF1-nonMUT (n = 28) tumors. Mean age (62 years) and level of pretreatment (majority 2L+) were similar between the groups. Compared to NF1-nonMUT, NF1-MUT pts had a shorter median rwTTNT on CDK4/6i regimens (4.2 vs. 12.4 mo, weighted log-rank p< 0.0001) and worse rwOS (15.8 vs 45.2 mo, weighted log-rank p=0.016). In MCF7 cells, NF1-KO exhibited a palbociclib IC₅₀ 11- to 13-fold higher than NF1-WT controls. In estrogen-deprived media, treatment with 250 nM palbociclib for 6 days reduced MCF7 NF1-WT cell viability 75% but only 5-20% in NF1-KO cells. As expected, phosphorylation of ERK and AKT were strongly induced in NF1-KO cells relative to NF1-WT. Conclusions: Using multicenter clinical and real-world evidence, we demonstrate that NF1-MUT is associated with inferior duration and worse outcomes on CDK4/6i in MBC. Pts with baseline pNF1-MUT on 1L CDK4/6i and endocrine therapy had a median PFS below typical responses expected in clinical practice. A link between NF1 loss and CDK4/6i resistance was supported by in vitro experiments in HR+ breast cancer cells. NF1 deletion was accompanied by activation of ERK and AKT, therefore, future directions include investigating alternative or combination treatment strategies targeting the MAPK and/or PI3K/AKT pathways in these tumors.

*MRL and RCP contributed equally. ABH and SAW are co-senior authors.

PO1-23-10

Multi-omics analysis identifies the mechanism in cross-resistance to endocrine therapy and CDK4/6 inhibitor in breast cancer

Presenting Author(s) and Co-Author(s):

M. Hou. Kaohsiung Medical University Hospital, Kaohsiung, Taiwan (Republic of China)

C. Li. Division of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, 80756, Taiwan, United States

C. Chiang. Division of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, 80756, Taiwan, United States

Background

In advanced/metastatic breast cancer (MBC) or recurrent breast cancer on prior endocrine therapy (ET), selective estrogen receptor downregulator (SERD) of fulvestrant and CDK4/6i are the mainstream therapy regimen. In the clinical, fulvestrant combined with CDK4/6i is the second-line therapy for breast cancer (BC) that had progressed during previous endocrine therapy. The alternation of backbone from aromatase inhibitor or tamoxifen (endocrine sensitive) to fulvestrant (endocrine resistance) partially comes from the mechanism of ET resistance. Moreover, in the PALOMA-2 trial, approximately 30% of patients developed into recurrence after two years of CDK4/6i treatment, indicating that the ET backbone may affect CDK4/6i efficacy, bringing an emerging clinical issue of cross-resistance. However, whether the cross-resistance of ET would be more sensitive to CDK4/6i or impair the efficacy of CDK4/6i is still an ambiguous and heterogeneous issue. Also, in CDK4/6i resistance, whether the mechanism of ET resistance is associated with the dysregulation of the cell cycle or activation of other “bypass” signaling pathways is not fully understood. Methods

We use a 3D and 2D culture of ET-sensitive cell S0.5, tamoxifen-resistant cell TAM, and fulvestrant-resistant cell 182R6 as our model. The 3D culture was performed by using the Tools 3d culture plus kit. Drug responses to fulvestrant and ribociclib were conducted by using CCK-8 assay. The potential target and pathway involved in the mechanisms of cross-resistance were analyzed by using multi-omics analysis of sequential window acquisition of all theoretical mass spectra (SWATH-MS), RNA-seq, micro-western array (MWA), traditional western blots, and open access database. Results

In comparison with S0.5, the sensitivity to fulvestrant was indeed reduced in 182R6 cell; however, we found the sensitivity to ribociclib was also reduced in 182R6 cell, which was in contrast to the ribociclib-sensitive TAM cell. The different response to ribociclib between 182R6 and TAM, indicating that cross-resistance between fulvestrant and ribociclib existed in the model of 182R6 and TAM would be another control for 182R6 to find the target with or without cross-resistance. With multi-omics analysis of SWATH-MS, RNA-seq, MWA, western blots, and open access database, we found some unique or high expression of targets and pathways including EGFR, HER2, CDK6, CDK2, MAPK, and TNF- α pathways in cross-resistance R6 cell than in parental and TAM cell. We reconfirmed the above targets by 3D culture and found MAPK signaling pathway of p-ERK was not affected under ribociclib treatment, indicating the important role of the MAPK signaling pathway in ribociclib resistance. Conclusion

To our knowledge, these results provide the first preliminary mechanism of cross-resistance between fulvestrant and ribociclib. We found fulvestrant resistant cell R6 exhibited the phenomenon of cross-resistance to ribociclib, which was in contrast to ribociclib-sensitive TAM cell. We also found some unique or high expression of target and pathway in cross-resistance R6 cells than in parental and TAM cells. In the future, with compound library screening and in

vivo animal models, we expect to discover an FDA-approved drug or potential compound to overcome the cross-resistance between fulvestrant and ribociclib.

PO1-23-11

Differential m6A modification identified by direct RNA sequencing in endocrine-resistant and sensitive breast cancer cells

Presenting Author(s) and Co-Author(s):

B. Petri. University of Louisville School of Medicine, Kentucky, United States

B. Valdes. University of Louisville School of Medicine, United States

K. Piell. University of Louisville School of Medicine, United States

E. Rouchka. University of Louisville School of Medicine, United States

C. Klinge. University of Louisville School of Medicine, Louisville, Kentucky, United States

A major limitation of current adjuvant treatments for the ~ 70% of breast cancer patients with estrogen receptor α -expressing (ER+) primary breast tumors is the development of acquired and adaptive endocrine therapy (ET) resistance and metastatic spread. Chemical modifications of transcribed RNAs alters their cellular location, stability, and, for mRNAs, translation into proteins. N-6 methyladenosine (m6A) is the most common modification of mRNA. We tested the hypothesis that m6A epitranscriptomic changes alters the transcriptome resulting in changes in targets in pathways contributing to the metastatic cascade in ET-resistant breast cancer cells. We used an unbiased approach of direct mRNA sequencing using the Oxford Nanopore MinION platform on polyA-selected mRNA from MCF-7 luminal A breast cancer cells and ER+, ET-resistant LCC9 breast cancer cells treated with vehicle control or 100 nM 4-hydroxytamoxifen (4-OHT) for 24 h. In addition, MCF-7 cells were treated with the METTL3 (the catalytic methyltransferase that adds the methyl group from S-adenosylmethionine (SAM) to the adenosine on the N6 position) inhibitor STM2457 to identify m6A positions and transcripts directly regulated by METTL3 activity. Computational analysis directly identified m6A locations in transcripts. We examined the differential modification rate (DMR) between MCF-7 cells +/- STM2457 treatment, between MCF-7 and LCC9 cells with vehicle control treatment or with 4-OHT treatment and within each cell line with 4-OHT treatment. We identified 183 and 3,097 genes with m6A DMRs between vehicle-treated and 4-OHT-treated MCF-7 and LCC9 cells, respectively. For 4-OHT-treated cells, we identified 2,401 and 2,638 genes with m6A DMRs in MCF-7 and LCC9 cells respectively with 1,760 genes in common. We identified many genes with multiple m6A modifications, e.g., AMIGO2 appeared to have 14 m6A sites at DRACH motifs in MCF-7 cells, but none were m6A modified in LCC9 cells. Enrichment by Pathway Maps, Process Networks, and GO Processes were performed. Overall, our data suggest a role for altered m6A positions in transcripts and pathways involved in ET-resistance in breast cancer.

PO1-24-01

ADAR1 drives ribosomal biogenesis by regulating NOP14 and stabilizing FBL-NOP58 complex in breast cancer

Presenting Author(s) and Co-Author(s):

L. Wangxu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, 200032 China, United States

H. Ren. Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

Z. Shao. Fudan University Shanghai Cancer Center, China (People's Republic)

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Y. Chi. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

Background

Breast cancer (BC) has been widely accepted as a highly heterogeneous disease. Transcriptional and translational dysregulation is commonly found in BC patients. Adenosine-to-inosine (A-to-I) editing on RNA is the most abundant RNA editing form in human, mediated mainly by ADARs. Though the role of ADAR1 in RNA editing and immune response has been deeply investigated, the change of the translational profile and the biology sequelae after base editing are still unclear. In this study, we uncovered a previously unknown role of ADAR1 in the regulation of ribosome biosynthesis and translational dysregulation in BC cells.

Method

RNA-seq was used for gene set enrichment analysis (GSEA) and A-to-I editing analysis. Transmission electron microscopy (TEM) was conducted to visualize the nucleolar architecture. Nuclear rRNA abundances of 18S and 28S rRNAs were monitored using Qsep100. Ribosomal fractions were isolated with a Beckman SW41Ti rotor and quantified on a 2100 Bioanalyzer. 3' Untranslated region (3'UTR) reporter construction and dual-luciferase reporter assay were used to validate the correlation. In-vitro transcription, RNA pull-down assay and sanger sequencing were used to directly confirm the direct interaction and A-to-I editing status. Cell proliferation, migration assay, apoptosis assay in vitro and xenograft mouse model in vivo were performed for phenotype study. Co-immunoprecipitation (Co-IP) was used to identify the interactive protein. Immunofluorescence (IF) assay was applied to indicate the co-localization. Immunohistochemistry (IHC) staining was applied to tissue microarrays and assess of expression. Survival analysis was made by Kaplan-Meier method. RNA polymerase I inhibitor CX-5461 was used for treatment.

Result

Through bioinformatic analysis with RNA-seq data from cell lines and clinical samples, we found the expression of ADAR1 was correlated with signatures of ribosomes. Consistently, BC cells with overexpression of ADAR1 showed larger nucleoli and contained more 18S and 28S rRNAs. To uncover the potential ribosomal genes involved in this process, we analyzed the transcriptional profile of 88 BC samples in combination with ADAR1 editing profiles identified by comparing ADAR1-null and control cells. Nucleolar Protein 14 (NOP14), a nucleolar ribosome

biogenesis gene, was found to be hyper-edited. Phenotype experiments revealed that NOP14 promotes tumor growth and invasion in vitro and in vivo. The RNA and protein level of NOP14 is regulated by ADAR1 through A-to-I editase activity. Mechanically, ADAR1 binds directly with NOP14 transcripts in the 3'UTR region through Sanger sequencing and RNA-pull down. The binding region of NOP14 with ADAR1 was also a target of miR-939-3p, while the ADAR1 mediated-editing led to less binding of miR-939-3p with NOP14 and resulted in NOP14 up-regulation. Notably, NOP14 facilitates the assembly of the box C/D small nucleolar ribonucleoprotein (snoRNP) and stabilize the interaction of fibrillarin (FBL)-nucleolar Protein 58 (NOP58) with this complex. Loss of NOP14 impaired the nucleolar distribution of FBL and the abundance of ribosomes. CX-5461, an RNA polymerase I inhibitor, suppressed the overexpression of ribosomes in ADAR1 high cells and displayed a strong inhibition efficacy on tumor growth both in vitro and in vivo.

Conclusion

Taken together, these results shed light on the role of ADAR1 in ribosomal biogenesis in breast cancer. The promising results also provide potential targets in BCs with high ADAR1 by suppressing translational dysregulation.

PO1-24-02

Enhancement of TGF- β Receptor Inhibitor Efficacy through CD44 Suppression in Claudin-low Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Matsunuma. Department of Breast Surgery, Shizuoka General Hospital, Shizuoka, Japan

S. Imada. Shizuoka General Hospital, Japan

S. Sato. Shizuoka General Hospital, Japan

R. Hayami. Shizuoka General Hospital, Japan

M. Tsuneizumi. Department of Breast Surgery, Shizuoka General Hospital, Japan

Introduction:

Claudin-low breast cancer is mostly classified as triple-negative breast cancer and is known to possess cancer stem cell properties with high expression of epithelial-to-mesenchymal transition (EMT) markers. However, specific therapeutic targets for this subtype have not yet been identified. While reports suggest that inhibition of EMT using EMT inhibitors can suppress cell and tumor proliferation, monotherapy may not be sufficient. The expression of CD44, a surface marker of cancer stem cells, has been reported to be involved in multiple signaling pathways, promoting cancer growth and invasion. In this study, we focus on CD44 and the TGF- β receptor, which is involved in EMT, to investigate the effect of inhibiting TGF- β receptor through CD44 inhibition in Claudin-low breast cancer and validate its potential as an effective treatment.

Methods:

SUM159 and MDA-MB-231 cell lines were used as Claudin-low breast cancer cell models. CD44 knockdown cells were established to examine the effects of TGF- β receptor inhibition and downstream signaling.

Results:

CD44 knockdown did not affect the expression of TGF- β receptor. Both SUM159 and MDA-MB-231 cells showed comparable cell growth inhibition through CD44 knockdown and TGF- β receptor inhibition, with enhanced effects observed in CD44 knockdown cells in response to TGF- β receptor inhibition. Furthermore, CD44 knockdown combined with TGF- β receptor inhibition significantly reduced the expression of Smad2/3.

Conclusion:

In Claudin-low breast cancer cells, CD44 knockdown enhances the effectiveness of TGF- β receptor inhibition and significantly influences the expression level of Smad2/3.

PO1-24-03

The clinicopathological and prognostic significance of HER2-low breast cancer: A comparative analysis between HER2-low and HER2-zero subtypes

Presenting Author(s) and Co-Author(s):

R. Nishimura. Social Medical Corporation Hakuaiikai, Sagara Hospital, Kagoshima City, Japan

Y. Fujiki. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

T. Taira. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

T. Miyaki. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

S. Kanemitsu. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

D. Yotsumoto. sagara hospital Hakuaiikai social medical corporation, kagoshima city, Kagoshima, Japan

M. Teraoka. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

J. Kawano. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

N. Gondo. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

R. Mitsueda. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

S. Baba. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

Y. Ohi. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

Y. Rai. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

Y. Sagara. Social Medical Corporation Hakuaiikai, Sagara Hospital, United States

Y. Sagara. Hakuaiikai Sagara Hospital, Kagoshima, Kagoshima, Japan

Background: HER2-low breast cancer (BC) is a newly defined subset of HER2-negative BC that has a HER2 immunohistochemical (IHC)-1+ or 2+/ISH negative phenotype. Recent clinical trials have demonstrated the clinical benefits of novel HER2 directing ADCs in treating this group. It is uncertain whether HER2-low BC represents a distinct biological/clinical subgroup or if the HER2-low categorization has any prognostic significance. We retrospectively investigated the clinicopathological and prognostic significance of HER2-low BC and compared it with HER2-0 BC.

Methods: Primary BC patients who underwent surgery from January 2000 to March 2023 were enrolled in this retrospective study. A total of 10,215 invasive BC cases with Stage I-III were analyzed. The HER2 status was divided into 3 groups: HER2-0, HER2-low, and HER2-positive (3+ or 2+ with positive ISH). The clinicopathological factors investigated were age, nodal status, tumor size, nuclear grade (NG), ER/PgR (cutoff points; 1% and 10%), and the Ki-67 index value (cutoff points: 15% and 30%). The pCR rate in patients who underwent neoadjuvant chemotherapy (NAC) was examined. The disease-free (DFS) and overall survival (OS) were calculated using the Kaplan-Meier method and tested with the log-rank procedure. Uni- and multivariate analyses for recurrent factors were performed using the Cox proportional hazard model.

Results:

1. The HER2 status was classified as follows; HER2-0 in 1,227 cases (12.0%), HER2-low in 7,209 cases (70.6%), and HER2-positive in 1,779 cases (17.4%). In the recurrent cases, HER2-low was observed in 648 cases (66.1%), and in cases treated with NAC, HER2-low was observed in 544 cases (52.7%).

2. The HER2 status significantly correlated with age, tumor size, lymph nodal status, ER, PgR, NG, and the Ki-67 index value. A comparison between HER2-low and HER2-0 revealed that patients with HER2-low tumors were significantly more likely to be under 50 years of age and had more positive nodes. Moreover, HER2-low was significantly associated with positive ER/PgR, lower NG, and lower Ki-67 index values.
3. There was no significant difference in terms of DFS between the three HER2 groups. However, a difference was observed between the three groups in terms of OS. HER2-0 had the lowest OS rate. Moreover, there was a significant difference in OS after recurrence between HER2-0 and HER2-low.
4. When the DFS for the ER status was examined, a significant difference between the HER2 status in cases with ER < 1.0% and ER>10% was observed. Moreover, the DFS in the HER2-low cases was equivalent to the DFS in the HER2-0 cases. However, the DFS in HER2-low was lower in the ER 1-10% group. Although all the HER2 groups showed a significant difference in OS, HER2-low in the ER 1-10% group had the lowest OS, and HER2-0 in the ER>10% group had the lowest OS and was significantly different from HER2-low in the same group.
5. A multivariate analysis revealed that there was no significant difference between HER2-low and HER2-0 as a prognostic factor after recurrence.
6. The pCR rate for NAC was lowest in the HER2-low group, and the pCR rate in the HER2-low group was significantly lower than the HER2-0 group.
7. The DFS after NAC was significantly better in all the pCR cases, regardless of the HER2 status. However, the DFS was significantly lower in the HER2-low non-pCR cases.

Conclusion: HER2-low accounted for 70% of the cases. There were more cases with positive ER/PgR, lower NG, and lower Ki-67 index values in the HER2-low group. The HER2-low group had a significantly better OS than the HER2-0 group. However, the response to NAC was low in the HER2-low group and this group had the poorest prognosis among all the non-pCR cases. These findings indicate that HER2-low has a different biology and prognosis compared to HER2-0 and it may be a new subtype.

PO1-24-04

Gedatolisib, a pan-PI3K/mTOR inhibitor, shows superior potency and efficacy relative to other PI3K/AKT/mTOR pathway inhibitors in breast cancer models

Presenting Author(s) and Co-Author(s):

S. Rossetti. Celcuity, United States

A. Broege. Celcuity, United States

A. Sen. Celcuity, United States

S. Khan. Celcuity, United States

I. MacNeil. Celcuity, United States

J. Molden. Celcuity, United States

I. Gorbachevsky. Celcuity, Inc., Minneapolis, MN, United States

B. Sullivan. Celcuity, Inc., Minneapolis, MN, United States

L. Laing. Celcuity, United States

Background: The PI3K, AKT, and mTOR (PAM) pathway is frequently activated in breast cancer (BC). Current standard-of-care therapy options for patients with advanced BC (ABC) include PAM inhibitors (PAMi), such as everolimus and alpelisib, and hormonal therapy, such as letrozole and fulvestrant. Most PAMi selectively inhibit one or only a few PAM pathway components, which can lead to drug resistance. To minimize drug resistance, a more comprehensive inhibition of the multiple PI3K isoforms and downstream mTOR complexes may be required. We hypothesized that gedatolisib, which potently inhibits all Class I PI3K isoforms, as well as mTORC1 and mTORC2, can be more effective in BC cells than a PAMi targeting single PAM pathway components. Methods: A panel of BC cell lines with mutated or non-mutated PAM pathway genes (PIK3CA, PTEN, AKT) were evaluated for their sensitivity to gedatolisib and other PAMi (PI3K- α : alpelisib; AKT: capivasertib; mTORC1: everolimus; pan-PI3K/mTOR: gedatolisib). Cell viability, growth rate inhibition, and cell death were evaluated by luciferase- and fluorescence-based assays, both in monolayer cultures and three-dimensional (3D) cultures on reconstituted basement membrane. Flow cytometry analytical assays were conducted to assess DNA synthesis (EdU incorporation), protein synthesis (OPP incorporation), and PAM pathway activity (RPS6 and 4EBP1 phosphorylation). BC xenograft studies evaluating gedatolisib in vivo were also performed. Results: Gedatolisib strongly inhibited PAM pathway activity and reduced cell viability and growth rate in the cell lines tested. Compared to the other PAMi, gedatolisib exhibited more potent and efficacious anti-proliferative and cytotoxic effects, regardless of the cell lines' PI3K pathway mutational status. Gedatolisib effects were confirmed in 3D culture on reconstituted basement membrane, where gedatolisib inhibited tumor cell spheroid growth and induced regression. Mechanistically, gedatolisib decreased both DNA and protein synthesis more effectively than the other PAMi tested. Gedatolisib also exerted superior anti-proliferative and cytotoxic effects relative to the other PAMi tested in estrogen receptor-positive BC cell lines concomitantly treated with fulvestrant. BC xenografts confirmed growth inhibitory effects of gedatolisib in vivo. Conclusions: The pan-PI3K/mTOR inhibitor, gedatolisib, may more effectively address potential drug resistance mechanisms associated with narrowly targeted PAM inhibitors. Gedatolisib has previously demonstrated promising preliminary clinical efficacy and safety data in ABC in combination with hormonal therapy. A Phase 3 study (VIKTORIA-1) evaluating gedatolisib plus fulvestrant with and without palbociclib is underway in patients with ABC.

PO1-24-05

EZH2 histone methyltransferase activity promotes spindle metaplastic breast carcinoma metastasis and is induced by CCN6 knockout / b-catenin / TCF axis.

Presenting Author(s) and Co-Author(s):

M. Gonzalez. University of Michigan, United States

A. Eido. University of Michigan, United States

G. AUGIMERI. Department of Pharmacy and Health and Nutritional Sciences, University of Calabria, United States

C. Kleer. Department of Pathology, University of Michigan, Ann Arbor, Michigan, United States

Background: Metaplastic breast carcinomas (mBrCAs) are a highly aggressive subtype of triple negative breast cancer with histological evidence of deregulated differentiation towards non-glandular components. Previous studies have demonstrated that human mBrCA often exhibit activation of differentiation pathways, including canonical Wnt/b-catenin and EZH2-mediated transcriptional repression. Our lab has identified CCN6 as a tumor suppressor in mBrCA. MMTV-Cre;Ccn6fl/fl (CCN6KO) mice develop spindle mBrCAs and CCN6 is reduced/lost in 68% of human mBrCAs. Recently, we have demonstrated that the tumor suppressor function of CCN6 in spindle mBrCA requires activation of Wnt/b-catenin signaling pathway. Here, we tested the hypothesis that CCN6 KO leads to the upregulation of EZH2 histone methyltransferase promoting mBrCA. Furthermore, we investigated the requirement for the activation of the Wnt/b-catenin pathway in this mechanism. Methods: To test the effect of CCN6/b-catenin on EZH2 gene and protein expression we performed IHC, IF, qRT-PCR, ChIP-Seq, RNA-seq, invasion and adhesion assays, EZH2 reporter assay and immunoblots in mBrCA cell lines and MMTV-Cre;Ccn6fl/fl tumors. To investigate the role of CCN6KO-induced b-catenin activation on EZH2 activity and neoplastic functions we employed three independent approaches: i) Expression of a dominant-negative Tcf4 (dnTcf4) rescued with EZH2-WT, dSET and dNLS domain mutants versus vector in MMTV-Cre;Ccn6fl/fl tumor-derived cells; ii) Expression of a constitutively active mutant (S33Y) b-catenin in concert with treatment with recombinant human CCN6 (rhCCN6; 500 ug/ml) versus control; iii) Syngeneic orthotopic mammary tumor transplants of MMTV-Cre;Ccn6fl/fl were used for in vivo rescue experiments with rhCCN6 or BSA. To assess the therapeutic benefit of inhibiting EZH2 methyltransferase activity, MMTV-Cre;Ccn6fl/fl tumor cells (CCN6KO cells) were implanted orthotopically or intracardially in FVB mice, followed by treatment with EPZ-6438 (a selective EZH2 methyltransferase inhibitor) or vehicle. We tested CCN6, b-catenin, and EZH2 expression by IHC in a cohort of 27 human mBrCA tumor samples. Results: CCN6KO-induced b-catenin/TCF activation mediates EZH2 transcriptional upregulation and the deposition of repressive H3K27me3 in spindle mBrCAs. We found that the invasion program triggered by CCN6KO-induced Wnt/b-catenin requires EZH2 catalytic activity as WT-EZH2 (but not dSET-EZH2) rescued the reduced invasion of CCN6KO-dnTcf4 cells. RNA-seq and 3H3K27 ChIP-seq of CCN6KO-dnTcf4 cells transduced with EZH2-WT or dSET-EZH2 identify specific CCN6KO-b-catenin/Tcf targets that require EZH2 transcriptional repressor function. In vivo, administration of CCN6 protein to MMTV-Cre;Ccn6fl/fl tumor transplants reduces tumor growth and nuclear b-catenin, EZH2 and 3H3K27 in the tumors. Pharmacologic inhibition of EZH2 reduces the growth and metastasis of CCN6KO mBrCA tumors and improves survival. We identify a subset of human spindle mBrCA (54%) that display a CCN6Low/nuclear b-cat/EZH2High phenotype. Conclusion: We found a critical role for EZH2 activation in CCN6-deficient mBrCA tumor phenotypes via b-catenin/TCF Wnt canonical signaling. We demonstrate the effectiveness of pharmacological inhibition of EZH2 methyltransferase activity in reducing primary tumor growth

and distant metastasis in mouse models of spindle mBrCA. In clinical samples, low CCN6 is significantly associated with activated b-catenin and high EZH2 in spindle mBrCAs compared to other subtypes. These data reveal a novel tumor suppressor mechanism of CCN6 and provide compelling evidence supporting the potential therapeutic value of CCN6 restoration, b-catenin or EZH2 inhibition as promising approaches for the treatment of spindle mBrCAs.

PO1-24-06

Prolactin Hormone-Induced Mammary Differentiation and Anti-tumorigenic Role in Breast Cancer

Presenting Author(s) and Co-Author(s):

D. Hamam. McGill University, Montreal, Quebec, Canada

S. Ali. McGill University, United States

The premise of differentiation therapy in cancer is a strategy that aims at engaging-forward differentiation and cellular reprogramming restricting the proliferative, tumor repopulation, stemness, EMT and metastatic capacities of tumor cells leading to the cessation of the aggressive tumor phenotype and offering the cancer patients improved survival for decades. Therefore, deciphering molecular mechanisms deriving differentiation in normal mammary and breast cancer cells may allow the discovery of innovative differentiation-based biomarkers and therapeutics in breast cancer.

Lactation is an intricate process that results in the ability of the breast cells to produce a complex nutritious biological fluid to nurse the new-born. While the beneficial effects of breastfeeding to the infant is irrefutable, its effects on maternal health are less investigated especially in relation to breast cancer that still affects 1 in 8 women in high income countries and 1 in 20 globally. Importantly, epidemiological studies have linked breastfeeding to reduced risk of breast cancer by promoting terminal differentiation of the breast epithelial cells. While breastfeeding process is regulated by multiple hormones, growth factors, and transcriptional regulators, the lactation hormone prolactin (PRL) is known to be directly implicated in the hormonal control of breastfeeding. Extensive research including our own work has shown that PRL/PRL receptor (PRLR) pathway derives mammary gland development and importantly mammary epithelial cell terminal differentiation allowing successful lactation. In contrast the role of PRL in breast cancer is still to be fully defined. Importantly, we have accumulated compelling evidence using in-silico publicly available patient data sets and molecular data implicating this pathway as a clinically relevant pro-differentiation pathway driving differentiation and cellular reprogramming suppressing stemness, EMT, metastasis and tumorigenesis in breast cancer. To better characterize PRL signaling mediating its pro-differentiation effects, we used large-scale unbiased proteomics analysis of PRLR/interacting proteins in breast cancer cells. Our analyses revealed several novel PRLR-interactors. We have further confirmed these interactions through co-immunoprecipitations/western blotting analyses in breast cancer cells representative the different breast cancer subtypes. We also examined their functional contributions to mammary differentiation and tumorigenesis using in vitro and in vivo assays. Moreover, we defined their potential clinical relevance using bioinformatics in silico databases of breast cancer. Together our study delineates novel PRL/PRLR-downstream signaling mediators important for mammary differentiation and tumorigenesis and may thus be useful as biomarkers and/or therapeutic targets in breast cancer.

PO1-24-07

LYSOSOMAL-ASSOCIATED TRANSMEMBRANE 4B (LAPTM4B) AS POTENTIAL BIOMARKER IN BREAST CANCER

Presenting Author(s) and Co-Author(s):

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

A. Gasol Cudós. Hospital Universitari Arnau de Vilanova de Lleida, United States

N. Tuset Der-Abraín. Hospital Universitari Arnau de Vilanova de Lleida, United States

I. Urdanibia. Hospital Universitari Arnau de Vilanova de Lleida, United States

A. Velasco Sánchez. Hospital Universitari Arnau de Vilanova de Lleida, United States

LAPTM4B is a transmembrane that promotes autophagy and renders tumor cells resistant to metabolic and genotoxic stress. Increased expression of LAPTM4B has been found in breast, liver, lung, ovarian, uterine and gastric cancers. Overexpression of LAPTM4B contributes to chemotherapy resistance, proliferation and metastases.

We analyze the expression of LAPTM4B in serum by ELISA method in a series of breast cancer patients in different clinical situations to assess its possible potential as a biomarker.

A total of 135 patients were analyzed, 95 patients were in early breast cancer and 50 in metastatic disease. Of the 95 patients with early disease, 52 had a luminal A phenotype, 19 luminal B, 15 HER2 positive and 9 triple negative. And of the other 50 they were luminal in 34, HER2 positive in 11 and triple negative in 5.

The attached table specifies the values of the LAPTM4B expression in the different clinical situations.

	GLOBAL	LUMINAL A	LUMINAL B	HER2	TRIPLE NEGATIVE										
SITUATIONS	Laptm4b	n	Laptm4b	n	Laptm4b	n	Laptm4b	n	Laptm4b	n					
EARLY	9,6	ng/ml	95	7,7	ng/ml	52	12,8	ng/ml	19	13,4	ng/ml	15	7,1	ng/ml	9
METASTATIC	16,8	ng/ml	50	13,7	ng/ml	34	7,2	ng/ml	11	58,9	ng/ml	5			

We found a statistic difference in the expression of LAPTM4B in patients with early and metastatic disease (ANOVA test $p:0,028$). LAPTM4B was higher in the luminal B and HER2 subtypes in early breast cancer while in metastatic disease was overexpressed in triple negative.

An interesting finding was that in metastatic disease, LAPTM4B was overexpressed in patients with progression compared to patients in response. 30 ng/ml vs 10 ng/ml (ANOVA test $p:0,011$)

LAPTM4B expression may be a potential biomarker in breast cancer since its expression is statistically different in early and metastatic disease (9,6 vs 16,8 ng/ml). In addition, patients with metastatic breast cancer who are in response also have lower levels of LAPTM4B compared with patients in progression. Monitoring the levels of LAPTM4B in serum can help us to predict the treatment response.

PO1-24-08

Targeting of HER3 potentiates the antitumor activity of paclitaxel against triple negative breast cancer

Presenting Author(s) and Co-Author(s):

H. Lyu. LSU Health New Orleans, United States

S. Ruan. LSU Health New Orleans, United States

C. Tan. LSU Health New Orleans, United States

A. Thor. University of Colorado, Anschutz Medical Campus, United States

B. Liu. LSU Health New Orleans, Louisiana, United States

Background: Triple negative breast cancer (TNBC) is characterized by the absence of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) overexpression. This aggressive form of breast cancer carries a higher risk of recurrence compared to other subtypes, presenting a significant clinical challenge. Although chemotherapy is commonly used as the primary treatment for a substantial number of TNBC patients, it is often accompanied by drug resistance and frequent tumor recurrence. Urgent efforts are needed to identify novel molecular targets specific to TNBC and develop effective therapies to combat this aggressive disease. The ultimate objective is to discover treatments capable of overcoming drug resistance and improving the overall survival of patients with TNBC. Methods: Immunohistochemistry was performed to examine the expression of HER3 in TNBC samples. Western blots were used to assess protein expression and activation. Cell proliferation and viability were determined by cell growth (MTS) assays. TCGA databases were analyzed to correlate HER3 mRNA expression with the clinical outcomes of TNBC patients. Specific shRNA was used to knockdown HER3 expression. LIVE/DEAD Cell Imaging was to detect live and dead cells. Orthotopic tumor models were established in nude mice to determine the capability of TNBC cells forming tumors and to test if our newly developed anti-HER3 monoclonal antibody (mAb) 4A7 could potentiate the antitumor activity of paclitaxel in vivo. Results: The chemo-resistant subline HCC1806-TR was obtained by subjecting TNBC HCC1806 cells to prolonged treatment with paclitaxel. In comparison to the parental cell line HCC1806-P, HCC1806-TR exhibited enhanced HER3 expression and activation. It is noteworthy that approximately half of the tested TNBC specimens and cell lines displayed elevated expression of HER3. Analyzing TCGA databases revealed that TNBC patients with high levels of HER3 mRNA expression in their tumors had significantly poorer overall survival (OS) and relapse-free survival (RFS) compared to those with low HER3 expression. Specifically knockdown of HER3 markedly inhibited TNBC cell proliferation and mammosphere formation in vitro and tumor growth in vivo. Blockade of HER3 signaling with our mAb (4A7) in combination with paclitaxel exerted significant antitumor activity against TNBC in vitro and in vivo. Conclusions: Our data demonstrate that increased HER3 is an effective therapeutic target for TNBC and our anti-HER3 mAb (4A7) may enhance the efficacy of paclitaxel in TNBC. Keywords: HER3, Antibody, Chemotherapy, Triple Negative Breast Cancer

PO1-24-10

B cell-mediated immunity predicts survival of patients with ER-positive breast cancer

Presenting Author(s) and Co-Author(s):

S. Lee. Department of Genomic Medicine, Seoul National University, United States

B. Kang. Ewha Woman's University, United States

H. Lee. Seoul National University Hospital, United States

W. Han. Seoul National University Hospital, Seoul, Republic of Korea

I. Kim. Department of Radiation Oncology, Seoul National University Bundang Hospital, Seongnam, Korea, Republic of Korea

Background: The estrogen receptor-positive (ER+) breast cancer (BC), which constitutes the majority of BC cases, exhibits highly heterogeneous clinical behavior. To aid precision treatments, we aimed to find molecular subtypes of ER+ BC representing the tumor microenvironment.

Methods: We analyzed RNA-seq data of 113 BC patients and classified them according to the PAM50 intrinsic subtypes using gene expression profiles. Among them, we further focused on 48 patients with luminal-type (ER+) BC for subclassification. The Cancer Genome Atlas (TCGA) data of BC patients were utilized as a validation dataset to verify the new classification.

Results: Principal component analysis clearly divided the patients into two subgroups separately from the luminal A and B classification. The top differentially expressed genes between the subgroups were distinctly characterized by immunoglobulin and B cell-related genes. We could also cluster a separate cohort of patients with luminal-type BC from TCGA into two subgroups based on the expression of a B cell-specific gene set, and patients with high B cell immune activity had better prognoses than other patients.

Conclusions: Our transcriptomic approach defines a novel molecular phenotype of B cell immunity in ER+ BC that may help to predict disease prognosis. Although further researches are required, B cell immunity for ER+ BC patients may be helpful for identifying patients who are good responder to chemotherapy or immunotherapy. Work supported by grants from the National Research Foundation of Korea (NRF-2023R1A2C3003782)

PO1-24-11

Distinct patterns of MHC class I, PD-L1 expression, and T-cell infiltration in different subtypes of ductal carcinoma in situ of the breast

Presenting Author(s) and Co-Author(s):

n. kim. Chonnam National University Hwasun Hospital, United States

m. park. Chonnam National University Hwasun Hospital, United States

j. lee. Chonnam National University Hwasun Hospital, United States

Background: Ductal carcinoma in situ (DCIS) of the breast encompasses various subtypes with distinct behaviors. Immune cell infiltration within the tumor microenvironment is thought to influence DCIS progression. Tumor-infiltrating lymphocytes (TILs) serve as a surrogate marker for the adaptive immune response. The interaction between programmed death 1 (PD-1) and its ligand PD-L1 suppresses effector T-cell function. Major histocompatibility complex (MHC) class I molecules play a critical role in presenting tumor antigens to cytotoxic T cells. Despite the significance of PD-L1 and MHC class I in immune evasion, limited data exist on their correlation with T-cell infiltration in DCIS subtypes. **Methods:** Using immunohistochemistry, we examined MHC class I and PD-L1 expression, along with CD3+ and CD8+ T lymphocytes, in 131 DCIS cases through tissue microarrays. DCIS subtypes included hormone receptor-positive (HR+)/human epidermal growth factor 2-negative (HER2-), HR+/HER2+, HR-/HER2+, and triple-negative (TN) subtypes. **Results:** Among the 128 interpretable cases, the distribution was as follows: HR+/HER2- (50.8%), HR+/HER2+ (14.1%), HR-/HER2+ (26.5%), and TN (8.6%). HER2+ subtypes (HR+/HER2+ and HR-/HER2+) exhibited higher stromal TILs, CD3+ T cells, and CD8+ T cells compared to HR+/HER2- subtype. MHC class I loss was observed in 16.4% (21/128) of cases, with the highest frequency in the HR+/HER2- subtype (29.2%), followed by HR-/HER2+ (5.9%), HR+/HER2+ (0%), and TN (0%) subtypes. DCIS cases lacking MHC class I expression displayed lower stromal CD8+ T cell infiltration than those with intact MHC class I. PD-L1 expression in immune cells ($\geq 1\%$) was detected in 18.8% (24/128) of cases and correlated with increased stromal TILs, CD3+ T cells, and CD8+ T cells. PD-L1 expression was more prevalent in HER2+ subtypes than in HR+/HER2- subtype. PD-L1-positive DCIS cases mostly retained MHC class I expression (95.8%), except for one case (4.2%) in the HR-/HER2+ subtype. The highest numbers of stromal CD3+ and CD8+ T cells were observed in DCIS cases with intact MHC class I and positive PD-L1 expression. The correlation between MHC class I and PD-L1 expression and infiltration of CD3+ and CD8+ T cells was maintained in HR+/HER2- and HR-/HER2+ subtypes. Notably, tumoral CD3+ and CD8+ T cells showed no significant association with MHC class I or PD-L1 expression. Furthermore, MHC class I and PD-L1 expression did not predict tumor recurrence. **Conclusion:** We observed distinct patterns of MHC class I and PD-L1 expression and T-cell infiltration among DCIS subtypes. Enhancing our understanding of MHC class I, PD-L1, and immune subsets, including CD8+ T cells, may contribute to the development of immune modulating therapies for DCIS, particularly in the HER2+ subtype.

PO1-24-12

Investigating the immunological function of alpha-2-glycoprotein 1, zinc-binding in regulating tumor response in the breast cancer microenvironment

Presenting Author(s) and Co-Author(s):

T. Hanamura. Tokai University School of Medicine, Japan

K. Yokoyama. Tokai University School of Medicine, United States

S. Kitano. The Cancer Institute Hospital of JFCR, Ariake, Koto-ku, Toikeyo, Japan, Tokyo, Japan

H. Kagamu. Division of Respiratory Medicine, Saitama Medical University International Medical Center, Japan

M. Yamashita. Division of Cancer Immunotherapy Development, Center for Advanced Medical Development, The Cancer Institute Hospital of JFCR, Japan

M. Terao. Department of Breast Oncology, Tokai University School of Medicine, Japan

T. Okamura. Department of Breast Oncology, Tokai University School of Medicine, Kanagawa, Japan

N. Kumaki. Department of Pathology, Tokai University, School of Medicine, Japan

K. Hozumi. Department of Immunology, Tokai University School of Medicine, Japan

T. Iwamoto. Okayama University Hospital, Breast and Endocrine Surgery, Japan

C. Honda. Department of General Surgical Science, Gunma University Graduate School of Medicine, Japan

S. Kurozumi. Department of Breast Surgery, International University of Health and Welfare, Japan

J. Richer. University of Colorado Anschutz Medical Campus, Aurora, Colorado, United States

N. Niikura. Tokai University School of Medicine, Isehara-shi, Isehara, Kanagawa, Japan

Purpose: Tumor immunology has attracted considerable attention as an innovative therapeutic strategy for various types of cancer. Elucidating the unique immunoregulatory mechanisms in the breast cancer microenvironment will assist in the development of novel treatment strategies. Recently, we and other researchers have found that androgen receptor (AR) expression is associated with the immunosuppressive phenotype in the breast cancer microenvironment, suggesting some immunoregulatory function in breast cancer; however, the mechanism remains unclear. Here, we focused on AR-dependent secreted protein, alpha-2-glycoprotein 1, zinc-binding (ZAG) encoded by the AZGP1 gene in breast cancer, which is structurally similar to HLA class I and is implicated in immune regulation. In this study, we investigated the immunological function of AZGP1/ZAG in the breast cancer microenvironment. **Methods:** We performed a gene set enrichment analysis (GSEA) to screen the biological processes associated with AZGP1 expression using a gene expression profile dataset of the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC). Subsequently, we analyzed the correlation between AZGP1 expression and the immune cell composition in breast cancer tissues estimated with the CIBERSORTx using METABRIC and another dataset of The Sweden Cancerome Analysis Network-Breast. In our previous study of 45 breast cancer tissue samples, we evaluated the infiltration of 11 types of immune cells using flow cytometry (FCM). ZAG expression was further evaluated by immunohistochemistry, and the relationship between ZAG expression and the immune cell composition in breast cancer tissue was analyzed. Based on the results of this analysis (shown in the results section) we hypothesized that ZAG has some effect on the macrophage (M ϕ). The action of ZAG in M1/M2 polarization

models constructed using primary culture of human peripheral blood mononuclear cells (PBMC)-derived M ϕ was assessed based on the expression of M1/M2 differentiation markers (CD86, CD80/CD163, MRC1) and HLA class I/II expression evaluated by FCM (n=15 each). Results: GSEA demonstrated that AZGP1 expression was negatively correlated with multiple gene sets representing immunological processes, including inflammatory response, allograft rejection, interferon gamma response, IL6/JAK/STAT3 signaling, complement, and IL2/STAT5 signaling. Analysis by CIBERSORTx showed that AZGP1 expression was negatively correlated with the absolute score (the absolute abundance of total immune cell infiltration), M ϕ M1, NK cells activated, CD4+ T memory activated, and CD8+ T ($r < -3$ and $p < 0.05$). Analyses of our in-house dataset using breast cancer tissue showed that ZAG expression was associated with decreased infiltration of monocytes/macrophages, non-classical monocytes, and myeloid-derived suppressor cells in breast cancer tissues assessed by FCM. In the in vitro analyses, ZAG decreased the expression of CD80, CD163, MRC1, and HLA classes I and II in the M1 polarization model and the expression of CD163 and MRC1 in the M2 polarization model. Conclusion: AZGP1/ZAG was associated with an immunosuppressive phenotype and reduced infiltration of specific immune cell subsets, particularly M ϕ , into breast cancer tissues. In the in vitro analysis, ZAG demonstrated some regulatory effects on the phenotypic change of M ϕ . Our findings strongly suggest ZAG is a novel mediator of AR-dependent immunomodulation in the breast cancer microenvironment, laying the foundation for future studies to elucidate the immunological role of ZAG in breast cancer.

PO1-25-01

LMTK3 promotes macrophage M2 polarisation and suppresses monocyte infiltration in breast cancer by altering the proteomic cargo of exosomes

Presenting Author(s) and Co-Author(s):

M. Samuels. University of Sussex, United States

W. Jones. University of Sussex, United States

C. Turner. University of Sussex, United States

G. Giamas. University of Sussex, United States

Background:

Breast cancer (BC) is a leading cause of cancer death and despite numerous treatment advancements, metastatic BC is incurable. Extracellular vesicles (EVs) are lipid-delimited particles released from cells which contain bioactive protein and nucleic acid cargo. Numerous studies have shown their importance in facilitating communication between cancer cells and the tumour microenvironment, implicating them as mediators of many aspects of carcinogenesis. EV-mediated communication between BC and the innate immune system plays a crucial role in BC progression, metastasis and the maintenance of an immunosuppressive microenvironment. LMTK3 overexpression in BC promotes therapy resistance, disease progression and invasion and metastasis, leading to a poorer prognosis in patients. Analysis of deconvoluted TCGA data indicated that LMTK3 overexpression also correlates with exclusion of M1 macrophages from the tumour microenvironment. This study aimed to explore the role of LMTK3 in EV-mediated communication between BC and immune cells.

Methods

EVs were collected from conditioned media of wild-type and LMTK3-overexpressing BC cells through differential ultracentrifugation, then characterised by transmission electron microscopy, nanoparticle tracking analysis, quantitative mass spectrometry and Western blotting. Monocytes were treated with EVs and proteomic and phosphoproteomic changes were analysed. 3D coculture models of BC and immune cells were used to assess monocyte and macrophage infiltration, polarisation and anti-cancer activity. Immunofluorescence and flow cytometry was used to assess macrophage polarisation. Bioinformatic analysis of TCGA datasets validated the findings in a clinical setting and the data was also validated in vivo, using syngeneic immunocompetent mouse models.

Results

LMTK3 overexpression in BC cells promotes the upregulation of a subpopulation of large (80-150nm) CD81+ EVs which are significantly enriched in oncogenic and immunoregulatory proteins, including LDHB, ARHGEF15, PSAT1 and HIC2. EVs from LMTK3-overexpressing but not control BC cells strongly reduce the ability of monocytes to infiltrate BC tumour spheroids and migrate through Matrigel. Proteomics analysis of the monocytes showed an enrichment in M2 polarisation proteins and a downregulation of proteins essential for migration, including S100A8, KLF13 and TRPC3. LMTK3 overexpression in BC also promotes M2 polarisation and exclusion of M1 macrophages in vivo.

Summary

LMTK3 overexpression in BC correlates with poor prognosis and reduced overall survival. We hypothesise that this is, in part, due to monocyte M2 polarisation and exclusion of M1

macrophages from the TME, mediated by LMTK3-dependent alterations in EV cargo, contributing to tumour immune evasion.

PO1-25-03

Programmed Death-Ligand 1 and Receptor Tyrosine Kinases in Breast Cancer

Presenting Author(s) and Co-Author(s):

N. Ayoub. Jordan University of Science and Technology, Irbid, Irbid, Jordan

M. Al-Diabat. Jordan University of Science and Technology, Irbid, Irbid, Jordan

M. Al-Shorman. Jordan University of Science and Technology, Irbid, Irbid, Jordan

L. Al-Eitan. Jordan University of Science and Technology, Irbid, Irbid, Jordan

Programmed death-ligand 1 (PD-L1) is an immune checkpoint expressed in a wide range of malignancies leading to immune tolerance and cancer cell immune evasion. Receptor tyrosine kinases (RTKs) are key regulators of cancer cell proliferation, survival, and invasion. The Hepatocyte Growth Factor (HGF) receptor, MET, and the Epidermal Growth Factor Receptor (EGFR) are RTKs known for their tumorigenic potential in a variety of human malignancies. This study aimed to evaluate the effect of the small-molecule tyrosine kinase inhibitors (TKIs) on the expression of PD-L1 in breast cancer cells and the effect of their combination with inflammatory cytokines. The study also assessed the association of the expression of the tumoral PD-L1 mRNA with each of MET and EGFR mRNA expression and the tumor features and treatment outcomes in breast cancer patients using the METABRIC dataset publicly available from cBioPortal for Cancer Genomics. The TKIs crizotinib [a MET inhibitor] and gefitinib [an EGFR inhibitor] were used as a single treatment and in combination with the cytokines; tumor necrosis factor- α (TNF- α) or interferon- γ (INF- γ) in MCF7 and MDA-MB-231 breast cancer cells in vitro. The cells were also treated with the mitogens HGF and EGF. The viability of cells after the different treatments was determined using the MTT viability assay. The effects of the combination treatments were analyzed using combination index (CI) analysis. The expression level of PD-L1 in cancer cells was assessed using Western blotting.

The combination treatment of crizotinib with TNF- α and INF- γ produced a synergistic growth inhibition of MCF7 and MDA-MB-231 cells with CI values of 0.31 and 0.55, respectively. Alternatively, combined crizotinib and TNF- α produced an antagonist effect on the viability of MCF7 cells (CI=2.49). The combination of gefitinib with TNF- α produced a synergistic growth inhibition in both MCF7 and MDA-MB-231 cells with CI values of 0.39 and 0.78, respectively. Alternatively, gefitinib resulted in an additive effect when combined with INF- γ (CI=0.99) and an antagonistic effect when combined with TNF- α (CI=2.68) in MCF7 and MDA-MB-231 cells, respectively. Treatment with HGF (50 and 100 ng/ml) increased the protein levels of PD-L1 while EGF (50 and 100 ng/ml) reduced its levels in MDA-MB-231 cells. Treatment with the TKIs crizotinib (0.1-4 μ M) and gefitinib (1-40 μ M) significantly reduced PD-L1 levels in MDA-MB-231 cells compared to vehicle-treated cells.

The analysis of the METABRIC dataset revealed that the mRNA expression of PD-L1 was positively correlated with the mRNA expression of the EGFR gene ($r=0.081$, $p<0.001$) but not the MET gene. A double-high PD-L1/MET expression was significantly associated with younger age at diagnosis, high-grade carcinoma, greater tumor size, hormone receptor-negative status, HER2-positivity, and non-luminal disease compared to patients with a double-low PD-L1/MET expression. Similar findings were reported for patients with a double-high PD-L1/EGFR expression compared to patients with a double-low PD-L1/EGFR expression. Nevertheless, the mRNA expression of the PD-L1, MET, and EGFR genes as well as the co-expression of PD-L1/MET or PD-L1/EGFR genes did not affect the overall survival of breast cancer patients. Collectively, MET and EGFR TKIs could modulate the effects of inflammatory cytokines differently based on the type of cytokine and the molecular subtype of breast cancer cells. The expression of PD-L1 in breast cancer cells was upregulated by HGF while TKIs reduced its

expression. The co-expression of the PD-L1 gene with MET and EGFR genes in breast cancer was associated with advanced disease presentation and worse prognosticators in patients. Together, TKIs that target MET or EGFR could be an appealing therapeutic target in breast cancer, particularly in younger patients with the non-luminal disease.

PO1-25-04

PTN-positive luminal progenitors induce angiogenesis and metastasis in inflammatory breast cancer

Presenting Author(s) and Co-Author(s):

M. Zhang. Breast Disease Center, The First Affiliated Hospital of Sun Yat-sen University, China (People's Republic)

K. Zhou. Breast Disease Center, The First Affiliated Hospital of Sun Yat-sen University, United States

T. Liu. Breast Disease Center, The First Affiliated Hospital of Sun Yat-sen University, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

W. Chen. Dana-Farber Cancer Institute, United States

Q. Chen. Department of Breast Oncology, Traditional Chinese Medicine Hospital of Guangdong Province, United States

X. Li. Department of Breast Oncology, Jiangmen Central Hospital, United States

Z. Yuan. Department of Medical Oncology, Sun Yat-sen University Cancer Center, United States

J. Xu. Department of Breast Oncology, Maternal and Child Health Care Hospital of Guangdong Province, United States

Z. Cai. Department of Breast Oncology, Jieyang People's Hospital, United States

J. Guo. Institute of Precision Medicine, The First Affiliated Hospital of Sun Yat-sen University, United States

n. shao. First Affiliated Hospital of Sun Yat-sen University, United States

Y. Lin. The First Affiliated Hospital of Sun Yat-sen University, United States

Background

Inflammatory breast cancer (IBC) is a lethal subtype of breast cancer characterized by rapidly arising diffuse erythema and edema of the overlying skin that was thought to contribute to rapid metastasis. Dissecting the intricate cellular ecosystems within tumors and affected skin and their complex interplay may be pivotal in unraveling the aggressive nature of IBC.

Methods

Integrative analysis containing single-cell RNA sequencing, bulk RNA sequencing, and whole exome sequencing, was performed on paired tumor and skin samples from 17 treatment-naive IBC patients and 5 non-IBC patients from multiple centers. Meanwhile, paraffin sections and serum specimens from two centers were conducted to validate the omics results. Additionally, public single-cell transcriptomic data of non-IBC tumors and normal mammary glands, RNA microarray data from IBC cases, and the Cancer Genome Atlas (TCGA) database were utilized to validate the characteristics of IBC microenvironment. The regulatory mechanism was verified by in vitro experiments.

Results

We delineated the landscapes of IBC tumor and affected skin microenvironment at the single-cell level and demonstrated that the luminal progenitors (LP) cells highly expressing pleiotrophin (PTN) were most significantly enriched in IBC tumors compared to non-IBC tumors and normal mammary glands, in two independent cohorts. Moreover, the serum concentrations of PTN were significantly higher in IBC patients compared with non-IBC patients. Notably, PTN

secreted by PTN+ LP cells interacted with Neuropilin 1(NRP1) receptor on endothelial tip cells in both tumor and affected skin of IBC. Moreover, in vitro assay demonstrated knocking down the expression of NRP1 on human umbilical vein endothelial cells significantly blocked PTN-induced migration, tube formation and sprouting, which might be independent of VEGFA. In addition, two immature phenotypes of PVL_MMP9 and PVL_CCL19 cells recruited by endothelial tip cells via PDGFB/PDGFRB axis were accumulated in affected skin of IBC, which might be associated with promotion of malignant cell metastasis. Finally, we revealed that malignant cells in affected skin of IBC had a higher ability of epithelial-mesenchymal transition than IBC intratumoral malignant cells and identified enhanced crosstalk between immature PVL cells and malignant cells in the skin affected with IBC, through TNFSF12-TNFRSF12A, TGFB-TGFR1/TGFR2, MDK-SDC1/4/NCL/ (ITGA6+ITGB1).

Conclusion

We identified a unique, non-malignant epithelial cell subpopulation PTN+ LP cells, which induce massive angiogenesis via the PTN-NRP1 axis, recruit the immature phenotype PVL cells accumulated in affected skin of IBC thus promoting tumor progression. Our findings offer comprehensive insights into the pathogenesis of IBC and uncover a previously unknown, promising therapeutic target.

Patient of discovery cohort details

Patient ID	Gender	Tissue Acquired in scRNA-seq	Tissue Acquired in WES	Tissue Acquired in Bulk RNA-seq	Age	Grade	ER	PR	HER2	VEGF	PDGFR	Metastasis	Subtype	Treatment status	Stage
IB21	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	40	3	-	-	0	Non-Amplified	CC	None	IBC	None	T4A0M
IB22	Female	Tumor/Skin/Skin with erythema and edema	Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	40	3	-	-	0	Amplified	CC	None	IBC+EDC	None	T4A0M
IB23	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor	38	3	-	-	0	Non-Amplified	CC	None	IBC	None	T4A0M
IB24	Female	Tumor/Skin/Skin with erythema and edema	Tumor	Tumor	45	3	20+	20+	1+	Non-Amplified	Mesenchymal carcinoma	None	IBC	None	T4A0M
IB25	Female	Tumor/Skin/Skin with erythema and edema	Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	56	3	40+	80+	0	Non-Amplified	CC	None	IBC+EDC	None	T4A0M
IB26	Female	Tumor/Skin/Skin with erythema and edema	Tumor	Tumor	76	3	-	-	0	Amplified	CC	None	IBC+EDC	None	T4A0M
IB27	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	56	3	-	-	0	Amplified	CC	None	IBC+EDC	None	T4A0M
IB28	Female	Tumor	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	56	3	-	-	0	Amplified	CC	None	IBC+EDC	None	T4A0M
IB29	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	40	3	-	-	0	Non-Amplified	CC	None	IBC	None	T4A0M
IB30	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	48	3	-	-	0	Non-Amplified	CC	None	IBC	None	T4A0M
IB31	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	NA	54	3	20+	-	1+	Non-Amplified	CC	None	IBC+EDC	None	T4A0M
IB32	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	39	3	30+	<10+	1+	NA	CC	None	IBC+EDC	None	T4A0M
IB33	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	56	3	85+	10+	1+	Non-Amplified	CC	None	IBC+EDC	None	T4A0M
IB34	Female	Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	58	3	80+	50+	0	Non-Amplified	CC	None	IBC+EDC	None	T4A0M
IB35	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	57	3	-	-	0	NA	CC	None	IBC	None	T4A0M
IB36	Female	Tumor	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	40	3	40+	10+	0	Amplified	CC	None	IBC+EDC	None	T4A0M
IB37	Female	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	Tumor/Skin/Skin with erythema and edema	57	3	20+	-	0	NA	CC	None	IBC	None	T4A0M
IB38	Female	Tumor/Skin/Skin with lymph	Tumor/Skin/Skin with lymph	Tumor/Skin/Skin with lymph	72	3	-	-	0	Amplified	CC	None	IBC+EDC	None	T4A0M
IB39	Female	Tumor/Skin/Normals skin	Tumor/Skin/Normals skin	Tumor/Skin/Normals skin	59	3	-	-	0	Amplified	CC	None	IBC+EDC	None	T4A0M
IB40	Female	Tumor/Skin/Normals skin	Tumor/Skin/Normals skin	Tumor/Skin/Normals skin	54	3	80+	80+	0	Amplified	CC	None	IBC+EDC	None	T4A0M
IB41	Female	Tumor/Skin/Skin with lymph	Tumor/Skin/Skin with lymph	Tumor/Skin/Skin with lymph	56	3	85+	70+	0	Non-Amplified	CC	None	IBC+EDC	None	T4A0M
IB42	Female	Tumor/Skin/Skin with lymph	Tumor/Skin/Skin with lymph	Tumor/Skin/Skin with lymph	56	3	80+	10+	1+	Non-Amplified	CC	None	IBC+EDC	None	T4A0M

Clinical and pathology details for inflammatory breast cancer(IBC) and non-IBC patients analysed by single-cell RNA sequencing(scRNA-seq), bulk RNA sequencing(bulk RNA-seq) and whole exome sequencing(WES) in this study.

Clinical/pathological feature of validation cohort

Characteristic	IBC (n=52)	non-IBC (n=61)
Age at diagnosis (median [range])	52[29-89]	54[26-80]
Histology		
IDC	50(96.15)	60 (98.36)
ILC	1(1.92)	0 (0)
MBC	1(1.92)	0 (0)
Invasive papillary carcinoma	0(0)	1 (1.64)
Histologic grade (%)		
2	12 (23.08)	19 (31.15)
3	13(25.00)	21 (34.43)
NA	28(53.85)	21 (34.43)
T (%)		
1	0 (0)	4 (6.56)
2	0 (0)	20 (32.79)
3	0 (0.0)	5 (8.20)
4	52 (100)	32 (52.46)
N (%)		
0	2(3.85)	14 (22.95)
1	22 (42.31)	20 (32.79)
2	10 (19.23)	12 (19.67)
3	18(34.62)	15 (24.59)
M (%)		
0	36(69.23)	49 (80.33)
1	16(30.77)	12 (19.67)
Stage (%)		
IIA	0 (0.0)	13 (21.31)
IIB	0 (0.0)	7 (11.48)
IIIA	0 (0.0)	7 (11.48)
IIIB	31 (59.62)	18 (29.51)
IIIC	5(9.52)	4 (6.56)
IV	16(30.77)	12 (19.67)
ER status (%)		
negative	35 (67.31)	30 (49.18)
positive	17 (32.69)	31 (50.81)
PR status (%)		
negative	36(69.23)	31 (50.81)
positive	16 (30.77)	30 (49.18)
HER2 status (%)		
negative	33 (63.46)	38 (62.30)
positive	19 (36.54)	23 (37.70)
Ki67 (%)		
≤ 30%	14(26.92)	31 (50.81)
> 30%	34(65.38)	30 (49.18)
NA	4(7.69)	

PO1-25-05

Adipose-enriched peri-tumoral stroma prognosticates poorer survival in breast cancers

Presenting Author(s) and Co-Author(s):

H. Lau. Department of Physiology, National University of Singapore; Division of Cellular & Molecular Research, National Cancer Centre Singapore, United States

V. Tan. National Cancer Centre Singapore, United States

B. Tan. National Cancer Centre Singapore, United States

Y. Sim. Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, Singapore

J. Quist. Breast Cancer Now Unit, King's College London Faculty of Life Sciences and Medicine, London; School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, United States

A. Thike. Division of Pathology, Singapore General Hospital, United States

P. Tan. Singapore General Hospital, United States

S. Pervaiz. Department of Physiology, National University of Singapore; NUS Centre for Cancer Research (N2CR), Yong Loo Lin School of Medicine, National University of Singapore, United States

A. Grigoriadis. King's College London, Comprehensive Cancer Centre, Faculty of Life Sciences and Medicine, London; School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom

K. Sabapathy. Division of Cellular & Molecular Research, National Cancer Centre Singapore; School of Biological Sciences, Nanyang Technological University, United States

Background: Adjuvant breast cancer therapy is informed by whether a tumour is positive or negative for the biomarkers ER, PgR, and HER2, often without regard to level of positivity. Quantitation has been proposed to improve therapeutic management. Adjunctive statistical standardization has been proposed to improve inter-laboratory comparability of biomarkers results. Methods: This primary report utilized adjunctive statistical standardization of machine-quantitated image analysis biomarker assessments. CCTG MA.27 (NCT00066573) is an adjuvant phase III trial of exemestane versus anastrozole in postmenopausal women with ER+ and/or PgR+ tumours. IHC ER, PgR, and HER2 were centrally assessed, with FISH (HER2;HER2/CEP17) determinations for equivocal IHC HER2. HSCOREs were statistically standardized to a mean of 0, standard deviation of 1 following Box-Cox variance stabilization transformations of square for ER and natural logarithm for PgR (0.1 was added to 0 HSCOREs). The primary endpoint was STEEP distant disease-free survival (DDFS) at the longest trial follow-up of median 4.1 years. Survival was described with Kaplan-Meier plots. The univariate Wilcoxon (Peto-Prentice) test statistic was used with usual designation of negative/positive (0; >0), and standardized cut-points at standard deviations about mean of 0 (<-1; (-1,0]; (0,1]; >1). Cox multivariate regressions adjusted for age, T and N stage, grade, lymphovascular invasion, treatment, and baseline patient demographics, utilized likelihood ratio tests. Nominal significance was $p=0.05$. Results: Of the 7576 women accrued, 3048 had machine-quantitated image analysis results: 2900 (95%) for ER; 2726 (89%) for PgR. Only 8 women were ASCO/CAP ER- (HSCORE 0); PgR HSCORE was 0 for 533. Statistically standardized units differentiated DDFS ER levels ($p < 0.001$) and PgR levels ($p < 0.001$).

Biomarker	N	DDFS 5-year (%)	DDFS 95% CI
ER total	2900		
ER <-1	506	86	(82, 91)
ER (-1, 0]	934	94	(92, 96)
ER (0, 1]	919	94	(92, 96)
ER 1	541	96	(93, 98)
PgR total	2726		
PgR <-1	734	89	(86, 92)
PgR (-1, 0]	439	92	(89, 95)
PgR (0, 1]	967	95	(93, 96)
PgR 1.0	586	98	(97, 100)

similar patient populations.

In adjusted multivariate analyses, higher ER HSCORE was associated with better DDFS (p=0.05) with weak evidence of an association (p=0.11) for standardized HSCORE, and no significant association (respectively, p=0.28, p=0.54) in models with PgR. Higher PgR was associated with better DDFS (p=0.001) in all multivariate assessments, including those with ER.

Conclusions: DDFS was superior for patients with higher ER and PgR standardized units compared with those with HSCOREs <-1. Adjunctive statistical standardization, similar to that mandated for clinical practice by the World Health Organization for BMD, should improve inter-laboratory comparability of biomarker results for

PO1-25-06

Integrated analysis of single-cell RNA and VDJ-sequencing data to identify T cell marker expressed on antigen-specific T cells

Presenting Author(s) and Co-Author(s):

B. Jeong. Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Republic of Korea

Y. Kim. NeogenTC Corp., United States

J. Park. NeogenTC Corp., United States

B. Ham. NeogenTC Corp., United States

J. Kim. NeogenTC Corp., United States

C. Lim. NeogenTC Corp., United States

H. Lee. University of Ulsan College of Medicine, Asan Medical Center, United States

Background

In recent years, the advancement of adoptive cell transfer-based immunotherapies has significantly contributed to the evolution of cancer treatment. The crucial step in achieving successful treatment lies in the identification of T cells that exhibit reactivity towards tumor-specific antigens. However, the heterogeneous composition of tumor antigen-specific T cells poses a challenge as there are no standardized biomarkers available for their identification. To overcome this limitation, we investigated alternative approaches, employing single cell RNA and VDJ sequencing to identify antigen-specific T cells.

Methods

First, peripheral blood mononuclear cells (PBMCs) obtained from healthy human donors were stained with carboxyfluorescein succinimidyl ester (CFSE) to facilitate the identification of proliferating antigen-specific T cells. Then the PBMCs were exposed to 1 ug/ml of CMV pp65 peptide. After a 2-day incubation period with the CMV peptide, interleukin-2 (IL-2) was administered to stimulate T cell expansion. At various time points (0, 1, 2, 3, 5, and 7 days) following the CMV peptide treatment, CD8+ T cells were isolated through fluorescence-activated cell sorting (FACS) analysis. On day 7, the CD8+ T cells were further segregated into CFSE- and CFSE+ cell populations. The single-cell transcriptomes and T cell receptor (TCR) repertoire of the CD8+ T cells were subsequently examined using the Chromium Single Cell Reagent Kit.

Results

The TCR repertoire analysis of CD8+ CFSE- T cells revealed the dominance of 10 major clones, accounting for 93.9% of the total cells. These clones were confirmed to be CMV-specific through various in vitro assays, including NFAT-luciferase, IFN- γ ELISA, and cytotoxicity assay. In contrast, CD8+ CFSE+ T cells did not exhibit significant overlap with the major TCR clones found in CFSE- CD8+ T cells, comprising only 0.02% of the total cells. Gene set enrichment analysis demonstrated that the upregulated genes in CFSE- CD8+ T cells, when compared to CFSE+ T cells, were related to cell cycle proliferation and T cell cytotoxicity. Furthermore, these genes exhibited a matching upregulation pattern with CFSE- T cells from another batch of the same donor, as well as from two other healthy donors. In addition, there was a moderate increase in the expression of the upregulated genes in CFSE- CD8+ T cells at day 3 compared to day 0-2. In this end, we selected a set of nine genes that were consistently upregulated in CFSE- CD8+ T to serve as markers for antigen-specific T cells, employing a

logistic regression model. This gene set showed high sensitivity (97.7%) and specificity (95.6%) in identifying T cell clones that respond to CMV antigen at day 3.

Conclusions

We have discovered potential markers for antigen-specific CD8+ T cells. These results can offer the promising opportunity for earlier isolation of T cells that exhibit reactivity towards tumor-specific antigens. This breakthrough has significant implications, as it can potentially contribute to cost savings in adoptive cell transfer-based immunotherapies.

PO1-25-07

Obesity, breast cancer, and adipose-derived mesenchymal stem/stromal cells: The complex cross-signaling in the tumor microenvironment

Presenting Author(s) and Co-Author(s):

A. Ritter. University Hospital Frankfurt, Hessen, Germany

C. Solbach. University Hospital Frankfurt, Frankfurt, Germany

J. Yuan. University Hospital Frankfurt, United States

Objective:

Breast cancer is the most frequently diagnosed cancer and a common cause of cancer related death in women. The breast cancer microenvironment (TME) is mainly composed of adipose tissue, consisting of adipocytes, adipose-derived mesenchymal stem/stromal cells (bASCs) and immune cells. Interestingly, it is well recognized that obesity, as indicated by increased body mass index (BMI \geq 30), is associated with an enhanced risk of more aggressive breast cancer (BC) as well as reduced patient survival. Therefore, we asked how BC affects the biological functionality of bASC, how obesity fuels this process, and on the other hand how these cells influence BC cells.

Methods:

Multiple molecular biological approaches as transcriptomic profiling and diverse functional assays were conducted to characterize at least 5 lean and obese patients derived bASCs samples near the TME (lean/obese-aT) or distant (lean/obese-dT). Afterwards, these cells were used to investigate the interaction with BC cells in 2-dimensional and 3-dimensional cell culture experiments. Moreover, immunohistological analyses were conducted in 16 lean and 16 obese breast cancer patients (grade 3-4).

Results:

The TME shifts bASCs towards cancer supporting phenotypes into an inflammatory cancer-associated phenotype, whereas ob-aT bASCs are prone to be cancer-educated into a myofibroblastic phenotype with a significant deregulated gene expression, cytokine/chemokine secretion, and reduced differentiation capacity. In corroboration, these BMI dependent de-differentiation processes could be confirmed in breast cancer tissue. Moreover, the cell-cell interaction of BC cells with aT-bASCs increased their proliferation, motility, and chemoresistance.

Conclusions:

The study found multiple pathways deregulated in bASCs associated with tumor promoting effects. Additionally, it revealed the role of aT-bASCs in promoting breast cancer progression on a functional and molecular level.

PO1-25-08

Evaluating the role of CDK4/6 inhibition on STAT3 activation in a transgenic mouse model of HER2-positive breast cancer

Presenting Author(s) and Co-Author(s):

T. Adesoye. UT MD Anderson Cancer Center, United States

L. Luo. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Bui. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Kim. 2Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, United States

H. Wingate. Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Keyomarsi. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background: The human epidermal growth factor receptor 2 (HER2) is a receptor tyrosine kinase overexpressed in approximately 20-25% of breast cancers with varying biological differences according to hormone receptor (HR) positive status. Combination of chemotherapy with dual HER2 blockade and endocrine therapy (adjuvant) or CDK4/6 inhibitor (CDK4/6i) therapy (metastatic) is standard of care for HER2-positive/HR-positive breast cancer. However, de-escalation of chemotherapy remains of significant interest given associated toxicities and, as a result, alternative therapeutic strategies are needed. One such strategy is targeting the signal transducer and activator of transcription 3 (STAT3) which is constitutively activated in the HER2 positive setting. Moreover, there is preclinical evidence to suggest that phosphorylated STAT3 (pSTAT3) induces overexpression of cyclin D1 (CCND1), which along with CDK4 may mediate resistance to targeted therapy for HER2-positive breast cancer. However, it is unclear if pSTAT3 plays a significant role in tumorigenesis or the development of resistance to therapy in HER2-positive disease. We aim to evaluate the effect of CDK4/6i therapy with palbociclib on tumor growth in an inducible transgenic HER2-positive mouse model and the impact on pSTAT3 and cyclin D1 levels.

Methods: Using an inducible transgenic mouse mammary tumor virus (MMTV) model of HER2-positive breast cancer, we evaluated STAT3 phosphorylation in tumors driven by HER2 expression in addition to the impact of CDK4/6 inhibition with palbociclib on tumorigenesis and pSTAT3 activation. To model tumor recurrence, doxycycline was withdrawn from tumor bearing mice and tumor regression was observed. Subsequently, the mice developed recurrent mammary tumors. Given recurrent tumors in this model are driven by a HER2-independent mechanism, we examined expression of cell cycle proteins together with STAT3 phosphorylation to determine association with recurrence.

Result: In addition to expressing HER2, the primary tumors expressed estrogen receptor (ER α), Rb, cyclin D1, and CDK4/6 proteins. STAT3 phosphorylation was also observed. Treatment with palbociclib decreased Rb phosphorylation and decreased tumor growth compared to vehicle treated mice (%TGI 79.37% after 21 days). Furthermore, pSTAT3 levels were not

altered with palbociclib therapy. When recurrent tumors were analyzed, they lacked HER2 expression but expressed cyclin D1 and CDK4/6 supporting that tumor growth is driven by cyclin D1/CDK4 pathway. Recurrent tumors also demonstrated pSTAT3 despite lack of HER2 expression suggesting that STAT3 phosphorylation in the recurrent tumors is mediated by an alternative mechanism, potentially the CDK4/6 pathway.

Conclusion: We demonstrate STAT3 activation in a mouse model of HER2 driven breast cancer and show persistent activation in recurrent tumors lacking HER2 expression rendering them resistant to HER2-targeted therapy. We also demonstrate the anti-tumor effect of palbociclib in primary tumors with HER2-dependent proliferation. Taken together, our findings suggest that pSTAT3 is a viable therapeutic target and provides the rationale for combination therapy with CDK4/6 inhibition using palbociclib and STAT3 inhibition with a novel STAT3 inhibitor in HER2-positive breast cancer. This therapeutic approach may represent a potential chemotherapy de-escalation strategy.

PO1-25-09

A new generation of breast cancer modeling has been achieved through somatic precision gene editing, offering high flexibility and efficiency

Presenting Author(s) and Co-Author(s):

W. Bu. Baylor College of Medicine, United States

Y. li. Baylor College of Medicine, United States

Breast cancer, along with many other cancers, is primarily caused by genetic mutations, typically involving the alteration of nucleotides (A, G, C, T) within genes (with a total of 12 possible mutations). Gene sequencing advancements have facilitated the identification of numerous gene mutations in tumor samples. However, comprehending the precise mechanisms through which these gene mutations contribute to tumor initiation, development, and their impact on tumor characteristics cannot be solely determined from these findings. Therefore, it is crucial to observe the influence of mutations on tumor initiation and development from the moment they occur. Since conducting such observations in human subjects is impractical, animal models with simulated gene mutations have become essential for studying tumor initiation and development.

Mice, with a genome comprising approximately 2.7 billion nucleotides, are commonly used as animal models in cancer research due to their cost-effectiveness and high similarity to humans. About 90% of their genes share similar functions, particularly those associated with cancer development. However, achieving precise alterations to specific nucleotides among the 2.7 billion nucleotides within live mouse cells (with a total of 12 possible changes) has presented significant technical challenges. In this study, we present modifications to the CRISPR/Cas9 vector system, enabling homology-directed repair-mediated precise editing of any proto-oncogene in murine somatic mammary epithelial cells, thereby generating mammary tumor models with exceptional flexibility and efficiency. The resulting tumors exhibit significant advantages over traditional mouse models. This technological breakthrough bridges the gap between the potential of CRISPR technology and the accuracy of mouse models, facilitating the study of human tumor evolution and preclinical drug testing.

PO1-25-11

Deciphering biological differences between normal breast tissues in men and women using single cell sequencing and in vitro modeling

Presenting Author(s) and Co-Author(s):

P. Bhat-Nakshatri. Indiana University School of Medicine, Indianapolis, Indiana, United States

B. Fischer. Indiana University School of Medicine, United States

A. Khatpe. Indiana University School of Medicine, United States

A. Adebayo. Indiana University School of Medicine, United States

H. Gao. Indiana University School of Medicine, United States

Y. Liu. Indiana University School of Medicine, United States

M. Cote. Indiana University School of Public Health, United States

H. Nakshatri. Indiana University School of Medicine, Indianapolis, Indiana, United States

Breast cancer in men is relatively rare but outcome from the disease is worse than in women. Although 87% breast cancers in men are Estrogen Receptor-positive (ER+), anti-estrogen therapy is less efficacious in men compared to women with similar breast cancer subtype. Recent genomic analysis of breast tumors in men and women have identified overlapping as well as unique genomic aberrations in breast tumors of men. It is unclear whether genomic aberrations enriched in breast cancers of men uniquely affect the biology and thus alter response to antiestrogen therapy. This lack of knowledge is mainly due to scarcity of model systems. To overcome this limitation, we collected ultrasound guided breast biopsies of healthy men and characterized breast epithelial cells grown from these biopsies. Biopsies were also subjected to single nuclei sequencing. Single nuclei breast atlas of men is currently being superimposed on single nuclei breast atlas generated from breast biopsies of healthy women to determine whether distinct cell types exist in men and to distinguish ductal and lobular breast epithelial cells. Breast epithelial cells of men expressed higher levels of ER compared to similarly propagated breast epithelial cells of women. Expression of ER in a subpopulation of cultured breast epithelial cells was confirmed by immunofluorescence. Among the pioneer factors that determine genome wide binding pattern of ER, TBX3 is expressed at a higher level but FOXA1 is expressed at a lower level in breast epithelial cells of men compared to women. Comparative RNA-seq analysis of breast epithelial cells of men and women revealed elevated non-genomic ER signaling in men compared to women, which could be responsible for limited response of breast tumors of men to anti-estrogen therapy. Additional pathways uniquely upregulated in breast epithelial cells of men include non-canonical Wnt, HIF1A, JUN, NF-kB, TGFb, and FOXO1 signaling. Expectedly, breast epithelial cells of men expressed 15 Y chromosome associated genes including the epigenetic regulators KDM5D and UTY, which have recently been shown to be responsible for sex-specific differences in outcome from other cancer types and loss of Y chromosome could be driver event in certain cancer types. We have created immortalized and transformed variants of breast epithelial cells of men to further aid in mechanistic investigation and drug discovery. Furthermore, our tissue bank currently has breast biopsies of ~30 healthy men to be used as controls for breast cancer studies in men. To our knowledge, this is the first model system to study breast cancer in men starting with breast tissues of healthy men.

PO1-25-12

Metformin enhances response to chemotherapy combined with immunotherapy in a triple negative breast cancer in vivo model

Presenting Author(s) and Co-Author(s):

P. Zamora. Hospital Universitario La Paz, Madrid, Spain, Madrid, Spain

A. Gamez Pozo. Molecular OncologyLab, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain, United States

L. Vega-Clemente. 3New Therapies Laboratory, Health Research Institute-Fundación Jiménez Díaz University Hospital (IIS-FJD), Madrid, Spain, United States

E. Lopez-Camacho. Molecular OncologyLab, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain, United States

L. trilla-Fuertes. Molecular OncologyLab, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain, United States

D. Alonso-Martin. New Therapies Laboratory, Health Research Institute-Fundación Jiménez Díaz University Hospital (IIS-FJD), Madrid, Spain, United States

J. Fresno Vara. Molecular OncologyLab, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain, United States

M. Garcia-Arranz. New Therapies Laboratory, Health Research Institute-Fundación Jiménez Díaz University Hospital (IIS-FJD), Madrid, Spain, United States

E. Espinosa. Hospital Universitario La Paz, Madrid. GEICAM Spanish Breast Cancer Group, Madrid, Spain, United States

Background

Triple-negative breast cancer (TNBC) is a heterogeneous group comprising several well-defined molecular subtypes. Classical chemotherapy remains the standard of care for advanced TNBC, although blockade of the PD-1/PD-L1 axis has emerged as a promising therapeutic option to enhance antitumor immunity. Atezolizumab is an immune checkpoint inhibitor targeting PD-L1 that has been approved for use in combination with paclitaxel for the treatment of advanced TNBC. Metformin (MTF) is a prescribed drug for type 2 diabetes with well-tolerated side-effects and has been reported to have anticancer effects. Xenograft mouse models studies of breast, lung and prostate cancer, have reveal a synergistic effect of MTF when combined with paclitaxel, carboplatin or doxorubicin and has been reported to enhance the efficacy of immunotherapy. In this work we want to explore the effect of including MTF in a chemo-immunotherapy scheme using an in vivo model. Methods 1×10^6 EMT6 TNBC cell line (ATCC® CRL-2755™) were implanted subcutaneously in the back of immunocompetent BALB/c mice. Treatment began when tumours reached a volume size of 30-100 mm³. At that moment, mice received the drug, or drugs combinations, for 21 days. All drugs were administered intraperitoneally, except for MTF, which was given orally in drinking water at a concentration of 1g/L. The anti PD-L1 drug anti-hPD-L1-mIgG1 (mATZ, 300 mg/week) was administered twice per week and doxorubicin (DOXO) every three days (0.3 mg/Kg or 6 mg/kg). The primary outcome will be tumour response. Tumour size was measured using a digital caliper every day until mice were euthanized. For tumour volume determination (mm³), two measures were taken (length and width). Volume was calculated as $(\text{length} \times \text{wide}^2)/2$. We tested three different arms: DOXO(0,3mg/Kg)+m-ATZ, DOXO(0,3mg/Kg)+m-ATZ+MTF, and DOXO(6mg/Kg)+m-ATZ. Each arm included 10 mice. Differences in tumour volume and mice weight were assessed by Kruskal-Wallis analysis. Results EMT6 cells produced a tumour

mass in twenty seven out of thirty mice. Follow-up in mice in the DOXO(0.3mg/Kg)+m-ATZ and DOXO(6mg/Kg)+m-ATZ arms was interrupted in two weeks due to extended tumour growth and quality of live criteria, respectively. Mice in the DOXO(0.3mg/Kg)+m-ATZ+MTF arm were followed for three weeks. Increase of tumoral volume was assessed at 14 days. Mean increase was 205, 1096 and 365 mm³ in the DOXO(6mg/Kg)+m-ATZ, DOXO(0,3mg/Kg)+m-ATZ, and DOXO(0,3mg/Kg)+m-ATZ+MTF arms respectively, being the volume increase between DOXO(0,3mg/Kg)+m-ATZ treated mice significantly higher. Regarding mice, mean weight at the beginning of the treatments was 19.8 gr for the complete mice population, whereas mean weight after 14 days of treatment was 15.4, 20.9 and 21.7 gr in the DOXO(6mg/Kg)+m-ATZ, DOXO(0,3mg/Kg)+m-ATZ, and DOXO(0,3mg/Kg)+m-ATZ+MTF arms respectively, showing a significant decrease of body weight in mice receiving a high dose of DOX, while no differences associated to the inclusion of MTF in the treatment scheme was found. Conclusions MTF addition to a combination of chemotherapy and immunotherapy in the treatment of TNBC increased therapy efficacy, with no added side effects. These result paves the way to explore treatment schemes with lower chemotherapy doses, decreasing toxicity side effects.

PO1-26-01

Leveraging Clinicopathological Factors and Deep Learning-Based Morphometrics for PDX Engraftment Success Prediction in Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Lee. Asan Medical Center, United States

G. Lee. Asan Medical Center, United States

G. Gong. Asan Medical Center, United States

H. Lee. University of Ulsan College of Medicine, Asan Medical Center, United States

Background: Patient-derived xenografts (PDXs) are pivotal in cancer research. Despite histopathological insights into factors driving PDX success, the role of artificial intelligence (AI) in predicting PDX engraftment remains unexplored. We aimed to bridge this gap by integrating clinicopathological data and AI-based morphometric analysis to predict PDX success in breast cancer.

Methods: PDXs were generated from tumor tissues derived from breast cancer patients who had undergone surgical intervention. Clinicopathological information including subtypes, pathological diagnosis, modified Bloom-Richardson system histologic grades, treatment with neoadjuvant chemotherapy (NAC), Miller Payne grade, residual cancer burden score, invasive tumor size, lymphovascular invasion status, AJCC 8th T and N stages and the percentage of tumor infiltrating lymphocytes were collected and analyzed. For the image analysis component, whole-slide images (WSIs) of hematoxylin and eosin-stained tissue samples from 64 surgically resected breast cancer patients were used as a training set for an AI model under the supervision of 2 pathologists to extract morphometric features. The model transformed image tiles into patches of morphologically similar patterns, and categorized them into adipose tissue, background, necrosis, invasive carcinoma, carcinoma in situ, stroma, and terminal ductal lobular unit. This trained model was subsequently applied to the WSIs employed in the establishment of PDXs. The classified patches and their relative ratios within the invasive tumor boundary were compiled. The consolidated data from clinicopathological and image analyses were subjected to logistic regression to discern correlates of successful PDX engraftment.

Results: Out of the 311 patient tumor samples used for generating PDXs, (131 post-chemotherapy, 180 chemo-naïve), 47 PDXs were successfully established (15.1%). Logistic regression revealed several factors for successful engraftment including NAC treatment with an odds ratio of 6.71 (28.2% vs 5.6%, 95% CI: 2.53 - 17.80, $p < 0.001$), higher histologic grades (25.3% vs 2.2%, OR = 5.80, 95% CI: 1.49 - 22.63, $p = 0.01$), triple negative breast cancer compared to hormone receptor-positive cancers (32.0% vs 3.3%, OR = 10.99, 95% CI: 1.26 - 95.89, $p = 0.03$), and tumors of larger size (OR = 1.34, 95% CI: 1.02 - 1.76, $p = 0.03$). Interestingly, the percentage of specific tissue patch types within tumor did not significantly impact the likelihood of successful PDX engraftment. However, in our logistic regression analysis based solely on morphometric features, presence of necrosis within the tumor notably enhanced PDX establishment. Specifically, each percent increase in necrosis within tumor boosted the odds of successful PDX creation by 0.01% (OR = 1.0001, 95% CI: 1.00003 - 1.00024, $p = 0.01$).

Conclusions: PDXs are often successfully established from clinically aggressive breast cancers, particularly those with NAC treatment, higher histologic grades, TNBC subtype, and larger tumor size. While morphometric features contribute to the prediction of PDX engraftment

success, their importance is surpassed by these clinicopathological factors. However, presence of necrosis emerged as a key morphometric predictor of successful PDX engraftment.

Keywords: breast cancer; patient-derived xenograft (PDX); Breast Cancer Morphometrics; Cancer Predictive Modeling.

PO1-26-02

Enfortumab vedotin (EV): Correlation of estrogen receptor status and Nectin-4 expression with single agent efficacy in breast XPDX models

Presenting Author(s) and Co-Author(s):

C. Moreno. XenoSTART, United States
J. Flores. XenoSTART, United States
A. Simonson. XenoSTART, United States
M. DeBoer. XenoSTART, United States
N. Banos. XenoSTART, United States
A. Diaz III. XenoSTART, United States
M. Lynch. XenoSTART, United States
J. Lund. XenoSTART, United States
L. Leykum. XenoSTART, United States
T. Rouzbahan. XenoSTART, San Antonio, Texas, United States
M. Pedregal. START Madrid, United States
K. Papadopoulos. START San Antonio, United States
A. Lang. The START Center, United States
A. Rosenthal. The START Center, United States
D. Rasco. START San Antonio, United States
G. Rodriguez. The START Center, United States
L. Rodriguez. The START Center, United States
N. Lakhani. START Midwest, United States
M. Beeram. The START Center, United States
A. Patnaik. START San Antonio, United States
M. De Miguel. START-CIOCC HM Sanchinarro, Madrid, Spain
R. Drengler. The START Center, United States
S. Abbate. The START Center, United States
B. Doger de Speville Uribe. START Madrid FJD - Oncology Phase I, Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain, United States
M. Wick. XenoSTART, United States

EV is a Nectin-4 targeting antibody-drug conjugate (ADC) with an MMAE payload, recently approved for treatment of bladder cancer patients. To better understand the potential for EV in treatment of breast cancer, we evaluated 175 breast XPDX models, including hormone receptor positive and negative cancer, some with actionable mutations, representing primary and metastatic disease from naïve or clinically treated patients. Each model was stained and scored for Nectin-4 protein and evaluated in vivo against single agent EV and activity correlated with ER status, Nectin-4 staining and known variants.

175 breast XPDX models were evaluated in this study, approximately 35% representing estrogen receptor positive and 20% clinically HER2+ cancers. Nectin-4 protein expression based on intensity and proportion was determined on a scale of 0+-3+, and models profiled

using WES and RNA_{seq}. For in vivo studies, models were evaluated against single agent EV administered by intravenous injection once weekly for three cycles at 3 mg/kg. Endpoints included tumor volume and time from treatment initiation with %T/C values and tumor regression reported at study completion; a T/C of $\leq 20\%$ versus control was considered sensitive. Tumor regression (%T/C < 0%) versus Day 0 tumor volume was also reported.

Overall, 40% of breast models stained positive for Nectin-4 including 50% of ER- and 20% of ER+ and 50% of HER2+ models. For ER- models, 50% were negative and 40% stained 1+ while 80% of ER+ models were negative and 15% stained 1+. In vivo, 25% of models were sensitive to EV, with 65% of these models ER- and < 10% HER2+. Nectin-4 staining did not directly correlate to model sensitivity although models with known drivers such as AKT1 and ESR1 were insensitive as were several models established from post CDK4/6i patients.

We have characterized a panel of breast XPDX models based on Nectin-4 staining and in vivo sensitivity to EV and correlated activity with protein and receptor staining and known mutations. This data is a valuable tool in further developing EV and identifying its potential in treating breast cancer.

PO1-26-03

Activity of alpelisib in a panel of breast XPDX models harboring hotspot and uncommon PIK3CA mutations

Presenting Author(s) and Co-Author(s):

M. Castaneda. XenoSTART, United States
A. Simonson. XenoSTART, United States
J. Flores. XenoSTART, United States
M. DeBoer. XenoSTART, United States
J. Lund. XenoSTART, United States
T. Rouzbahan. XenoSTART, San Antonio, Texas, United States
K. Papadopoulos. START San Antonio, United States
A. Lang. The START Center, United States
G. Rodriguez. The START Center, United States
M. Elmi. The START Center, United States
A. Rosenthal. The START Center, United States
D. Rasco. START San Antonio, United States
V. Moreno. START Madrid, United States
A. Patnaik. START San Antonio, United States
T. Hernandez. START Barcelona, United States
E. Calvo. START Madrid-CIOCC, United States
L. Smith. The START Center, United States
M. Sharma. START Midwest, United States
M. Beeram. The START Center, United States
M. Wick. XenoSTART, United States

Background: Therapies targeting mutated phosphoinositide 3-kinase (PI3K) p110 α catalytic subunit (PIK3CA) cancers remain an active field of research. Alpelisib was approved in combination with fulvestrant in ER+/HER2- breast cancer patients harboring PIK3CA mutations on hotspot amino acids E542, E545 Q546 or H1047. While mutation at these sites have been widely studied, they only comprise ~25% of identified variants in this protein. Recent studies have reported other mutations, including those at the c-terminus, which can lead to constitutive activation of PIK3CA; however, whether these variants are sensitive to agents like alpelisib is unclear. To better understand these variants and their role in PIK3CA-mediated breast cancer, we established a panel of PIK3CA-mutated ER+ and ER- breast XPDX models and evaluated each in vivo with single agent alpelisib. Methods: Ninety previously developed XPDX models representing PIK3CA-mutated ER+ and ER- breast cancer were evaluated in this study. Models were grown subcutaneously in female athymic nude mice supplemented with estradiol in drinking water when necessary and ER expression confirmed at multiple passes; PIK3A variants were determined by WES and RNA_{seq}. For in vivo studies, alpelisib was administered once daily by oral gavage at 35 mg/kg through study completion. Endpoints included tumor volume and time from treatment initiation with %T/C values and tumor regression reported at study completion; a T/C of $\leq 20\%$ versus control was considered sensitive. Tumor regression (%T/C < 0%) versus Day 0 tumor volume was also reported. Results: 60% of PIK3CA-mutated

models were found ER+ with 40% also HER2+ while 20% of ER- PIK3CA-mutated models were also HER2+. H1047X mutations accounted for 40% of all PIK3CA variants, 75% of which were single or dual PIK3CA^{H1047R}. Several hotspot-mutated models were sensitive to alpelisib some with regressions including ST986 (E542K), ST1097 (E454K) and STF040 (H1047R), as well as ST1245C (R88Q/N1044H), ST2076 (102-103ins/R357Q) and ST4176 (E726K/H1047R). HER2+ models were less sensitive to alpelisib although STM148D (H1047L) reported tumor regressions. Interestingly, ST1799/PBR (E542K/H1065L), a palbociclib resistant clone of the ER+ parent ST1799 model was resistant to alpelisib while the parent was found sensitive. Conclusion: We have benchmarked a panel of PIK3CA-mutated breast XPDX models with alpelisib and compared activity of models harboring hotspot versus uncommon PIK3CA mutations with ER and HER2 expression. This data is a valuable tool in further developing PIK3CA inhibitors and identifying new variant targets in breast cancer.

PO1-26-04

Patient-derived organotypic tissue cultures for organoid isolation and probing unique metabolic features of individual breast cancer patients

Presenting Author(s) and Co-Author(s):

T. Fan. University of Kentucky, Lexington, Kentucky, United States

C. Goncalves. University of Kentucky, United States

J. Yan. University of Kentucky, United States

J. Islam. University of Kentucky, United States

P. Lin. University of Kentucky, United States

M. Kaddah. University of Kentucky, United States

R. Higashi. University of Kentucky, United States

A. Lane. University of Kentucky, United States

C. Zhu. University of Kentucky, United States

Patient-derived organotypic tissue cultures (PD-OTC) are unique models for probing how individual patient's tumor microenvironment (TME) influences cancer development and treatment responses. They retain the patient tumor architecture and TME, that are difficult to recapitulate in other models, while affording flexible treatment options and comparison of cancer (CA) versus matched non-cancer (NC) tissue responses to treatments. We have developed a culturing method for establishing PD-OTC of breast cancer patients that exhibit CA tissue growth and extensive metabolic reprogramming between CA versus matched NC tissues while enabling patient-derived organoids (PDO) and fibroblasts to be isolated. Pairs of CA and NC tissues freshly resected from six patients bearing early-stage estrogen receptor/progesterone receptor positive ductal carcinoma were sliced at 750 μm , embedded in Matrigel, and cultured in a 6-well plate with a Biopore membrane insert and custom medium at 37°C/5% CO₂ with gentle rocking (16-40 mg wet weight; n=3). Excess tissue slices were cryopreserved and kept at -196 °C. Culture media were sampled periodically for metabolite analysis by NMR. Microscopic examination revealed significant tissue, organoid-like, and fibroblast outgrowth after 1-1.5 month of culturing. Two to three days prior to the harvest of two patients' (CZ16 and 17) OTC, the culture medium was replaced with [U-²H]-glucose + [U-¹³C,¹⁵N]-glutamine-containing medium to allow the two stable isotope tracers to be metabolized, followed by Stable Isotope-Resolved Metabolomic (SIRM) analysis by NMR and ion chromatography coupled with ultra high-resolution Fourier transform mass spectrometry (IC-UHRFTMS). Two separate pieces of the OTC were cut and each was assayed for glucose uptake and mitochondrial membrane potential by live fluorescence spectroscopy via a portable custom-built fluorescence microscope, and by histochemical analysis. Histological analysis showed that both CA and NC OTC of all patients maintained their structural integrity. SIRM analysis of two patients' OTC revealed active catabolic and anabolic metabolism including glucose uptake/glycolysis, the Krebs cycle/mitochondrial membrane potential, the pentose phosphate pathway (PPP), gluconeogenesis, glycogen synthesis, and purine/pyrimidine/sugar nucleotides synthesis. The CA OTC of both patients showed enhanced glucose uptake, glycolysis, mitochondrial membrane potential/Krebs cycle, PPP, glycogen synthesis, and purine nucleotide synthesis, when compared with the matched NC OTC. Treatment-naïve CA OTC of CZ16 showed much more significant metabolic reprogramming (NAD⁺ metabolism, in particular) than CA OTC of CZ17 who has undergone neoadjuvant treatment, chemotherapy, and hormone therapy prior to surgery. Distinct metabolic features of breast CA tissues can be

exploited as therapeutic targets. Organoids and fibroblasts were isolated from CA and/or NC OTC cultures and their characterization is in progress. When revived, cryopreserved OTC exhibited active metabolism and tissue/organoid/fibroblast outgrowth similarly to fresh OTC. In conclusion, our culturing method enables PD-OTC models to be established efficiently for early-stage breast cancer patients for downstream functional studies including live cell imaging and SIRM analysis. Organoids and fibroblasts can also be derived from < 20 mg of tissues for further studies. Future direction includes therapeutic studies on these patient-derived models to better understand and predict individual patient's responses to therapy.

PO1-26-05

Animal Study Compares CAR T cell Exhaustion & Ability to Kill Low Antigen expressing breast cancer cells among three CAR constructs including one with 1XX mutations

Presenting Author(s) and Co-Author(s):

C. Bamdad. Minerva Biotechnologies, Waltham, Massachusetts, United States

A. Stewart. Minerva Biotechnologies, United States

B. Smaghe. Minerva Biotechnologies, United States

M. Carter. Minerva Biotechnologies, United States

D. Walkley. Minerva Biotechnologies, United States

K. Yi. Minerva Biotechnologies, United States

J. Nash. Minerva Biotechnologies, United States

M. Nash. Minerva Biotechnologies, United States

T. Grant. Minerva Biotechnologies, United States

G. Riley. Minerva Biotechnologies, United States

Background: CAR T cells for the treatment of solid tumor cancers has not yet achieved the same success as CAR T cells for treatment of blood cancers. Two of the hurdles that must be cleared for effective use of CAR T cells for solid tumor cancers are: 1) CAR T cell exhaustion; and 2) failure to recognize and kill low antigen expressing cancer cells. A promising approach to overcoming CAR T cell exhaustion, referred to as "1XX" was developed in the Sadelain Lab at MSKCC. Mutation of Tyrosines to Phenylalanine in ITAMs 2 and 3, of the CD3z signaling domain, restrict signaling to ITAM 1. This slowing down of signaling has been reported to be effective at eliminating or greatly reducing CAR T cell exhaustion in blood cancers [Feucht, et al 2019; Park et al 2022; Schoutrop, et al 2023]. Purpose: To evaluate the potential of the 1XX mutations to overcome CAR T cell exhaustion and inability to kill low antigen expressing cells in an animal model of breast cancer. Specifically, we tested the ability of three different CARs to eliminate human breast tumors that expressed variable levels of the target antigen, MUC1*, and their ability to suppress tumor recurrence over approximately 100 days. Methods: All three CARs were targeted to the tumor by the same antibody fragment, huMNC2, that recognizes MUC1*, which is the transmembrane cleavage product of MUC1 that functions as a potent growth factor receptor. The CARs are: 1) huMNC2-41BB-CD3z; 2) huMNC2-CD28-CD3z; and 3) huMNC2-CD28-1XX. Heterogeneous tumors expressing different levels of target antigen were made as follows. T47D breast cancer cells were engineered to express even more of the target, MUC1*, and were also engineered to fluoresce green. T47D wild type cells were engineered to fluoresce red. Heterogeneous tumors consisting of 250,000 cells were implanted sub-cu into female NSG mice bearing 90-day estrogen pellets. The tumors comprised either 70% wild-type/30% overexpressing cells, or 85% wild-type/15% overexpressing cells or 92.5% wild-type/7.5% overexpressing cells. Tumor engraftment was verified by bioluminescence at Day 6 post implantation. There was a total of 150 animals, 5 animals per group. Animals were administered a single dose of CAR T cells into the tail vein on Day 7, wherein the Effector to Target ratio was either 10:1, 5:1 or 1:1. Tumor volume was measured weekly by Luciferase/Luciferin bioluminescence on an IVIS instrument. In addition, the red versus green fluorescence of the tumor was tracked periodically as an indicator of which cells, high or low antigen expressing, were being killed. Between Day 93 and Day 96, animals were sacrificed, cells were recovered from blood and spleen, recovered tumors were weighed, tumor cells dissociated and fluorescent images were captured to determine which cells escaped CAR T cell

killing. Conclusions: The CAR with the 1XX mutations in CD3z, huMNC2-CD28-1XX, was much more effective at suppressing breast tumor recurrence than either CAR with wild-type CD3z. At sacrifice, significantly more CAR T cells were recovered from huMNC2-CD28-1XX than from huMNC2-41BB-CD3z or huMNC2-CD28-CD3z. At high dose, the CARs with wild-type CD3z effectively suppressed the high antigen expressing cells, but the recurrent tumors were essentially made up of the low antigen expressing cells that had escaped CAR T cell killing. At low CAR T cell dose, the CARs with wild-type CD3z appeared to become exhausted about 40 days post treatment, when tumors began to recur. Post sacrifice analysis of the recurrent tumors showed that they were made up of both high and low antigen expressing cells. huMNC2-CD28-1XX effectively killed both the high antigen and low antigen expressing cells as evidenced by the live fluorescent imaging and the post-sacrifice analysis of residual tumor.

PO1-26-06

The effect of localized radiotherapy in combination with chemoimmunotherapy in a humanized triple-negative breast cancer mouse model

Presenting Author(s) and Co-Author(s):

A. Schreiber. University of Colorado Anschutz Medical Center, United States

S. Bagby. University of Colorado Anschutz Medical Campus, United States

S. Smoots. University of Colorado Anschutz Medical Campus, United States

A. Dominguez. University of Colorado Anschutz Medical Campus, United States

C. Fisher. University of Colorado Anschutz Medical Center, United States

J. Lang. University of Colorado Anschutz Medical Center, United States

T. Pitts. University of Colorado Anschutz Medical Center, United States

J. Diamond. University of Colorado Anschutz Medical Center, United States

Background: Metastatic triple-negative breast cancer (TNBC) is an aggressive sub-type of breast cancer that is challenging to treat. While the addition of immunotherapy (IT) with pembrolizumab (pembro) to chemotherapy prolongs overall survival in patients with programmed death-ligand 1 positive (PD-L1+) TNBC, few patients obtain long-term benefit. Radiotherapy (RT) can stimulate cellular damage, release of tumor antigens and promote the T cell anti-tumor response including at distant sites (abscopal response) when used with IT. The purpose of this study was to investigate the combination of RT with pembro and paclitaxel (pac) in a TNBC humanized mouse model.

Methods: Human Immune System BRGS (BALB/c, Rag2^{-/-}, IL2RγC^{-/-}, NOD^{SIRPα}) mice were engrafted with TNBC MDA-MB-231 cells in bilateral flanks. Treatments included: vehicle, pac 10 mg/kg intra-peritoneal (IP) weekly, pembro 15 mg/kg IP weekly, and RT 8 Gy x 3 fractions every other day the first week of treatment to one-sided tumors (contralateral tumors received no RT). Mice were treated and analyzed in the following groups: vehicle, pac + pembro, RT + pac, and RT + pac + pembro. Treatments began when tumors reached 100-300 mm³ and tumors were measured twice weekly. At the end of study, sera, lymph nodes (LNs), spleen, and tumor tissue were collected for immunohistochemistry, single cell suspensions, and flow cytometry analysis for immune cell populations.

Results: All treatment arms resulted in a decrease in tumor volume when compared to vehicle with the greatest reduction in the RT + pac and RT + pac + pembro arms. Combination therapy with RT + paclitaxel (p=0.0002) and RT + pac + pembro (p=0.008) resulted in a statistically significant decrease in specific growth rate (SGR) when compared to vehicle. An abscopal effect was not observed in the non-RT tumors compared to RT-tumors in either group. RT + pembro was associated with an increase in hCD45 T cells in LNs and spleens but not in tumors. In mice that received RT, a decrease was noted in HLA-ABC class I and Intermediate Class II major histocompatibility complex (MHC). In addition, RT-tumors had reduced expression of PD-L1 and polio virus receptor (PVR) and increased expression of PD-1. The percentage of interferon gamma (IFNγ+), tumor necrosis factor alpha (TNFα+) CD8+ T cells increased with radiation. This percentage was the highest in the triplet therapy with RT+ pembro + pac.

Conclusion: Combination treatment with RT + immunochemotherapy resulted in a significant

increase in anti-tumor activity when compared to immunochemotherapy alone, however, an abscopal effect was not observed in contralateral non-RT tumors. RT resulted in down-regulation of immune inhibitory receptors and tumor MHC.

PO1-27-01

Comparing the Efficacy and Safety of TQB2440 versus the Reference Pertuzumab for the Treatment of HER2-Positive Early or Locally Advanced Breast Cancer: A Multicenter, Randomized, Double-Blind, Parallel-Controlled Phase 3 Trial

Presenting Author(s) and Co-Author(s):

- Q. Zhang. Harbin Medical University Cancer Hospital, United States
- S. Wang. Sun yat-sen university cancer center, United States
- N. Li. Xijing Hospital, United States
- Q. Cheng. The First Affiliated Hospital of Chongqing Medical University, United States
- Y. ren. The First Affiliated Hospital of Xi'an Jiaotong University, United States
- X. Cao. Tianjin Medical University Cancer Institute and Hospital, United States
- J. Huang. Affiliated Hospital of Guizhou Medical University, United States
- C. Liu. Shengjing Hospital of China Medical University, United States
- H. Yang. Suining Central Hospital, United States
- L. Wei. The First Affiliated Hospital of Henan Science and Technology University, United States
- Z. Song. Shaanxi Provincial People's Hospital, United States
- H. Zhao. Tangdu Hospital, The Airforce Medical University, United States
- F. Ning. Binzhou Medical University Hospital, United States
- X. Wang. Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, United States
- D. Zou. Cancer Hospital of the University of Chinese Academy of Sciences/Zhejiang Cancer Hospital, United States
- X. Zeng. Chongqing University Cancer Hospital, United States
- J. Hao. Gansu Provincial Hospital, United States
- Y. Liu. The Fourth Hospital of Hebei Medical University, United States
- H. Wang. Gansu Wuwei Tumor Hospital, United States
- n. jianyun. Department of Breast Surgery, Breast Cancer Clinical Research Center, Cancer Hospital, Kunming Medical University, China (People's Republic)
- L. Li. Meizhou People's Hospital (Huangtang Hospital), Meizhou Academy of Medical Sciences,, United States
- L. Liu. Nanyang Second General Hospital, United States
- T. Sun. Cancer Hospital of China Medical University/Liaoning Cancer Hospital, United States
- X. Hu. Hunan Cancer Hospital, the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University,, United States
- Z. Zhai. The First Affiliated Hospital of Jinzhou Medical University, United States
- H. Xiong. Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology,, United States
- Y. Zhang. Affiliated Hospital of Guangdong Medical College, United States
- E. Zhou. The Second Xiangya Hospital, Central South University, United States

j. sun. Anyang Cancer Hospital, Henan, China., United States
 Z. Cai. Department of Breast Oncology, Jieyang People's Hospital, United States
 A. Zhang. Maternal and Child Health Care Hospital of Guangdong Province, United States
 S. Wang. Jiangsu Cancer Hospital & the Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, United States
 J. Mo. Liuzhou People's Hospital, United States
 Q. Su. Jilin Guowen Hospital Co., LTD, United States
 X. Qi. Hebei Petrochina Central Hospital, United States
 G. zhou. Jiangsu Cancer Hospital & the Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, United States
 S. Zhang. The Second Affiliated Hospital of Xi'an Jiaotong University, United States
 G. Cui. Cangzhou Central Hospital, United States
 W. Wang. Kashgar First People's Hospital, United States
 M. Fan. Kashgar First People's Hospital, United States
 X. Qian. Hangzhou First People's Hospital, Hangzhou Cancer Hospital, United States
 X. Wu. Hubei Cancer Hospital, China
 Z. Wang. The Affiliated Tumor Hospital of Guizhou Medical University, United States
 J. zhao. Affiliated Hospital of Qinghai University, United States
 Y. Luo. Second Affiliated Hospital of Nanchang University, United States
 Y. Zhang. Linfen Central Hospital, United States
 F. Tian. Shanxi Provincial Cancer Hospital, United States
 J. Zhang. Sanmenxia Central Hospital, United States
 D. Chai. Xiamen Maternity and Child Healthcare Hospital, United States
 Q. Li. Affiliated Hospital of Chengde Medical University, United States

Background: Pertuzumab is a recombinant humanized monoclonal antibody targeting the extracellular dimerization domain II of HER2. On September 30, 2013, the FDA have granted accelerated approval of a pertuzumab regimen for neoadjuvant treatment of patients (pts) with high-risk, HER2-positive early stage breast cancer. TQB2440 is a pertuzumab (Perjeta[®], Roche) biosimilar. This study aimed to compare the efficacy and safety of TQB2440 and the reference pertuzumab combined with trastuzumab and docetaxel in pts with HER2-positive early or locally advanced breast cancer. Methods: In this multicenter, randomized, double-blind phase 3 study, eligible pts were aged 18-75 with operable HER2-positive (IHC 3+ or ISH+) clinical stage II-IIIc breast cancer negative for ER/PR and had an ECOG PS of 0-1. The pts were randomly assigned to receive either TQB2440 or the reference pertuzumab (Perjeta[®]) (840 mg on day 1, cycle 1, followed by 420 mg on cycle 2-4, q3w) added to trastuzumab (8 mg/kg on day 1, cycle 1, followed by 6 mg/kg for cycles 2-4, q3w) + docetaxel (75 mg/m², cycle 1-4, q3w). The pts then underwent surgery followed by adjuvant treatment with FEC regimens (fluorouracil 600 mg/m², epirubicin 90 mg/m², cyclophosphamide 600 mg/m², cycle 5-7, q3w), then TQB2440 (840 mg on day 1, cycle 8, followed by 420 mg on cycle 9-20, q3w) + trastuzumab (8 mg/kg on day 1, cycle 8, followed by 6 mg/kg for cycles 9-20, q3w) or until disease progression or intolerable toxicity. The primary endpoint was total pathologic complete response (tpCR) by independent review committee (IRC). Equivalence was established if the 90% confidence intervals (CIs) of the relative ratio [RR] within the interval of 0.76 to 1.32. Secondary endpoints included breast pathologic complete response (bpCR) by IRC, tpCR &

bpCR by investigator, breast conserving surgery (BCS) rates, objective response rate (ORR), event-free survival (EFS), disease-free survival (DFS), OS and safety. Results: Between October 21, 2020, and November 21, 2022, 412 pts were enrolled (TQB2440 group, n=207; the reference pertuzumab group, n=205). Data cutoff was November 30, 2022. In the intention-to-treat (ITT) population, the tpCR by IRC of the TQB2440 group and the reference drug group were 58.94% and 58.05%, respectively. The RR was 1.02 (90% CI, 0.89, 1.16), which was within the predefined equivalence interval of 0.76 to 1.32. There was no statistically significant difference in the bpCR by IRC between the TQB2440 group and the reference pertuzumab group (67.63% [95% CI, 60.80%, 73.95%] vs. 63.90% [95% CI, 56.92%, 70.48%], P=0.4249). The BCS rate also comparable between the two groups with 13.04% (95% CI, 8.77%, 18.41%) vs. 13.17% (95% CI, 8.86%, 18.58%) (P=0.9695). Additionally, the results of the PP (per-protocol) population were similar to those of the ITT population. The incidence of treatment-related adverse events (TRAEs) and grade ≥ 3 TRAEs were similar between the TQB2440 group and the reference pertuzumab group with 79.71% vs. 75.98% and 49.28% vs. 41.67%, respectively. Conclusion: In patients with HER2-positive early or locally advanced breast cancer, TQB2440 demonstrated equivalent efficacy and similar safety to the reference pertuzumab. Clinical trial information: NCT05985187. Research Sponsor: Chia

Endpoints	TQB2440 (n=207)	The Reference Pertuzumab (n=205)	RR (90% CI)	P value
ITT Population				
tpCR by IRC, %	58.94	58.05	1.02 (0.89-1.16)	/
tpCR by investigator, %	60.39	58.05	1.04 (0.91-1.19)	/
bpCR by IRC, % (95% CI)	67.63 (60.80-73.95)	63.90 (56.92-70.48)	/	0.4249
bpCR by investigator, % (95% CI)	65.70 (58.80-72.14)	61.95 (54.93-68.62)	/	0.4284
BCS rates, % (95% CI)	13.04 (8.77-18.41)	13.17 (8.86-18.58)	/	0.9695
Median EFS, mo	NR	NR	/	0.4886
Median DFS, mo	NR	NR	/	0.4656

Tai Tianqing Pharmaceutical Group Co., Ltd

PO1-27-03

Studies on factors for pathological complete response after neoadjuvant chemotherapy in relation to HER2 status in primary breast cancer

Presenting Author(s) and Co-Author(s):

N. Arima. Kumamoto Breast and Gastrointestinal Surgical Hospital, Kumamoto, Kumamoto, Japan

R. Nishimura. Social Medical Corporation Hakuaiikai, Sagara Hospital, Kagoshima City, Japan

K. Muramoto. Kumamoto Breast and Gastrointestinal Surgical Hospital, Japan

A. Inayoshi. Kumamoto Breast and Gastrointestinal Surgical Hospital, Japan

T. Tanigawa. Kumamoto Breast and Gastrointestinal Surgical Hospital, Japan

S. Watanabe. Kumamoto Breast and Gastrointestinal Surgical Hospital, Japan

Background: Neoadjuvant chemotherapy (NAC) has been increasingly used as the frontline therapy for the management of high-risk localized breast cancer (BC). Achieving pathological complete response (pCR) following NAC is associated with significantly better disease-free (DFS) and overall survival (OS), particularly for triple negative (TN) and HER2+ breast cancer. Among HER2 negative BC, HER2-low BC is a newly defined subset that has a HER2 immunohistochemical (IHC)-1+ or 2+/ISH negative phenotype. HER2 status is divided into 3 categories: HER2 positive, HER2-low, and HER2-zero. In this study, we investigated factors for pCR in relation to HER2 status and survival after NAC. Methods: A total of 197 cases with primary BC from January 2013 to July 2023 were enrolled in this study. There were 83 HER2 positive cases (including 7 HER2 2+/ISH+ cases) and 114 HER2 (78 HER2-low and 36 HER2-0) negative cases. HER2 3+ was dichotomized according to the staining cell rate (cut-off point; 90%) into the following two groups; HER2 3+ >90% (70 cases) and HER2 3+ < 90% (6 cases). The chemotherapy regimen was anthracycline and taxane with the addition of anti-HER2 therapy if the cases were HER2-positive. The clinicopathological factors examined were age, nodal status, tumor size, ER/PgR (cut-off points; 1% and 10%), and the Ki-67 index value (cut-off points: 20% and 40%). pCR was defined as the absence of residual invasive cancer on H&E evaluation of the complete resected breast specimen (ypT0/Tis). We investigated the correlation between pCR and clinicopathological factors. The DFS and OS were calculated using the Kaplan-Meier method and analyzed using the log-rank procedure. Uni- and multivariate analyses of factors for pCR were performed using regression analysis. Results: 1. pCR was observed in 48 cases (57.8%) after NAC in the HER2 positive group and 17 cases (14.9%) in the HER2 negative group. 2. There was no significant relationship between the pCR rate and ER, PgR, Ki-67, menopausal and nodal status in the HER2 positive group. However, pCR was significantly observed more often in smaller tumors. HER2 3+ (>90%) had a significantly higher pCR rate than HER2 3+(≤90%) and HER2 2+(ISH+). Multivariate analysis revealed that HER2 3+ (>90%) and tumor size (≤5cm) were significant factors for pCR in HER2 positive BC cases. 3. Patients with pCR after NAC had significantly better DFS in HER2 positive BC cases. 4. There was a significant correlation between the pCR rate and ER≤10%, PgR≤10% and tumor size < 5cm in the HER2 negative BC cases. There was no relationship between the pCR rate and the HER2 status; 19.4% in HER2-0 and 12.8% in HER2-low. 5. Multivariate analysis revealed that the PgR status and tumor size were significant factors for pCR in the HER2 negative BC cases. 6. There was no significant difference in DFS between patients with pCR and non-pCR, especially in the luminal type BC cases. Moreover, no significant difference was observed between HER2-low and HER2-0. Conclusion: pCR rate after NAC was 57.8% in the HER2 positive cases and 14.9% in the HER2 negative cases.

Moreover, the HER2 3+ (>90%) group had a significantly higher pCR rate than the HER2 3+(≤90%) and HER2 2+(ISH+) groups. There was no correlation between the HER2 status (HER2-low and HER2-0) and pCR rate in the HER2 negative BC cases. In addition, the ER/PgR negativity (≤10%) was a significant factor for pCR in the HER2 negative cases. These findings suggest that the IHC data on the HER2 and ER/PgR status may be effective in predicting the pCR rate after NAC in BC cases.

PO1-27-05

De-escalated neoadjuvant weekly nab-paclitaxel with trastuzumab and pertuzumab in HER2-positive early breast cancer (HELEN-006):a randomized,phase 3 trial

Presenting Author(s) and Co-Author(s):

Z. Liu. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

X. Chen. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

J. Qiao. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

J. Dechuang. Henan cancer hospital, United States

C. Wang. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

X. Sun. Affiliated Cancer Hospital of Zhengzhou University, United States

Z. Lu. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

L. Li. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

C. Zhang. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

M. Yan. Henan Cancer Hospital, Henan, China

Y. Wei. Anyang Cancer Hospital, United States

C. Bo. Department of Breast Surgery, The First Hospital of China Medical University, Shenyang, United States

Y. Feng. Department of Breast Surgery, Xinxiang Central Hospital, Xinxiang, China, United States

M. Deng. Department of Breast Surgery, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, China, United States

M. Ma. Department of Thyroid and Breast surgery, Huaihe Hospital of Henan University, United States

Background: Chemotherapy de-escalation is currently under investigation as a treatment approach for HER2-positive early-stage breast cancer(EBC). We conducted a phase 3 clinical trial to evaluate the effectiveness of a weekly regimen of nab-paclitaxel monotherapy in combination with dual HER2 blockade for HER2-positive EBC. Methods: We conducted a multicenter, randomized, open-label Phase 3 trial at six hospitals in China. Eligible participants were women aged 18-70 with locally confirmed, HER2-positive, stage II-III, invasive, operable breast cancer and an Eastern Cooperative Oncology Group performance status of 0 or 1. Participants were randomly assigned (1:1) using central block randomization, with block sizes of four, stratified by hormone receptor status, tumor stage, and node status. They were assigned to receive either intravenous nab-paclitaxel (125mg/m² on days 1, 8, and 15) for six 3-week cycles (group A), or intravenous docetaxel (75mg/m² on day 1) and carboplatin (area under the concentration-time curve 6mg/mL per min on day 1) for six 3-week cycles (group B). Both groups received concurrent trastuzumab (8mg/m² loading dose, 6mg/m² maintenance dose on day 1) and pertuzumab (intravenous 840mg loading dose, 420mg maintenance dose on day 1). The primary endpoint was the proportion of patients achieving a pathological complete response(pCR) in the breast and axilla (ypT0/is ypN0) as determined by a local

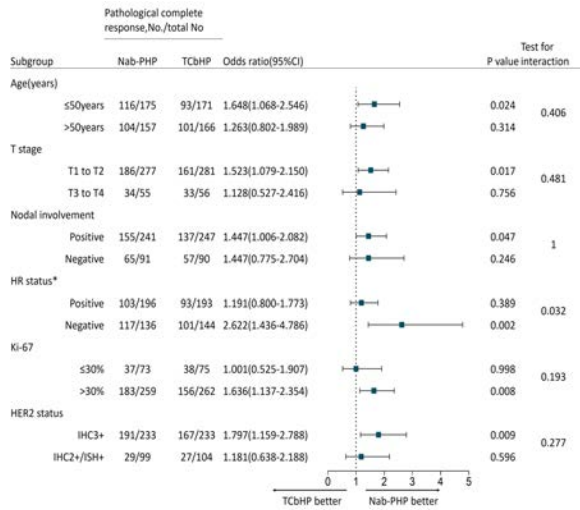
pathologist after surgery, assessed using a modified intention-to-treat analysis. To test for non-inferiority, we used a closed test procedure, considering the nab-paclitaxel group non-inferior to the docetaxel plus carboplatin group if the lower 95% confidence interval(CI) for the odds ratio (OR) was above 0.802, which accounted for a 5.5% non-inferiority margin (10% of the 55% pCR rate for docetaxel plus carboplatin and dual HER2 blockade regimen). We planned to test for superiority only if the non-inferiority test was positive, using an alpha value of 0.05. Safety was assessed in all patients who received the study drug. The trial is registered with ClinicalTrials.gov, with the registration number NCT04547907. Findings: Between September 10, 2020, and March 1, 2023, we randomly assigned 689 women, of whom 669 started treatment (332 with nab-paclitaxel and 337 with docetaxel plus carboplatin). The nab-paclitaxel group had a higher proportion of patients achieving a pCR (220 [66.3%, 95% CI 61.2-71.4]) compared to the docetaxel plus carboplatin group (194 [57.6%, 52.3-62.9]). The OR for pCR was 1.448 (95% CI 1.058-1.981), indicating a statistically significant difference (unadjusted p=0.021). Overall, 228 (34.1%) patients were noted to have at least one grade 3 or 4 event, 100(30.1%) in the nab-paclitaxel group and 128 (38.0%) in the docetaxel plus carboplatin group (P=0.032). The most common grade 3 or 4 events overall were nausea (98[14.6%] of 669 patients), diarrhea (80 [12.0%]), and neuropathy (51 [7.6%]).However, no treatment-associated deaths were identified. Conclusions: In neoadjuvant treatment of HER2-positive EBC, 18 weeks of nab-paclitaxel monotherapy combined with dual HER2 blockade has shown significantly higher pCR rates and improved tolerability compared to the standard docetaxel plus carboplatin and dual HER2 blockade regimen. These findings could potentially reshape preferences for neoadjuvant therapy in HER2-positive EBC.

Patient Characteristics

Characteristics	Nab-PHP(n=332)	TcHP(n=337)
Age (years), median [IQR]	50(41-55)	50(44-56)
Age(years)		
≤50years	175(52.7%)	171(50.7%)
>50years	157(47.3%)	166(49.3%)
T stage		
T1 to T2	277(83.4%)	281(83.4%)
T3 to T4	55(16.6%)	56(16.6%)
Nodal involvement		
Positive	241(72.6%)	247(73.3%)
Negative	91(27.4%)	90(26.7%)
HR status*		
Positive	196(59.0%)	193(57.3%)
Negative	136(41.0%)	144(42.7%)
Ki-67		
≤30%	73(22.0%)	75(22.3%)
>30%	259(78.0%)	262(77.7%)
HER2 status		
IHC3+	233(70.2%)	233(69.1%)
IHC2+/ISH+	99(29.8%)	104(30.9%)

Abbreviation:Nab-PHP,nanoparticle albumin-bound paclitaxel plus trastuzumab and pertuzumab; TcHP,docetaxel plus carboplatin ,trastuzumab and pertuzumab; IQR,interquartile range; HR,hormone receptor; IHC,immunohistochemistry.
*estrogen and/or progesterone receptor positive is classified as hormone receptor positive,estrogen and progesterone receptor negative is classified as hormone receptor negative

pCR by clinical-pathological variables



Abbreviation:Nab-PHP,nanoparticle albumin-bound paclitaxel plus trastuzumab and pertuzumab; TCbHP,docetaxel plus carboplatin ,trastuzumab and pertuzumab; HR,hormone receptor; IHC,immunohistochemistry.

*estrogen and/or progesterone receptor positive is classified as hormone receptor positive;estrogen and progesterone receptor negative is classified as hormone receptor negative

Adverse events

Event	NO (%)							
	Nab-PHP group				TCbHP group			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Haematological								
Anaemia	253(76.2%)	45(13.5%)	2(0.7%)	0(0.0%)	127(37.5%)	162(48.1%)	13(3.9%)	0(0.0%)
Leukopenia	59(17.8%)	55(16.6%)	1(0.3%)	0(0.0%)	100(29.7%)	20(5.9%)	17(5.0%)	0(0.0%)
Neutrophilia	174(52.3%)	62(18.7%)	9(2.7%)	0(0.0%)	180(53.4%)	26(7.6%)	20(5.9%)	0(0.0%)
Febrile neutropenia			5(1.5%)	0(0.0%)			13(3.9%)	0(0.0%)
Thrombocytopenia	115(34.6%)	1(0.3%)	5(1.4%)	0(0.0%)	127(37.5%)	16(4.6%)	15(4.5%)	2(0.7%)
Non-haematological								
Nausea	138(41.6%)	91(27.4%)	22(6.6%)	0(0.0%)	97(28.6%)	136(40.3%)	76(22.6%)	0(0.0%)
Vomiting	63(19.0%)	18(5.4%)	4(1.2%)	0(0.0%)	123(36.6%)	51(15.1%)	27(7.9%)	0(0.0%)
Diarrhea	178(53.6%)	88(26.5%)	25(7.5%)	0(0.0%)	152(45.2%)	109(32.4%)	55(16.3%)	0(0.0%)
Constipation	63(19.0%)	6(1.8%)	0(0.0%)	0(0.0%)	84(24.9%)	6(1.9%)	0(0.0%)	0(0.0%)
Abdominal pain	142(42.8%)	24(7.2%)	3(0.9%)	0(0.0%)	146(43.3%)	46(13.6%)	4(1.1%)	0(0.0%)
Myalgia	148(44.7%)	62(18.7%)	1(0.4%)	0(0.0%)	156(46.4%)	67(20.0%)	4(1.1%)	0(0.0%)
Arthralgia	117(35.4%)	41(12.4%)	4(1.2%)	0(0.0%)	118(35.0%)	46(13.6%)	4(1.1%)	0(0.0%)
Neuropathy	116(35.0%)	150(45.2%)	43(13.0%)	0(0.0%)	152(45.2%)	79(23.4%)	8(2.3%)	0(0.0%)
Dysgeusia	206(62.2%)	117(35.2%)	0(0.0%)	0(0.0%)	160(47.5%)	169(50.1%)	0(0.0%)	0(0.0%)
Mucositis or stomatitis	88(26.5%)	19(5.7%)	3(0.9%)	0(0.0%)	81(24.1%)	32(9.4%)	4(1.1%)	0(0.0%)
Laboratory-assessed items								
Increased ALT	168(50.6%)	35(10.4%)	13(3.9%)	0(0.0%)	132(39.2%)	4(1.2%)	3(1.0%)	0(0.0%)
Increased AST	152(45.7%)	12(3.5%)	13(3.9%)	0(0.0%)	122(36.2%)	6(1.8%)	0(0.0%)	0(0.0%)
Increased alkaline phosphatase	170(51.3%)	5(1.4%)	0(0.0%)	0(0.0%)	123(36.6%)	2(0.6%)	0(0.0%)	0(0.0%)
Increased creatinine	10(3.1%)	0(0.0%)	0(0.0%)	0(0.0%)	37(10.9%)	1(0.3%)	0(0.0%)	0(0.0%)
Hypokalemia	5(1.4%)	16(4.8%)	1(0.3%)	0(0.0%)	72(21.4%)	8(2.4%)	0(0.0%)	0(0.0%)
Hyponatremia	31(9.3%)	0(0.0%)	1(0.3%)	0(0.0%)	30(8.9%)	2(0.6%)	0(0.0%)	0(0.0%)
Hypocalcemia	18(5.5%)	2(0.7%)	1(0.3%)	1(0.3%)	19(5.6%)	6(1.8%)	0(0.0%)	0(0.0%)

Abbreviation:Nab-PHP,nanoparticle albumin-bound paclitaxel plus trastuzumab and pertuzumab; TCbHP,docetaxel plus carboplatin ,trastuzumab and pertuzumab;ALT,alanine aminotransferase;AST,aspartate transaminase.

PO1-27-06

HER2 Amplification Level and Focal/Broad Region Size as Predictors of Treatment Response in Neoadjuvant Chemotherapy and Anti-HER2 Therapy for HER2-Positive Breast Cancer

Presenting Author(s) and Co-Author(s):

N. Liao. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

G. Zhang. Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China, Guangdong, China (People's Republic)

X. Lv. Burning Rock Biotech, Guangzhou, China, United States

K. Li. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

T. Hou. Burning Rock Biotech, Guangzhou, China, United States

Z. Zhang. Burning Rock Biotech, Guangzhou, China, United States

Background: Neoadjuvant chemotherapy combined with anti-HER2 therapy has become the standard treatment approach for HER2-positive breast cancer. However, not all HER2-positive patients can achieve pathological complete response after neoadjuvant therapy. This raises the question of which subset of HER2+ patients derive the greatest benefit from pre-operative HER2-targeted treatment. Therefore, this study aims to determine whether the level and amplification region size of HER2 amplification are associated with the efficacy of neoadjuvant chemotherapy combined with anti-HER2 therapy. Methods: A total of 523 breast cancer samples were collected from 2017 to 2018, among which 202 cases were HER2-positive patients. Among these, 55 HER2-positive patients received neoadjuvant chemotherapy combined with anti-HER2 targeted therapy. The amplification status of HER2 was assessed using immunohistochemistry/fluorescence in situ hybridization (IHC/FISH) and next-generation sequencing (NGS). The HER2/CEP17 ratio, determined by FISH, was used to represent the amplification level of HER2. The size of the amplification region was calculated using NGS and neighboring genes located in chr17q. Amplification regions smaller than 1 Mb were classified as focal amplification, while those larger than 1 Mb were classified as broad amplification.>

Results: We compared the HER2/ERBB2 status of 523 breast cancer patients using different detection methods and found a high concordance between ERBB2 amplification detected by NGS and HER2-positivity detected by IHC and FISH, with a sensitivity of 96.0%, specificity of 97.8%, and overall concordance of 97.1%. Based on the HER2/CEP17 ratio determined by FISH, we observed that using a threshold of 6 for classification, the high amplification group had a significantly higher pCR rate compared to the low amplification group (86.7% vs. 41.7%; $p=0.037$, odds ratio [OR]=0.121, 95% confidence interval [CI]: 0.009-0.919). Moreover, the focal amplification group showed a higher pCR rate compared to the broad amplification group (65.9% vs. 30.8%, $p=0.051$, OR=0.237, 95% CI: 0.045-1.035). Additionally, within the low amplification group (HER2/CEP17 < 6), the pCR rate was 66.7% for focal amplification and 20% for broad amplification, suggesting that focal amplification of ERBB2 may further guide clinical benefit in the low HER2/CEP17 ratio group. Conclusion: This study demonstrates a high concordance between ERBB2 amplification determined by NGS and HER2-positivity determined by IHC/FISH. High HER2/CEP17 ratio and focal amplification of ERBB2 are

associated with a higher pCR rate in neoadjuvant chemotherapy combined with anti-HER2 targeted therapy.

PO1-27-07

Is HER2-low a biologically distinct breast cancer (BC) subtype? Prognosis and pathological complete response rate after neoadjuvant treatment (NAT) in early breast cancer (BC) HER2 negative.

Presenting Author(s) and Co-Author(s):

A. Gil-Torralvo. Instituto de Biomedicina de Sevilla IBiS. Hospital Universitario Virgen del Rocío / CSIC / US, Molecular and translational research in oncology, Seville, Spain., United States

Y. Rodriguez. Hospital Juan Ramón Jiménez, United States

A. Falcon. Virgen del Rocío Hospital (Seville), United States

D. Morales. Hospital Universitario Juan Ramon Jimenez. GEICAM Spanish Breast Cancer Group, Huelva, Spain

M. Cejuela. Virgen del Rocío Hospital (Seville), United States

I. Miras. Hospital Virgen del Rocío, United States

M. Amérigo. Hospital Virgen del Rocío, United States

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

J. Bayo. Hospital Juan Ramón Jiménez, United States

F. Salvador Bofill. Hospital Universitario Virgen del Rocío, Seville, Spain, Andalucía, Spain

Background: Overexpression of HER2 is a significant prognostic and predictive factor in early breast cancer. HER2 positive tumors are those scored by immunohistochemistry (IHC) 3+ or 2+ with amplification by in situ hybridization (ISH). These tumors may benefit from HER2-targeted treatment and additionally, in early HER2-positive BC, achieving a complete pathological response after neoadjuvant treatment improves patient survival. In recent years, new anti-HER2 antibody-drug conjugates have proven effective for HER2 low BC (defined as IHC score 1+ or 2+ not amplified) in the metastatic disease setting; however, in HER2-low early BC, studies testing novel anti-HER2 antibody-drug conjugates as neoadjuvant therapy (NAT) are ongoing. Currently, we don't know exactly whether HER2 expression can influence the pathological response rate after NAT or disease-free survival (DFS) in these patients compared to HER2-zero (IHC 0). The aim of our study is to determine the impact on response rate to NAT and survival outcomes in early HER2-negative BC. Methods: We conducted a retrospective study in two hospitals in Andalucía, Spain. Patients with early HER2 negative BC treated with NAT from January 2015 to June 2022 were included. Patients were divided into HER2 low patients (IHC 1+ or 2+ not amplified) and HER2 0 (IHC 0). We collected clinical and pathological characteristics, pathological response rate using the Residual Cancer Burden (RCB) system where a complete pathological response (pCR) was defined as ypT0/ypTis and ypN0, and survival outcomes. The primary objective of the study was to analyze the pCR rate after NAT according to HER2 score, and secondary objectives were to assess disease-free survival and overall survival (DFS and OS rates). Results: 574 patients were included (100% women). 397 patients had hormone receptors (luminal BC) on these tumors, and 177 did not have them, i.e., triple-negative BC (TNBC). 225 patients were HER2-zero, and 312 patients were HER2-low (253/312 patients had luminal BC and 59/312 patients were TNBC). The pCR in HER2-low patients was 17.3% and 23.1% in HER2-zero patients ($p=0.047$). For luminal BC patients, the pCR was 16.7% in HER2-low tumors and 13.7% in HER2-zero tumors ($p=0.29$). Similarly, there was no difference in pCR rates in TNBC patients (45.8% in HER2-low and 53.8% in HER2-zero tumors, respectively, ($p=0.958$)). The overall survival (OS) at 96 months was 88.7% (95% CI 85.6%-92%). Regarding survival outcomes, neither HER2 expression level

was associated with higher 8-year DFS: 81.1% in HER2-low patients (95% CI 75.7%-86.8%) and 74.9% in HER2-zero patients (95% CI 62.3%-90.1%) $p=0.64$. There was no difference between histological subtypes at 8-years regarding DFS rate: 80.5% (95% CI 74.3%-87.2%) in luminal HER2-low patients and 76.3% (95% CI 60.8%-95.7%) in luminal HER2-zero patients, $p=0.22$; 83.8% in TNBC HER2-low (95% CI 74.5%-94.2%) and 77.5% in TNBC HER2-zero patients (95% CI 69.4%-86.6%) $p=0.26$. We also didn't find significant differences in terms of OS. For HER2-low patients, the 8-year OS was 90.9% (95% CI 87%-94.9%) and for HER2-zero patients, it was 86.4% (95% CI 80.8%- 92.5%) $p=0.46$. There were also no differences in OS for different histological subgroups with an 8-year OS in luminal HER2-low breast cancer patients of 92.5% (95% CI 88%-96.7%) and 87% in HER2-zero (95% CI 78.9%-96.1%) $p=0.91$. In patients with triple-negative breast cancer phenotype, the OS was 84.2% for HER2-low (95% CI 74.5%-95.2%) and 85.3% for HER2-zero (95% CI 77.9%-93.4%) $p=1$. Conclusions: We found no difference in survival outcomes and response rate to conventional NAT between HER2-low and HER2-zero expression levels. Therefore, our data do not support the hypothesis of HER2-low as a biologically specific breast cancer subtype. Further research on this approach with HER2 antibody-drug conjugate schemes as an alternative to traditional NAT schemes is warranted.

PO1-27-09

TRIPTORELIN (11.25MG) vs TRIPTORELIN (3.75MG) IN PREMENOPAUSAL WOMEN WITH HIGH-RISK EARLY STAGE BREAST CANCER RH(+) and HER2(-) REAL WORLD EXPERIENCE. TRIPTO3 RESULTS

Presenting Author(s) and Co-Author(s):

R. LIMON. CLINICA DE LAS AMERICAS, United States

M. LOPEZ-PEREYRA. ecancer, Lima, Peru

M. GIANELLA. CENTRO MASTOLOGIA Y ONCOLOGIA, Santa Cruz, Bolivia

N. ESPINOZA. PERINAT, Santa Cruz, Bolivia

D. RAMIREZ. PERINAT, Santa Cruz, Bolivia

C. ANTELO. ONCOBOLIVIA, Santa Cruz, Bolivia

C. SITIC. PERINAT, Santa Cruz, Bolivia

W. CORTEZ. CENTRO MASTOLOGIA Y ONCOLOGIA, Santa Cruz, Bolivia

O. NIÑO DE GUZMAN. NIÑO DE GUZMAN CENTER, COCHABAMBA, Cochabamba, Bolivia

S. Neciosup. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

N. VALDIVIESO. ecancer, Lima, Peru

Background. Premenopausal women with high risk early stage BC HR+/Her2- present as a complex disease and generally have worse survival outcomes compared to postmenopausal women with the same disease. There are pathological clinical factors and genomic platforms that help us in therapeutic decisions. The use of triptorelin 3.75mg associated with AI promotes favorable results in terms of survival for premenopausal women with high-risk Early stage BC. TEXT/SOFT trial. TRIPTO3 study evaluates the use of Triptorelin 11.25mg vs. Triptorelin 3.75mg in this specific patient population. Methods: We reviewed medical records of premenopausal female patients with high-risk early stage breast cancer who have been treated and received triptorelin 3.75mg and triptorelin 11.25mg as part of their treatment. All patients were treated at a private Oncology Center between 2013 and 2020. The primary objective was disease-free survival. Results: 52 patients were found who met the inclusion criteria. 28(53.8%) patients received triptorelin 11.25mg and 24(46.2%) patients received triptorelin 3.75mg respectively. The median follow-up was 63 months and the disease-free survival for the Triptorelin 11.25mg group was 91.2% and for the Triptorelin 3.75mg group was 86.8% respectively (Hazard Ratio of disease-free survival was 1.2; 95% IC (0.2-7.2)). Disease-free survival for both groups regardless of triptorelin dose was 89% at 5 years. The median disease-free survival was not reached in both groups. Conclusions: Our findings show that triptorelin 11.25 mg is similar to the use of triptorelin 3.75 mg in terms of disease-free survival for premenopausal women with high-risk early stage breast cancer.

PO1-27-10

Adjunctive statistical standardization of quantitated machine image analysis of Estrogen and Progesterone Receptors: CCTG MA.27 trial

Presenting Author(s) and Co-Author(s):

J. Chapman. Canadian Cancer Trials Group, Queen's University, Kingston, ON (retired), Kitchener, Ontario, Canada

J. Bayani. Diagnostic Development, Ontario Institute for Cancer Research Toronto, Ontario, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto. Toronto, Ontario, Canada, United States

S. SenGupta. Queen's University, Kingston, Ontario, Canada

J. MS Bartlett. University of Edinburgh, Scotland, United Kingdom, United Kingdom

T. Piper. University of Edinburgh, Edinburgh, United Kingdom

M. Quintayo. Ontario Institute for Cancer Research, Toronto, Ontario, Canada

S. Virk. Canadian Cancer Trials Group, Queen's University, Kingston, ON, Kingston, Ontario, Canada

P. Goss. Harvard University, Boston, Massachusetts, United States

J. Ingle. Mayo Clinic, Rochester, Minnesota, United States

M. Ellis. AstraZeneca, Washington, District of Columbia, United States

G. Sledge Jr. Caris Life Sciences, United States

G. Budd. Cleveland Clinic, Cleveland, Ohio, United States

M. Rabaglio. Department of Medical Oncology; Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland

R. Ansari. Indiana School of Medicine, South Bend, Indiana, United States

R. Tozer. McMaster University, Hamilton, Ontario, Canada

D. D'Souza. London Regional Health Science Centre, London, Ontario, Canada

H. Chalchal. Alan Blair Cancer Center, Regina, Saskatchewan, Canada

S. Spadafora. Algoma Regional Cancer Centre, Sault St. Marie, Ontario, Canada

V. Stearns. Johns Hopkins University, Baltimore, Maryland, United States

E. Perez. Bolt Biotherapeutics, United States

K. Gelmon. BC Cancer Agency, Vancouver, British Columbia, Canada, United States

T. Whelan. McMaster University, Hamilton, Ontario, Canada

C. Elliott. Canadian Cancer Trials Group, Queen's University, Kingston, Ontario, Canada

L. Shepherd. Canadian Cancer Trials Group, Queen's University, Kingston, Ontario, Canada, United States

B. Chen. Canadian Cancer Trials Group, United States

K. Taylor. University of Edinburgh Cancer Research Centre, Institute of Genetics and Cancer, United States

Background: Adjuvant breast cancer therapy is informed by whether a tumour is positive or negative for the biomarkers ER, PgR, and HER2, often without regard to level of positivity. Quantitation has been proposed to improve therapeutic management. Adjunctive statistical

standardization has been proposed to improve inter-laboratory comparability of biomarkers results. Methods: This primary report utilized adjunctive statistical standardization of machine-quantitated image analysis biomarker assessments. CCTG MA.27 (NCT00066573) is an adjuvant phase III trial of exemestane versus anastrozole in postmenopausal women with ER+ and/or PgR+ tumours. IHC ER, PgR, and HER2 were centrally assessed, with FISH (HER2;HER2/CEP17) determinations for equivocal IHC HER2. HSCOREs were statistically standardized to a mean of 0, standard deviation of 1 following Box-Cox variance stabilization transformations of square for ER and natural logarithm for PgR (0.1 was added to 0 HSCOREs). The primary endpoint was STEEP distant disease-free survival (DDFS) at the longest trial follow-up of median 4.1 years. Survival was described with Kaplan-Meier plots. The univariate Wilcoxon (Peto-Prentice) test statistic was used with usual designation of negative/positive (0; >0), and standardized cut-points at standard deviations about mean of 0 (<-1; (-1,0]; (0,1]; >1). Cox multivariate regressions adjusted for age, T and N stage, grade, lymphovascular invasion, treatment, and baseline patient demographics, utilized likelihood ratio tests. Nominal significance was p=0.05. Results: Of the 7576 women accrued, 3048 had machine-quantitated image analysis results: 2900 (95%) for ER; 2726 (89%) for PgR. Only 8 women were ASCO/CAP ER- (HSCORE 0); PgR HSCORE was 0 for 533. Statistically standardized units differentiated DDFS ER levels (p< 0.001) and PgR levels (p< 0.001).

Biomarker	N	DDFS 5-year (%)	DDFS 95% CI
ER total	2900		
ER <-1	506	86	(82, 91)
ER (-1, 0]	934	94	(92, 96)
ER (0, 1]	919	94	(92, 96)
ER >1	541	96	(93, 98)
PgR total	2726		
PgR <-1	734	89	(86, 92)
PgR (-1, 0]	439	92	(89, 95)
PgR (0, 1]	967	95	(93, 96)
PgR >1.0	586	98	(97,100)

In adjusted multivariate analyses, higher ER HSCORE was associated with better DDFS (p=0.05) with weak evidence of an association (p=0.11) for standardized HSCORE, and no significant association (respectively, p=0.28, p=0.54) in models with PgR. Higher PgR was associated with better DDFS (p=0.001) in all multivariate assessments, including those with ER. Conclusions: DDFS was superior for patients with higher ER and PgR standardized units compared with those with HSCOREs <-1. Adjunctive statistical standardization, similar to that mandated for clinical practice by the World Health Organization for BMD, should improve inter-laboratory comparability of biomarker results for similar patient populations.

PO1-27-11

Survival Benefit of Adjuvant Endocrine Therapy in Patients with Estrogen Receptor Low-Positive Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Lee. Seoul National University Hospital, Seoul, Seoul-t'ukpyolsi, Republic of Korea

H. Ryu. Seoul National University Hospital, United States

M. Jang. Medical Research Collaborating Center, Seoul National University Hospital, Seoul-t'ukpyolsi, Republic of Korea

K. Lee. Seoul National University Hospital, United States

H. Lee. Seoul National University Hospital, United States

Background: Estrogen receptor (ER) low-positive (1–10%) breast cancer is a very rare subtype that accounts for only 2–5% of all breast cancer cases and was introduced as a new category in the 2020 American Society of Clinical Oncology/College of American Pathologist Guidelines. There are limited data on the overall benefit of endocrine therapy for patients with ER low-positive cancers. The objective of this study was to analyze the clinicopathological characteristics and treatment patterns in patients with ER low-positive breast cancer and to compare disease-free survival (DFS) between patients who received and did not receive endocrine therapy. **Methods:** A retrospective search of the prospectively maintained database of our institution identified consecutive women with ER low-positive (1–10%) primary invasive breast cancer who underwent curative surgery at Seoul National University Hospital (Seoul, Korea) between January 2010 and April 2021. Standard immunohistochemical staining techniques were used to assess the level of ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, and semiquantitative scores (0–100%) were reported for ER and PR. DFS was defined as the time from surgery to the development of any recurrence and was compared between women who received and did not receive adjuvant endocrine therapy using univariable and multivariable Cox proportional hazards regression. **Results:** A total of 721 women (median age, 51 years; range, 24–83 years) with ER low-positive cancer were included in the analysis. Overall, 28% (203/721) had AJCC stage I, 42% (304/721) had stage II, and 30% (214/721) had stage III. PR expression was negative (< 1%) in 79% (571/721), low-positive (1–10%) in 12% (90/721), and high-positive (>10%) in 8% (60/721). HER2 expression was negative in 54% (390/721) and positive in 46% (331/721). Most women (88% [634/721]) received adjuvant endocrine therapy, including all women with PR expression >10%. Of the 661 women with PR expression ≤10%, 87 (13%) did not receive adjuvant endocrine therapy. HER2-targeted therapy was performed in 81% (268/331) of women with HER2-positive cancer. During a median follow-up of 5.7 years, 98 (14%) had recurrence (25 locoregional/contralateral and 73 distant metastases). AJCC stage III (HR, 3.6; 95% CI: 2.4, 5.4; P < .001) and receiving total mastectomy (HR, 1.8; 95% CI: 1.2, 2.8; P = .004) were associated with worse DFS. Receiving adjuvant endocrine therapy was independently associated with better DFS in the entire cohort (HR, 0.46; 95% CI: 0.28, 0.76; P = .002) and in the HER2-negative subgroup (HR, 0.40; 95% CI: 0.22, 0.75; P = .004). In the HER2-positive subgroup, receiving adjuvant endocrine therapy was not significantly associated with better DFS (HR, 0.55; 95% CI: 0.23, 1.32; P = .18). **Conclusion:** In this large cohort of women with ER low-positive breast cancers, adjuvant endocrine therapy was administered in the majority of cases, including those with PR >10% expression. Receiving adjuvant endocrine therapy was associated with better DFS, especially when HER2 expression was negative.

PO1-28-01

MammaPrint and Blueprint identify racial disparities among women with HR+HER2-early-stage breast cancer

Presenting Author(s) and Co-Author(s):

S. Reid. Vanderbilt-Ingram Cancer Center, United States

X. Shu. Vanderbilt University Medical Center, United States

L. Venton. Vanderbilt University Medical Center, United States

J. Haan. Agendia NV, United States

A. Menicucci. Agendia Inc, United States

P. Dauer. Agendia Inc., United States

W. Audeh. Agendia Inc., United States

T. Pal. Vanderbilt University Medical Center, United States

INTRODUCTION: Black women are 41% more likely to die from breast cancer compared to White women yet remain underrepresented in clinical trials and population studies. We have previously shown a higher proportion of Black women with HR+HER2- tumors further classify as Basal-Type compared with White women, using Blueprint molecular subtyping. Other studies have demonstrated higher 3-year recurrence rates in patients with Blueprint Basal-Type tumors compared to Luminal-Type. To determine whether the increased frequency of HR+/Basal-Type tumors impacts long-term outcomes in this cohort, we compared 3-year outcomes with Blueprint and the risk of distant recurrence signature, MammaPrint (MP), between Black and White women with HR+HER2- breast cancer. We also evaluated the association of MP and Blueprint with 10-year outcomes in a subset of Black women.

METHODS: This study included 635 women with stage I-III, HR+HER2- breast cancer, of whom, 135 Black women were enrolled in the BEST study between 2005-2015 (R01-CA204819), and 120 Black women and 380 White women are enrolled in the ongoing FLEX study (NCT03053193). Each patient had MP and Blueprint testing. MP classifies tumors as having a Low Risk or High Risk of distant recurrence. Blueprint categorizes tumors as Luminal-Type, HER2-Type, or Basal-Type. Together, MP and Blueprint further stratify Luminal tumors into Luminal A-Type (MP Low Risk) and Luminal B-Type (MP High Risk). Recurrence-free survival (RFS) was the primary endpoint. Overall survival (OS) at 10 years was the secondary endpoint for those with long-term follow up. RFS and OS are defined per STEEP criteria. Survival curves were estimated using Kaplan-Meier analyses, and significance between groups was determined using log-rank test. **RESULTS:** Among all patients, 14.5% of Black women had Blueprint Basal-Type tumors compared to 5.8% of White women ($p < 0.001$). Median follow up was 3.0 years for patients in FLEX, and 10.1 years for patients in BEST. The unstratified 3-year RFS was 93.6% (95% CI 90.7 – 96.7) for Black patients and 93.6% (95% CI 91.1 – 96.3) for White patients. When further stratified by MP and Blueprint, 3-year RFS for patients with HR+HER2- tumors significantly differed ($p=0.002$). Patients with HR+/Luminal A tumors exhibited the best 3-year RFS (96.9%; 95% CI 95.0 – 98.9), followed by HR+/Luminal B tumors (91.6%; 95% CI 88.2 – 95.1), and HR+/Basal tumors (85.8%; 95% CI 77.2 – 95.5). For a subset of patients with 10-year follow up, we evaluated the association of MP and Blueprint with RFS ($n=135$) and OS ($n=134$). The unstratified 10-year RFS and OS rates for Black women were 88.4% (95% CI 82.9 – 94.2) and 89.0% (95% CI 83.7 – 94.7), respectively. When stratified by MP and Blueprint, Black patients with HR+/Luminal A tumors had a 10-year RFS of 97.7% (95% CI 93.4 – 100), versus 83.5% (95% CI 74.8 – 93.1) for patients with HR+/Luminal B, and 85.0% (95% CI 70.7 – 100) for patients with HR+/Basal tumors ($p=0.080$). Similarly, Black

patients with HR+/Luminal A tumors exhibited excellent 10-year OS (100%), whereas OS for patients with HR+/Luminal B (83.5%; 95% CI 74.8 – 93.1) and HR+/Basal tumors (85.0%; 95% CI 70.7 – 100) were significantly lower ($p=0.026$). CONCLUSION: Survival outcomes at 3 years were comparable between Black and White patients. MP and BluePrint more precisely stratified tumors resulting in distinct 3- and 10-year outcomes, independent of race, beyond clinical subtype alone. Additionally, the subset of Black patients with Low Risk, Luminal A-Type tumors had excellent 10-year survival outcomes. Patients with HR+ tumors that further classify as Basal-Type, which occur more frequently in Black patients, have worse outcomes compared to Luminal A-Type tumors, and may warrant more aggressive treatment. These data highlight the importance of genomic testing to help optimize treatments and reduce outcome disparities in Black women.

PO1-28-03

Impact of the Oncotype DX® test over time and association with clinicopathological characteristics of Peruvian patients with early breast cancer: Experience in the last 15 years

Presenting Author(s) and Co-Author(s):

S. Gonzalez Bocanegra. Clínica Ricardo Palma, Lima, Lima, Peru

G. Valencia Mesías. Instituto Nacional de Enfermedades Neoplásicas, United States

Y. Ferreyra Chombo. Universidad de Ingeniería y Tecnología, United States

K. Meza Garcia. Clínica Ricardo Palma, United States

M. Lopez-Pereyra. ONCOCENTER PERU S.A.C., United States

J. Torres Maldonado. Instituto Nacional de Enfermedades Neoplásicas, United States

E. Yan Quiroz. Hospital de Alta Complejidad EsSalud Virgen de la Puerta, United States

Z. Morante Cruz. Instituto Nacional de Enfermedades Neoplásicas, United States

J. cotrina concha. Instituto Nacional de Enfermedades Neoplásicas, United States

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

G. Calderon Valencia. Instituto Nacional de Enfermedades Neoplásicas/ Clínica Internacional Lima Peru, United States

M. León Rivera. Clínica Ricardo Palma, Lima, Lima, Peru

Introduction: Gene expression assays provide prognostic and therapy-predictive information that complements management of early breast cancer patients. Oncotype DX® had showed prognostic and prediction of adjuvant chemotherapy benefit. The present study evaluates the impact of Oncotype DX® on therapeutic decision-making for 15 years and explores the association of clinicopathological characteristics with the Recurrence Score (RS) in Peruvian patients with early breast cancer. **Material and methods:** A retrospective multicenter analysis of 759 breast cancer patients treated in three oncological centers in Lima-Peru (Instituto Nacional de Enfermedades Neoplásicas, Oncosalud and Ricardo Palma) between 2007 and 2022 was conducted. Risk groups were classified according to Oncotype DX® result and menopausal status. For premenopausal women ≤ 50 years: low (RS=0-20), intermediate (RS=21-25) and high-risk (RS=26-100). A descriptive analysis was evaluated to observe the trend and profile of the patients who used the Oncotype test in 5 time periods (2007-2009, 2010-2013, 2014-2016, 2017-2019, 2020-2022). Subsequently, chi-square, t-test, analysis of variance and Poisson linear regression tests were applied to compare clinicopathological features with RS. Finally, univariate and multivariate analyses were performed using Cox logistic regression to identify the probability of association with the high-risk group. **Results:** 642 patients were included, 78.5% were postmenopausal, and 64.2% had clinical stage (CS) I. Overall, 63.4% had no recommendation for chemotherapy and only 5.6% had recurrence. 74.8% were classified as low-risk according to the Oncotype DX® result. Postmenopausal patients had negative lymph nodes (95.4%), the majority had undergone conservative surgery (71.8%) and had a low rate of breast reconstruction (11.9%). An increase in the use of Oncotype DX® was observed over time, especially in premenopausal patients (from 4.5% in 2007 to 36.9% in 2022). A significant association was found between luminal B subtype ($p < 0.0001$), histological grade 3 ($p < 0.0001$) and T3 vs. T1/2 ($p = 0.025$). In univariate analysis, luminal B subtype (vs. luminal A, OR=5.56, 95% CI, 2.80-12.3, $p < 0.001$), T3 (vs. T1/2, OR=2.84, 95% CI, 0.13-30.0, $p = 0.006$), histological grade 3 (vs. 1/2, OR=13.1, 95% CI, 5.35-39.6, $p < 0.001$) and histology (other vs.

ductal/lobullar/mucinous, OR=2.94, 95% CI, 0.57-13.5, p=0.003) provided a higher probability of obtaining a high-risk RS result. Similar results were found in multivariate analysis. Conclusion: The use of the Oncotype DX® had a significant impact on therapeutic decision-making in Peruvian patients with early breast cancer, with an increase of use in the last 15 years. A high-risk RS was associated with luminal B subtype, histological grade 3 and T3 tumor size, which could facilitate risk stratification and provide valuable information for the need of adjuvant chemotherapy. Keywords: Early breast cancer, Oncotype DX®, clinicopathological characteristics, Recurrence Score (RS), Peru

Oncotype PERU Table

General characteristics	Overall, N = 642*	Postmenopausal, N = 322	Premenopausal, N = 320	p-value**
Age (years)	56.0 (46.0, 65.0)	60.0 (52.0, 68.0)	43.0 (35.2, 47.0)	<0.001
Age groups				
<45	48 (7.5%)	13 (2.6%)	35 (25.4%)	
45-55	435 (67.6%)	232 (69.9%)	103 (74.8%)	
≥55	159 (24.8%)	77 (23.5%)	0 (0.0%)	
Period of diagnosis				<0.001
2007-2009	134 (20.9%)	147 (20.2%)	7 (0.1%)	
2010-2012	270 (42.1%)	73 (14.3%)	45 (25.8%)	
2013-2015	97 (15.1%)	164 (20.2%)	63 (35.4%)	
2016-2018	127 (19.8%)	91 (13.8%)	44 (25.0%)	
2019-2022	105 (16.4%)	91 (13.8%)	24 (13.7%)	
Clinical stage				0.14
I	410 (64.2%)	330 (65.6%)	80 (58.8%)	
II	218 (34.2%)	127 (23.2%)	91 (64.8%)	
III	10 (1.6%)	6 (1.2%)	4 (2.9%)	
Tumor size (mm)	15.0 (11.0, 22.0)	15.0 (11.0, 21.0)	17.0 (11.0, 25.0)	0.2
T				0.6
T1	427 (66.5%)	340 (67.4%)	87 (64.4%)	
T2	204 (32.6%)	140 (27.8%)	46 (33.4%)	
T3	3 (0.5%)	2 (0.4%)	0 (0.0%)	
Histological grade				0.0
I	86 (13.7%)	66 (13.4%)	20 (14.8%)	
II	437 (68.1%)	249 (48.2%)	98 (70.8%)	
III	105 (16.7%)	86 (17.4%)	19 (14.2%)	
Histological type				0.053
Ductal/DCIS	517 (80.5%)	418 (82.1%)	99 (72.8%)	
Lobular/L	77 (12.1%)	55 (10.9%)	22 (16.2%)	
Mixed	50 (7.8%)	13 (2.6%)	37 (27.0%)	
Other	7 (1.1%)	4 (0.8%)	3 (2.2%)	
Tubular/Cribri	1 (0.2%)	1 (0.2%)	0 (0.0%)	
Lymph node status				0.009
Positive	604 (94.1%)	481 (94.4%)	123 (89.1%)	
Negative	38 (5.9%)	23 (4.6%)	15 (10.9%)	
Focality				0.5
Multiple	9 (1.4%)	6 (1.2%)	3 (2.2%)	
Unifocal	19 (2.9%)	16 (3.1%)	3 (2.2%)	
Axillary management				0.11
BSAC	528 (82.8%)	422 (82.6%)	106 (76.6%)	
OPA	35 (5.5%)	24 (4.7%)	11 (8.0%)	
Tam				0.4
T1/NO/NO	410 (64.2%)	329 (65.4%)	81 (59.4%)	
T2/NO/NO	24 (3.8%)	18 (3.5%)	6 (4.4%)	
T3/NO/NO	174 (27.2%)	122 (23.8%)	41 (29.7%)	
T3/NO/NO	24 (3.8%)	16 (3.1%)	8 (5.9%)	
T3/NO/NO	3 (0.5%)	5 (1.0%)	0 (0.0%)	
T3/NO/NO	2 (0.3%)	2 (0.4%)	0 (0.0%)	
Surgery type				0.007
Conservative	443 (69.2%)	361 (70.8%)	82 (59.8%)	
Medical	197 (30.8%)	142 (28.2%)	55 (40.1%)	
Breast reconstruction				<0.001
Yes	159 (24.8%)	125 (24.5%)	33 (23.9%)	
No	480 (75.2%)	177 (34.5%)	22 (16.1%)	
Treatment				0.12
HT	208 (32.4%)	172 (34.1%)	36 (26.1%)	
HT+FT	1 (0.2%)	1 (0.2%)	0 (0.0%)	
CT	1 (0.2%)	1 (0.2%)	0 (0.0%)	
CT+FT	145 (22.6%)	119 (23.3%)	26 (18.8%)	
CT+HT+FT	88 (13.7%)	62 (12.1%)	26 (18.8%)	
CT+FT	1 (0.2%)	1 (0.2%)	0 (0.0%)	
Chemotherapy treatment				0.8
Yes	407 (63.4%)	321 (63.7%)	86 (62.3%)	
No	235 (36.6%)	180 (36.3%)	52 (37.7%)	
Radiotherapy treatment				<0.001
Yes	287 (44.9%)	240 (47.6%)	47 (34.6%)	
No	355 (55.1%)	212 (41.4%)	76 (55.4%)	
Hormonal therapy				<0.5
Yes	3 (0.5%)	3 (0.6%)	0 (0.0%)	
No	639 (99.5%)	501 (99.4%)	138 (100.0%)	
Risk group				<0.001
Low	480 (74.8%)	411 (80.6%)	69 (50.0%)	
Intermediate	44 (6.9%)	13 (2.5%)	31 (22.5%)	
High	118 (18.4%)	98 (19.0%)	20 (14.5%)	
Recurrence score	16.0 (11.0, 22.0)	16.0 (11.0, 22.0)	15.9 (11.0, 22.8)	0.8
Recurrence status				0.12
Yes	606 (94.4%)	472 (92.7%)	134 (97.1%)	
No	36 (5.6%)	32 (6.3%)	4 (2.9%)	

*Median (IQR); n (%).

**Wilcoxon rank-sum test; Pearson's Chi-squared test; Fisher's exact test.

PO1-28-04

PILHLE-001: neoadjuvant pyrotinib combined with chemotherapy in HR-positive, HER2-low (IHC 2+/FISH-negative) early breast cancer

Presenting Author(s) and Co-Author(s):

C. Gong. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Y. Xia. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China, United States

Y. Zhu. Clinical Research Design Division, Clinical Research Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Y. Yang. Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, United States

W. Yang. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China, United States

L. Chow. UNIMED Medical Institute Comprehensive Centre For Breast Diseases, Hong Kong

L. Ling. Department of Medical Statistics, School of Public Health, Sun Yat-sen University, Guangzhou, China, United States

Y. Zeng. Department of Pathology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

J. Zhong. Department of Pathology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Z. Cheng. Department of Radiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

J. Shen. Department of Radiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Q. Lin. Breast Tumour Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Y. Zeng. Breast Tumour Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Q. Liu. Breast Tumour Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, Afghanistan

E. Song. Breast Tumour Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Background: Hormone receptor (HR)-positive/HER2-low (IHC 2+/FISH negative or IHC 1+) breast cancers (BCs) represent the largest proportion of breast carcinomas. However, its response to neoadjuvant chemotherapy or endocrine therapy is the lowest, with a residual cancer burden (RCB) 0/I rate around 15%. Previous studies have demonstrated that pyrotinib (P), a pan-HER tyrosine kinase inhibitor, exhibits excellent response in HER2-positive early or advanced BC (E/ABC). In-vitro experiments have shown that pyrotinib can effectively inhibit colony formation in HER2-low (IHC 2+/FISH negative) BC cells. This PILHLE-001 study (NCT05165225) aimed to evaluate the efficacy and safety of neoadjuvant pyrotinib plus chemotherapy in HR-positive/HER2-low (IHC 2+/FISH negative) EBC patients with potential biomarkers. Methods: PILHLE-001, as a single-arm, single-center phase II trial, enrolled patients with previously untreated HR-positive (ER or PR > 1%) and HER2-low (IHC 2+/FISH negative) invasive EBC (TNM stage II-III) to receive pyrotinib 320mg QD and four Q3W of

epirubicin-cyclophosphamide followed by four Q3W of docetaxel. MammaPrint/Blueprint at baseline (t0) was assessed. Breast magnetic resonance imaging (MRI) was conducted at t0, the end of cycle 2 neoadjuvant therapy (t1), and the end of all neoadjuvant therapy. Immune cell subpopulations assay and gene sequencing of tumor tissues with whole blood control samples were performed at t0 and surgery (t2). Additional core biopsy was administered to reassess Ki67 and tumor infiltrating lymphocytes (TILs) at t1. The primary outcome was RCB 0/I rate. The short-term secondary outcomes included pathological complete response (pCR, ypT0/is ypN0) rate, objective response rate (ORR), breast conservation surgery (BCS) rate, safety, and exploratory biomarkers analysis. Results: From July 2021 to March 2023, 48 patients were enrolled and treated. The median age of the patients was 48 years (range 28-66), 43 (90%) had cT₁₋₂ tumors, 30 (63%) showed no node involvement, 37 (77%) had tumours with TNM stage II, and 47 (98%) had ER expression \geq 50%. Twenty-eight (61%) of 46 patients had MammaPrint high risk. Out of the 48 patients, 26 (54.2%) achieved RCB 0/I, with a 95% confidence interval of 39.2% to 68.6%. The RCB 0/I rate was particularly higher in tumors with no lymph node involvement (73.3%), TNM stage II (64.9%), or abundant tumor-infiltrating lymphocytes (66.7%). Three (6.3%) patients obtained a pCR. The rate of BCS was 60.4% (29/48). The ORR was 45.8% (22/48) at t1 and 81.3% (39/48) at the end of all neoadjuvant therapy, respectively. No patients had progressive disease. All treatment-related adverse events (AEs) were mostly of grade 1 or 2 severity. Grade \geq 3 AEs occurred in 21 (44%) patients, with the most prevalent being diarrhea [10 (21%)]. All AEs were reversible with symptomatic treatment and no treatment-related deaths occurred. Patients with MammaPrint risk-low BC had a lower RCB 0/I rate than those with risk-high BC (60.7% vs. 44.4%), although the difference was not statistically significant. Baseline specific immune cell subpopulations (lower PD-1, higher CD3, etc.) or the presence of non-altered PIK3CA were significantly associated with a higher likelihood of achieving RCB 0/I. Similarly, objective response, greater declines in specific MRI quantitative parameters (K^{trans} and K_{ep}), greater declines in Ki67, or more increased TILs at t1 were also significantly associated with a higher rate of RCB 0/I. Conclusions: The PILHLE-001 trial first revealed that neoadjuvant pyrotinib plus chemotherapy has encouraging efficacy and acceptable toxicity in patients with HR-positive/HER2-low (IHC 2+/FISH negative) EBC, and this regimen warrants further investigation in phase III randomized controlled trials.

PO1-28-05

Preventive Microsurgery in Breast Cancer Treatment

Presenting Author(s) and Co-Author(s):

V. Vorotnikov. Clinic RZD-Medicine Moscow, United States

A. Soynov. Clinic RZD-Medicine Moscow, United States

A. Soynov. Clinic RZD-Medicine Moscow, United States

R. Pakhomova. Russian Biotechnological University, United States

A. Gugnina. Clinic RZD-Medicine Moscow, United States

S. Abdugafforov. Clinic RZD-Medicine Moscow, Tashkent, Toshkent Shahri, Uzbekistan

S. Kim. Saint-Petersburg State Pediatric Medical University, United States

T. Mchedlidze. Clinic RZD-Medicine Moscow, United States

Relevance: Breast cancer (breast cancer) ranks first among all oncological diseases in women in the world. In 2020, 2.3 million people worldwide were diagnosed with breast cancer. The most common complication after radical breast surgery is violation of lymph outflow in the form of lymphatic edema (lymphedema) of the limb. The probability of developing lymphedema according to scientific literature is from 12 to 60%. Treatment of this complication is carried out conservatively and surgically. According to a review of international experience, a preventive microsurgical technique for restoring lymph outflow from the upper limb – the application of lymphovenous anastomoses (LVA) has a positive result for the prevention of lymphedema, similar to a sentinel lymph node biopsy and can be considered as an addition to standard axillary lymph dissection (ALD). Objective: To evaluate the effectiveness of preventive microsurgical application of LVA after ALD in breast cancer. Methods: From August 2022 to June 2023, 44 operations were performed with preventive microsurgical application of lymphovenous anastomoses on the basis of the Department of Tumors of the Female Reproductive System of the Central Clinical Hospital “RZD-Medicine”, Moscow. In 39 patients, surgery was performed during the primary treatment: disease stage cT1-4N1-3M0. Organ-preserving resection with lymph node dissection (9), mastectomy with lymph node dissection (30). In 14 patients, a biopsy of the sentinel lymph node was performed at the first stage; according to the result of a lesion of 2 or more, ALD and LVA were performed. In 5 patients, ALD was performed for local recurrence of the disease in the axillary region. All patients underwent immediate microsurgical restoration of lymphatic outflow from the upper limb during one operation in the axillary region after the stage of lymph node dissection. A fluorescent dye was used for reverse mapping of lymphatic pathways from the upper limb. Isotopes + fluorescent dye were used to determine the sentinel lymph node. Lymphatic venous anastomoses were applied end-to-end, end-to-side, side-to-side and by the Optocus technique. Results: The median follow-up was 5.5 months. The duration of the operation increased by an average of 70 minutes: at the same time, the ALD time increased by an average of 14 minutes for gentle skeletonization of the veins for the subsequent application of LVA. In 4 patients, the integrity of the recipient vein was damaged during lymph node dissection and restored microsurgically. No surgical complications were observed. The average duration of lymphorrhea in the postoperative period was 2.3 days (without LVA 13.9 days). Conclusions: The preventive microsurgical technique for restoring lymph drainage from the upper limb has a number of technical limitations, requires special training and microsurgical equipment. Nevertheless, the technique is safe, feasible and effective in the early postoperative period. The application of LVA led to a significant decrease in lymphorrhea in the postoperative period, a reduction in hospital stay, but an increase in the duration of the operation. Longer follow-up is

required to assess the overall effect of LVA on the incidence of lymphedema.

PO1-28-06

Development of a plasma-based real-time qPCR gene expression assay for targeted screening and diagnosis of early-stage breast cancer.

Presenting Author(s) and Co-Author(s):

M. Keiser. IV BioHoldings (IVBH), United States

E. Cormier-May. Mammogen, United States

M. Alderdice. Sonrai Analytics, United States

J. Kavanagh. Sonrai Analytics, United States

W. Guesdon. Sonrai Analytics, United States

H. Healy. P4 Diagnostix, United States

N. Jean-Charles. P4 Diagnostix, United States

J. Harness. Mammogen, United States

Background Over 12 million US women undergo follow-up breast imaging and exams annually due to breast cancer suspicions, incurring an \$8 billion total cost, of which \$2.18 billion is attributed to false-positive breast biopsies. Recent updates published to the Mammography Quality Standards Act (MQSA) now recommend supplemental imaging for women with heterogeneously dense and extremely dense breasts, regardless of suspicious findings. Given sensitivity limitations associated with mammography in dense-breasted women, as low as 30-47%, and non-specificity associated with ultrasound and MRI, these recent recommendations are likely to further strain the healthcare system and place substantial burden on patients and providers. With an estimated 25 million dense-breasted women who regularly screen for breast cancer now considered at-risk, there is a critical need for affordable and highly accurate testing, offering better specificity without sacrificing sensitivity. To address this gap, we developed an affordable and accurate plasma-based gene expression assay using real-time qPCR for targeted screening and diagnosis of early-stage breast cancer. **Methods** In previous studies, 26 cross-correlated mRNA gene targets were discovered and independently validated for non-invasive breast cancer detection across five independent patient cohorts using microarray gene expression profiling, comprised of peripheral blood mononuclear cells (n=337) and saliva (n=20), demonstrating strong efficacy, reproducibility, and concordance across bio-fluids and assay platforms in all studies. A sixth independent validation cohort comprised of 203 plasma samples was subsequently obtained for real-time qPCR clinical assay development and validation in our CLIA laboratory. The CLIA validation cohort was designed to be representative of different diagnosis status, stage, and ethnicity, and included Caucasian, Black/African American, Hispanic, and Asian women. After normalizing mRNA expression and clustering analysis, the signature was refined to 8 target genes and was assessed in a cohort of 87 plasma samples [Table 1] to verify the assay's diagnostic performance for stage I breast cancer detection, under locked laboratory protocols. We leveraged machine learning methods derived from XGBoost classification, a supervised-learning algorithm that uses sequentially built shallow decision trees to provide accurate results and avoidance of overfitting. **Results** The XGBoost model, selecting from the 8 mRNA gene targets and patient age, achieved >99% sensitivity, 89% specificity for stage I breast cancer detection in the held-out test set, with an overall diagnostic accuracy of 94.5%. Normalized data showed significant differences in gene expression between healthy controls and stage I patients, and distinct clustering was observed for the 8 mRNA gene signature, including patient age. **Conclusions** Our plasma-based real-time qPCR gene expression clinical assay, with machine learning, is positioned as a highly accurate non-invasive tool for targeted screening and diagnosis of early-stage breast cancer.

Furthermore, a clinically validated assay in this space addresses the need for more targeted diagnostics, while serving as a promising tool for clinicians as they make critical care decisions across the breast health continuum, accelerating time to earlier and more precise intervention and treatment, mitigating unnecessary healthcare expenditures, and reducing the mental, emotional, and financial burden on patients and their families.

	Breast Cancer	Healthy Control	P
n=87	30	57	
Stage at Diagnosis (%)			<0.001
Healthy Control	0 (0.0)	57 (100.0)	
IA	27 (90)	0 (0.0)	
IB	2 (6.7)	0 (0.0)	
IB (left) + IA (right)	1 (3.3)	0 (0.0)	

PO1-28-07

Neoadjuvant docetaxel plus cisplatin versus docetaxel plus doxorubicin and cyclophosphamide in early-stage triple-negative breast cancer (HNBC-001): results from a multicenter, randomized controlled, open-label phase II trial

Presenting Author(s) and Co-Author(s):

D. Jiao. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

J. Qiao. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

C. Wang. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

J. Li. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

X. Sun. Affiliated Cancer Hospital of Zhengzhou University, United States

Z. Lu. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

C. Zhang. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

L. Li. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

M. Yan. Henan Cancer Hospital, Henan, China

Y. Feng. Department of Breast Surgery, Xinxiang Central Hospital, Xinxiang, China, United States

Y. Zhou. Department of Breast Surgery, Xinxiang Central Hospital, Xinxiang, China, United States

M. Deng. Department of Breast Surgery, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, China, United States

X. Liu. Department of Oncology, General Hospital of Ningxia Medical University, Yinchuan, China, United States

M. Ma. Department of Thyroid and Breast surgery, Huaihe Hospital of Henan University, United States

H. Jia. Department of Breast Surgery, Anyang Tumor Hospital, Anyang, China, United States

Q. Xia. Department of Pathology, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China, United States

X. Chen. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

Z. Liu. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

Background: Adding platinum to anthracycline- and taxane-based neoadjuvant chemotherapy has improved pathological complete response (pCR) in patients with triple-negative breast cancer (TNBC). However, the efficacy of combining docetaxel and platinum without anthracycline remains controversial. Methods: The HNBC-001 trial was a randomized, phase 2 controlled, and open-label investigation carried out in China at 6 hospitals. The participants who were aged 18–70 years, were histologically confirmed for TNBC clinical stage II–III, suitable for potentially curative surgery, and had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1 were selected for this trial. Participants were randomly categorized

into two equal groups; those who received docetaxel plus cisplatin (75 mg/m², respectively) and those who received docetaxel plus doxorubicin and cyclophosphamide (docetaxel 75 mg/m², doxorubicin 50 mg/m², and cyclophosphamide 500 mg/m²). These regimens were given every 3 weeks for 6 cycles. Randomization was stratified by tumor size and nodal status. The primary endpoint was the number of individuals achieving a pCR (ypT0/is ypN0). The trial was registered with chictr.org (number ChiCTR-1800019501). Results: Between November 28, 2018, and June 11, 2022, 212 patients were selected (n=106/treatment). The number of individuals who achieved pCR after docetaxel plus cisplatin treatment was 51.9%, and that of those who attained pCR after docetaxel plus doxorubicin and cyclophosphamide was 35.8% (P=0.019). After 21 months of median follow-up [interquartile range (IQR), 13 to 33], 11 of 106 patients (10.4%) in the docetaxel plus cisplatin group and 14 of 106 patients (13.2%) in the docetaxel plus doxorubicin and cyclophosphamide group had event-free survival (EFS) events [95% confidence interval (CI) =0.360 to 1.783, hazard ratio (HR) =0.801, P=0.585]. The incidence of grade 3 or 4 events was similar in both groups [57 (54%) vs. 51 (48%)]. However, no treatment-associated deaths were identified. Conclusions: In stage II to III TNBC, the docetaxel plus cisplatin regimen achieved higher pCR rates than docetaxel plus doxorubicin and cyclophosphamide, with a manageable toxicity profile. Consistent with the literature, the docetaxel plus cisplatin regimen demonstrated a favorable risk-to-benefit profile and could serve as an optimal neoadjuvant chemotherapy option for patients with high-risk TNBC.

table 1: Patient characteristics

Characteristics	Docetaxel+ cisplatin (n=106)	Docetaxel+doxorubicin +cyclophosphamide (n=106)
Mean age,(SD)	50(43-55)	50(43-55)
Age(years)		
≤50years	54(50.9%)	54(50.9%)
>50years	52(49.1%)	52(49.1%)
T stage		
T1 to T2	93(87.7%)	94(88.7%)
T3 to T4	13(12.3%)	12(11.3%)
Nodal involvement		
Positive	68(64.2%)	66(62.3%)
Negative	38(35.8%)	40(37.7%)
ER and PR status		
ER and/or PR 1%-9%	12(11.3%)	10(9.4%)
ER and PR<1%	94(88.7%)	96(90.6%)
Ki-67		
≤50%	26(24.5%)	30(28.3%)
>50%	80(75.5%)	76(71.7%)
gBRCA1/2 status		
Mutant	14(13.2%)	15(14.2%)
Wild-type	75(70.8%)	66(62.3%)
Missing	17(16.0%)	25(23.6%)

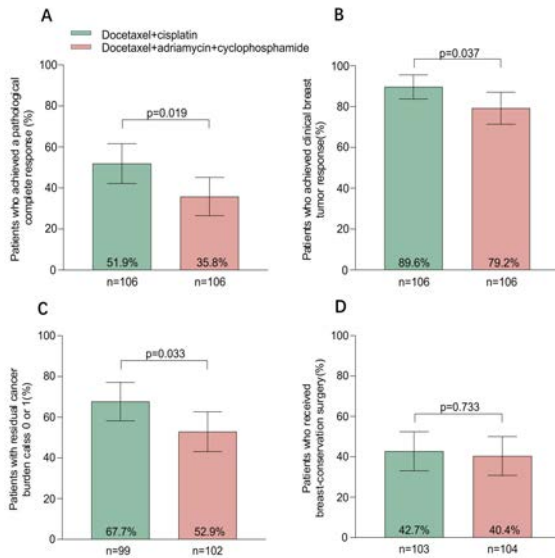


figure 1: Study endpoints

Error bars denote 95% CIs based on normal approximation. p values were calculated from the Chi-square test.

(A) Frequency of patients who achieved a pathological complete response per treatment group (primary endpoint).

(B) Frequency of patients who achieved a clinical breast tumour response per treatment group, assessed by serial MRI scans after completion of neoadjuvant treatment.

(C) Frequency of patients who achieved a minimal residual disease (residual cancer burden class 0 or 1).

(D) Frequency of patients who received breast-conservation surgery.

table 2: Treatment-emergent adverse events

	Docetaxel + cisplatin(n=106)			Docetaxel +doxorubicin + cyclophosphamide(n=106)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Haematological						
Leucopenia	22(21%)	3(3%)	2(2%)	13(12%)	4(4%)	4(4%)
Neutropenia	10(9%)	3(3%)	0(0%)	5(5%)	2(2%)	3(3%)
Febrile neutropenia	1(1%)	0(0%)	0(0%)	1(1%)	0(0%)	0(0%)
Anaemia	68(64%)	4(4%)	0(0%)	60(57%)	3(3%)	0(0%)
Thrombocytopenia	8(8%)	2(2%)	2(2%)	7(7%)	1(1%)	3(3%)
Non-haematological						
Nausea	54(51%)	23(22%)	0(0%)	65(61%)	8(8%)	0(0%)
Vomiting	55(52%)	15(14%)	0(0%)	33(31%)	5(5%)	0(0%)
Stomatitis	30(28%)	1(1%)	0(0%)	32(30%)	3(3%)	0(0%)
Constipation	45(42%)	0(0%)	0(0%)	40(38%)	1(1%)	0(0%)
Diarrhea	58(55%)	7(7%)	0(0%)	51(48%)	13(12%)	0(0%)
Abdominal pain	48(45%)	0(0%)	0(0%)	55(52%)	2(2%)	0(0%)
Myalgia	49(46%)	0(0%)	0(0%)	47(44%)	2(2%)	0(0%)
Arthralgia	40(38%)	0(0%)	0(0%)	44(42%)	2(2%)	0(0%)
Neuropathy	46(43%)	3(3%)	0(0%)	44(42%)	0(0%)	0(0%)
Dysgeusia	17(16%)	0(0%)	0(0%)	14(13%)	0(0%)	0(0%)
Pneumonitis	0(0%)	0(0%)	0(0%)	1(1%)	0(0%)	0(0%)
Laboratory-assessed items						
Increased ALT	26(25%)	0(0%)	0(0%)	38(36%)	2(2%)	0(0%)
Increased AST	16(15%)	0(0%)	0(0%)	33(31%)	1(1%)	2(2%)
Increased bilirubin	10(9%)	0(0%)	0(0%)	2(2%)	0(0%)	0(0%)
Increased creatinine	18(17%)	0(0%)	0(0%)	2(2%)	1(1%)	0(0%)
Increased urea nitrogen	14(13%)	0(0%)	0(0%)	5(5%)	0(0%)	0(0%)
Increased uric acid	31(29%)	0(0%)	0(0%)	12(11%)	0(0%)	0(0%)
Hyponatraemia	9(8%)	3(3%)	2(2%)	1(1%)	1(1%)	0(0%)
Hypokalaemia	13(12%)	6(6%)	0(0%)	4(4%)	0(0%)	0(0%)
Hypercalcaemia	11(10%)	0(0%)	0(0%)	9(8%)	0(0%)	0(0%)
Hypocalcaemia	15(14%)	1(1%)	0(0%)	11(10%)	0(0%)	0(0%)

PO1-28-08

The Efficacy and Safety Results of Neoadjuvant Phase II study of Anlotinib plus Sintilimab Combined with Chemotherapy in Triple-negative Breast Cancer (NeoSACT)

Presenting Author(s) and Co-Author(s):

L. Zhang. Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China, United States

M. Yang. Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China, United States

C. Yang. Guangdong Provincial People's Hospital, Guangdong, China (People's Republic)

T. Zhu. Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, United States

H. Gao. Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, United States

K. Wang. Guangdong Provincial People's Hospital, Guangzhou, Guangdong, China, Guangdong, China (People's Republic)

Background: In triple-negative breast cancer (TNBC), the co-administration of programmed mortality 1 (PD-1) inhibitors and chemotherapy has demonstrated enhanced pathological complete response (pCR) rates and improved event-free survival (EFS).

Previous research has suggested that antiangiogenic agents possess the ability to normalize aberrant tumor vasculature, thereby converting the immune-suppressive tumor microenvironment into an immune-supportive one. This study aims to assess the effectiveness and safety of combining the neoadjuvant small-molecule antiangiogenic drug Anlotinib with the PD-1 inhibitor Sintilimab and chemotherapy. Methods: In this study, a single-arm, open-label, phase II trial was conducted to evaluate the effectiveness of Anlotinib plus Sintilimab, in conjunction with nab-paclitaxel and carboplatin, followed by epirubicin and cyclophosphamide, in eligible patients with stage II-III TNBC. The treatment regimen consisted of four cycles of nab-paclitaxel (100 mg/m² on day 1, 8 and 15) plus carboplatin (AUC 5) every 21 days, followed by four cycles of epirubicin (90 mg/m²) plus cyclophosphamide (600 mg/m²) every 21 days. Additionally, patients received Sintilimab (200mg) every 21 days and Anlotinib (12mg, po on day 1-14, every 21 days) for eight cycles. Patient enrollment was conducted according to a Simon two-stage design. The primary endpoint was the rate of pCR based on the definition of ypT0/Tis ypN0. Secondary endpoints included residual cancer burden (RCB), EFS, overall survival (OS), adverse events (AE), and immune response biomarkers. Results: Between September 2021 and August 2023, a cohort of 31 patients was enrolled, with a median age of 48 years (range: 30-70 years). Among the participants, 21 out of 31 (67.8%) presented with clinical stage II disease, 23 out of 31 (74.2%) had T2 tumors, and 19 out of 31 (61.3%) exhibited clinically positive lymph nodes. In the initial phase of the study, a total of 11 patients were evaluated, out of which 7 patients achieved a pathological complete response (pCR) after surgery. Consequently, 20 patients were included in the subsequent stage, and among the 19 patients who were evaluable, 13 achieved pCR. One participant withdrew from the study prematurely following the third cycle due to grade 3 liver impairment, resulting in the discontinuation of study therapy as well as subsequent surgery. In the intention-to-treat (ITT) population, the overall pCR rate was determined to be 64.5% (20/31, 95% CI 45.4% - 80.8%). Additionally, 80.6% (25/31, 95%CI 62.5% - 92.5%) of the patients were assessed as having a

RCB score of 0 or 1. A total of 31 patients were subjected to adverse event assessment. Among them, 12 patients (38.7%) experienced one or more grade 3/4 adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The grade 3/4 AEs encompassed rash (7 patients, 22.6%), anemia (4 patients, 12.9%), thrombocytopenia (3 patients, 9.7%), neutropenia (2 patients, 6.4%), leukopenia (2 patients, 6.4%), hypothyroidism (2 patients, 6.4%), and elevated AST/ALT (1 patient, 3.2%).

Conclusions: The neoadjuvant regimen comprising the combination of Anlotinib and Sintilimab alongside chemotherapy demonstrated a pCR rate of 64.5%, with no observed emergence of novel toxicity signals. Ongoing investigations encompass biomarker assessments and survival analyses. Pertinent clinical trial details can be found under the identifier NCT04877821.

PO1-28-09

Rethinking the value of pathologic complete response rate for the survival outcomes of early triple-negative breast cancer treated with neoadjuvant chemotherapy: a systematic review and network meta-analysis

Presenting Author(s) and Co-Author(s):

X. Qiao. Breast Center - Peking University People's Hospital, -- Select one --, United States

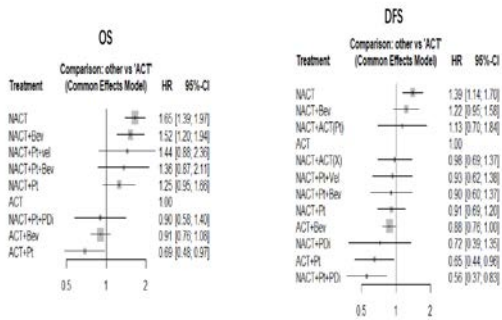
S. Wang. Breast Center - Peking University People's Hospital, Beijing, United States

T. Hu. Breast Center - Peking University People's Hospital, United States

B. Liang. School of Public Health, Peking University, United States

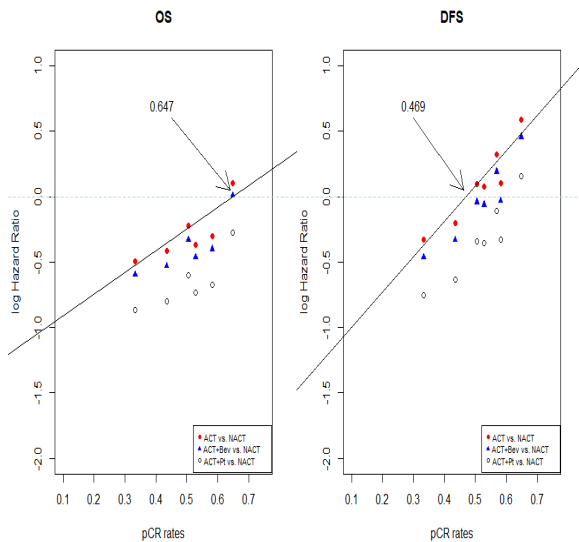
Abstract Background: Neoadjuvant chemotherapy (NACT) has been more frequently used in breast cancer, but it's controversial whether NACT or adjuvant chemotherapy (ACT) is more effective in improving survival outcomes for triple-negative breast cancer (TNBC) patients. Recent studies also proposed pathologic complete response (pCR) could not be a robust surrogate for survival outcomes in certain types of breast cancer. To address these questions, a general meta-analysis and a network meta-analysis (NMA) were conducted to compare the survival outcomes of patients with pCR, non-pCR after NACT and ACT. The cut-off pCR rate was also declared to indicate when NACT produces equivalent survival outcomes to ACT (Registration: PROSPERO CRD42022336732). **Methods:** Databases including PubMed, Embase, Web of science and Cochrane library were searched up to June 2023 to investigate studies comparing NACT and ACT, as well as randomized controlled trials (RCTs) comparing different regimens in NACT or ACT settings in early operable TNBC patients. Heterogeneity was assessed using χ^2 based Q-test and I^2 , combined with hazard ratios (HRs) with 95% confidence intervals (CI) computed for overall survival (OS), and disease-free survival (DFS, or event-free survival). The NMA with a Bayesian framework was conducted using both random and fixed effect model. The Weighted Least Square method and the Least Absolutely Deviation method were used to determine the cut-off pCR rates of OS and DFS. **Results:** A total of 35 studies involving 21 RCTs and 34143 TNBC patients were included. The general meta-analysis comprised 14 cohort studies. Eight high-quality cohort studies with propensity score matching and 21 RCTs were included in NMA. The pooled pCR rate for NACT was 42.2% (95% CI 37.8%-46.8%). Overall, the NACT cohort showed significantly worse OS and DFS than ACT cohort (HR=1.67, 95% CI 1.22-2.31; HR=1.37, 95% CI 1.14-1.64). However, patients with pCR after NACT showed improved OS than ACT (HR=0.58, 95% CI 0.50-0.66), while the patients without pCR after NACT had poorer OS than ACT (HR=2.03, 95% CI 1.88-2.19). As for DFS, there was no statistically difference between pCR after NACT and ACT groups (HR=1.04, 95% CI 0.63-1.73), while patients without pCR after NACT had significantly worse DFS than ACT (HR=2.65, 95% CI 1.98-3.55). From the NMA, the OS and DFS were better when combining modern target therapy such as Bevacizumab, PARPi, and PD-1/PD-L1 inhibitor (Figure 1), but not achieving pCR completely negated the benefits of newer drugs. Adding adjuvant capecitabine to patients not achieving pCR seemed to favor the OS. It was predicted that when the pCR rates were 64.7% and 46.9% (Figure 2), respectively, the OS and DFS of patients treated with NACT would be the same as those of patients treated with ACT. **Conclusions:** Higher pCR rate after NACT was associated with improved OS compared with ACT in TNBC patients. However, failure to achieve pCR after NACT resulted in worse survival outcomes than ACT. NACT had similar survival outcomes with ACT only when the pCR rate was at least 46.9%. The development of effective NACT regimens is beneficial for breast cancer patients.

Figure 1. Forest plot of the Hazard Ratio for OS and DFS in TNBC patients



pCR: pathological complete response; Bev: Bevacizumab; Pt: platinum; NACT: neoadjuvant chemotherapy; ACT: adjuvant chemotherapy; vel: veliparib; PDi:PD1/PDL1 inhibitor; X: capecitabine

Figure 2. The cut-off value of pCR when NACT and ACT have the same Hazard Ratio based on OS and DFS.



pCR: pathological complete response; Bev: Bevacizumab; Pt: platinum; NACT: neoadjuvant chemotherapy; ACT: adjuvant chemotherapy

PO1-28-10

Tumor Infiltrating Lymphocytes identify patients with stage I TNBC with excellent outcome without chemotherapy

Presenting Author(s) and Co-Author(s):

V. Geurts. Netherlands Cancer Institute, Amsterdam, The Netherlands, United States

S. Balduzzi. Netherlands Cancer Institute, United States

H. Horlings. Netherlands Cancer Institute, Amsterdam, The Netherlands, United States

T. Steenbruggen. Netherlands Cancer Institute, United States

S. Siesling. Netherlands Comprehensive Cancer Organization (IKNL) | University of Twente, Department of Health Technology and Services Research, Utrecht & Enschede, Netherlands

S. Adams. NYU Perlmutter Cancer Center, NYU Langone Health, United States

G. Sonke. Netherlands Cancer Institute, Amsterdam, Netherlands

R. Salgado. GZA-ZNA-Hospitals, Antwerp, Belgium; Peter Mac Callum Cancer Centre, Temse, Belgium

M. Kok. Netherlands Cancer Institute, Amsterdam, Noord-Holland, Netherlands

Introduction International guidelines recommend chemotherapy for most patients with stage I triple negative breast cancer (TNBC), except for special histological subtypes. However, the absolute benefit of systemic treatment for all stage I TNBC patients is not well known and no tools are yet available to select patients with an excellent prognosis for whom the chemotherapy can be safely omitted. High levels of stromal tumor infiltrating lymphocytes (sTILs) are strongly associated with favorable prognosis in TNBC, however, data solely focusing on patients with stage I TNBC who did not receive chemotherapy are lacking. Methods Patients with pT1N0M0 TNBC diagnosed between 2005 and 2015 not treated with (neo)adjuvant chemotherapy were identified from the nationwide Netherlands Cancer Registry (NCR) and linked to the national pathology database (PALGA). Newly sectioned hematoxylin & eosin (H&E) slides were used for central review of the histology and sTILs scoring following the International TIL working group guidelines (www.tilsinbreastcancer.org). Cause of death was provided by Statistics Netherlands (CBS). Primary endpoint was breast-cancer specific survival (BCSS) at 5-, 10- and 15-years for prespecified sTILs cut-offs of 30%, 50% and 75% sTILs. Results sTILs were evaluated for 1,041 patients with stage I TNBC who did not receive (neo)adjuvant chemotherapy. Mean age at diagnosis was 64.4 years [range 26 – 96] and median sTILs value was 5%. Most tumors (91.5%) were invasive ductal adenocarcinomas of no special type (NST) and 6.6% were of histological special types. In 52% of the patients the tumor was >1cm (pT1cN0). Median follow-up was 9.4 years in which 335 patients had died, of whom 107 due to breast cancer. Patients with pT1abN0 tumors had a favorable prognosis compared with patients with a pT1cN0 tumor (HR 0.47, CI 0.32- 0.72). 10-year BCSS in patients with pT1ab was 91.8% and 85.8% in patients with pT1c tumors. In the overall cohort, sTILs-levels of at least 30% were associated with better BCSS compared to sTILs < 30% (HR 0.45, CI 0.26 – 0.77), with 10year-BCSS of 96% and 87%, respectively (table 1). Patients with TNBC of special histological subtype had low sTILs (median 1%). A univariate cox model showed no association between sTILs (continuous) and BCSS in TNBC of special histological subtype ($p = 0.56$). Next, the prognostic value of sTILs was evaluated separately for pT1ab and pT1c. High sTILs $\geq 50\%$ were not associated with improved BCSS compared to low sTILs < 50% in patients with pT1ab (HR 1.35, CI 0.65 – 2.82, $p = 0.42$). In contrast, high sTILs $\geq 50\%$ showed a strong prognostic importance over low sTILs < 50% (HR 0.27, CI 0.10 – 0.74) in patients with pT1C tumors. We

found excellent 10year-BCSS of 95% for patients if sTILs $\geq 50\%$, which further increases to 98% with sTILs $\geq 75\%$ contrasting 10year-BCSS of 83% for patients with sTILs $< 30\%$. Conclusions sTILs-levels provide important prognostic information in patients with stage I TNBC who did not receive (neo)adjuvant chemotherapy. The outcome of patients with pT1c TNBC and sTILs $\geq 50\%$ was excellent, with 10year-BCSS of 95%, and 98% if sTILs $> 75\%$. This large registry study provides a foundation for clinical trials in patients with stage I TNBC with high TILs to prospectively confirm their excellent survival without chemotherapy.

Table 1: BCSS for overall cohort

	sTILs <30%	sTILs 30-49%	sTILs 50-69%	sTILs 70-89%	sTILs $\geq 90\%$
5y	93.5% (0.92 - 0.95)	93.8% (0.92 - 0.94)	96.6% (0.93 - 0.99)	95.7% (0.93 - 0.98)	94.9% (0.92 - 0.98)
10y	87.0% (0.84 - 0.90)	87.9% (0.86 - 0.90)	94.4% (0.90 - 0.96)	95.7% (0.93 - 0.98)	92.0% (0.88 - 0.94)
15y	86.0% (0.82 - 0.88)	86.0% (0.83 - 0.89)	94.4% (0.90 - 0.96)	93.0% (0.90 - 0.97)	92.7% (0.88 - 0.94)

Table 1: BCSS for overall cohort

PO1-29-01

Single agent and combinatorial efficacy with imipridone ONC206 via inhibition of mitochondrial function in preclinical models of chemorefractory triple negative breast cancer

Presenting Author(s) and Co-Author(s):

L. Baek. Baylor College of Medicine, Houston, Texas, United States

L. Dobrolecki. Baylor College of Medicine, United States

S. Faucher. Baylor College of Medicine, United States

C. Sallas. Baylor College of Medicine, United States

N. Griffith. Baylor College of Medicine, United States

V. Prabhu. Chimerix, United States

B. Lim. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Lewis. Baylor College of Medicine, Houston, Texas, United States

G. Echeverria. Baylor College of Medicine, United States

Breast cancer remains a major global health concern, with triple-negative breast cancer (TNBC) being one of the most aggressive subtypes associated with limited targeted therapies. Chemotherapy resistance in TNBC patients poses a significant clinical challenge and is associated with poor progression-free and overall survival. Thus, exploring novel approaches to improve chemotherapeutic efficacy is of paramount importance. We previously demonstrated a role for mitochondrial fusion in supporting oxidative phosphorylation (oxphos) activity and cell survival in residual TNBC (PMID: 30996079 and 36813854) cells refractory to chemotherapy treatments. Based on these observations, we sought to inhibit mitochondrial function to improve chemotherapeutic efficacy. We used ONC206, a novel agonist of mitochondrial serine protease, ClpP (Caseinolytic Mitochondrial Matrix Peptidase Proteolytic Subunit) to induce mitochondrial proteotoxic stress. ONC201, a parent molecule of ONC206, has shown efficacy in TNBC as a single agent or when combined with a MEK inhibitor in vitro (PMID: 34680527). We demonstrate treatment of TNBC cell lines with ONC206 results in reduced mitochondrial fusion and OXPHOS. Furthermore, ONC206 co-treatment enhanced chemo-sensitivity in vitro. Based on these promising findings, we tested this in orthotopic patient-derived xenograft (PDX) mouse preclinical trials. Three PDX models of TNBC were tested, BCM-2665, BCM-5471, and BCM-0002. ONC206 as a single agent (twice weekly for 4 weeks, oral gavage, 100mg/kg) significantly decreased tumor growth in all three PDX models. Remarkably, treatment ONC206 achieved nearly complete tumor regression as a single agent or when combined with carboplatin in BCM-2665. Regressed tumors did re-grow, but this was significantly delayed when combined with carboplatin. Treatment with ONC206 in BCM-5471 resulted in a modest but significant reduction in tumor growth rate as a single agent. However, ONC206 did not improve carboplatin (weekly, i.p., 50mg/kg) nor docetaxel (weekly, i.p., 20mg/kg) efficacy in this model. ONC206 treatment of BCM-0002 resulted in prolonged tumor stasis and a slight enhancement of docetaxel and carboplatin efficacy. Interestingly, the efficacy of ONC206 in these PDX models correlates with their relative mRNA expression of ClpP. The mice demonstrated tolerance to ONC206 as a single agent or when combined with chemotherapy during the course of treatment. Our study underscores the potentially crucial role of mitochondria in driving chemotherapy resistance in TNBC and provides novel insights into mitochondria-targeted therapeutic approaches. We report a novel targeting option for TNBC and anticipate that these findings will stimulate further research into innovative combination

therapies for TNBC patients, and may lead us to a viable inhibitor.

PO1-29-02

Two and a half years follow-up data of HER2-targeted bispecific antibody KN026 combined with docetaxel as first-line treatment for HER2-positive recurrent/metastatic breast cancer.

Presenting Author(s) and Co-Author(s):

Q. Zhang. Harbin Medical University Cancer Hospital, Harbin, United States

J. Wang. Harbin Medical University Cancer Hospital, United States

Q. Ouyang. Department of Medical Oncology, Hunan Cancer Hospital, United States

X. Wang. Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, United States

J. Wang. Linyi Cancer Hospital, Linyi, United States

L. Gan. The First Affiliated Hospital of Chongqing Medical University, United States

D. Lin. Jiangmen Central Hospital, United States

Z. Ouyang. The First Affiliated Hospital of Xiamen University, United States

T. Xu. Jiangsu Alphamab Biopharmaceuticals Co.,Ltd., Suzhou, China, United States

Y. Liu. Jiangsu Alphamab Biopharmaceuticals Co.,Ltd., Suzhou, China, United States

Y. Lv. Jiangsu Alphamab Biopharmaceuticals Co.,Ltd., Suzhou, China, United States

Background:

- KN026 is a novel bispecific HER2-targeted antibody. Fully humanized, IgG1-like antibody binds to two distinct HER2 epitopes, the same domains as trastuzumab and pertuzumab.
- Preliminary safety and efficacy results (data as of Aug 18, 2022) were presented at SABCs 2022(PD18-08), showed promising efficacy and tolerability.
- Herein, we update the 2.5-year follow-up results.

Methods:

- Eligible subjects with recurrent/metastatic breast cancer, HER-2 positive and treatment-naïve were enrolled.
- Subjects received KN026 30 mg/kg combined with docetaxel 75 mg/m² Q3W until disease progression, unacceptable toxicity, or other reasons.
- The primary endpoints were ORR and DoR. The secondary endpoints included safety, PFS and OS.

Results:

- As of data cut-off date (Sep 15, 2023), 57 subjects were enrolled, the median age was 52 years (min:30, max:67), 100% were female, and 91.2 % (52/57) were stage IV. There were 34 and 23 subjects with and without visceral metastasis, respectively. 48 subjects with high HER2 expression (IHC 3+), and the other 9 subjects with HER2 expression 2+ or 1+.
- The confirmed ORR within 55 evaluable subjects was 76.4% (42/55). The DoR was not reached yet with a median follow-up of 27.0 mons (95% CI: 26.28, 28.98).

- The median study follow-up was 30.6 mons (95% CI: 29.11 , 31.77). The mPFS was 27.7 mons (95% CI:17.97, NE) and the mOS was not reached. The OS rates at 12m, 24m and 30m were 93.0% (95% CI: 82.37, 97.31), 84.2% (95% CI: 71.85, 91.45) and 78.5% (95% CI: 65.25, 87.21).
- The mPFS of subjects with or without visceral metastasis were 23.6 mons and not reached. The mPFS of subjects with or without brain metastasis were 13.7 mons and 28.1 mons, respectively. The mPFS of 48 subjects with high HER2 expression (3+) was 28.1 months.
- The incidence of KN026-related Grade \geq 3 TRAE was 43.9% (25/57), including neutrophil count decreased 24.6% (14/57), white blood cell count decreased 12.3% (7/57), hypokalaemia 7.0% (4/57), diarrhoea 3.5% (2/57) and others less than 2%.
- The incidence of serious adverse events related to KN026 was 12.3% (7/57).
- There was no KN026 -related death.

Conclusions: KN026 in combination with docetaxel is well tolerated and has shown promising clinical benefit as 1L treatment for HER2-positive BC. After 2.5 years follow-up, mPFS was 27.7 mons and the 24-months OS rate was 84.2%, which is very promising. No new safety signals were observed. Robustness of efficacy and safety results will be further confirmed in an ongoing randomized phase 3 clinical trial with PTH as control.

PO1-29-03

Efficacy, Safety, and Immunogenicity of TQ-B211 (a Trastuzumab Biosimilar) Plus Docetaxel versus Herceptin® Plus Docetaxel for HER2-positive Metastatic Breast Cancer: a Double-blind, Randomised, Multicenter, Phase 3 Trial

Presenting Author(s) and Co-Author(s):

- X. Hu. Shanghai Cancer Center, Fudan University, Shanghai, China
Q. Zhang. Harbin Medical University Cancer Hospital, United States
S. Wang. Sun Yat-Sen University Cancer Center, United States
T. Sun. Cancer Hospital of China Medical University/Liaoning Cancer Hospital, United States
X. Zeng. Chongqing University Cancer Hospital, Chongqing, Chongqing, China (People's Republic)
W. Xie. Guangxi Medical University Affiliated Tumour Hospital, United States
Z. Tong. Tianjin Medical University Cancer Institute & Hospital, United States
H. Cao. Guizhou Provincial People's Hospital, United States
H. Xiong. Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology,, United States
X. wang. Qilu Hospital of Shandong University, United States
J. Yang. First Affiliated Hospital of Xi'an Jiaotong University, United States
S. Zhang. The Second Affiliated Hospital of Xi'an Jiaotong University, United States
Y. Wang. Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, United States
C. Hu. The second Xiangya Hospital of Central South University, United States
K. Lei. The Second People's Hospital of Yibin, United States
B. Ma. Affiliated Tumor Hospital of Xinjiang Medical University, United States
W. Liu. Affiliated Tumor Hospital of Xinjiang Medical University, United States
Z. Yu. Shandong Cancer Hospital, United States
P. Peng. The Fifth Affiliated Hospital of Sun Yat-sen University, United States
H. Yang. Suining Central Hospital, United States
Z. Yuan. Hunan Cancer Hospital, the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University,, United States
X. Wang. Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, United States
X. Wang. The Second People's Hospital of Neijiang, United States
H. Wang. Department of Medical Oncology, The Third Hospital Of Nanchang, Nanchang, Jiangxi, China (People's Republic)
Y. Shu. The First Affiliated Hospital of Nanjing Medical University, United States
N. Li. Xijing Hospital, United States
W. Yue. Puyang Oilfield General Hospital, United States
J. Wang. Linyi Cancer Hospital, Linyi, United States
D. Wang. Hengshui People's Hospital, United States

Z. Luo. Taihe Hospital Affiliated Hospital of Hubei University of Medicine, United States

J. Mo. Liuzhou People's Hospital, United States

Y. Li. Second Hospital of Jilin University, United States

L. Sheng. The First Affiliated Hospital of Wannan Medical College, United States

Background: Breast cancer is one of the most common malignant tumors in women worldwide. In China, the incidence of breast cancer has been steadily increasing. Approximately 30% of human breast cancers exhibit human epidermal growth factor receptor 2 (HER2) positivity, which is closely associated with tumor aggressiveness, high recurrence rate and high mortality. This study aimed to evaluate the efficacy, safety, and immunogenicity of TQ-B211 (a trastuzumab biosimilar) compared to the reference trastuzumab in combination with docetaxel as first-line treatment for patients with HER2-positive metastatic breast cancer. **Methods:** This randomized, multicenter, double-blind phase III equivalence study enrolled HER2+ metastatic breast cancer patients aged 18-75, ECOG PS \leq 1, no prior systemic chemotherapy, biologic, or targeted therapy for recurrent or metastatic disease, and at least one measurable lesion (RECIST 1.1). The patients were randomly assigned to two groups: the experimental group received TQ-B211 (8 mg/kg iv on day 1, cycle 1, followed by 6 mg/kg q3w for cycles 2-8) in combination with docetaxel (75 mg/m² on day 2, cycle1, followed by 75 mg/m² on day 1 for cycles 2-8), while the control group received Herceptin® in combination with docetaxel. For subjects who completed 8 cycles of treatment without disease progression and demonstrated tolerability, they were subsequently administered TQ-B211 as monotherapy until disease progression or unsuitable for further treatment. The primary efficacy endpoint was ORR up to week 24 (ORR_{24w}). Equivalence was declared if the 90% confidence interval (CI) of relative ratio (RR) value was within the range of 0.8 to 1.25. Secondary efficacy endpoints included duration of response (DoR); progression-free survival (PFS); disease control rate (DCR); overall survival (OS), safety and immunogenicity. **Results:** Between December 6, 2018 and July 31, 2021, a total of 386 patients (pts) were enrolled (192 pts in the TQ-B211 group and 194 pts in the Herceptin® group). In the intention-to-treat (ITT) population, the ORR_{24w} of the TQ-B211 group was 67.19% (95% CI: 60.55, 73.83), while the ORR_{24w} of the Herceptin® group was 65.98% (95% CI: 59.31, 72.65). The RR of the confirmed ORR_{24w} between the two groups was 1.02 (90%CI, 0.90, 1.15), which fell entirely in the predefined equivalence margins (0.8, 1.25), indicating comparable efficacy of the two drugs. In the ITT population, the DCR of the TQ-B211 group and the Herceptin® group were 83.85% (78.65, 89.06) and 78.35% (72.56, 84.15) respectively, with no statistically significant difference between the two groups (P=0.1940). By the data cutoff date of October 31, 2021, the median PFS was not statistically different (P=0.6834); the median OS was not reached in both groups (P=0.9246). Additionally, the data results of the per-protocol (PP) population were similar to those of the ITT population. In total, similar rates of treatment-related grade \geq 3 adverse events (41.05% vs. 46.39%) occurred in the TQ-B211 and Herceptin® groups, respectively. The incidence and magnitude of immunogenicity were low in both of the two groups (ADA: 0.53% vs. 0%, Nab: both negative). **Conclusion:** Equivalence for efficacy was demonstrated between TQ-B211 and Herceptin® on the basis of ORR_{24w}. Safety and immunogenicity were comparable.

PO1-29-04

Spatial tumor microenvironment profiling identifies immune features that correlate with response to T-DXd treatment in patients with metastatic breast cancer

Presenting Author(s) and Co-Author(s):

H. Zhao. Houston Methodist, United States

M. Vasquez. Houston Methodist Research Institute, United States

J. Zhang. Houston Methodist Research Institute, United States

G. Das. Houston Methodist Research Institute, United States

J. Lee. Georgia Institute of Technology, United States

Y. Gao. Emory University, United States

J. Zhang. Emory University, United States

X. Li. Emory University, United States

J. Chang. Houston Methodist Hospital, United States

S. Wong. Houston Methodist, United States

Objective: It is unclear which patients with metastatic breast cancer respond to the new antibody drug conjugate T-DXd treatment. Methods: We profiled 22 pre-T-DXd treatment metastatic tissue samples from patients using Nanostring GeoMX digital spatial profiler of tumor infiltrating immune cells and stroma components. Among the 22 metastatic samples, 10 were bone metastases 7 of the patients were defined as responder (R) and 3 were defined as non-responder (NR) to T-DXd treatment; 4 brain metastases with 2 R and 2 NR; 4 lymph node metastases with 2 R and 2 NR, and 3 liver metastases with all patients were NR to T-DXd. In each metastatic tissue section, 6-8 circular regions of interest (ROI) with 300 μ m diameter were selected by tumor epithelial marker (pan CK) and immune cells marker (CD45) throughout different areas of the tumor. The spatial quantification of 22 immune markers and 3 stroma elements (fibronectin, fibroblast activation protein, and smooth muscle actin) in each ROI was analyzed. Results: Based on the segmented CD45-positive cell numbers, a total of 144 ROIs were classified into high tumor-infiltrating immune ROIs (high-TIL, n=47) and low-TIL ROIs (n=97). Within the high-TIL ROIs, none immune markers showed significant difference in either the R or NR group across all metastasis sites ($P > 0.05$, Figure 1). Within the low-TIL ROIs, several immune markers, including PD-L1, PD-1, CD3, CD56, CD20, CD14, CD11c, CTLA-4, CD45, and B2M (Beta-2-microglobulin, an antigen presentation marker) showed significant elevation in the R group than those in the NR group ($P < 0.05$, Figure 2). Other immune markers including CD4 and CD8 were not significantly different in the R vs. NR groups in the low-TIL ROIs. High Ki-67 was correlated with R in both high and low-TIL ROIs. None of the three stroma markers was associated to treatment response to T-DXd. Conclusions: Enrichment of PD-L1, PD-1, CD3, CD56, CD20, CD14, CD11c, CTLA-4, CD45, and B2M in the metastatic tumor sites favors the treatment response to T-DXd in patients with metastatic breast cancer. Our study provides novel evidence that immune-suppression is associated with patients' response to T-DXd treatment, which may due to the unique mechanism of action of T-DXd.

RF01-01

SERENA-3: A randomized pre-surgical window of opportunity study assessing dose and duration of camizestrant treatment in post-menopausal women with ER-positive, HER2-negative primary breast cancer

Presenting Author(s) and Co-Author(s):

J. Robertson. University of Nottingham, Nottingham, UK; University Hospitals of Derby and Burton, Derby, England, United Kingdom

T. Gogitidze. LTD Brothers, Batumi, Ajaria, Georgia

Z. Katashvili. Acad. Fridon Todua Medical Center, United States

J. Bargallo Rocha. Instituto Nacional de Cancerologia (INCAN), Mexico City, Mexico

E. Arkania. Helsicore Israeli Gergian Medical Research Clinic, Tbilisi, Georgia

I. Moppett. Injury, Recovery and Inflammation Sciences, University of Nottingham, Nottingham, United Kingdom

K. Cheung. School of Medicine, University of Nottingham, Royal Derby Hospital Centre, Derby, United Kingdom

G. Nemsadze. The Institute of Clinical Oncology, Tbilisi, Georgia

M. Ajimi. AstraZeneca, United States

i. irurzun-Arana. AstraZeneca, Cambridge, United Kingdom

J. Lindemann. AstraZeneca, Cambridge, United Kingdom

T. Klinowska. AstraZeneca, Cambridge, United Kingdom

A. Mathewson. Research and Early Development, Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. Morrow. AstraZeneca, Cambridge, United Kingdom

M. Nikolaou. Research and Early Development, Oncology R&D, AstraZeneca, Cambridge, United Kingdom

G. Dzagnidze. LTD S. Khechinashvili University Hospital, Tbilisi, Georgia

Background Camizestrant, a next-generation oral selective estrogen receptor (ER) degrader (SERD) and pure ER antagonist, has demonstrated statistically significant and clinically meaningful progression-free survival (PFS) benefit over fulvestrant at both 75 and 150 mg once-daily doses in the Phase 2 SERENA-2 (NCT04214288) study in post-menopausal women with ER+ HER2- advanced breast cancer. SERENA-3 (NCT04588298) was established to explore the biological effects of three camizestrant dose levels in post-menopausal women with ER+ HER2- primary breast cancer. **Methods** Post-menopausal women with ER+ HER2- primary breast cancer scheduled to undergo curative intent surgery were randomly assigned in Stages 1 and 2 to pre-surgical treatment with camizestrant at 75, 150 or 300 mg once daily for 5 to 7 days or, in a sequential Stage 3, randomly assigned to camizestrant at 75 or 150 mg once daily for 12 to 15 days. Image-guided tumor biopsies were accessed as pre-treatment samples, while on-treatment ultrasound-guided tumor biopsies were obtained on the last day of camizestrant treatment. The primary objective was to explore the effect of camizestrant on ER expression by comparison of pre-treatment and on-treatment biopsies as assessed by immunohistochemistry (IHC) H-score. Secondary objectives included assessment of Ki67 and progesterone receptor (PgR) expression, and also of safety and tolerability, with exploratory pharmacodynamic (PD) assessment using other transcriptomic and proteomic technologies.

The study was undertaken in 17 centers across 3 countries (Georgia, Mexico and the United Kingdom). Results 135 patients were randomized and received treatment. 76 patients received camizestrant for 5 to 7 days at doses of 75 mg (n=30), 150 mg (n=33), and 300 mg (n=13); 59 received camizestrant for 12 to 15 days at doses of 75 mg (n=30) and 150 mg (n=29). Baseline disease characteristics, and ER, Ki67 and PgR levels were well balanced across arms and stages. Pharmacokinetic (PK) observations in all stages were commensurate with steady-state predictions derived from previous studies. PD data for ER and Ki67 are shown in Table 1. Camizestrant reduced ER H-score by approximately 65% irrespective of dose or duration. While the 75 mg dose reduced Ki67 score to a lesser degree than 150 mg and 300mg after 5–7 days exposure, after 12–15 days exposure 75 and 150 mg reduced Ki67 score to a similar substantial degree (82% reduction). PD results assessed by additional transcriptomics and proteomics assays were concordant with the IHC analyses. No serious adverse events were reported. All treatment-emergent adverse events were grade 1, apart from one patient with a grade 2 visual impairment, and one patient with grade 3 diarrhea. Conclusions SERENA-3 is the first study investigating the effect of multiple dose levels of camizestrant with different treatment durations on ER, Ki67 and PgR expression in post-menopausal women with primary ER+ HER2- breast cancer. SERENA-3 demonstrated that the 75 mg dose of camizestrant achieves maximal levels of ER degradation and Ki67 suppression. Together with SERENA-2, this provides strong evidence supporting 75 mg as the optimal dose of camizestrant, including for the early disease setting, and highlights the additive value of a specifically designed multi-dose pre-surgical PD study for optimal dose selection.

Table 1

Dose (duration) n ^a	Camizestrant 75mg (5-7 days) 26	Camizestrant 150mg (5-7 days) 31	Camizestrant 300mg (5-7 days) 11	Camizestrant 75mg (12-15 days) 24	Camizestrant 150mg (12-15 days) 26
Baseline ER H-score ^b	270.0 (259.8, 280.2)	277.9 (270.2, 285.6)	282.3 (279.1, 295.5)	282.1 (274.5, 289.7)	285.0 (278.8, 291.2)
On-treatment ER H-score ^b	100.2 (86.1, 114.3)	108.2 (93.9, 122.6)	95.5 (79.3, 115.6)	94.8 (77.2, 112.4)	101.3 (85.5, 117.1)
% change in ER H-score ^b	-62.7% (-67.5, -57.9)	-62.8% (-67.1, -58.4)	-67.2% (-74.5, -59.7)	-66.9% (-72.1, -61.5)	-65.0% (-70.3, -59.8)
n ^c	18	28	11	18	20
Baseline Ki67 ^d	22.1% (17.3, 28.2)	19.6% (17.2, 22.5)	18.7% (14.2, 24.7)	23.0% (17.1, 31.0)	21.5% (16.5, 27.8)
On-treatment Ki67 ^d	3.7% (0.2, 16.8)	3.8% (2.9, 5.0)	3.6% (1.9, 6.8)	4.1% (2.7, 6.2)	4.0% (2.7, 5.9)
% change in Ki67 ^d	-82.2% (-83.3, -79.8)	-81.3% (-85.1, -76.5)	-80.9% (-85.4, -69.6)	-81.7% (-86.5, -75.2)	-81.9% (-86.4, -75.9)
% on treatment <10% ^e	50.0% (31.9, 67.1)	81.1% (69.4, 91.1)	63.6% (40.1, 83.1)	77.8% (60.4, 89.9)	80.0% (63.9, 91.0)
% on treatment <2.7% ^e	5.0% (0.6, 19.9)	39.3% (26.7, 53.2)	54.5% (31.8, 75.9)	44.4% (27.9, 62.0)	45.0% (29.3, 61.5)

^a PD analysis set
^b Patients with Ki67 <1% at baseline excluded.
ER is presented as arithmetic mean (95% CI) for baseline/on-treatment score and least square mean (95% CI) for % change
^c Ki67 data are presented as geometric mean (95% CI) for baseline/on-treatment score and % change, and absolute % (95% CI) for % thresholds

Disclosure(s):

John Robertson, MB ChB BSc MD FRCS: Advisory Committee/Board Member: Carrick Therapeutics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): AstraZeneca (Terminated, October 29, 2023), Takeda (Terminated, October 29, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual

property or other ownership interest excluding diversified mutual funds): Carrick Therapeutics (Ongoing), FaHRAS (Ongoing), Oncimmune (Ongoing)

RF01-02

A randomized Phase I pre-operative window trial of transdermal endoxifen in women planning mastectomy: evaluation of dermal safety, intra-mammary drug distribution, and biologic effects

Presenting Author(s) and Co-Author(s):

O. Lee. Northwestern University, Chicago, Illinois, United States

L. Bazzi. Northwestern University, United States

Y. Xu. Northwestern University, United States

E. Pearson. Northwestern University, United States

M. Wang. Northwestern University, United States

O. Hosseini. Northwestern University, United States

A. Akasha. Northwestern University, United States

J. Choi. Northwestern University, United States

M. Kocherginsky. Northwestern University, United States

K. Benante. Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, United States

T. Helland. Haukeland University Hospital, Bergen, Norway

G. Mellgren. Haukeland University Hospital, Bergen, Norway

E. Dimond. National Cancer Institute, DCP, MD, United States

M. Perloff. National Cancer Institute Division of Cancer Prevention, United States

B. Heckman-Stoddard. National Cancer Institute, United States

S. Khan. Northwestern University, Chicago, Illinois, United States

S. Karlan. Cedars-Sinai Medical Center, United States

M. Pilewskie. University of Michigan, Ann Arbor, Michigan, United States

Background: Breast cancer prevention requires only local exposure of the breast to active drug but oral preventive agents entail systemic exposure, with resultant adverse effects, limiting acceptance by high-risk women. Drug-delivery through the breast skin is an attractive option, but requires demonstration of dermal safety and drug distribution throughout the breast. We formulated the tamoxifen metabolite (E/Z)-endoxifen in a hydroalcoholic/oleic acid gel for transdermal delivery. We tested this in a placebo-controlled, double-blinded Phase I trial with dose escalation from 10 to 20 mg daily and evaluated dermal safety, intra-mammary drug distribution, and biologic effects in DCIS or invasive cancers. Methods: Women planning mastectomy for therapy for Stage 0-III breast cancer, or surgical risk reduction (N=32) were randomized (2:1) to placebo-gel or endoxifen-gel applied to the skin of both breasts for 3-5 weeks. Our primary endpoint, dermal safety was evaluated using the modified NCI Common Terminology Criteria for Adverse Events version 4. Endoxifen concentration, and modulation of circulating tamoxifen biomarkers were evaluated to demonstrate minimal systemic effects. Plasma and tissue concentration of endoxifen were determined using Liquid Chromatography – Tandem Mass Spectrometry. Tamoxifen-responsive circulating markers, insulin-like growth factor 1 (IGF1) and sex hormone-binding globulin (SHBG), were measured with enzyme-linked immunosorbent assays. Finally, we explored anti-cancer efficacy in tumors by measuring the modulation of tumor cell proliferation (Ki67 labeling index) and gene expression associated with tamoxifen response in proliferation (BIRC5, MKI67, MYBL2, CCNB1, AURKA), cell cycle

(UBE2C, PLK1, CEP55, CDK1, RRM2, TOP2A, PTTG1), cancer-associated stromal genes of invasion (FN1, SERPINH1, PLOD2, PDGFA, ITGAV) and extracellular matrix (COL11A1, SPP1, COMP, BGN). Within-participant changes between baseline and post-treatment were assessed using the Wilcoxon signed rank test. Differences between treatment arms were assessed using the Wilcoxon rank sum test and the Kruskal-Wallis test. Results: endoxifen-gel at both doses incurred no dermal or systemic toxicity nor change in circulating biomarkers (IGF1, SHBG) compared to placebo. All treated breasts contained endoxifen at each of five sampling locations; the median per-person tissue concentration in the treated participants was 0.6 ng/g (IQR 0.4-1.6), significantly higher ($p < 0.001$) than the median plasma concentration (0.2 ng/mL, IQR 0.2-0.2). The median ratio of the more potent (Z)-isomer to (E)-isomer at each breast location was 1.5 (IQR 0.96-2.54, $p < 0.05$). We observed non-significant overall reduction in tumor Ki67 LI (median change -1.7 with IQR -5.8, 3.6) and gene expression of MKI67 and the genes associated with proliferation, and cell cycle. However, downregulation of invasion signature genes (FN1, SERPINH1, PLOD2, PDGFA, ITGAV) was significant ($p=0.03$) and a cluster of six participants demonstrated a consistent reduction of MKI67 and multiple gene signatures suggesting the possibility that their tumors might be early responders to low endoxifen exposure within 3 to 4 weeks of treatment. Conclusions: our evaluation of transdermal (E/Z) endoxifen 10 and 20 mg in hydroalcoholic/oleic acid formulation demonstrates lack of early dermal toxicity, and good tolerability over a month or so of therapy. Our findings warrant development of transdermal formulations of (Z)-endoxifen with better dermal permeation for a Phase 2 breast cancer prevention trial compared to low-dose oral SERMs so that women at high-risk for breast cancer may have a range of cancer prevention options available to them.

Disclosure(s):

Oukseub Lee, PhD: No financial relationships to disclose

Seema Khan, MD: No financial relationships to disclose

Melissa Pilewskie, MD, FACS: No financial relationships to disclose

RF01-03

PARSIFAL-LONG: Extended follow-up of hormone receptor-positive /HER2-negative advanced breast cancer patients treated with fulvestrant and palbociclib vs. letrozole and palbociclib in the PARSIFAL study

Presenting Author(s) and Co-Author(s):

A. Llombart-Cussac. 17 Medical Oncology Department, Hospital Arnau de Vilanova, Valencia, Comunidad Valenciana, Spain

J. Pérez-García. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Catalonia, Spain

M. Bellet- Ezquerro. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

M. Gil-Gil. Institut Català d'Oncologia, Institut d'Investigació Biomèdica Bellvitge. GEICAM Spanish Breast Cancer Group, United States

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

J. Gavilá. Medical Oncology Department, Fundación Instituto Valenciano de Oncología, Valencia, Spain; SOLTI Cancer Research Group, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

P. Zamora. Hospital Universitario La Paz, Madrid, Spain, Madrid, Spain

D. Wheatley. Royal Cornwall Hospitals NHS Trust, Truro, England, United States

E. Martínez-de Dueñas. Consorcio Hospitalario Provincial de Castellón. GEICAM Spanish Breast Cancer Group, Castellón, Spain

K. Amillano. Hospital Universitari Sant Joan de Reus, Spain

A. Antón. Miguel Servet University Hospital, Zaragoza, Aragon, Spain

P. Cottu. Institut Curie, Paris, Paris, Ile-de-France, France

G. Viñas. Medical Oncology, Catalan Institute of Oncology, Hospital Universitari Dr. Josep Trueta, Girona, Spain; Precision Oncology Group (OncoGIR-Pro), Institut d'Investigació Biomèdica de Girona (IDIBGI, Salt, Spain

T. Petit. Centre Paul Stauss, Strasbourg, France

P. Tesarová. 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

J. Cueva. 18. Complejo Hospital Universitario de Santiago de Compostela, Santiago de Compostela, Spain

M. Colleoni. Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Lombardia, Italy

M. Purificación Martínez del Prado. Hospital de Basurto, Bilbao, Spain

R. Andrés. Hospital Clínico Lozano Blesa, Spain

M. Díaz Cabo. MEDSIR, United States

S. Victorino. MEDSIR, United States

M. Sampayo-Cordero. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US; Department of Medicine, Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Madrid, Spain., Barcelona, Catalonia, Spain

Background: The Phase 2 PARSIFAL study assessed whether fulvestrant (FUL) or letrozole (LET) was the optimal endocrine partner for the cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) palbociclib (PAL) in patients (pts) with untreated, endocrine-sensitive, hormone receptor-positive (HR+)/HER2-negative (HER2-) advanced breast cancer (ABC) in the first-line setting. This trial failed to demonstrate an improvement in progression-free survival (PFS) of PAL+FUL over PAL+LET (Llombart-Cussac et al. *Jama Oncol* 2021). Following progression on CDK4/6i-based regimens in the metastatic setting, the EMERALD study (Bardia et al, SABCS 2022 GS3-01) identified early progressions (< 12 months [mo]) as a strong predictor of resistance to subsequent endocrine therapies. Here, we report updated PFS and overall survival (OS) from PARSIFAL, exploring a PFS <12 mo threshold as a prognostic factor for poor outcomes. **Methods:** This was an observational, international, multicenter study that included pts from the prospective PARSIFAL study, in which pts were randomly assigned (1:1) to receive PAL (oral 125 mg/day, 28-day cycles; 3 weeks on, 1 week off) plus FUL or LET at conventional doses. The primary objective was to extend the assessment of OS of PARSIFAL study with a longer median follow-up. Secondary objectives included extended PFS, other post-progression efficacy data, and the identification of new prognostic and predictive markers. The design had a planned recruitment of at least 388 pts with 195 deaths. The 2-sided stratified log-rank test ($\alpha = 0.05$) had a 70% power to detect a hazard ratio ≤ 0.70 in favor of FUL + PAL arm. **Results:** A total of 389 pts (80.5%) from the PARSIFAL study were included in this analysis, involving 32 of the 47 original sites. Pts signed a new informed consent form according to local regulations. Demographic and baseline disease characteristics were similar between the PARSIFAL-LONG and the overall PARSIFAL intention-to-treat populations. At the time of analysis, after a median follow up of 5.0 years (range, 0.1-7.3), 241 and 213 events were reported for PFS and OS, respectively. No differences in efficacy were observed between treatment arms whether for PFS (hazard ratio, 1.0, $p=0.985$) or OS (hazard ratio, 0.94, $p=0.635$). In accordance with the protocol for PARSIFAL-LONG, both arms were combined for subsequent analysis. The median PFS (mPFS) for the first-line PAL-based regimen population was 33.2 mo (95%CI, 27.7-39.5), with a median OS (mOS) of 65.4 mo (95%CI, 57.8-72.0). A total of 86 pts (22.1% of the population) had a mPFS time <12 mo (early progressors). mOS and mPFS for this early progressor subgroup were 24.0 mo (95%CI, 17.3-30.1) and 7.0 mo (95%CI, 5.6-8.3), respectively, and only 11 pts (12.8%) were still alive at the time of analysis. The remaining 303 pts (77.9%) were progression-free on PAL-based regimens at 12 mo (PFS \geq 12). The number of events for PFS and OS at this time were 165 (54.5%) and 138 (45.5%), respectively. mOS from randomization for the PFS \geq 12 subgroup was 81.5 mo (95%CI, 70.2-not achieved) and the mPFS was 49.8 mo (95%CI, 40.9-59.8). Following progression on PAL-based regimens, the PFS \geq 12 criteria was a strong predictor for mOS, with 27.0 vs 18.0 mo (hazard ratio, 0.67, 95%CI, 0.51-0.90, $p=0.007$) for PFS \geq 12 and early progressors, respectively. These differences may increase in the future, as 54.5% of pts with PFS \geq 12 are still alive compared to 12.8% of pts with an early progression. **Conclusions:** Extended follow-up analysis from PARSIFAL study confirms no major differences between LET or FUL when combined with PAL. mPFS and mOS results are consistent with those reported in other first-line trials involving different CDK4/6i. Progression within the first year of first-line CDK4/6i-based regimen for HR+/HER2-ABC pts may be prognostic of less favorable outcomes.

Disclosure(s):

Antonio Llombart-Cussac, MD, PhD: Advisory Committee/Board Member: DAIICHI-ASTRAZENECA (Ongoing), Eli Lilly & Company (Ongoing); Consulting Fees (e.g., advisory boards): DAIICHI-ASTRAZENECA (Ongoing), Eisai Europe Ltd. (Ongoing), Eli Lilly & Company (Ongoing), Exact-Sciences (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gilead (Ongoing), Guardant Health Inc. (Ongoing), Menarini/Stemline (Ongoing), MSD Co., Ltd. (Ongoing), Novartis Pharma GmbH (Ongoing), Pfizer, Inc. (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Agendia Inc (Ongoing), DAIICHI-ASTRAZENECA (Ongoing), Eli Lilly & Company (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gilead (Ongoing), MSD Co., Ltd. (Ongoing), Pfizer, Inc. (Ongoing), SeaGen (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Agendia Inc (Ongoing), DAIICHI-ASTRAZENECA (Ongoing), Eli Lilly & Company (Ongoing), Exact-Sciences (Ongoing), Gilead (Ongoing), GlaxoSmithKline (GSK) (Ongoing), Guardant Health Inc. (Ongoing), MSD Co., Ltd. (Ongoing), Novartis Pharma GmbH (Ongoing), Pfizer, Inc. (Ongoing)

Peter Schmid, MD, PhD: Consulting Fees (e.g., advisory boards): Eli Lilly & Company (Ongoing), Gilead Science (Ongoing)

Paul Cottu, MD, PhD: No financial relationships to disclose

Javier Cortés, MD, PhD: No relevant disclosure to display

RF01-04

Final results from the phase 2, open-label FOENIX-MBC2 study: efficacy and safety of futibatinib in adult patients with locally advanced/metastatic HR+/HER2- breast cancer harboring high-level FGFR1 gene amplification

Presenting Author(s) and Co-Author(s):

S. Damodaran. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France

N. Unni. University of Texas Southwestern Medical Center, Dallas, Texas, United States

M. Ferreira. Instituto Português de Oncologia do Porto FG, Porto, Portugal

K. Giridhar. Mayo Clinic, Rochester, Minnesota, United States

B. Daniel. Duke University Medical Center, University of Tennessee Health Science Center College of Medicine, Chattanooga, TN, United States

M. Colleoni. Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Lombardia, Italy

L. Costa. Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal

T. Bachelot. Medical Oncology, Centre Léon Bérard, Lyon, France

C. O'Brien. Christie Hospital NHS Foundation Trust, University of Manchester, Manchester, United Kingdom

G. Wright. Florida Cancer Specialists, New Port Richey, FL, United States

M. Shimura. Taiho Oncology, Inc., Princeton, New Jersey, United States

G. Tomlinson. Taiho Oncology, Inc., Princeton, New Jersey, United States

M. Gil. Taiho Oncology, Inc., Princeton, New Jersey, United States

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background: Fibroblast growth factor receptor 1 (FGFR1) gene amplification and overexpression is associated with an adverse prognosis in hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer and is observed in ~10% of all invasive breast cancers. The phase 2 FOENIX-MBC2 study (NCT04024436) was designed to evaluate the effect of futibatinib, a highly selective and potent irreversible covalent inhibitor of FGFR1-4 (FDA-approved for intrahepatic cholangiocarcinoma), used either alone or in combination with fulvestrant in patients with metastatic breast cancer. Here, we report final efficacy and safety data for the cohort of patients receiving futibatinib plus fulvestrant for HR+/HER2- breast cancer harboring high-level FGFR1 gene amplification. **Methods:** Patients were eligible if they had disease progression after prior therapy for advanced/metastatic disease, had measurable disease per RECIST v1.1, had an ECOG performance status of 0 or 1, were fulvestrant-naïve, and had previously received 1-2 endocrine-containing therapies, ≤1 chemotherapy regimen, and a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor for advanced cancer (unless ineligible). High-level FGFR1 gene amplification, determined in tumor tissue using next-generation sequencing, fluorescence in situ hybridization (FISH), or similar assays, was defined as FGFR1/centromere 8 ratio ≥5 or FGFR1 copy number ≥10 signals per cell. Local FGFR1 determination results were confirmed in tumor tissue by a central laboratory using FISH. Patients received oral futibatinib 20 mg once daily

and standard fulvestrant dosing until disease progression, unacceptable toxicity, or other discontinuation criteria were met. The primary endpoint was the 6-month progression-free survival (PFS) rate. Key secondary endpoints included objective response rate (ORR), PFS, and overall safety. Results: Overall, 22 female patients were enrolled in this cohort. Patients were a median age of 58 years, had received a median of 3 lines of any prior systemic anticancer therapy, and had all received CDK4/6 inhibitor pretreatment. PFS at 6 months was observed in 10 (45.5%) patients (95% CI: 24.4, 67.8) and the median PFS was 7.2 (95% confidence interval [CI]: 2.1, 7.6) months. Four patients had a confirmed partial response (ORR: 18.2%; 95% CI: 5.2, 40.3). The median duration of response was 6.3 (range: 3.3–12.8) months. All patients had ≥ 1 treatment-related adverse event (TRAE), the most common being hyperphosphatemia (95.5%), alopecia (54.5%), constipation (45.5%), and dry mouth (40.9%). There were 5 (22.7%) patients with a Grade 3 TRAE (no Grade 4 or 5). TRAEs leading to study treatment interruption or reduction were seen in 9 (40.9%) and 15 (68.2%) patients, respectively. There were 2 (9.1%) patients who had TRAEs leading to study treatment discontinuation. No treatment-related serious adverse events were reported. Conclusions: Futibatinib plus fulvestrant showed antitumor activity in patients with advanced HR+/HER2– breast cancer with FGFR1 amplification progressing on prior CDK4/6 inhibitors, with a numerically higher ORR and doubling in PFS relative to historical fulvestrant results in post-CDK4/6 patients. The safety profile was consistent with those of the individual study drugs. Further biomarker work is ongoing.

Disclosure(s):

Senthil Damodaran, MD, PhD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Daiichi-Sankyo (Ongoing), DualityBio (Ongoing), EMD Serono (Ongoing), Guardant Health Inc. (Ongoing), Medilink Therapeutics (Ongoing), Novartis Pharma GmbH (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), TAIHO Oncology (Ongoing)

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Guardant Health (Ongoing), Invitae (Ongoing), Natera (Ongoing), Personalis (Ongoing)

RF01-05

Functional assessment of RAD51 foci and replication fork dynamics in PARPi resistant BRCA1/2 mutated breast cancer

Presenting Author(s) and Co-Author(s):

E. Harvey-Jones. King's College London, Great Maze Pond, England, United Kingdom

M. Raghunandan. Institute of Cancer Research, United States

L. Robbez-Masson. Institute of Cancer Research, United States

T. Alaguthurai. King's College London, United States

A. Llop-Guevara. Val D'Hebron Institut D'Oncologia, United States

J. Trendell. King's College London, United States

O. Rodriguez. Val D'Hebron Institut D'Oncologia, United States

M. Guzman. Val D'Hebron Institut D'Oncologia, United States

D. Weekes. Institute of Cancer Research, United States

C. deRenty. Astra Zeneca, United States

E. Knight. Institute of Cancer Research, United States

R. Marlow. Institute of Cancer Research, United States

C. Starling. Institute of Cancer Research, United States

R. Liu. King's College London, United States

N. Ravindran. Institute of Cancer Research, United States

I. Roxanis. The Institute of Cancer Research, United States

N. Lukashchuk. Astra Zeneca, United States

V. Serra. Val D'Hebron Institut D'Oncologia, United States

S. Pettitt. Institute of Cancer Research, United States

C. Lord. Institute of Cancer Research, London, United States

A. Tutt. Institute of Cancer Research, King's College London and Guy's Cancer Centre, London, United States

Background: Although platinum salts (Pt) or Poly (ADP-Ribose) Polymerase inhibitors (PARPi) are effective in treating homologous recombination defective (HRD) breast cancer, resistance often emerges, especially in advanced disease. Predicting response and relapse is complex, even in patients with germline BRCA1/2 mutations (gBRCA1/2m). Clinically approved HRD detection methods are limited to identification of pathogenic mutations in HR genes or mutational signatures in the genome of tumors caused by HRD. In PDX models derived from HRD breast cancer, the restoration of nuclear RAD51 foci formation, a key feature of functional HR, can predict resistance to HRD-targeted treatment.¹ In addition, the restoration of replication fork stability, despite PARPi or induction of Pt adducts that induce replication fork arrest and collapse, confers resistance in pre-clinical models²; to date this resistance mechanism has not been clinically validated. Here we analyse RAD51 foci in FFPE samples and DNA replication fork dynamics, using DNA fibre combing assays, in patient derived organoids (PDO) relating these to clinical response to illustrate how such assays might predict clinical HRD-targeted therapy resistance in metastatic breast cancer (MBC). Patients and Methods: We used immunofluorescent detection of RAD51 foci as a marker for HR proficiency (HRP) in tumors

from 29 patients with gBRCA1/2m with MBC treated with HRD-targeted treatment (n=6 PARPi, n=2 Pt and n=21 both agents in sequence). All patients developed resistance that was either de novo or acquired. RAD51 and BRCA1 foci were scored in a minimum of 50 geminin (a marker of S/G2 phase) positive tumor cells; cells with ≥ 5 foci were classified as positive, and tumours where $\leq 10\%$ or $>10\%$ of cells were positive were considered HRD or HRP, respectively. DNA replication fork dynamics were assessed in with or without PARPi using thymidine analogue labelling. DNA fibre analysis was performed in PDOs developed from fresh tumor sampling of HRD-targeted treatment sensitive or resistant tumors, to determine the relationship between replication fork dynamics, stability and PARPi sensitivity. Results: RAD51 analysis was performed on 9 treatment naïve samples (n=9 patients), 8 samples obtained after HRD-targeted treatment resistance (n=8 patients) and 27 samples obtained pre and post HRD-targeted treatment resistance (n=12 patients). Functional HRD by RAD51 in treatment naïve samples was seen in 100% (n=17) of patients with acquired resistance and 66% of patients with de novo resistance. All patients, whether with de novo or acquired resistance, exhibited high RAD51 scores in post-resistance tumour samples, suggesting restoration of HR function is the dominant mechanism of PARPi resistance. As such, RAD51 analysis shows potential as a biomarker of clinical PARPi resistance. Replication fork stability fibre was analysed after exposure to potent PARP1 trapping inhibitors or an ATRi control in 3 PDOs (2 gBRCA1m, 1 BRCAwt). As controls we used an isogenic 2D cell line with and without a CRISPR engineered BRCA1 reversion mutation (SUM149 parental BRCA1m and SUM149BS*1 revertant) or with a PARP1 mutation (SUM149 TR2 clone) that prevents PARP1 being trapped on DNA. These experiments indicate that replication fork dynamics can be assessed in “patient derived” models of breast cancer and that PARPi sensitivity was associated with PARPi induced replication fork instability (median ratio IdU:CldU in resistant lines: 0.98, sensitive lines: 0.60). Conclusion: We show that HRP restoration and RAD51 foci in advanced BRCA1/2m breast cancers is the dominant form resistance to HRD-targeted treatment. We also demonstrate for the first time that analysis of DNA replication fork dynamics can be carried out in breast cancer PDOs and could be further explored as a functional predictive biomarker of PARPi resistance. 1.Pellegrino et al, 2022 (PMID: 35425960) 2.Chaudhuri et al, 2016 (PMID: 27443740)

Disclosure(s):

Elizabeth Harvey-Jones, MBChB, MRCP: No financial relationships to disclose

RF01-06

Efficacy and safety of toripalimab plus metronomic chemotherapy in HER2 negative metastatic breast cancer: a multicenter phase II trial based on a Bayesian adaptive randomized design.

Presenting Author(s) and Co-Author(s):

H. Mo. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

X. Sun. Cancer Hospital of Huanxing Chaoyang District Beijing, Beijing, China

J. Zhai. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

J. Han. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

H. Ge. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

Y. Wei. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

X. Guan. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

H. Qian. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

F. Ma. Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: Combining Immune checkpoint blockade (ICB) with chemotherapy may significantly improve efficacy in patients with breast cancer. Metronomic chemotherapy is based on more frequent and low-dose drug administrations compared with conventional chemotherapy. Some clinical studies with small samples have tried the combination of metronomic chemotherapy and ICB in patients with advanced tumors. However, whether metronomic chemotherapy is more suitable for ICB than conventional chemotherapy is still unclear. Thus, we performed the first clinical trial, to our knowledge, of metronomic chemotherapy combined with PD-1 blockade comparing with the efficacy of combined conventional chemotherapy and ICB. **Methods:** This study is a multicenter randomized phase 2 trial using a multi-arm design with Bayesian adaptive randomization and efficacy monitoring. Eligible patients have advanced HER2 negative breast cancer, with no more than one prior line of standard chemotherapy. Patients were randomized to 5 groups: ① metronomic vinorelbine (NVB, 40 mg/day, TIW) monotherapy (the control cohort); ② NVB + Toripalimab (anti-PD1 antibody, 240 mg Q3W); ③ Bevacizumab (5 mg/kg Q3W) + NVB + Toripalimab (the BEV cohort); ④ Cisplatin (50mg/m Q3W) + NVB + Toripalimab (the DDP cohort), ⑤ Cyclophosphamide (50mg/day, QD) + Capecitabine (500 mg, TID) + NVB + Toripalimab (the VEX cohort). The primary endpoint is disease control rate (DCR), and secondary endpoints are objective response rate (ORR), progression free survival (PFS), and overall survival (OS). The safety profile has also been assessed. Mass cytometry time-of-flight (CyTOF) analyses of paired blood samples were performed to demonstrate dynamic changes in systemic immune profile. **Results:** A total of 103 patients were randomized. Characteristics were as expected for advanced breast cancer and balanced between cohorts. Adverse events of any grade occurred in 64 patients, with 5.2% grade >3. The rate of nausea was significantly higher in the cisplatin

cohort than in the others ($P < 0.001$). Toripalimab was not associated with any previously unreported toxicity. Among the five treatment cohorts, the VEX cohort and the cisplatin cohort had the highest DCR, 69.7% (95% CI 51.7–85.9%) and 73.7% (95% CI 56.1–88.7%), respectively. Followed by the bevacizumab cohort, DCR is 55.7% (95% CI 37.4%–73.6%). Most objective responses were observed in the VEX cohort (ORR: 18.5%; 95% CI 5.6–34.1%), followed by cisplatin (ORR 14.5%; 95% CI 3.3–29.0%). It is worth noting that the PFS of patients in the VEX cohort was the longest, reaching 6.6 months (95% CI 4.0-5.9), followed by 4.0 months (95% CI 2.4-10.4) in patients of the bevacizumab cohort. The PFS of patients receiving the cisplatin regimen was relatively short, only 3.5 months (95% CI 2.2-5.3). Similarly, patients in the cisplatin cohort had shorter OS than those in the VEX and bevacizumab cohorts. In the TNBC subgroup, again, patients in the VEX cohort had the highest DCR (74.1%, 95%CI 47.9%-95.4%) and longest PFS (9.8 months, 95%CI 3.8-21.9). We obtained over 63 million cells in total and clustered CD45+ immune cells into 32 clusters. The systemic immune profile of patients changed dramatically over 2 cycles of PD-1 blockade. However, only the change of cluster 30 differed between responders and non-responders. This is a group of intermediate monocytes with a high expression of CD38, which decreased in responders but significantly increased in non-responders. CD38-NAD+ axis regulates the PD1+ exhausted T cell function. Meanwhile, the overall expression of CD38 in monocytes was significantly increased by DDP and BEV treatment compared with baseline, but not in the VEX groups. DDP significantly increased the expression level of CD38 on NK cells, while BEV or VEX treatment did not affect it. Conclusions: These data suggest promising clinical efficacy and evidence of cooperativity between metronomic VEX chemotherapy and PD-1 blockade.

Disclosure(s):

Hongnan Mo, MD: No financial relationships to disclose

RF01-07

The efficacy and safety of tinengotinib in patients with advanced or metastatic HR+/HER2- breast cancer or TNBC

Presenting Author(s) and Co-Author(s):

P. Sarina. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Y. Fan. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Y. Yuan. Cedars-Sinai Cancer, Los Angeles, California, United States

S. Lavasani. UCI Health, United States

J. Mortimer. City of Hope, Duarte, California, United States

S. Goel. Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, United States

A. Tsimberidou. The University of Texas MD Anderson Cancer Center, Houston, TX, United States

N. Ibrahim. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Abouharb. The University of Texas MD Anderson Cancer Center, Houston, TX, United States

C. Barcenas. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Iheme. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Karp. The University of Texas MD Anderson Cancer Center, Houston, TX, United States

J. Rodon Ahnert. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

E. Dumbrava. The University of Texas MD Anderson Cancer Center, Houston, TX, United States

J. Fan. TransThera Sciences (US), Inc., United States

P. Peng. TransThera Sciences (Nanjing), Inc., China (People's Republic)

C. Sun. TransThera Sciences (Nanjing), Inc., China (People's Republic)

H. Wang. TransThera Sciences (Nanjing), Inc., China (People's Republic)

K. Hennessy. TransThera Sciences (US), Inc., United States

X. Fu. TransThera Sciences (Nanjing), Inc., China (People's Republic)

R. Xu. TransThera Sciences (Nanjing), Inc., China (People's Republic)

S. Ni. TransThera Sciences (Nanjing), Inc., China (People's Republic)

F. Wu. TransThera Sciences (Nanjing), Inc., China (People's Republic)

F. Meric-Bernstam. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background: Tinengotinib is a novel multiple kinase inhibitor that strongly inhibits Aurora A/B, FGFR1/2/3, VEGFRs, JAK1/2, and CSF1R. Here we present the preliminary safety,

pharmacokinetic and efficacy data of tinengotinib in patients (pts) with hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC) and triple-negative BC (TNBC) from Phase I TT420X2101 (NCT03654547) and Phase Ib/II TT420X1103 (NCT04742959) trials. Methods: Eligible pts with HR+/HER2- BC or TNBC who have no available standard therapeutic treatment options were enrolled to the TT420X2101 and TT420X1103 trials. Tinengotinib was given as monotherapy at different dose levels (5 mg QD, 10 mg QD and 12 mg QD); different dosing schedule (6 mg BID); and as combination (tinengotinib 8 mg QD and Abraxane 100 mg/m²). Recruitment spanned from January 2019 to March 2023. Results: As of June 2023, 36 pts with metastatic BC were treated: 30 with tinengotinib monotherapy at dose levels of 5 mg QD (n=1), 8 mg QD (n=4), 10 mg QD (n=5), 12 mg QD (n=18), 6 mg BID (n=2) and 6 with tinengotinib 8 mg QD in combination with nab-paclitaxel 100 mg/m². Median age 51 years (range 24-75), ECOG PS 1 in 83.3% of pts, median lines of prior therapy were 5, and 77.8% of pts had prior taxanes. Of 30 pts receiving tinengotinib monotherapy, treatment related adverse events (TRAEs) were reported in 26 (86.7%) pts. 43.4% were Grade (G) 1-2, 43.3% were G3. No G4 or G5 TRAEs were reported. Common TRAEs (≥20%) of tinengotinib monotherapy were hypertension (60.0%), stomatitis (50.0%), palmar-plantar erythrodysesthesia syndrome (46.7%) and diarrhea (20.0%). All six (100%) pts receiving tinengotinib in combination with nab-paclitaxel experienced TRAEs, 16.7% were G1, 66.7% were G3, no G4 TRAEs, and one pt had G5 (pulmonary hemorrhage). Common TRAEs (≥20%) of tinengotinib in combination with nab-paclitaxel were neutrophil count decreased/neutropenia (50.0%), stomatitis (50.0%), hypertension (33.3%), hyponatremia (33.3%), hypokalemia (33.3%), and nausea (33.3%). Twenty-eight pts receiving tinengotinib monotherapy were efficacy evaluable. 11 pts with HR+/HER2- BC achieved objective response rate (ORR) of 45.5%, clinical benefit rate (CBR, CR+PR+SD ≥ 24 weeks) of 54.5% and median progression-free survival (mPFS) of 5.55 (95% CI 1.97-6.18) months. Partial responses were seen in 3 pts with HER2-zero (n=5) and 2 pts with HER2 low (1+/2+) pts (n=6), respectively. 17 pts with TNBC had ORR of 23.5%, CBR of 29.4% and mPFS of 2.73 (95% CI 1.68-6.41) months. In 6 pts treated with tinengotinib in combination with nab-paclitaxel, one out of 2 pts with HR+/HER2- BC achieved PR for 13 weeks as of data cutoff; two out of 4 pts with TNBC had SD. No significant difference in exposure was observed between tinengotinib monotherapy and tinengotinib in combination with nab-paclitaxel. Conclusions: Tinengotinib for the treatment of HR+HER2- BC or TNBC, whether as monotherapy or in combination with nab-paclitaxel, had manageable side effects. Tinengotinib has shown promising clinical benefit in heavily pre-treated pts with refractory HR+HER2- BC or TNBC. Clinical benefit was similar across the subgroups of pts with HR+ HER2-zero and HR+ HER2 low disease.

Disclosure(s):

Piha-Paul A. Sarina, MD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AbbVie, Inc. (Ongoing), ABM Therapeutics, Inc. (Ongoing), Acepodia, Inc. (Ongoing), Alkermes, Inc (Ongoing), Aminex Therapeutics (Ongoing), BioMarin Pharmaceutical, Inc. (Ongoing), Boehringer Ingelheim (Ongoing), Bristol Myers Squibb (Ongoing), Cerulean Pharma, Inc. (Ongoing), Chugai Pharmaceutical Co., Ltd. (Ongoing), Curis, Inc. (Ongoing), Cyclacel Pharmaceuticals (Ongoing), Daiichi Sankyo, Inc. (Ongoing), Eli Lilly (Ongoing), ENB Therapeutics (Ongoing), Epigenetix Inc. (Ongoing), Five Prime Therapeutics (Ongoing), F-Star Beta Limited (Ongoing), F-Star Therapeutics, Limited (Ongoing), Gene Quantum Healthcare (Ongoing), Genmab A/S (Ongoing), Gilead Sciences, Inc. (Ongoing), Glaxo Smith Kline (Ongoing), Helix BioPharma Corp. (Ongoing), Hengrui Pharmaceuticals, Co., Ltd. (Ongoing), HiberCell, Inc. (Ongoing), Immunomedics, Inc. (Ongoing), Incyte Corp. (Ongoing), Jacobio Pharmaceuticals Co., Ltd. (Ongoing), Jiangsu

Simcere Pharmaceutical Co., Ltd. (Ongoing), Loxo Oncology, Inc. (Ongoing), Lytix Biopharma AS (Ongoing), Medimmune, LLC (Ongoing), Medimmune, LLC (Ongoing), Medivation, Inc. (Ongoing), Merck Sharp and Dohme Corp. (Ongoing), NCI/NIH (Ongoing), Nectin Therapeutics, Ltd. (Ongoing), Novartis Pharmaceuticals (Ongoing), Nurix Therapeutics (Ongoing), Pfizer, Inc. (Ongoing), Phanes Therapeutics (Ongoing), Pieris Pharmaceuticals (Ongoing), Principia Biopharma, Inc. (Ongoing), Puma Biotechnology, Inc. (Ongoing), Purinomia Biotech, Inc. (Ongoing), Rapt Therapeutics, Inc. (Ongoing), Replimune (Ongoing), Roche/Blueprint (Ongoing), Seattle Genetics (Ongoing), Shasqi, Inc. (Ongoing), Silverback Therapeutics (Ongoing), Synlogic Therapeutics (Ongoing), Taiho Oncology (Ongoing), Tesaro, Inc. (Ongoing), Theradex Oncology (Ongoing), Toragen Therapeutics, Inc. (Ongoing), TransThera Bio (Ongoing), Xencor, Inc. (Ongoing), ZielBio, Inc. (Ongoing)

Yuan Yuan, MD PhD: Advisory Committee/Board Member: Astra Zeneca (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Stemline Therapeutics (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Astra Zeneca (Terminated, February 1, 2023), Daiichi Sankyo (Terminated, February 1, 2023), Merck (Terminated, February 1, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Merck (Terminated, February 1, 2023)

Joanne Mortimer, MD, FACP, FASCO: Consulting Fees (e.g., advisory boards): GE Healthcare (Ongoing)

RF01-08

A randomized, open-label phase III trial Evaluating Low-Dose Vs standard-dose Olanzapine with triple Antiemetic therapy for Prevention of highly emetogenic chemotherapy- induced Nausea and vomiting in solid tumors (OLAnzaPiNE)

Presenting Author(s) and Co-Author(s):

J. Bajpai. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India

V. Kapu. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India

S. Rath. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India

S. Kumar. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), United States

A. Sekar. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), United States

S. Anne. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), United States

A. Pawar. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), United States

S. Srinivas. Tata memorial hospital, United States

P. Bhargava. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), United States

S. Gulia. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), United States

R. Sarin. Tata Memorial Hospital, United States

R. Badwe. Tata Memorial Centre, Mumbai, India

S. Gupta. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), United States

Background Chemotherapy induced nausea and vomiting (CINV) is a major adverse event for cancer patients. Olanzapine (OLZ) in standard 10 mg dose along with triple antiemetics (TAE), has shown effectiveness in treating CINV with highly emetogenic chemotherapy (HEC), however, significant day time somnolence (DTS) precludes its widespread use. Steroids related side effects are another major concern. Hence, a lower dose of OLZ, with single dose (SD) steroid use is worth exploring in a randomized fashion. Methods Solid tumors planned for anthracycline-cyclophosphamide & high-dose cisplatin chemotherapy was randomized (1:1) to receive either 10mg OLZ (standard arm) or 2.5mg (experimental arm) till day 4 with TAE regimen [5-hydroxytryptamine type 3 (5-HT3) receptor antagonists, dexamethasone (SD, without delayed doses), and neurokinin-1 (NK1) receptor antagonists] in both arms. Primary objective was to evaluate Complete control rate (CCR) defined as proportion of subjects with no emetic episodes (EE), no use of rescue medications (RM), no or mild nausea assessed in overall phase (OP) =0-120 hours(h) in both groups. Secondary objectives were to compare two groups for the CCR in acute(AP) and delayed phase(DP); Complete response rate (CRR)=no EE and no use of RM in AP(0- 24h), DP(25-120h) and OP; Total control rate(TCR)= no EE, no use of RM, and no nausea) in AP, DP, OP; Time to treatment failure(TTF), defined as mean duration from chemotherapy initiation to first episode of nausea, EE, use of RM; Incidence of significant daytime somnolence(DTS). Tertiary objectives were effect on appetite loss. Subjects maintained a daily record of nausea, EE, RM use with the severity graded on a four-category scale. Statistical analysis CCR, CRR, TCR are given in counts and proportions. Occurrence of nausea, EE, DTS and their grades were compared using Chi-square test. Results A total of 275 subjects were enrolled, among them 267 were analyzable, inclusive of 132 subjects in 2.5mg and 135 in 10mg arms with well-balanced baseline characteristics (Table 1) Proportion of

patients with CCR in OP (Primary end point) in 2.5mg vs. 10mg arms were, 44.7 % vs. 43.7 % (P = 0.87) respectively. CCR in 2.5mg vs. 10mg arms in AP, DP were 50% vs. 48.9%(p=0.856) and 50.8% vs. 58.5% (P=0.203) respectively. CRR in 2.5mg vs. 10mg in AP, DP and OP were 56.1% vs. 57 % (P=0.872), 55.3% vs. 63% (P = 0.203), and 50.8 % vs. 51.1% (P=0.954), respectively. TCR in 2.5mg vs. 10mg in AP, DP, and OP were 25% vs. 23 % (P=0.697), 20.5% vs. 22% (P = 0.725), and 13.6 % vs. 15.6% (P=0.657), respectively. Subjects receiving 2.5 mg as compared with those receiving 10 mg, had statistically significant decreased DTS on overall grades 65.2% vs 89.6% vs. (p < 0.001); severe grade DTS was more on day1 i.e., 4.5% vs. 40% (p < 0.001) and although successively reduced from day 2-5 in both the arms, however, 2.5 mg fared better on all the days (table 1). No statistically significant effect of reduced appetite noted in 2.5mg vs. 10mg i.e., 17.4% vs. 24.4 % (p=0.208) Conclusion Low dose olanzapine (2.5mg) is non inferior to 10mg olanzapine in controlling CINV without requirement of delayed steroids, and is superior with respect to DTS (all days, all grades, severe grades) in subjects receiving HEC. This merits wide recognition as a new steroid sparing antiemetic regimen of choice with HEC.

Demographic data, Clinical characteristics and Outcomes

Demographic data, Clinical characteristics and Outcomes			
Characteristics	Experimental 2.5mg arm (n=132)	Standard arm 10mg (n=135)	Total (n=267)
Age in years(mean)	43.5	43.4	43.45(0.127)
Gender			
Male	64 (5%)	90 (7%)	156 (6%)
Female	126(95.5%)	126(93.3%)	252(94.4%)
ECOG			
0	69(52.3%)	62(45.9%)	131(49.1%)
1	57(43.2%)	73(54.1%)	130(48.7%)
2	6(4.5%)	0(0%)	6(2.2%)
Comorbidities			
Diabetes	3(2.3%)	6(4.4%)	9(3.4%)
Hypertension	11(8.4%)	10(7.4%)	21(7.8%)
Hypothyroidism	11(8.4%)	10(7.4%)	21(7.8%)
Asthma	1(0.8%)	1(0.7%)	2(0.7%)
Diagnoses			
Breast	121(91.7%)	121(89.6%)	242(90.6%)
Other cancers:			
Sarcoma	6(4.5)	11(8.1%)	17(6.4%)
Head and neck cancer	4(3)	3(2.2%)	7(2.6%)
Germ cell tumours	1(0.8%)	0	1(0.4%)
Chemo regimen			
Antihydroxyline based	123(92.8%)	122(90.9%)	245(91.8%)
Cisplatin based Chemotherapy	9(7.2%)	13(9.1%)	22(8.2%)
OUTCOMES	Experimental 2.5mg arm	Standard 10mg arm	P value
Primary Endpoint			
Overall (0-120 hrs)	44.7%	43.7%	P=0.87
Secondary Endpoint			
CCR			
Overall (0-120 hrs)	50%	48.9%	P=0.856
Delayed (24-120 hrs)	50.8%	58.5%	P=0.203
CRR			
Overall (0-120 hrs)	56.1%	51.1%	P=0.364
Delayed (24-120 hrs)	55.3%	63%	P=0.203
TCR			
Overall (0-120 hrs)	13.6%	15.6%	P=0.697
Delayed (24-120 hrs)	20.5%	22%	P=0.725
TTP in days (Median IQR)			
Nausea	1(1, 1)	1(1, 1)	P=0.8921
Vomiting	1(1, 1)	1(1, 1)	P=0.384
Need for rescue medications	4.5(4.2, 4.8)	4(3.2-4.8)	P=0.479
Daytime somnolence(Overall/grade)			
Severe grade Day 1	6(4.5%)	59(8%)	P=0.001
Severe grade Day 2	4(3.0%)	54(40%)	P=0.004
Severe grade Day 3	1(0.8%)	31(23%)	P=0.001
Severe grade Day 4	0(0%)	18(13.3%)	P=0.001
Severe grade Day 5	1(0.8%)	11(8.1%)	P=0.004

Disclosure(s):

Jyoti Bajpai, DM Medical Oncology: No financial relationships to disclose

PO2-01-01

Biophysical simulation using DCE-MRI to forecast response to NAT in HER2+ patients, with glucose characterization and orthogonal validation using FDG-PET

Presenting Author(s) and Co-Author(s):

J. Whitman. SimBioSys, Inc., Chicago, Illinois, United States

V. Adhikarla. Beckman Research Institute, United States

R. Rockne. Beckman Research Institute, United States

L. Tumyan. City of Hope, United States

J. Mortimer. City of Hope, Duarte, California, United States

W. Huang. Oregon Health & Science University, United States

J. Peterson. SimBioSys, Inc., Chicago, Illinois, United States

D. Lopez-Ramos. SimBioSys, Inc., Chicago, Illinois, United States

J. Cole. SimBioSys, Inc., Chicago, Illinois, United States

Background: Metabolic reprogramming and tumor angiogenesis are two tightly linked hallmarks of cancer. Regions of high metabolic activity within a tumor can become hypoxic or nutrient starved, eliciting a cascade of pro-angiogenic signals that can lead to increased tumor perfusion and in turn greater metabolic activity. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and ¹⁸Fluorodeoxyglucose (FDG) positron emission tomography (PET) are two imaging methods commonly used in the diagnosis of cancer; the former can be also used to identify the perfusion of the tumor microenvironment (TME) and the latter provides a coarse readout of glucose metabolic activity. Here, we are presented with a unique cohort of patients who underwent DCE-MRI, ¹⁸FDG-PET and ⁶⁴Cu-DOTA-Trastuzumab offering potential to perform a pilot analysis. First, we characterize the performance of our perfusion model SimBioSys- Microvasculature (SBS-MV) through a stability analysis, as well as comparison with two PET modalities. Finally, we use this model in 3D simulations of individual HER2+ breast cancer patients to forecast responses to neoadjuvant chemotherapy (NAT). Methods: SBS-MV is a modified Tofts model for pharmacokinetic modeling of DCE-MRI data, utilizing a tissue segmentation model developed in-house to inform parameter fits and ensure that the derived parameters fall within acceptable values on a tissue-by-tissue level, in addition its function for standard fitting of DCE time-course data. We first evaluated the stability of the SBS-MV model by analyzing a separate cohort of 10 patients who underwent ultrafast DCE-MRI. Temporal undersampling was performed on the original high temporal resolution data to mimic low temporal resolution from standard-of-care (SoC) DCE studies. Both datasets were processed with SBS-MV model. Next, we analyzed data from a cohort of 18 patients, each of whom underwent a pre-NAT SoC DCE-MRI study, a mid-treatment FDG PET/CT study, and a mid-treatment ⁶⁴Cu-DOTA-Trastuzumab/CT study during treatment. Tissue segmentation and SBS-MV fits were performed on the pre-NAT DCE MRI. Tightly cropped boxes encompassing the tumor in the 3D SBS-MV volumes as well as the PET volumes were created. Using these identified regions, all summary statistics were calculated and cross-correlated between imaging modalities. Results: SBS-MV was stable to SoC-mimicking temporally undersampled ultrafast DCE MRI series, demonstrating relatively little variability in the output parameters (a voxel wise median deviation of approximately 0.005 min⁻¹). Further, we demonstrate that SBS-MV parameters (K^{trans} , v_e) are correlated with FDG SUV_{SA} and ⁶⁴Cu SUV_{SA}. In addition, the glucose concentrations used in the biophysical simulations were correlated with FDG SUV_{SA},

indicating that downstream applications of the SBS-MV models still carry this information about perfusion.

Finally, using SBS-MV, our biophysical simulations of HER2-targeted therapy accurately predict patient response. In this small cohort, our biophysical simulation platform performed well, yielding predictive accuracy of 0.83, with sensitivity and specificity of 0.83 and 0.83, respectively. These performance metrics are in line with previously published reports. Conclusion: Our MV model is capable of extracting biologically meaningful perfusion parameters from standard clinical DCE MRI time series, providing the same benefits of a comprehensive kinetic analysis, without impacting current clinical workflow. This approach could be used in both the research and clinical settings, offering actionable information on what drives individual patient therapeutic response for a more personalized care.

PO2-01-02

Clinicopathologic features and prognosis of breast cancer with low HER2 expression evaluated by fluorescence in situ hybridization

Presenting Author(s) and Co-Author(s):

A. Sato. Teikyo University School of Medicine, United States

S. Naruse. Department of Surgery, Teikyo University School of Medicine, United States

Y. Isono. Department of Surgery, Teikyo University School of Medicine, United States

Y. Maeda. Department of Surgery, Teikyo University School of Medicine, United States

M. Yamada. Department of Surgery, Teikyo University School of Medicine, United States

A. Matsumoto. Teikyo University School of Medicine, United States

T. Ikeda. Teikyo University School of Medicine, United States

H. Jinno. Department of Surgery, Teikyo University School of Medicine, United States

Background

Although trastuzumab deruxtecan has been found to improve progression-free survival and overall survival of HER2-low breast cancer patients in DESTINY Breast04 trial, the characteristics and prognostic value of low HER2 expression remains to be elucidated. In this study, we retrospectively examined the clinicopathologic characteristics and prognosis of HER2-low expressing breast cancer. Methods

A prospective database of 1026 clinical stage I to III, HER2 negative breast cancer patients who underwent surgery from September 2012 to October 2022 at Teikyo University Hospital was analyzed. HER2 was evaluated by fluorescence in situ hybridization assay, and HER2-low and HER2-negative was defined as HER2/CEP17 ratio ≥ 1.0 , and < 1.0 , respectively. The chi-squared test was performed to estimate correlations between HER2-low status and clinicopathological factors. Distant-disease survival (DDFS) was calculated using the Kaplan-Meier curves and log-rank test. Multivariate logistic regression analyses were used to identify the independent prognostic factors. Results

Median age, tumor size and ki67 of the entire 1026 patients was 56.0 years (range=23.0-93.0), 2.0 cm (range=0.3-15.0 cm), and 15.0 % (range=0.5-99.0 %), respectively. 155 (15.1 %) patients had lymph node metastasis. 904 (88.1 %) patients revealed hormone receptor positive (estrogen receptor [ER] positive; 904 patients, progesterone receptor [PgR] positive; 810 patients). Neoadjuvant and adjuvant chemotherapy was performed in 197 (19.2 %) and 160 (15.6 %) patients, respectively. Among all patients, 904 (88.1 %) patients had HER2-low tumors and 122 (11.9 %) patients had HER2-negative tumors. Positive rate of ER and PgR was significantly higher in HER2-low compared to HER2-negative patients (ER: 804 [88.9 %] patients vs 100 [82.0 %] patients; $p=0.026$, PgR: 723 [80.0 %] patients vs 87 [71.3 %] patients; $p=0.028$). The median ki67 was significantly lower in HER2-low compared to HER2-negative patients (14.5 % vs 18.5 %, $p=0.013$). Pathologic complete response rates were not significantly different between HER2-low and HER2-negative patients (16.1 % [27/168 patients] vs 17.2 % [5/24 patients], $p=0.528$). With a median follow-up time of 39.7 months, DDFS was significantly better in HER2-low compared to HER2-negative patients (96.6 % vs 90.7 %, $p=0.027$). Multivariate logistic regression analyses showed that HER2-low expression was not independently related factors for DDFS. Conclusion

These data suggested that HER2-low expression might not have significant association with prognosis despite significant correlation with ki67 and hormone receptor expression.

PO2-01-03

Efficacy of dose-dense and anthracycline-free regimens in neoadjuvant chemotherapy of HER2-positive breast cancer: a single-center matched-cohort study. Preliminary results.

Presenting Author(s) and Co-Author(s):

E. Kovalenko. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

Y. Zhulikov. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

M. Khoroshilov. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

I. Vorotnikov. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

A. Petrovskiy. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

E. Artamonova. National Medical Research Center of Oncology na N.N. Blochin, United States

Introduction: The efficacy of dose-dense (dd) adjuvant chemo has been proved in numerous clinical trials and meta-analysis. However, it remains unclear whether the intensification of AC (doxorubicine/cyclophosphamide) regimen affects the rate of pathological complete response (pCR) in HER2+ subtype, since the efficiency of the ddAC-THP (docetaxel/trastuzumab/pertuzumab) regimen with dual anti-HER2-blocade in the neoadjuvant (NA) setting has not been assessed. Anthracycline (A)-containing and A-free regimens (TCHP -docetaxel/carboplatin/trastuzumab/pertuzumab) are considered equivalent, although there are no direct comparative studies to date. **Methods:** The aim of the study was to assess the rate of pCR of ddAC (once every 2 weeks)-THP NA regimen in comparison with ACq3w (once every 3 weeks)-THP and A-free TCHP regimen in HER2+ stage II-III breast cancer (BC). The study included patients with early HER2+ BC who received NA chemo in a single center from Jan 2017 to Nov 2022. **Statistical hypothesis.** The study has a 2-step design. It is assumed that the rate of pCR with ddAC will be $\geq 65\%$, and with ACq3w $\leq 50\%$. With a unilateral type I error (α) = 0.05 and a type II error (β) = 0.2, 170 patients should be included in each group. In the absence of significant differences between ddAC and 4ACq3w, groups may be merged into one cohort and compared with TCHP group. It is assumed that A-containing regimens (H1 - pCR 55%) are not inferior to A-free regimen (H0 - pCR 55%). A non-inferiority design is planned, with delta 15%, type I error (α) = 0.05 and type II error (β) = 0.2, 173 people in each group should be included. Here we present preliminary results. **Results:** A total of 400 patients were included, of which 138 received 4xddAC- 4xTHP, 102 – 4xACq3w-4 x THP, 160 – 6xTCHP. The pCR rate in the whole ddAC-THP group was 55,8%. The majority of patients (77,5%) had stage III disease. After propensity matching analysis to adjust for selection bias 102 patients in each A-containing group were included in the final analysis. The pCR rate was 50% in the ddAC group vs 48% in the ACq3w group ($p=0.67$). Subgroup analysis, including T, N stage, age, ER status, G, ki67 revealed no advantage of ddAC regimen. Next, both A-groups were merged and after propensity matching analysis 143 patients were included both in A- and TCHP-group. The pCR rate was 53,8% in the A-group vs 60,1% in the TCHP group ($p=0.34$). Subset analysis demonstrated no benefit of A-regimen across subgroups. **Conclusion:** Our preliminary results suggest that A-containing and TCHP regimens appear to be equivalent in terms of pCR. In case of choosing AC-THP for NA chemo there's no need to perform the AC arm in dd way

since it does not improve efficacy.

PO2-01-04

Efficacy and safety of anti-HER2 therapy in neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis

Presenting Author(s) and Co-Author(s):

L. Gan. The First Affiliated Hospital of Chongqing Medical University, United States

F. Li. The First Affiliated Hospital of Chongqing Medical University, United States

J. Su. The First Affiliated Hospital of Chongqing Medical University, China (People's Republic)

Background: Human epidermal growth factor receptor-2 overexpression or gene amplification (HER2+) breast cancer is considered to be a highly aggressive, dangerous and even fatal subtype. In recent years, with the application of large molecule anti-HER2 monoclonal antibody and its biosimilar in neoadjuvant therapy of HER2-positive breast cancer, small molecule tyrosine kinase inhibitors (TKIs) have also performed strong advantages of antineoplastic activity in breast cancer. At present, there is no direct evidence to demonstrate the differences in neoadjuvant efficacy of anti-HER2 monoclonal antibody and tyrosine kinase inhibitors (TKIs) in this subtype of breast cancer. We conducted a preliminary network meta-analysis to explore the difference of efficacy and safety between anti-HER2 monoclonal antibody and TKIs for neoadjuvant therapy in patients with HER2-positive early or locally advanced breast cancer.

Method: A systematic literature search in the Cochrane Central Register of Controlled Trials, PubMed, Embase and Web of Science was performed. Randomized or non-randomized controlled studies of neoadjuvant therapy for HER2-positive breast cancer including large molecules trastuzumab, pertuzumab and small molecules TKIs (pyrotinib, lapatinib, neratinib, etc.) were screened. Studies had to satisfy the following criteria: i) randomized or non-randomized controlled trials, ii) at least one treatment group received an anti-HER2 agent, iii) available information of any efficacy end-point. A network meta-analysis with a frequentist framework using random-effects model was used to pool direct and indirect evidence. Pathologic complete response (pCR) were the efficacy end-points of interest, and selected safety end-points were also analysed. Results: A total of 5885 published manuscripts were identified, and 19 studies including 6517 patients were finally included in our analysis. and 19 different regimens were evaluated. Dual anti-HER2-therapy, trastuzumab with pertuzumab or tyrosine kinase inhibitors, combined with chemotherapy was significantly superior to trastuzumab or TKIs and chemotherapy in terms of pCR (OR=2.20, 95%CI=1.92-2.52). In the comparison of dual-target treatment regimens, the efficacy of pyrotinib plus trastuzumab combined chemotherapy was superior to that of pertuzumab plus trastuzumab combined chemotherapy (OR=1.20, 95%CI=0.85-1.70), but the difference was not statistically significant. In addition, compared with pertuzumab combined with trastuzumab and chemotherapy, there was no significant difference in the efficacy aspect of TKIs combined with trastuzumab and chemotherapy (OR=1.15, 95%CI=0.88-1.51).

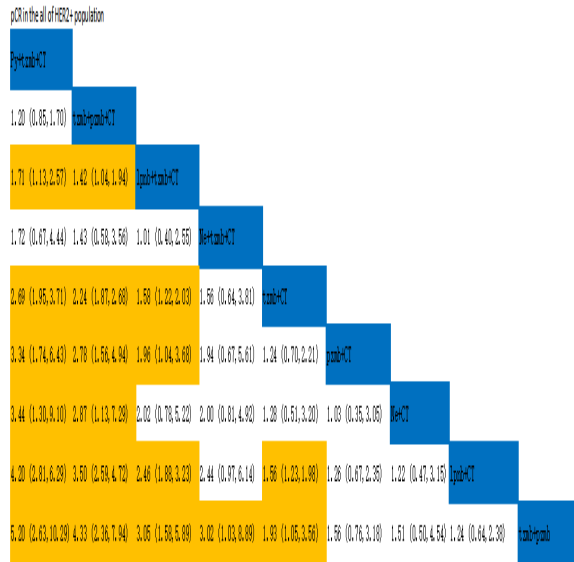
Conclusion: For the selection of neoadjuvant treatment for HER2-positive early or locally advanced breast cancer, trastuzumab plus pertuzumab combined with chemotherapy is still the preferred strategy at present. As our study showed that pyrotinib combined with trastuzumab and chemotherapy maybe could provide another option for neoadjuvant target therapy for HER2-positive breast cancer. **Keywords:** breast cancer, HER2-positive, neoadjuvant, network meta-analysis, target therapy.

Characteristics of eligible studies.

Publication	No. Of pts (n)	Clinical stage	NAC	Neo-adjuvant Anti-HER2	Arm (n)	pCR (%)	Duration (week)
ZHENG Xiangjin	2021	92	T2-T3N2/3,AM0 T4,any N,AM0	TCb	tzmb-Py	1.6	7
Xiaoyun Mao	2022	97	II-III	TCb	tzmb	1.8	4
				AC-T/T-AC	tzmb-Py	30	22
				T	tzmb-Py	29	13
				T	tzmb-Py	23	10
				T	tzmb-Py	178	73
				T	tzmb	177	39
				T	tzmb-Py	65	35
				T	tzmb-pzmb	198	112
				T	tzmb	284	93
				T	tzmb-Py	63	40
				T	tzmb-pzmb	50	27
				T	tzmb	53	14
				T	tzmb-pzmb	107	49
				T	tzmb	107	31
				T	tzmb	107	31
				T	pzmb	96	23
				T	tzmb-pzmb	107	18
				T	tzmb-pzmb	219	86
				T	tzmb	110	24
				T	tzmb-pzmb	399	227
				T	tzmb	399	140
				T	tzmb-pzmb	52	33
				T	tzmb	95	41
				T	tzmb-pzmb	170	100
				T	tzmb	807	271
				T	tzmb-pzmb	148	106
				T	tzmb-pzmb	93	41
				T	tzmb-pzmb	94	49
				T	tzmb-lpnb	119	60
				T	tzmb	117	51
				T	lpnb	62	17
				T	tzmb	48	23
				T	lpnb	51	12
				T	tzmb	301	93
				T	lpnb	308	70
				T	tzmb-lpnb	48	27
				T	tzmb	52	27
				T	lpnb	32	8
				T	tzmb-lpnb	148	68
				T	tzmb	140	40
				T	lpnb	130	30
				T	tzmb-lpnb	171	103
				T	tzmb	178	87
				T	lpnb	171	81
				T	tzmb-lpnb	58	30
				T	tzmb	34	16
				T	lpnb	36	9
				T	tzmb-Ne	42	21
				T	tzmb	41	16
				T	Ne	42	14

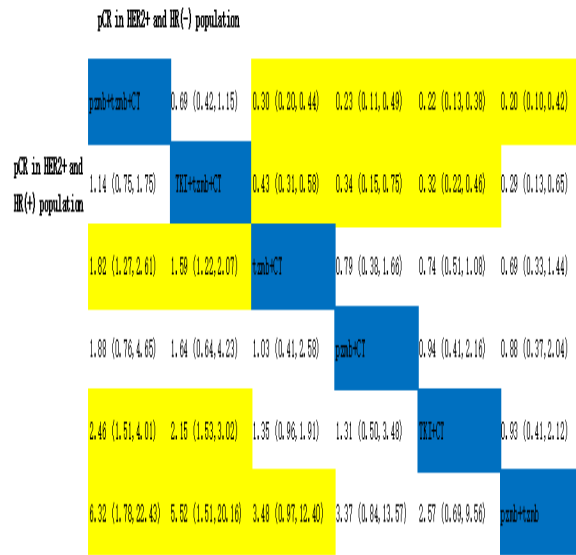
NAC=Neoadjuvant chemotherapy ; T=nab-paclitaxel,paclitaxel or Docetaxel ; F= fluorouracil ; E=epirubicin ; A=doxorubicin ; C=cyclophosphamide ; Cb=carboplatin ; tzmb=trastuzumb ; pzmb=pertuzumab;Py=pyrotinib ; lpnb=lapatinib ; Ne=neratinib.

Cross-comparison odds ratios (ORs) and their respective 95% CIs for pCR among different experimental arms.



CT=chemotherapy ; tzmb=trastuzumb ; pzmb=pertuzumab;TKI=tyrosine kinase inhibitors ; Py=pyrotinib ; lpnb=lapatinib ; Ne=neratinib.

Cross-comparison odds ratios (ORs) and their respective 95% confidence intervals (CIs) for pathologic complete response (pCR) in HR-positive and HR-negative subgroups.



CT=chemotherapy ; tzmb=trastuzumab ; pzmb=pertuzumab;TKI=tyrosine kinase inhibitors ; Py=pyrotinib ; lpb=lapatinib ; Ne=neratinib.

PO2-01-05

Neoadjuvant pyrotinib plus trastuzumab, and chemotherapy in patients with HER2-positive early breast cancer: a real-world study

Presenting Author(s) and Co-Author(s):

J. Zhou. Department of Breast Cancer, The first people's hospital of lianyungang, Lianyungang, Jiangsu, China (People's Republic)

R. Wang. Department of Breast Cancer, The first people's hospital of lianyungang, Lianyungang, Jiangsu, China (People's Republic)

Background Pyrotinib is a new oral, irreversible pan-ErbB receptor tyrosine kinase inhibitor that targets human epidermal growth factor receptor 1 (HER1), HER2, and HER4. Previous studies have confirmed it combined with capecitabine is safe and well-tolerated in advanced breast cancer. And also PHEDRA trial had demonstrated the efficacy and safety of pyrotinib combined with trastuzumab and docetaxel neoadjuvant therapy early HER2-positive breast cancer. However, the efficacy of pyrotinib plus trastuzumab-based in real-world neoadjuvant therapy for early breast cancer is unknown. **Purpose** The present study aimed to explore the efficacy of pyrotinib-based in neoadjuvant therapy for early breast cancer in real-world. **Method** This is investigator-initiated phase 2 real-world study recruited eligible patients, aged 18–70 years with invasive carcinoma, cT2-3N0-3M0 stage, HER2-positive breast cancer. The patients received 400 mg pyrotinib orally once per day for 21 days and trastuzumab (8 mg/kg loading dose, 6 mg/kg maintenance dose) plus different standard chemotherapy, including six 21-day cycles of docetaxel (75 mg/m²) plus carboplatin (6 mg/mL/min), or four cycles of epirubicin (90 mg/m²) plus cyclophosphamide (600 mg/m²) and four cycles paclitaxel (80 mg/m²). The primary endpoint was to calculate the number of patients who achieved a pathological complete response (pCR, ypT0/is, ypN0). (ChiCTR2100052892). **Result** The results of the 23 patients were reported, The pCR of 12 (52.2%) patients, who reached the threshold for the design, was noted. The study is ongoing. The most frequent grade 3 to 4 adverse events were diarrhea (35.6%), which all the patients received primary prevention of diarrhea, leukopenia (44.8%), and anaemia (23.7%). However, no treatment-related deaths were recorded. **Conclusion** Previous studies have shown the efficacy and safety of pyrotinib plus trastuzumab and docetaxel in neoadjuvant therapy of HER2-positive early breast cancer. The current trial suggests that pyrotinib plus trastuzumab-based standard chemotherapy in real-world has promising efficacy and manageable toxicity in patients with HER2-positive early breast cancer in a neoadjuvant setting, the trial is ongoing, we will enroll more patients.

PO2-01-06

Prognostic value of residual disease (RD) biology and gene expression changes during the neoadjuvant treatment in HER2+ early-breast cancer (EBC).

Presenting Author(s) and Co-Author(s):

A. Fernandez-Martinez. 1 Lineberger Comprehensive Center, University of North Carolina, Chapel Hill, NC, USA. 2 Department of Genetics, University of North Carolina, Chapel Hill, NC, USA., United States

M. Tanioka. Medical AI project, Okayama University, United States

S. Gwe Ahn. 4 Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea., United States

P. Zagami. 1 Lineberger Comprehensive Center, University of North Carolina, Chapel Hill, NC, USA. 5 University of Milan, Milan, Italy., North Carolina, United States

T. Pascual. SOLTI Cancer Research Group, Barcelona, Spain /Department of Medical Oncology, Hospital Clínic de Barcelona, Spain / Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

M. Rediti. 9 Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B), Université Libre de Bruxelles (ULB), Brussels, Belgium., Belgium

G. Tang. NRG Oncology Statistics and Data Management Center Department of Biostatistics, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

K. Hoadley. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, United States

D. Venet. Breast Cancer Translational Research Laboratory J-C Heuson, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

N. Rashid. Biostatistics, lineberger cancer center, university of North Carolina, Chapel Hill, United States

P. Spears. University of North Carolina, Chapel Hill, North Carolina, United States

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

J. Huober. Kantonsspital St.Gallen, Brustzentrum, Departement Interdisziplinäre medizinische Dienste, St. Gallen, Switzerland

P. Rastogi. UPMC Hillman Cancer Center and NRG Oncology, Pittsburgh, Pennsylvania, United States

M. Islam. 15 Genomics and Epigenomics Shared Resource (GESR), Georgetown University Medical Center, Washington, DC, USA., United States

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

A. Llombart-Cussac. 17 Medical Oncology Department, Hospital Arnau de Vilanova, Valencia, Comunidad Valenciana, Spain

S. Swain. Georgetown University Medical Center, Lombardi Comprehensive Cancer Center and MedStar Health, Washington, DC, USA, United States

C. Sotiriou. Breast Cancer Translational Research Laboratory J.-C. Heuson, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Not Applicable, Belgium

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

C. Perou. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA, United States

L. Carey. UNC-Lindberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

Title Prognostic value of residual disease (RD) biology and gene expression changes during the neoadjuvant treatment in HER2+ early-breast cancer (EBC). **Background** In HER2+ EBC, neoadjuvant trastuzumab-based therapy is the standard of care, with adjuvant therapy determined by whether residual disease (RD) is present. Patients (pts) with RD have significantly higher relapse rates than pts with pathologic complete response. Differences in tumor and immune biology between pre-treated and post-treated tumors after HER2-blockade have been described, but little is known about how these changes can affect long-term outcomes or can be leveraged to tailor adjuvant treatment. Here we evaluate the biology of RD using gene expression analyses of pre- and post-treated HER2+ tumors, and their prognostic value to predict event-free survival (EFS) in a pooled analysis of 4 neoadjuvant studies in which single-agent trastuzumab or combined with lapatinib was explored, with and without chemotherapy: CALGB 40601 (Alliance), PAMELA, NeoALTTO, and NSABP B-41. **Methods** Gene expression profiling by RNA sequencing was assessed on 497 pre-treated samples from pts with RD, and on pre-treated and RD in 171 tumor pairs. Intrinsic subtypes and 22 tumor and immune gene expression signatures (GESs) were evaluated. We studied and compared the association of gene expression biomarkers with EFS in different cohorts and time points, including when GESs were calculated at baseline (N=497), in the 171 paired baseline and RD samples, and the nature of biomarker changes during neoadjuvant therapy. Association between GESs and EFS was explored by uni- and multivariable Cox regression models adjusted by clinical parameters (i.e., study, treatment arm, hormone receptor status, clinical tumor size, and clinical node involvement), and the performance of the models was assessed by the c-index. **Results** In 497 baseline untreated samples from pts with RD after neoadjuvant therapy (N=497), intrinsic subtypes were significantly associated with EFS (log-rank [LR] P 0.007), with Luminal A showing the best prognosis and Basal-like the worst. Among 171 paired tumors, HER2-Enriched tumors were more common in baseline (50.3%) with change to Normal-like (49.7%) and Luminal A (18.7%) in RD (chi-square P < 0.001). This luminal phenotypic change was also confirmed by a significant reduction in the correlation to the HER2-Enriched centroid and a significant increase in the correlation to the Luminal A centroid between pre- and post-treated samples; a significant decrease in ERBB2 gene expression and the HER2 amplicon gene expression signature was also observed (Wilcoxon P < 0.001). At an immune GES level, we found a significant increase in B cell, CD8+ T cell, and NK cell signatures in RD specimens. In contrast, T reg GES was significantly downregulated (Wilcoxon P < 0.05). In uni- and multivariable models, immune GESs provided more prognostic information when assessed in RD samples. In contrast, subtype-related biomarkers provided more prognostic information at baseline. From all the multivariable models, the best (c-index= 0.78) included the IgG signature assessed in RD (adjusted hazard ratio 0.46, 95% CI 0.30-0.70, adjusted P 0.005). IgG signature levels (tertiles) in RD could also stratify pts into different groups based on prognostic information (EFS at 7 years: 69% in IgG low vs. 91% in IgG high, LR P 0.02). **Conclusions** In pts with HER2+ EBC and RD after neoadjuvant treatment with HER2-blockade, tumor-related biomarkers seem to provide more prognostic information when calculated at baseline, whereas immune biomarkers in the RD perform better for EFS prognostication. This finding could be relevant for implementing RD biomarkers in the clinic to stratify pts into different prognostic groups and tailor the post-operative treatment strategy.

Supported in part by U10 CA180821, U10 CA180882, R01-CA229409

<https://acknowledgments.alliancefound.org>

PO2-01-07

Real-world efficacy of dual HER2-blockade in combination with anthracycline-containing and anthracycline-free neoadjuvant treatment in early breast cancer (BC).

Presenting Author(s) and Co-Author(s):

B. Alonso de Castro. Complejo Hospitalario Universitario A Coruña, United States

C. Reboredo. Oncology Department-Universitary Hospital A Coruña, A Coruña, Galicia, Spain

L. Calvo. Oncology Department-Universitary Hospital A Coruña, A Coruña, Galicia, Spain

M. Perez-Lopez. Hospital Universitario A Coruña, A Coruña, Spain., A CORUÑA, Galicia, Spain

M. Gomez Randulfe Rodriguez. Hospital Universitario A Coruña, United States

S. silva diaz. Oncology Department-Universitary Hospital A Coruña, A Coruña, Galicia, Spain

I. Parajo Vazquez. Complejo Hospitalario Universitario A Coruña, United States

S. Antolin Novoa. Complejo Hospitalario Universitario A Coruña (CHUAC). GEICAM Spanish Breast Cancer Group., Spain

BACKGROUND: Neoadjuvant therapy with antiHER-2 blockade is the standard of care for HER-2 positive early BC. The objective of this treatment is tumor downstaging to increase resectability and pathological complete response (pCR), a reliable surrogate endpoint for survival. Adding Trastuzumab (T) to chemotherapy resulted in an improvement in pCR, however, resistance to this agent is common and the incorporation of Pertuzumab (P) to the neoadjuvant scene demonstrated an increase in pCR in the Peony (39.3% vs 21.8%) and Neosphere trials (45.8% vs 29%). Across all studies, pCR is even higher in patients (pts) with negative hormonal receptor (HR) status (50%-63%) (3, 4). Tryphaena and Berenice found low rates of cardiotoxicity with T-P combination. Recently, TRAIN-2 data showed that anthracyclines and platinum have a similar pCR (67% vs 68%), but febrile neutropenia and cardiotoxicity is higher in the anthracycline group, concluding that omitting this therapy might be a preferred approach in the presence of dual HER2 blockade. Our study investigated the pCR benefit of dual HER2 blockade with anthracyclines and platinum in HER2 positive early BC.

METHODS: We conducted a retrospective, unicenter, observational study of pts, treated with neoadjuvant T-P plus chemotherapy, in HER-2 positive early BC, between April 2015 and December 2022 at University Hospital A Coruña (Spain). The primary endpoint was total pCR in breast and axila (tpCR: ypT0/is ypN0). Secondary endpoints were: association between clinicopathological characteristics and pCR; and between cardiotoxicity and treatment pattern. Statistical analyses were conducted with Statistical Package for the Social Science (SPSS).

RESULTS: During the study period, from April 2015 to May 2022, 154 pts were enrolled. The median age was 51,3 years [range 26 – 799 years], all patients were female. Infiltrating ductal carcinoma was present in 92.2% pts, and 5.8% were inflammatory BC. At diagnosis, 11.7%, 61.7% and 26.6% had stages I, II and III, respectively, and 51.3% revealed axillary node involvement. Among observed cases, 94 (61%) were positive HR; 68 (45%) had histological grade 2 and 83 (53.9%) histological grade 3 tumors; and 151 pts (99.3%) presented a ki-67 level >20%. HER2 by immunohistochemistry (IHC) resulted in 3+ for 133 pts (86.9%) and in 2+ for 20 pts (13.1%), all of them with positive result by in situ hybridation (ISH). P-T were mostly combined with anthracyclines (64.9%). tpCR rate was 50.6%, and it was not significantly different according chemotherapy approach. tpCR was significantly higher among HR negative tumours (73.3%) compared with HR positive (36.2%) ($p= 0.001$), and in HER2 positive 3+ (55.6%) compared with HER2 positive 2+ (15%) tumours ($p= 0.001$). Achievement of tpCR was not significantly associated with tumor size, stage, histological grade and ki-67 level. Breast pCR was higher than tpCR (54.2%). 13 pts (8.4%) presented recurrence disease, in 76.9% of

cases was a metastatic relapse. Cardiotoxicity was low during all stages of treatment and was not significantly associated with chemotherapy pattern. CONCLUSIONS: Neoadjuvant T-P plus chemotherapy with either anthracyclines or platinum therapy, demonstrated same efficacy and cardiac safety in our real-world study. pCR rates are lower in positive HR and HER2 positive 2+, needing more investigation with combination strategies including hormone therapy. Our results are similar to data from randomized trials and other real-world efficacy studies, but we need more follow-up to identify late cardiotoxicity by anthracyclines and recurrences in positive HR tumors.

PO2-01-08

Differential HOXB13 gene expression and promoter methylation analysis in breast cancer

Presenting Author(s) and Co-Author(s):

N. Siuliukina. Biotheranostics, A Hologic Company, San Diego, California, United States

Y. Zhang. Biotheranostics, A Hologic Company, United States

K. Treuner. Biotheranostics, A Hologic Company, United States

M. Pegram. Stanford School of Medicine, United States

Background: The Breast Cancer Index (BCI) is a gene expression-based signature comprising two functional biomarker panels: the Molecular Grade Index (MGI) and BCI (H/I), which is a ratio of the HOXB13 and IL17BR gene expression. Several studies have shown that BCI (H/I) is a predictive biomarker for extended adjuvant endocrine therapy benefit in hormone receptor-positive (HR+) early-stage breast cancer. Molecular mechanisms underlying endocrine responsiveness remain to be fully explored. The objective of this analysis is to evaluate the correlation between gene expression and methylation in breast cancer patients displaying different HOXB13 mRNA expression levels from The Cancer Genome Atlas (TCGA) project. **Methods:** Data from methylation microarrays and mRNA sequencing were examined in combination with clinical metadata from 1,095 TCGA breast cancer patients. After removing outliers, HR+ samples were ordered based on their HOXB13 expression levels and the top 10% of samples (HOXB13-high; n=95) and bottom 10% (HOXB13-low; n=95) were selected for further analysis. Differentially expressed genes (DEGs) were determined by comparing all protein-coding genes between the HOXB13-high and HOXB13-low sets, based on an absolute log-fold change above 2 and a Benjamini-Hochberg adjusted p-value threshold of 0.01. Among the subset of samples with matching methylation data (n=60 for the HOXB13-high group and n=48 for the HOXB13-low group), hypo-methylated and hyper-methylated differentially methylated probes (DMPs) were identified based on at least 10% change of β (i.e., average promoter methylation) and a Benjamini-Hochberg adjusted p-value threshold of 0.01. Motif and transcription factor (TF) enrichment analyses were identified at a minimum incidence of 10 and a lower boundary of 1.5 for the 95% confidence interval of the odds ratio. **Results:** Our analysis identified a total of 613 DEGs between the HOXB13-high and HOXB13-low groups. Gene ontology analysis of DEGs revealed a statistically significant enrichment of genes associated with PTK6 regulated cell cycle, oncogene-induced cellular senescence, and regulation of T cell activation. Analysis of protein-protein interactions of differentially expressed genes revealed differences in key biological processes including changes in cell cycle regulation, p53 pathway, and IL-17 signaling. A total of 5,295 hyper-methylated and 580 hypo-methylated DMPs were discovered when comparing HOXB13-high and HOXB13-low samples. Changes in global methylation patterns enabled classification of breast cancer samples with high or low HOXB13 expression with an accuracy of 0.90. Reconstruction of gene regulatory networks from DNA methylation and transcriptome profiles elucidated significant pairs of DMPs and differentially expressed genes. Specifically, a total of 197 differentially expressed genes were attributed to hyper-methylated DMPs, including genes involved in response to estrogen, activation of HOX genes during differentiation, and drug-mediated inhibition of CDK4/6 activity. Additionally, 8 differentially expressed genes were attributed to hypo-methylated DMPs and were associated with proteasomal protein catabolic processes. Lastly, motif analysis of transcriptional factors for the hyper-methylated DMPs revealed enrichment of binding motifs attributed to FOXA1, ESR1, XBR1, and FOXP1. **Conclusion:** A comprehensive and comparative analysis of mRNA expression levels and methylation patterns between TCGA breast cancer samples with high

and low expression of HOXB13 revealed key signaling pathways and biological processes that may provide insights on the molecular mechanism of HOXB13 in the regulation of response to endocrine therapy in HR+ breast cancer.

PO2-01-09

Patient preferences for CDK4/6 inhibitor treatments in HR+/HER2- early breast cancer: a discrete choice survey study

Presenting Author(s) and Co-Author(s):

E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

M. Smith. Research Advocacy Network, United States

A. Guerin. Analysis Group, Inc, United States

D. Latremouille-Viau. Analysis Group, Inc, United States

N. Hazra. Analysis Group, Inc, United States

Y. Meng. Analysis Group, Inc, United States

W. Qu. Analysis Group, Inc, United States

R. Bellefleur. Analysis Group, Inc, United States

V. Ganapathy. Novartis Pharmaceuticals Corporation, United States

L. Santarsiero. Novartis Pharmaceuticals Corporation, United States

R. Morlock. YourCareChoice, United States

m. lustberg. Yale Cancer Center, New Haven, Connecticut, United States

Background: Patients (pts) with stage II/III HR+/HER2- early breast cancer (EBC) are at risk of recurrence that persists over years. The addition of a CDK4/6 inhibitor (CDK4/6i) to adjuvant endocrine therapy (ET) was investigated in monarchE, evaluating abemaciclib (ABE) in lymph node (LN)+ high-risk pts, and NATALEE, using ribociclib (RIB) in stage II/III disease, including pts with N0 disease. ABE was FDA approved in this indication in 2021, while NATALEE recently reported statistically significant iDFS results. Both efficacy and tolerability are relevant for pts treated in a curative setting. This prospective study evaluated the extent pts with EBC value different treatment (tx) attributes and how these may translate into preferences between the two CDK4/6i in the US.

Methods: A web-based discrete choice experiment survey was conducted among pts with EBC between Jan and May 2023 before NATALEE results were available. Eligible pts were adult women in a US clinical practice setting with self-reported stage II/III HR+/HER2- EBC +/- prior chemotherapy receiving only adjuvant ET at the time of survey, who completed curative surgery 1-3 years ago. Pts selected the scenario that best reflected their preferences from a series of choice cards, each displaying a pair of hypothetical tx profiles. A total of 8 attributes related to efficacy (5-year iDFS), adverse events (AEs), monitoring requirements, tx duration, and schedule were included (Table 1). Attributes were included based on an initial pilot qualitative assessment that selected efficacy and safety attributes most relevant to pts, clinical input, and differentiating features between CDK4/6i. A conditional logit regression model was used to estimate preference weights and relative importance (RI) of each attribute. Utility scores, summarizing overall preference for CDK4/6i tx profiles, were estimated from the model, and various scenarios were tested. Subgroup analyses by menopausal status and BC stage will be presented.

Results: 409 pts participated in the survey (median age, 53 years; White/Black/other race, 59%/23%/18%; BC stage II/III, 48%/52%; employed, 38%). Pt preferences for attributes that significantly impacted tx decision, in order of high to low RI, were higher efficacy (iDFS), lower

risk of diarrhea, lower risk of fatigue, shorter tx duration, and lower risk of venous thromboembolic events. Attributes based on monitoring or schedule, including number of blood tests, number of EKGs, and tx schedule, did not affect tx choice (Table 2). Overall utility scores were consistently higher for reconstructed tx profiles that resembled RIB features, including under conservative scenarios where efficacy of RIB was assumed to be equivalent or lower than that of ABE.

Conclusions: This study showed that, driven by strong preference for lower risk of AEs, pts with HR+/HER2- EBC prefer tx profiles that more closely resemble the clinical experience of receiving RIB. These pt preferences are important for shared decision making when discussing the addition of a CDK4/6i to adjuvant tx for eligible pts with HR+/HER2- EBC.

Discrete Choice Experiment Attributes and Levels

Table 1: Discrete Choice Experiment Attributes and Levels

Attributes	Levels
Efficacy	75% 80% 85% 90%
Thromboembolic event	1% 3%
Diarrhea	10% 75%
Fatigue	10% 40%
Number of blood tests	Biweekly (first 2 months), monthly (next 2 months) Biweekly (first 2 months), monthly (next 4 months)
Number of EKGs	0 3 in the first month
Tx duration	2 years 3 years
Tx schedule	Once daily, with a 1-week break each month Twice daily

EKG, electrocardiogram; tx, treatment.

Estimated Preference Weight and Relative Importance

Table 2: Estimated Preference Weight and Relative Importance

Attributes	Preference weight	Relative importance, %
Efficacy	8.34*	33
Diarrhea	-1.50*	26
Fatigue	-1.77*	14
Venous thromboembolic event	-15.45*	8
Tx duration, years		
2 ^a		
3	-0.46*	12
Number of blood tests in first 6 months		
4 ^b		
6	0.12	3
Number of ECGs in first month		
0 ^b		
3	0.09	2
Tx schedule		
Once daily, intermittent ^c		
Twice daily, continuous	-0.03	1

EKG, electrocardiogram; tx, treatment.
^a Significant at 5% level. ^b Reference group.

PO2-01-10

21-Gene Recurrence Score Index (ONCOTYPE DX) as a predictive biomarker for neoadjuvant chemotherapy response and outcome in patients with HR+HER2- breast cancer

Presenting Author(s) and Co-Author(s):

- A. Gasol Cudós. Hospital Universitari Arnau de Vilanova de Lleida, United States
- S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain
- N. Tuset Der-Abraín. Hospital Universitari Arnau de Vilanova de Lleida, United States
- F. Vilardell Villellas. Hospital Universitari Arnau de Vilanova de Lleida, United States
- L. Arbones Cid. Hospital Universitari Arnau de Vilanova de Lleida, United States
- J. Melé Olivé. Hospital Universitari Arnau de Vilanova de Lleida, United States
- C. Canosa Morales. Hospital Universitari Arnau de Vilanova de Lleida, United States

Background: Hormone receptor positive (HR+), HER2- early stage breast cancer (EBC) has shown lower response to neoadjuvant chemotherapy (NCT) compared with other clinicopathologic subtypes. ONCOTYPE DX may help inform systemic treatment decisions for EBC and predicting likelihood of pathological complete response (pCR) or chemosensitivity. We analyze the pathologic response according ONCOTYPE RS and their prognostic value.

Methods: We included a serie of 139 consecutive patients with high clinical risk factor with criteria to received NCT than have performed an ONCOTYPE DX test previous to start NCT. The median age was 51 years with 65 patients (47%) less than 50 years. Median initial tumoral size was 25 mm (9-97), T1: 35%, T2: 51% and T3: 14%. 70 patients (50%) have initial axillary node involvement. Median ONCOTYPE DX score was 29 (12 – 76) , RS < 25 in 36% and RS < 30 in 54%. Complete pathologic response (pCR) was found in 35 patients (25%), and by RCB was: RCB:0 23%, RCB-1 18%, RCB-2 24% and RCB-3 34%.

Results: pCR score was correlated with ONCOTYPE DX (pearson : p:0,001) , patients with ONCOTYPE RS score superior to 30 has a total of 37% of pCR in contrast to a 14% in patients with ONCOTYPE RS score less than 30. Median follow-up was 32 months (5 -100). The rate of recurrence was similar independently the ONCOTYPE RS score (12% < 30 ; 15% >30) , but patients with ONCOTYPE RS < 30 with achieve pCR had better prognostic compared to patients that not achieve pCR (0% vs 14%). Patients with ONCOTYPE RS > 30 tumors that had a pCR the recurrence rate was 8% compared to 20% in patients with non pCR.

Conclusions: These data suggest ONCOTYPE DX predicts pCR in HR+HER2- BC patients, especially in patients with a RS superior to 30 with an high rate of pCR of 37%. Patients with ONCOTYPE DX less than 30 that achieved pCR had the better outcomes and patients with ONCOTYPE DX superior to 30 that not achieved pCR had the worst outcomes with a total of 20% of recurrence. ONCOTYPE DX predicts the possibility of achieve a pCR and patients with a high ONCOTYPE DX RS score with residual disease have a high recurrence despite receiving treatment with chemotherapy, which requires a better adjuvant treatment, possibly with CDK 4/6 cyclin inhibitors.

PO2-01-11

Demographic, Lifestyle, and Clinical Factors Associated with Early vs. Late Recurrence among Women with Early-Stage Estrogen Receptor-Positive Breast Cancer in the Prospective Pathways Study

Presenting Author(s) and Co-Author(s):

A. Chua. Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY, Amherst, New York, United States

H. Sheng. Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

M. Kwan. Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States

I. Ergas. Division of Research, Kaiser Permanente Northern California, United States

J. Roh. Division of Research, Kaiser Permanente Northern California, United States

C. Laurant. Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States

T. Khoury. Department of Pathology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

S. Gomez. Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, United States

C. Ambrosone. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

L. Kushi. Division of Research, Kaiser Permanente Northern California, United States

S. Yao. Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

Background: Although women diagnosed with early-stage estrogen receptor (ER)-positive breast cancer generally have a favorable prognosis, they face a lingering risk of late recurrence that can occur years to decades after diagnosis. Relatively little is known about the demographic, lifestyle, or clinical factors associated with the risk of late recurrence, or whether the associations differ between early vs. late recurrence.

Methods: We performed a comprehensive analysis of factors related to early vs. late recurrence in early-stage ER-positive breast cancer in the Pathways Study, an established prospective cohort of women diagnosed with invasive breast cancer at Kaiser Permanente Northern California (KPNC) between 2006 and 2013. Recurrences were identified through monthly searches of the KPNC Cancer Registry, follow-up interviews with participants, and confirmation with electronic medical records. For this analysis, 2,473 women with stage I-II B, ER-positive breast cancer were included, with ascertainment of recurrence and death through December 31, 2021. Univariate analysis and multivariable Cox regression models were used to examine the factors associated with early (< 5 years since diagnosis) and late (\geq 5 years since diagnosis) recurrence.

Results: The median age of diagnosis was 57 (\pm 10) years, with 35% diagnosed before menopause. While 64% of patients self-reported as White, 16% identified as Asian, 6% Black, 12% Hispanic, and 2% other ethnicity. After a median 13.3 (range: 0.6-16.8) years of follow up, a total of 341 (13.8%) recurrences occurred, with 158 before and 181 at or after 5 years from

diagnosis. Approximately a third of recurrences were local or regional and the other two thirds were distant. In univariate analysis, increasing stage and tumor grade were associated with higher risk of both early and late recurrence ($p < 0.05$). Progesterone receptor (PR) negativity was associated with only early (hazard ratio [HR]=1.49, 95% confidence interval [CI] 1.06-2.09) but not late recurrence (HR=0.90, 95% CI 0.63-1.28). In unadjusted models, receiving lumpectomy (vs. mastectomy), chemotherapy, radiation therapy, or endocrine therapy were associated with lower risk of both early and late recurrence. Among the demographic and lifestyle factors examined, postmenopausal status at diagnosis was associated with lower risk of early (HR=0.69, 95% CI 0.51-0.96) but not late recurrence (HR=1.00, 95% CI 0.73-1.36). No association was found with body mass index, socioeconomic measures (education, income, employment, marital status), smoking, alcohol intake, or physical activity assessed at the time close to diagnosis. Notably, minoritized racial/ethnic groups all had higher risk of early recurrence than White women (Asian: HR=1.76, 95% CI 1.16-2.66; Black: HR=2.33, 95% CI 1.38-3.93; Hispanic: HR=1.80, 95% CI 1.15-2.82), but no association was found with late recurrence (Asian: HR=0.99, 95% CI 0.65-1.51; Black: HR=0.80, 95% CI 0.41-1.58; Hispanic: HR=0.80, 95% CI 0.48-1.33). In multivariable Cox models adjusted for age, cancer stage, grade, PR status, surgery, radiation therapy, chemotherapy, and endocrine therapy, the trend of higher risk of early recurrence among minoritized racial/ethnic groups remained, although the association remained significant only in Black women (HR=1.89, 95% CI 1.08-3.31).

Conclusion: Most histopathological features and cancer treatment modality had similar impact on early vs. late recurrence among women with early-stage ER-positive breast cancer, although PR negativity might be an adverse risk factor for early recurrence only. The findings of higher risk of early but not late recurrence among Asian, Black, and Hispanic relative to White women provide some novel data on the racial/ethnic disparities of prognosis for ER-positive breast cancer and may warrant further investigation.

Financial Disclosure: The authors declare no financial conflict of interest related to this work.

PO2-01-12

Preoperative cryoablation in 52 Her2- Luminal invasive ductal carcinomas \leq 2cm. Analysis of the tumor specimen.

Presenting Author(s) and Co-Author(s):

M. Roca Navarro. Hospital Universitario La Paz, United States
P. Zamora. Hospital Universitario La Paz, Madrid, Spain, Madrid, Spain
Y. Navarro Monforte. Hospital Universitario La Paz, United States
D. Garrido Alonso. Hospital Universitario La Paz, United States
V. Córdoba Chicote. Hospital Universitario La Paz, United States
T. Diaz de Bustamante Durban. Hospital Universitario La Paz, United States
J. Oliver Goldaracena. Hospital Universitario La Paz, Madrid, Spain
L. Yebenes Gregorio. Hospital Universitario La Paz, United States
C. Marti. Hospital Universitario La Paz, United States
J. Sanchez-Mendez. La Paz University Hospital/ La Paz Institute for Health Research – IdiPAZ / Universidad Autónoma - Madrid (Spain), United States
E. Moreno. Hospital la Paz, Madrid, Madrid, Spain
L. Frías Aldeguer. Hospital Universitario La Paz, United States
A. Loayza Galindo. Hospital Universitario La Paz, United States
A. Berjón García. Hospital Universitario La Paz, United States
M. Melendez Gisper. Hospital Universitario La Paz, United States
C. Martín Hervás. Hospital Universitario La Paz, United States
L. Miralles. Hospital Universitario La Paz, United States
C. Escabias del Pozo. Hospital Universitario La Paz, United States
Y. Abadi. Hospital Universitario La Paz, United States
E. York pineda. Hospital Universitario La Paz, United States
G. Garzón Moll. Hospital Universitario La Paz, United States
D. Hardisson Hernáez. Hospital Universitario La Paz, United States
A. Hernández Gutiérrez. Hospital Universitario La Paz, United States
C. Casado Sánchez. Hospital Universitario La Paz, United States
V. Martínez Marín. Hospital Universitario La Paz, United States
S. zarbakhsh. Hospital Universitario La Paz, United States
J. Gomez Ramirez. Hospital Universitario La Paz, United States

Objective: 1st: Assess the presence of residual infiltrating component in the surgical specimen of patients with Luminal Her2- tumors \leq 2cm and ultrasound-negative axilla, following ultrasound-guided cryoablation. 2nd: Demonstrate that preoperative seed placement prior to cryoablation does not interfere with tumor cell elimination by freezing. Methods: Between April 2021 and April 2023, we performed preoperative cryoablation on 52 patients aged 53 to 79 years (mean 64) with 52 unifocal invasive ductal carcinomas (IDC) measuring 4 to 20 mm (mean 10), low grade (24 G1, 28 G2), 31 Luminal A and 21 B, Ki67 between 3 and 30% (mean 13). On ultrasound, all IDCs were visible and axilla-negative. 26 of them (50%) were referred

from the screening program of the Community of Madrid. The tumor-to-skin surface distance ranged from 2 to 18 mm (mean 9 mm). All patients underwent mammography-tomosynthesis, staging, and biopsy under ultrasound guidance. The minimum time elapsed until surgery was 6 days, and the maximum was 78 days (mean 22). All patients underwent mammography-tomosynthesis, staging, and biopsy under ultrasound guidance. MRI was performed to rule out extensive intraductal component in 17 out of 20 patients with associated intraductal carcinoma (IDC) in the diagnostic biopsy. Preoperative marking with ferromagnetic seed placement was performed in all cases prior to cryoablation, using a single dose of anesthesia and through the same skin access. We used the ICEfx Galil Boston Scientific cryoablation system with 17G or 14G needles, applying the standard triple-phase protocol: freezing-passive thawing-freezing for approximately 40 minutes. The correct placement of the seed was subsequently confirmed by mammography. Results: There were no significant complications in any case. Out of 52 low-risk unifocal IDCs: -32 were pure IDCs (without associated intraductal component in diagnostic biopsy): no residual IDC was identified in the tumor specimen. -20 were mixed IDCs (with associated IDC in the diagnostic biopsy): *In 4 cases, residual IDC was found in the surgical specimen, with some foci of IDC remaining at the periphery of the post-cryoablation necrosis. *In 8 patients, foci of IDC were detected distant from the cryoablation zone. The pathologist determined that all samples had tumor-free margins. Conclusions: Cryoablation is effective in 100% of cases for pure infiltrating tumors \leq 2cm. The presence of scattered IDC nests away from the cryoablation zone or at the margin of fat necrosis does not indicate technique failure, as all surgical specimens were determined to have tumor-free margins by the pathologist. For mixed infiltrating tumors, the ice ball should broadly cover the tumor size estimated by ultrasound and MRI. Standard adjuvant treatment will equalize the risk of recurrence with conventional lumpectomy.

Table 1: 52 cases IDC unifocal \leq 2cm

Age (years)	
Mean (range)	64 (50-79)
Median \pm SD	64,5 \pm 7,65
Tumor grade	
Low (G1)	24 (46%)
Moderate (G2)	28 (54%)
HR status	
Estrogen Receptors positive (ER+)	52(100%)
Progesteron Receptors positive (PR+)	46 (88%)
Her2 negative (Her2-)	52(100%)
Ki 67	
Mean (range)	13 (3-30%)
Subtype	
Luminal A	32
Luminal B	20
Tumor size by ultrasound (mm)	
Mean (range)	9,9 (4-20)
Median \pm SD	9 \pm 3,7
Cancer stage	
T1a \leq 5mm	5 (10%)
T1b >5mm-10mm	30 (58%)
T1c >10mm- \leq 20mm	17 (32%)
Distance to skin surface	
Mean	9,3mm (2-18)
Median \pm SD	9 \pm 3,3
Breast Laterality	
Right	30
Left	22
Screening Program (DEPRECAM)	26 (50%)
Adverse effects post-procedure	
Mild	3 (6%)
Time to surgery	
Mean	22 days (6-78)
Median \pm SD	18,5 \pm 14,3

Table 2: IDC Pure \leq 2cm. Table 3: IDC mixed: IDC+DCIs \leq 2cm

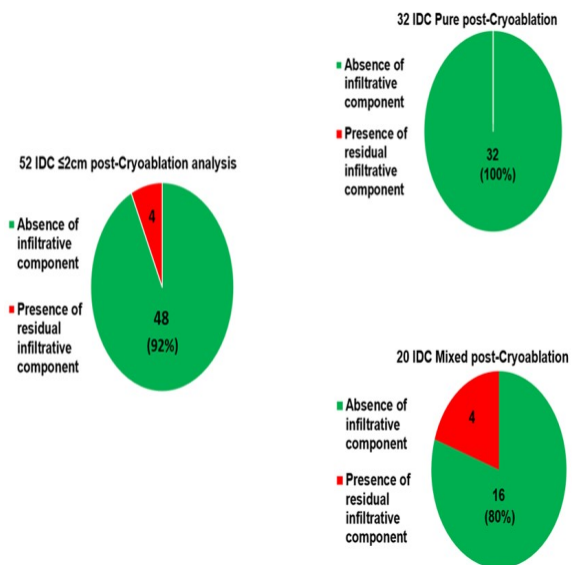
Tabla 2: IDC pure ≤ 2cm

IDC (pure) CNB specimen	32 (62%)
Tumor size	
Mean	9 mm (4-20)
Median ± SD	9 ± 3,7
Absence of residual infiltrating disease post-cryoablation	32 (100%)
DCIs nests post-cryoablation	3 (9%)

Tabla 3: IDC mixed: IDC+DCIs ≤ 2cm

IDC+DCIs CNB specimen	20 (38%)
Tumor size	
Mean	11 mm (5-19)
Median ± SD	10 ± 3,4
Absence of residual infiltrating disease post-cryoablation	16 (80%)
DCIs nests post-cryoablation	5 (25%)

Analysis of surgical specimen



PO2-01-13

Clinico-Pathological and Molecular Characterization of Early Hormone Receptor-Positive Breast Cancer in Young Women

Presenting Author(s) and Co-Author(s):

F. Muñoz-Carrillo. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain, Catalonia, Spain

J. Sola. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain ; Medical Oncology Department, Clínica Alemana, Santiago, Chile, United States

C. Crous. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain, United States

E. Sanfeliu. SOLTI Breast Cancer Research Group, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Faculty of Medicine and Pathology Department, Hospital Clínic of Barcelona, University of Barcelona, Barcelona, Spain., Catalonia, Spain

I. Garcia-Fructuoso. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain, United States

E. Seguí. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain and SOLTI Cancer Research Group, United States

T. Gorría. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain, United States

R. Gómez-Bravo. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain, United States

B. Adamo. Medical Oncology Department, Hospital Clínic de Barcelona ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain, Catalonia, Spain

T. Pascual. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; SOLTI Breast Cancer Research Group, Barcelona, Spain, Catalonia, Spain

O. Martínez-Sáez. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, United States

F. Schettini. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain and Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, United States

P. Rivera. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain, United States

R. Cayuela. Anesthesiology Department, Hospital Clínic of Barcelona, Barcelona, Spain, United States

M. Muñoz. SOLTI Breast Cancer Research Group, Hospital Clínic of Barcelona, Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research

Institute, Barcelona, Spain ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, Catalonia, Spain

N. Chic. Peter McCallum Cancer Centre, Melbourne, Australia ; SOLTI Breast Cancer Research Group, Barcelona, Spain, United States

M. Vidal. Medical Oncology Department, Hospital Clínic of Barcelona ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; SOLTI Breast Cancer Research Group ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Catalonia, Spain

Introduction Premenopausal women diagnosed with hormone receptor-positive (HR+)/HER2-negative (HER2-) early breast cancer (EBC) face a significantly higher risk of cancer recurrence and mortality compared to older women, particularly those diagnosed under the age of 40. The underlying causes behind this disparity remain largely unknown. **Material and methods** We retrospectively select tumour samples from patients (pts) diagnosed with HR+/HER2- EBC at Hospital Clinic (Barcelona, Spain) from May 2014 to March 2020 who had a PAM50/Prosigna assay (Veracyte) previously performed. This assay examines the expression of 50 genes involved in important breast cancer signaling pathways, as well as the intrinsic subtypes (IS) and the Risk of Recurrence (ROR) score. Our primary objective was to compare the distinct clinicopathological and molecular characteristics of HR+/HER2- EBC between two age groups: patients under 40 years old (Young EBC or YEBC) and those 40 years old and above (Older EBC or OEBC). Disease-free survival (DFS) was defined as the time between diagnosis and the first recurrence. Comparisons between groups were carried out using chi-square tests (categorical variables). Additionally, we performed a two-class unpaired Significance Analysis of Microarrays (SAM) with a false discovery rate (FDR) less than 5% to identify genes with significantly different expression between YEBC and OEBC. The statistical significance level was set at less than 0.05. **Results** A total of 441 tumor samples from 420 patients were included in the analysis, with 5% (22/441) corresponding to YEBC. With a median follow-up of 64.5 months, there were 20 breast cancer (BC) recurrences (4.8%), 12 second cancers (2.9%) and 5 BC-related deaths (1.2%), all occurring in the OEBC group. Table 1 provides an overview of the main clinico-pathological and molecular characteristics. YEBC tended to have larger tumors, with 45.5% (10/22) measuring over 2 cm compared to 36.1% (151/419) in OEBC ($p=0.376$). YEBC also had a higher proportion of grade 3 tumors (18.18% versus 3.1% in OEBC, $p=0.418$) and lower expression of estrogen receptor (ER) as determined by immunohistochemistry (mean of 72.28% vs 88.36%, $p=0.004$). Regarding the PAM50 IS, there was a difference observed between YEBC and OEBC ($p < 0.001$). Specifically, YEBC patients exhibited a tendency towards a higher proportion of Luminal B tumors (54.6% versus 38.9% in OEBC, $p=0.144$), as well as non-Luminal subtypes such as Basal-like (18.2% versus 0.95% in OEBC, $p < 0.001$) and HER2E (4.6% versus 0.7% in OEBC, $p=0.186$). YEBC tended to have higher ROR ($p=0.167$), and to receive chemotherapy in a higher proportion, especially in the intermediate-risk group ($p=0.004$). In YEBC tumours, SAM analysis ($p < 0.05$) showed an overexpression of genes mainly related with proliferation (i.e., RRM2, MELK, MIK67), cell cycle progression (i.e., KNTC2, CDC20, MYBL2) and apoptosis inhibition (i.e., BIRC5). In OEBC there were an overexpression of genes related with the oestrogen receptor-signalling pathway (i.e., ESR1, NAT1, FOXA1, PGR). Luminal B tumours in YEBC showed an upregulation of genes related to proliferation, migration, and poor prognosis (i.e., KRT17, KRT5) compared to OEBC. However, since there were no recurrences in the YEBC group, differences in terms of DFS between the groups could not be calculated. **Principio del formulario Final del formulario** **Conclusions** YEBC exhibited a more advanced stage and a more aggressive intrinsic phenotype compared to OEBC. Additionally, these tumors showed a tendency to upregulate genes involved in proliferation, cell cycle progression, and survival, while downregulating genes related to hormone signaling pathways. These molecular characteristics may help explain the

worse prognosis of YEBC compared to OEBC. However, further research is necessary to delve into the differential genomic characteristics that contribute to the unfavorable prognosis observed in patients diagnosed with HR+ EBC before the age of 40.

Key clinical and molecular features in 441 biopsies

	YEBC (n=22)	OEBC (n=419)	p-value
<i>Tumor size, cm</i>			
≤ 2	12 (54.55%)	267 (63.88%)	0.376
> 2	10 (45.45%)	151 (36.12%)	
Unknown	0 (0.00%)	1 (0.24%)	
<i>Lymph node status</i>			
Negative	17 (77.27%)	337 (80.43%)	0.904
Positive	5 (22.73%)	81 (19.35%)	
Unknown	0 (0.00%)	1 (0.24%)	
<i>Tumor grade</i>			
1	2 (9.09%)	142 (33.89%)	0.418
2	14 (63.64%)	236 (56.32%)	
3	4 (18.18%)	13 (3.10%)	
Unknown	2 (9.09%)	27 (6.44%)	
<i>HR-status</i>			
ER>10%	18 (81.82%)	403 (97.34%)	0.004
ER 1-10%	2 (9.09%)	5 (1.21%)	
RP>1%	19 (86.36%)	357 (86.23%)	1.000
RP negative	3 (13.64%)	53 (12.80%)	0.892
<i>Intrinsic subtypes</i>			
Luminal A	5 (22.7%)	249 (59.43%)	< 0.001
Luminal B	12 (54.55%)	163 (38.90%)	
HER2-Enriched	1 (4.55%)	3 (0.72%)	
Basal-like	4 (18.18%)	4 (0.95%)	
<i>ROR score</i>			
Low-risk	3 (13.64%)	150 (36.06%)	0.167
Intermediate-risk	9 (40.91%)	140 (33.65%)	
High-risk	10 (45.45%)	126 (30.29%)	
Unknown	0 (0.00%)	3 (0.72%)	
<i>Chemotherapy received</i>			
Low-risk	2 (9.09%)	14 (3.34%)	0.167
Intermediate-risk	8 (36.36%)	56 (13.37%)	0.004
High-risk	10 (45.45%)	116 (27.68%)	0.075
Luminal A	4 (18.18%)	46 (10.98%)	0.335
Luminal B	11 (50.00%)	136 (32.46%)	0.097

PO2-01-14

Development of Artificial Intelligence-based Machine Learning Models for Predicting Survival In Hormone-Receptor-Positive/HER2-Negative Early Breast Cancer undergoing Neoadjuvant Chemotherapy.

Presenting Author(s) and Co-Author(s):

L. Mastrantoni. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, United States

G. Garufi. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, United States

N. Maliziola. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, United States

E. Di Monte. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, United States

G. Arcuri. Università Cattolica del Sacro Cuore, United States

V. Frescura. Università Cattolica del Sacro Cuore, United States

A. Rotondi. Università Cattolica del Sacro Cuore, United States

G. Giordano. Università Cattolica del Sacro Cuore, United States

L. Carbognin. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, United States

A. Fabi. Precision Medicine in Breast Cancer, Fondazione Policlinico Universitario A. Gemelli, IRCCS Rome - Italy, Rome, Italy

I. Paris. Fondazione Policlinico Universitario A. Gemelli IRCCS Rome - Italy, United States

G. Franceschini. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Lazio, Italy

A. Orlandi. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, United States

A. Palazzo. Fondazione Policlinico Universitario A. Gemelli IRCCS Rome - Italy, United States

G. Scambia. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, United States

G. Tortora. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, United States

E. Bria. Università Cattolica Sacro Cuore Rome - Italy, United States

Background. In hormone-receptor positive (HoR)/HER2 negative early breast cancer (BC) multiple efforts have been made to predict disease recurrence and survival. Machine learning techniques have been used but few studies have looked into their applicability in predicting survival on the basis of clinico-pathological characteristics. The aim of this study was to evaluate a random survival forest model to predict the prognosis of this specific BC subtype. **Methods.** In this multicenter, retrospective study, patients who fulfilled the following inclusion criteria were included: (1) diagnosis of pathologically confirmed HoR-positive/HER2-negative invasive BC; (2) early or locally advanced, stage I-II-III (3) patients receiving neoadjuvant anthracycline and/or taxane-based chemotherapy, concurrently or sequentially; (4) patients undergoing surgery for primary BC. Survival endpoints were disease-free survival (DFS) and overall survival (OS). A random survival forest algorithm was used to develop the predictive model. Ten-fold cross-validation was performed. The C-index and the continuous rank

probability score (CRPS) were used to evaluate the discrimination of the predictive model, and a ROC curve was used to evaluate model precision. A cut point analysis based on maximally selected rank statistics was conducted to evaluate the best cut-off in the out-of-bag (OOB) mortality that could maximize DFS and OS prediction. Variable importance was assessed using Breiman-Cutler permutation importance. Results. Overall, 572 patients with HoR-positive/HER2-negative early BC were included. At univariate analysis age, T stage, N stage, grading, ER, PR and Ki67 were found to be significantly associated with DFS and ER, PgR, HER2, pCR ypT and ypN retained statistical significance at multivariate analysis. ER, pCR, pathological T and N stage were found to be significantly associated with OS at univariate and multivariate analysis. The following variables were included in the final model: menopausal status, age, histology, grade, clinical T/N, ER/PgR, Ki67 and HER2, pathological complete response (pCR), ypT and ypN. For DFS, the cross-validated C-index was 0.68 (95% CI 0.63-0.73) and the OOB CRPS was 0.15, with a OOB performance error of 0.31. The AUC calculated at 60 months was 0.91 (95% CI 0.88-0.94). Out-of bag RSF-based risk scores for individual patients were calculated and an optimal cut-off of 22.58 was identified. The HR between high risk and low risk group was 3.08 (95% CI 2.16-4.39, $p < 0.001$). For OS, the cross-validated C-index was 0.66 (95% CI 0.60-0.71) and the OOB CRPS was 0.17, with a OOB performance error of 0.35. The AUC calculated at 60 months 0.91 (95% CI 0.88-0.95). An optimal cut-off of 21.54 was identified and the HR between low risk and high risk group was 2.50 (95% CI 1.73-3.61, $p < 0.001$). For DFS, the most important variables were cN (9.00), ypN (7.35), ER (7.21), ypT (5.38), PgR (4.11), pCR (4.01) and age (2.82) while for OS the most important variables were cN (7.88), ER (5.37), PgR (3.61), age (3.37), pCR (2.80), ypT (2.64) and ypN (2.60). Discussion. We analyzed the performance of RSF in the prediction of DFS and OS based on the contribution of clinico-pathological features commonly available at the baseline of the NCT and post-surgery. By selecting patients with HoR-positive HER2-negative disease, we were able to show which clinico-pathological features within a ML model have greater predictive importance. The model could be integrated with image-based tumor and radiology features to improve its predictive accuracy. This retrospective multicenter study suggests that the combination of easily accessible clinico-pathological features within a ML model may reliably predict DFS and OS in the context of HoR-positive/HER2-negative BCs.

PO2-02-01

Online Virtual Patient Simulation CME Improves Clinical Decision-Making In The Management Of Patients With HR+/HER2- Early Breast Cancer

Presenting Author(s) and Co-Author(s):

N. Dorkhom. Medscape, United States

U. Patel. Medscape, United States

S. Baumhover. Medscape, United States

J. Cohen. Medscape, United States

Background:

The goal of this study is to assess whether an online, virtual patient simulation (VPS) continuing medical educational (CME) activity, improved the performance of oncologists in ordering appropriate diagnostic tests and managing and counselling patients with HR+/HER2- early breast cancer (EBC) at high risk of recurrence. Methods:

Two VPS educational activities were developed, the first VPS consisted of one patient case, focused on diagnosing patients with high risk of recurrence, while the other VPS consisted of 2 patient cases focused on the management and counselling of patients with HR+/HER2- EBC with high risk of recurrence. Physicians could make clinical decisions using complete open-field entries, based on the 3 performance based learning objectives. After each decision, learners received clinical guidance (CG) based on current evidence and expert recommendations. Pre- and post-CG clinical decisions were compared using a McNemar's test to determine P values ($P < .05$ is significant). Rationales for clinical decisions were collected in real time. Data were collected between November 2021 and August 2022 and are reported here as % point change per performance learning objective, P value.

Results:

A total of 922 oncologists were included in the analysis. There was a significant improvement across the 3 performance learning objectives analysed.

Please see table below for the results. Conclusions:

This analysis demonstrated the educational impact of an immersive, online VPS education which allowed physicians to improve evidence-based clinical decisions regarding diagnosing patients with HR+/HER2- early breast cancer at high risk of recurrence and managing and counselling them regarding their treatment.

Results

Results

	Pre-Activity Appropriate Clinical Decisions	Post-Activity Appropriate Clinical Decisions	P-value
Analyzing the risk factors that determine whether a patient with HR-positive, HER2-negative EBC is at high risk of recurrence (based on 1 clinical decision)	32%	57%	<.001
Preparing a management plan for patients with HR-positive, HER2-negative EBC at high risk of recurrence (based on 2 clinical decisions)	13%	46%	<.001
Counseling patients regarding potential outcomes and complications during management (based on 4 clinical decisions)	62%	76%	<.001

PO2-02-02

BREast Cancer Personalized NuTrition (BREACPNT): dietary intervention in HR+ breast cancer patients treated with endocrine therapy

Presenting Author(s) and Co-Author(s):

M. Rein. Weizmann institute of science, United States

M. Dadiani. Sheba Medical Center, Israel

A. Godneva. Weizmann institute of science, United States

M. Bakalenik-Gavry. Sheba Medical Center, United States

D. Morzaev-Sulzbach. Sheba Medical Center, United States

m. Lotan-Pompan. Weizmann institute of science, United States

A. Weinberger. Weizmann Institute of Science, United States

E. Segal. Weizmann Institute of Science, United States

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

BACKGROUND Breast cancer patients treated with adjuvant endocrine therapy commonly experience weight gain, which has been associated with low adherence to therapy and worse breast cancer prognosis. Dietary interventions are the first-line treatment for weight management in breast cancer patients and have beneficial results. Yet, the ability to maintain these outcomes requires further research. Here, we aimed to assess whether a personalized postprandial glucose targeting (PPT) diet is beneficial for weight management and metabolic health as compared with the recommended Mediterranean (MED) diet in this population. **DESIGN AND METHODS** BREACPNT is a phase-2 randomized trial in HR+ patients with breast cancer, treated with adjuvant endocrine therapy. We randomly assigned participants to follow a MED diet or a PPT diet for a 6-month dietary intervention and additional 6-month follow-up. The PPT diet is based on a machine-learning algorithm that integrates clinical and microbiome features to predict personal postprandial glucose responses (PPGRs). During the intervention, participants were monthly followed by a registered dietitian, they were additionally connected to a 2-week continuous glucose monitoring (CGM) on 3-timepoints, provided stool and blood samples and self-reported dietary intake using a smartphone application. **RESULTS** Among 127 randomized patients (mean \pm SD age 53 ± 10 years, BMI 28.6 ± 5 kg/m²), 103 (81%) completed the 6-month intervention period. A total of 94 participants provided 12-month follow-up data. Both interventions led to a significant weight loss. The PPT-diet showed numerically greater weight loss with median change of -1.45kg (IQR -3.75 – 0) compared to the MED-diet with median change of -1kg (IQR -3.2 - 0.1) , however this was not significant (p=0.9). Notably, at the 12-month time point , participants in the PPT arm were more likely to maintain the weight loss (median -1.2kg, IQR -4 - 0.1) compared to participants in the MED-arm (median -0.15kg , IQR -4.25 - 1.5), p=0.14) and had significantly improved waist circumference (median, IQR; -5 cm, -8-(-2) in the PPT arm, compared to -1cm, -6.5-3 in the MED arm, p=0.01). In terms of glucose metabolism the PPT-diet led to improved glycemic control as measured by CGM, with significant lower average postprandial glucose responses (PPGRs) and glucose coefficient of variation (CV) compared to the MED-diet arm (mean 6-month change in PPGR was 2.1 ± 7.5 mg/dL \times h for MED and -3.4 ± 5.6 mg/dL \times h for PPT, p< 0.001, and the 6-month mean change for CV was 0.15 ± 2.76 for MED and -1.37 ± 3.2 for PPT, p< 0.01). Within the entire cohort, participants who experienced the greatest weight loss (upper quartile) were more likely to be postmenopausal compared to participants in the lower quartile. Additionally, participants who

did not achieve weight loss (lower quartile) were significantly more likely to be treated with tamoxifen than AI ($p=0.015$). CONCLUSIONS In this dietary intervention in HR+ breast cancer patients, both PPT diet and MED diet led to weight loss and improved food quality, with a slight advantage to PPT diet. PPT diet additionally improved glycemic features as compared to MED diet, which are linked to lower risk of obesity and disease recurrence, suggesting an advantage in a glucose targeting approach. Premenopausal and Tamoxifen treated patients were less likely to lose weight through the intervention. These findings may have implications for dietary advice in clinical practice.

PO2-02-03

Clinical and pathological factors associated with Oncotype DX® 21-Gene recurrence score in patients diagnosed with early stage breast cancer in a low-middle income country

Presenting Author(s) and Co-Author(s):

C. Cavalcanti Gonçalves Ferreira. Beneficência Portuguesa de São Paulo, Brazil

J. Araujo. Hospital Beneficência Portuguesa, São Paulo, Brazil, Sao Paulo, Sao Paulo, Brazil

S. Brandão Rodrigues Moreira. Hospital Beneficência Portuguesa de São Paulo, United States

A. Buzaid. Centro Oncológico Antonio Ermírio de Moraes - Beneficência Portuguesa de São Paulo, United States

D. Gagliato. Hospital Beneficência Portuguesa, São Paulo, Brazil, Brazil

INTRODUCTION: Oncotype DX® recurrence score (ODX RS) is a 21-gene assay warranted to determine the the prognosis in patients with hormone receptor positive, HER-2 negative early stage breast cancer. In this context, the test is also predictive of benefit of adjuvant chemotherapy.^{1,2,3} **OBJECTIVES:** We aimed to correlate the clinical and pathological factors associated with Oncotype DX® 21-Gene in patients diagnosed with early stage Breast Cancer. Additionally, description of adjuvant treatment patterns and survival outcomes were described according to the Oncotype DX® 21-Gene result. **METHODS:** Data from medical records from a single center in Brazil were collected retrospectively from women over 18 years diagnosed with early breast cancer between 2012 and 2022. Included patients were diagnosed with stage T1-T2 breast cancer, hormone receptor positive, HER-2 negative, with up to three positive lymph nodes. All included patients had an Oncotype DX® test performed after definitive breast surgery. The ODX RS has been categorized into two levels according to menopausal status. Correlation between breast cancer recurrence and clinicopathological characteristics was done. The software SPSS was used for statistical analyzes with the significance of 0.05. **RESULTS:** From 197 patients, 20 have had breast cancer recurrence (10.15%) whom 10 were premenopausal and 10 were postmenopausal. The median ODX RS in these 20 patients was 15 (ranged from 9 to 31). The most common site of recurrence was breast and regional recurrence in 18 patients (90%). Adjuvant chemotherapy was omitted in 16 patients (80%) who have had breast cancer recurrence. Among premenopausal patients whose ODX RS was >20, 33 patients (91.66%) received adjuvant chemotherapy. Among postmenopausal patients whose ODX RS was >25, 19 (86.36%) received adjuvant chemotherapy. The probability of recurrence free survival was worse in premenopausal patients > 44-years-old compared to those with < =44 years-old ($p = 0.036$) and also worse in histological grade 3 tumors compared to grade 1 ($p=0.0048$). Tumor size >14 millimeters (mm) was correlated to worse recurrence free survival in premenopausal patients ($p=0.017$). Low estrogen and progesterone receptor was associated with a higher ODX RS ($p=0.0035$ and $p< 0.0001$, respectively) in premenopausal patients, but not associated with recurrence free survival. Clinicopathological characteristics and recurrence free survival correlation in postmenopausal patients were not significant. **CONCLUSION:** This retrospective analysis suggests that factors other than the Oncotype DX® score, such as age and grade contributed to worse survival outcomes among our patients population. Of note, age older than 44 years-old, histological grade 3 and tumor size >14 mm were associated with a higher probability of recurrence in premenopausal patients, despite the Oncotype DX® score. **REFERENCES:** 1. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* [Internet]. 2004;351(27):2817–26. Available from: <http://dx.doi.org/10.1056/NEJMoa041588>. 2. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant

chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med [Internet]. 2018;379(2):111–21. Available from: <http://dx.doi.org/10.1056/NEJMoa1804710>. 3. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. N Engl J Med [Internet]. 2021;385(25):2336–47. Available from: <http://dx.doi.org/10.1056/NEJMoa2108873>.

Table 1 – Clinical and pathological characteristics of 197 hormone receptor positive, HER-2 negative early breast cancer patients who did the Oncotype DX® 21-Gene Recurrence Score assay. Data from medical records collected retrospectively of women diagnosed with early breast cancer between 2012 and 2022 from a single center in Brazil.

Clinical characteristics	Clinical characteristics – description	N (%)
Breast cancer recurrence	Yes	20 (10.15%)
	No	177 (89.85%)
Recurrence site	Breast recurrence	12 (60%)
	Regional (regional lymph nodes)	6 (30%)
	Distance recurrence	2 (10%)
Menopausal status	Premenopausal	101 (51.27%)
	Postmenopausal	96 (48.73%)
Pathological tumor size (T stage)	pT1mic and pT1a	46 (23.35%)
	pT1b and pT1c	150 (76.14%)
	pT2	1 (0.51%)
Positive lymph node	Yes (01 lymph node)	22 (11.17%)
	Yes (02 lymph nodes)	2 (1.02%)
	Yes (03 lymph nodes)	1 (0.51%)
	No	172 (87.31%)
Histological grade	Grade 1	31 (15.74%)
	Grade 2	135 (68.53%)
	Grade 3	31 (15.74%)
Oncotype DX® 21-Gene Recurrence Score in premenopausal patients	RS <=20	65 (64.35%)
	RS >20	36 (35.64%)
Oncotype DX® 21-Gene Recurrence Score in postmenopausal patients	RS <=25	74 (77.08%)
	RS >25	22 (22.91%)
Adjuvant chemotherapy	Yes	59 (29.95%)
	No	138 (70.05%)
Chemotherapy regimen	TC x 6	33 (16.75%)
	TC x 4	14 (7.11%)
	AC-T	12 (6.09%)
Endocrine therapy	Aromatase inhibitor	83 (42.13%)
	Tamoxifen	111 (56.35%)
	No endocrine therapy	3 (1.52%)
Ovarian suppression in premenopausal patients	Yes	42 (41.58%)
	No	59 (58.42%)

Figure 1 – Probability of recurrence free survival in premenopausal patients according to age <=44 (blue line) or > 44-years-old (pink line). Data from medical records collected retrospectively of women with hormone receptor positive, HER-2 negative early breast cancer who did the Oncotype DX® 21-gene assay diagnosed between 2012 and 2022 from a single center in Brazil.

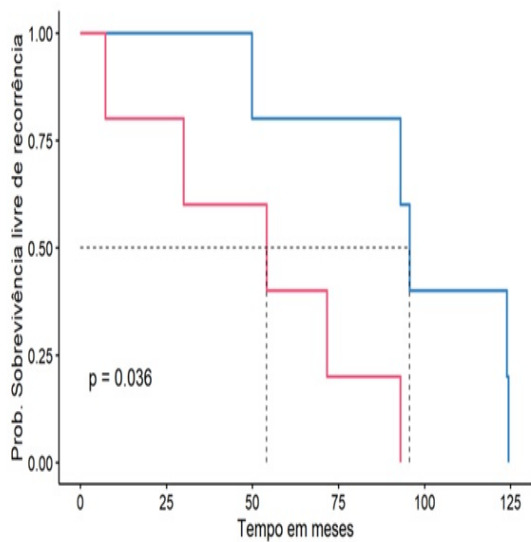
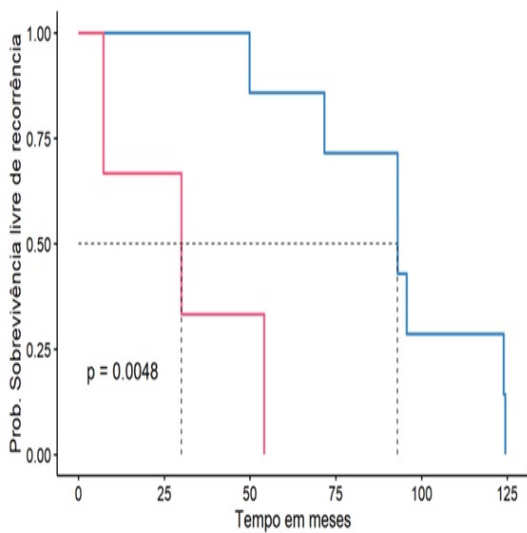


Figure 2 – Probability of recurrence free survival in premenopausal patients according to histological grade. Tumor with histological grade 1 (blue line) or histological grade 3 (pink line). Data from medical records collected retrospectively of women with hormone receptor positive, HER-2 negative early breast cancer who did the Oncotype DX® 21-gene assay diagnosed between 2012 and 2022 from a single center in Brazil.



PO2-02-04

The Impact of Statins on Breast Cancer Specific Mortality in a Diverse Patient Population with Stage I-III Hormone Receptor Positive, HER2 Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Sacks. Emory University / Winship Cancer Institute, Atlanta, Georgia, United States
M. Bliss. Emory University / Rollins School of Public Health, Atlanta, Georgia, United States
M. Streiff. Emory University / Rollins School of Public Health, Atlanta, Georgia, United States
L. Moubadder. Emory University, United States
M. Maliniak. Emory University, United States
T. Armidie. Emory University / Rollins School of Public Health, Atlanta, Georgia, United States
L. Collin. Huntsman Cancer Institute, University of Utah, United States
K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States
L. McCullough. Emory University, United States

Hormone receptor-positive (HR+), HER2 negative (HER2-) breast cancer has a long-term risk of recurrence, compared with other breast cancer subtypes, which ultimately impacts mortality outcomes. Although adjuvant endocrine therapy plays an integral role in risk reduction, disparities persist—with Black women experiencing higher mortality rates compared to White women. Multiple studies have demonstrated that statin use can lead to a reduction in breast cancer mortality, but there is limited information in relation to the impact of statins among diverse patient populations in the United States.

To assess whether statin use is associated with an improvement in breast cancer-specific mortality (BCSM), we conducted a large, observational study in women aged 66 and older diagnosed with Stage I–IIIC HR+, HER2- breast cancer between 2013 and 2017. We identified eligible women using the SEER-Medicare database and linked them to the BRIDGE (BReast cancer Investigation of Disparities in GEorgia) cohort, a survivorship cohort of the Georgia Cancer Registry. Patients needed to be continuously enrolled in Medicare Parts A, B, and D in the 12 months following a breast cancer diagnosis. We used Cox proportional hazards models to estimate the impact of statin use within 12 months of diagnosis on BCSM with adjustment for age, stage, and race using multivariable-adjusted hazard ratios (HRs).

A total of 2483 participants were identified, and of those, 303 (12.2%) were statin users, 383 (15.4%) were non-Hispanic Black women, and 1564 (63%) resided in census tract with greater than or equal to 10% poverty levels at the time of diagnosis. Distribution of age, stage, and race were similar between statin and non-statin users. Of the statin users, 41/303 (13.5%) were non-Hispanic Black women. The majority of statin users were prescribed lipophilic statins alone (169; 55.8%), and atorvastatin was the most commonly prescribed statin. There was no association between statin use and BCSM (HR 1.09; 95% CI 0.62-1.90) in the multivariable-adjusted model.

Although preliminary results suggest that there is no association between statin use and BCSM among women with Stage I–IIIC HR+, HER2- breast cancer, further analyses are planned to explore statin use as a time-varying exposure, which may provide additional insights into the potential relationship between statin use and BCSM. In addition, analyses examining potential heterogeneity by race, tumor and treatment characteristics, and comorbidities are forthcoming.

Given the low cost and relative accessibility of statins, we anticipate these findings will inform the clinical management of women with operable breast cancer, increasing parity in outcomes and potentially narrowing race disparities.

PO2-02-05

CDK4/6 inhibitor dalpiciclib combined with letrozole as neoadjuvant therapy in postmenopausal patients with hormone receptor-positive, HER2-negative stage II-III breast cancer: a single-arm exploratory trial

Presenting Author(s) and Co-Author(s):

L. Zhang. Breast Center, The Fourth Hospital of Hebei Medical University, China (People's Republic)

C. Yang. Breast Center, The Fourth Hospital of Hebei Medical University, China (People's Republic)

J. Ma. First Department of Breast Surgery, Tangshan People's Hospital, China (People's Republic)

Y. Li. Breast Center, The Fourth Hospital of Hebei Medical University, China (People's Republic)

R. Luo. Breast Center, Cangzhou Hospital of Integrated TCM-WM, China (People's Republic)

J. Han. Second Department of Breast Surgery, Affiliated Hospital of Hebei Engineering University, China (People's Republic)

X. Wang. Department of Breast Surgery, Affiliated Hospital of Hebei University, China (People's Republic)

Z. Zhang. Department of Breast Surgery, Affiliated Hospital of Hebei University, China (People's Republic)

L. Ma. Breast Center, The Fourth Hospital of Hebei Medical University, China (People's Republic)

H. Cai. Second Department of Breast Surgery, Tangshan People's Hospital, China (People's Republic)

X. Kong. Department of Breast Surgery, Xingtai People's Hospital, China (People's Republic)

Z. Wang. Third Department of Thyroid and Breast Surgery, Cangzhou Central Hospital, China (People's Republic)

X. Zhou. Department of Breast Surgery, Handan Central Hospital, China (People's Republic)

Y. Liu. Department of Pathology, The Fourth Hospital of Hebei Medical University, United States

J. Shi. The Fourth Hospital of Hebei Medical University, United States

Y. Zhang. Breast Center, The Fourth Hospital of Hebei Medical University, China (People's Republic)

M. Wang. Breast Center, The Fourth Hospital of Hebei Medical University, China (People's Republic)

J. Wang. Breast Center, The Fourth Hospital of Hebei Medical University, China (People's Republic)

C. Geng. Breast Center, the Fourth Hospital of Hebei Medical University, China (People's Republic)

Background: Patients with HR-positive, HER2-negative breast cancer respond poorly to neoadjuvant chemotherapy. The phase 3 DAWNA-1 and DAWNA-2 studies have proved that adding dalpiciclib (a CDK4/6 inhibitor) to endocrine therapy can significantly improve

progression-free survival in patients with hormone receptor (HR)-positive, HER2-negative advanced breast cancer. However, the evidence of dalpiciclib in the neoadjuvant setting is limited. This study aimed to explore the efficacy and safety of dalpiciclib plus letrozole as neoadjuvant therapy in patients with HR-positive, HER2-negative stage II-III breast cancer. Methods: In this multicenter, single-arm exploratory trial (NCT05512780), adult postmenopausal women with HR-positive (estrogen receptor >10%), HER2-negative stage II-III invasive breast cancer were enrolled. Patients received oral dalpiciclib (150 mg on days 1-21 of each 28-day cycle) and oral letrozole (2.5 mg once daily) for 4 cycles, followed by surgery. The primary endpoint was objective response rate (ORR), assessed by investigator according to the Response Evaluation Criteria In Solid Tumors version 1.1. Secondary endpoints included complete cell cycle arrest (CCCA, defined as Ki-67 < 2.7% on day 15 of the first cycle) rate, total pathological complete response (tpCR; ypT0/is ypN0) rate, residual cancer burden (RCB) 0-I rate, and safety.

Results: Between June 2022 and January 2023, 41 patients were screened at 9 sites, and 35 patients were enrolled and received at least one dose of study drug. The median age was 66 years (range, 52-83), and the median baseline Ki-67 level was 20% (range, 4%-40%). The majority of patients had T2 disease (65.7%), lymph node-positive disease (88.6%), and stage II disease (IIA: 45.7%; IIB: 40.0%). The ORR was 35.5% (11/31) at 8 weeks and 51.7% (15/29) at 16 weeks in patients with evaluable response. The CCCA rate was 70.0% (21/30) in patients with available data. Four patients refused surgery and chose to continue the drug therapy. Of 27 patients who had undergone surgery, one (3.7%) patient had tpCR and RCB 0. Of 35 patients, the most common adverse events were neutrophil count decreased (74.3%), white blood cell decreased (68.6%), anemia (34.3%), and fatigue (31.4%). The most common grade 3 or higher adverse event was neutrophil count decreased (45.7%). No febrile neutropenia or treatment-related deaths occurred.

Conclusions: This is the first prospective study of neoadjuvant dalpiciclib in patients with HR-positive, HER2-negative breast cancer. The findings suggest the promising tumor response to neoadjuvant dalpiciclib plus letrozole in postmenopausal patients with HR-positive, HER2-negative breast cancer, with a manageable safety profile. This combination can effectively suppress the tumor cell proliferation, as reflected by change in Ki-67 level.

PO2-02-07

**Clinicopathological Features and Prognostic Role of HER2 Low in Early Breast Cancer:
A real world study**

Presenting Author(s) and Co-Author(s):

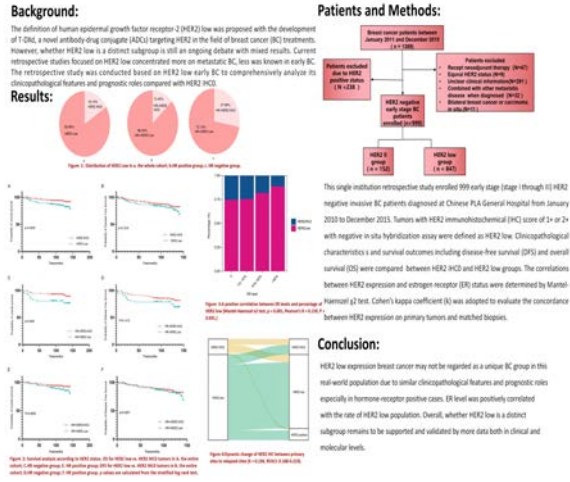
Z. Kong. Department of Medical Oncology, the First Medical Center, Chinese PLA General Hospital, United States

W. Zhao. Chinese PLA General Hospital, United States

Background: The definition of human epidermal growth factor receptor-2(HER2) low was proposed with the development of T-DXd, a novel antibody-drug conjugate (ADCs) targeting HER2 in the field of breast cancer (BC) treatments. However, whether HER2 low is a distinct subgroup is still an ongoing debate with mixed results. Current retrospective studies focused on HER2 low concentrated more on metastatic BC, less was known in early BC. The retrospective study was conducted based on HER2 low early BC to comprehensively analyze its clinicopathological features and prognostic roles compared with HER2 IHC0. Methods: This single institution retrospective study enrolled 999 early stage (stage I through III) HER2 negative invasive BC patients diagnosed at Chinese PLA General Hospital from January 2010 to December 2015. Tumors with HER2 immunohistochemical (IHC) score of 1+ or 2+ with negative in situ hybridization assay were defined as HER2 low. Clinicopathological characteristics and survival outcomes including disease-free survival (DFS) and overall survival (OS) were compared between HER2 IHC0 and HER2 low groups. The correlations between HER2 expression and estrogen receptor (ER) status were determined by Mantel-Haenszel χ^2 test. Cohen's kappa coefficient (k) was adopted to evaluate the concordance between HER2 expression on primary tumors and matched biopsies. Results: 999 patients were eligible for inclusion criteria, among which the percentages of HER2 low in the whole cohort, HR positive group and HR negative group were 83.6%, 86.54%, 72.14% respectively. It was observed the presence of a significant higher proportion of ER level > 10% ($p < 0.001$), PgR positive ($p < 0.001$) and more patients who received endocrine therapy ($p = 0.002$). In HR positive group, clinicopathological features were balanced between HER2 IHC0 and HER2 low. In HR negative group, HER2 low manifested a higher proportion of invasive ductal type ($p = 0.016$) compared with HER2 IHC0. Survival analysis showed a significantly longer OS in HER2 low BC than HER2 IHC0. (HR: 0.458, 95%CI: 0.262-0.800, $p = 0.0005$). Nevertheless, the independent role was not reached in DFS. When stratified by HR status, patients with HER2 low in HR positive group demonstrated a longer OS than HER2 IHC0 (HR: 0.55, 95%CI: 0.273-1.105, $p = 0.0385$). The same trend was observed in HR negative group (HR: 0.385, 95%CI: 0.158-0.939, $p = 0.0132$). Neither the HR positive group nor the HR negative group achieved significant DFS. Besides, a positive correlation was observed between ER status and the rate of HER2 low (Mantel-Haenszel c^2 test, $p < 0.001$, Pearson's $R = 0.159$, $P < 0.001$). No regularity of survival differences between HER2 IHC0 and HER2 low was found in each ER level in the exploratory study. Finally, 119 patients who developed relapsed or metastatic disease were identified, with the most prevalent metastatic site being bone (31.1%), following by lung (16.80%) and lymph node (13.44%). Among 52 patients with matched biopsy samples, dynamic changes of HER2 IHC status were confirmed in both primary and relapsed statuses, with an discordance rate of 28.84% ($K = 0.194$, 95%CI: 0.168-0.219). conclusion: HER2 low expression breast cancer may not be regarded as a unique BC group in this real-world population due to similar clinicopathological features and prognostic roles especially in hormone-receptor positive cases. ER level was positively correlated with the rate of HER2 low population. Overall, whether HER2 low is a distinct subgroup remains to be supported and

validated by more data both in clinical and molecular levels. Key words: HER2 low; Breast cancer; Clinicopathological Features; Prognosis; Molecular type
Clinicopathological Features and Prognostic Role of HER2 Low in Early Breast Cancer: A real world study

Clinicopathological Features and Prognostic Role of HER2 Low in Early Breast Cancer: A real world study
 Ziqing Kong, Li Jie, Weibing Zhang
 1 Medical School of Chinese PLA, Beijing, China 2 Department of Medical Oncology, the First Medical Center, PLA General Hospital

Clinicopathological Features and Prognostic Role of HER2 Low in Early Breast Cancer: A real world study

PO2-02-09

Pathological complete response to neoadjuvant systemic therapy and its predictive factors among early breast cancer subtypes: the emerging role of HER2

Presenting Author(s) and Co-Author(s):

M. Corianò. Breast Unit—Department of Medicine, The Royal Marsden NHS Foundation Trust, Sutton, London, UK, United Kingdom

N. Battisti. The Royal Marsden NHS Foundation Trust/ Breast Cancer Research Division – The Institute of Cancer Research, London, UK, England, United Kingdom

H. Aziz. Breast Unit - Department of Medicine, The Royal Marsden NHS Foundation Trust, United Kingdom, United States

N. Joharatnam Hogan. Breast Unit - Department of Medicine, The Royal Marsden NHS Foundation Trust, United Kingdom, United States

A. Musolino. University of Parma, United States

A. Ring. The Royal Marsden NHS Foundation Trust, Breast Unit - Department of Medicine, The Royal Marsden NHS Foundation Trust, London, UK/ Breast Cancer Research Division – The Institute of Cancer Research, London, England, United Kingdom

Purpose

Pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) for breast cancer (BC) is a prognostic factor for relapse-free and overall survival (OS). Despite recent therapeutic developments for early BC, there are still a significant proportion of patients who do not achieve pCR. In this study we established pCR rates in routine care and investigated possible predictive factors of pCR, including HER2 status.

Methods

We evaluated 980 stage I-III BC patients receiving NACT between 2013 and 2022. Patient characteristics, rates of pCR (ypT0-is ypN0), toxicities, treatment modifications and survival outcomes were recorded. Standard histopathological variables were recorded [with HER2-low status, defined as HER2 1+ on immunohistochemistry (IHC) or 2+ on IHC without in situ hybridization (ISH) gene amplification]. Overall survival (OS) and relapse-free survival (RFS) were calculated. Median follow-up time was 60.3 months (interquartile range 19.7-78.7).

Results

The mean age of the study population was 49.6 ± 11.2 years. 64% had stage II disease, 70.5% had grade 3 disease, and 90.5% had ductal histopathology. 34.6% had estrogen receptor (ER)-positive/HER2-negative, 27.1% had triple-negative (TN), and 38.3% had HER2-positive BC. 233 patients (23.8%) had HER2-low disease.

pCR rate was 35.8% in the overall population, 16.8% in ER-positive/HER2 negative BC, 32.7% in TNBC and 55.2% in HER2-positive BC.

pCR rate differed according to grade, histology, HER2 status, radiological and clinical response of disease ($p < 0.001$) and early discontinuation of NACT ($p = 0.001$), but not according to age, menopausal status, BRCA status, platinum use, NACT dose reduction or delays, neutrophils-to-lymphocytes, platelets-to-lymphocytes, or lymphocytes-to-monocytes ratios.

OS and RFS were better following pCR [HR 0.23 (95% CI, 0.14-0.38, $p < 0.001$) and HR 0.27 (95% CI, 0.18-0.40, $p < 0.001$), respectively].

Among HER2-negative BC patients (605, 61.7% of the entire cohort), there was a trend to lower pCR rate in HER2-low compared to HER2-negative (IHC 0) BC (19.7% vs 26.3%

respectively, $p = 0.06$). pCR rate was significantly lower in ER-positive/HER2-low compared to ER-positive/HER2-negative (IHC 0) BC (12.1% vs 20.9% respectively, $p = 0.031$), while no difference in pCR rates was observed in TNBC patients by HER2 status. Despite a lower rate of pCR, Kaplan-Meier curve showed that OS was significantly better in the HER2-low BC compared to HER2-negative (IHC 0) population at 100-months follow up. Multivariable Cox-regression model in the HER2-negative BC cohort demonstrated that HER2-low status was an independent predictor of OS (HR 0.59, 95% CI, 0.39-0.89 $p = 0.012$).

Conclusions

In our real-world analysis, pCR rates are consistent with the published data. Many patients still have residual disease following NACT, predicting worse outcomes, and may benefit from further adjuvant systemic therapies. Consistent with other studies, our findings suggest a possible prognostic and predictive role of HER2-low status especially among patients with ER-positive BC. This could lay the foundations for novel therapies targeting HER2 among HER2-low cancer subtypes.

PO2-02-10

Predicting the feasibility of breast conserving surgery using pre-treatment standard of care DCE-MRI: a novel clinical decision support tool for breast cancer surgical planning

Presenting Author(s) and Co-Author(s):

J. Pfeiffer. SimBioSys, Inc., Chicago, Illinois, United States

B. Feiger. SimBioSys, Inc., United States

A. Antony. SimBioSys, Inc., Chicago, Illinois, United States

J. Peterson. SimBioSys, Inc., Chicago, Illinois, United States

Background:

The decision-making process regarding breast cancer treatment options, specifically breast conserving surgery (BCS) versus mastectomy, is a complex and sensitive matter that takes into account the patient's preferences and their eligibility for BCS. A range of anatomical factors, such as tumor size, breast size, and proximity of the tumor to the skin, can influence the surgeon's recommendation regarding BCS or mastectomy. While mastectomy may be the only viable option for patients with large tumors, those with smaller tumors often have the opportunity to collaboratively decide with their surgeon on the most appropriate approach to ensure oncologic success and minimize potential cosmetic deformity. To facilitate this decision-making process, we developed a tool capable of providing informed recommendations on BCS or mastectomy based on standard of care imaging patient data. By integrating these recommendation capabilities, we aim to enhance the decision-making process and improve patient outcomes in breast cancer treatment.

Methods:

To assist surgeons and patients in determining a patient's eligibility for breast conserving surgery (BCS), we developed the BCS Feasibility Score. The BCS Feasibility Score is generated from a binary classifier machine learning model and is representative of the probability that a given patient could receive BCS. The score is based solely on the output from TumorSight Viz, a software platform that uses only pre-treatment T1-weighted DCE MRI and applies a suite of deep learning algorithms to segment the patient's disease and the surrounding breast tissues. From the multi-tissue segmentation generated using TumorSight Viz, we extracted 25 spatial morphology features to use in the model development process.

The training and testing sets were a subsample of a publicly available dataset (Saha, et al, 2018). We selected patients that received either BCS or mastectomy and had a viable T1-weighted DCE MRI. Bi-lateral cases were excluded. The total training/testing set consisted of $n = 749$ cases, 363 of which received mastectomy and 386 who received BCS. Before model training occurred, we split 20% of the sample to use as the test set. We then trained a random forest classifier across a range of pre-set hyper-parameters, using a total of 25 features as inputs, and using 5x cross-validation in the training set. We then assessed model performance in the testing set only.

Results:

In the test set, 76 cases received BCS versus 74 that received mastectomy. We successfully predicted BCS in 56 out of 76 cases (74%), and mastectomy in 46 out of 74 cases (62%). Overall, we observed an AUC = 0.76 and an F1 score = 0.66, indicating moderate to strong model performance. The most important features in the model, as measured by SHAP values, included the axis aligned tumor longest dimension (mm), the closest distance between the

tumor and the nipple (mm), the volume of the tumor convex hull (mL; dilated uni-centrally), and the ratio of tumor convex hull volume to breast volume.

We tested the model's performance in a fully independent holdout validation set of 579 cases. Within this validation set, 335 patients received BCS versus 244 received mastectomy. We successfully predicted BCS in 254 out of 335 cases (76%), and mastectomy in 149 out of 244 cases (61%). Overall, we observed an AUC = 0.75 and an F1 score = 0.63. Validation set performance mirrored results observed in the test set, indicating strong generalizability. In the validation set, comparing patients who underwent BCS to those who underwent mastectomy, we observed significant differences across all four of the most predictive features.

Conclusion:

TumorSight Viz and the BCS Feasibility Score help empower both patients and clinicians with information and tools to facilitate surgical planning decisions.

PO2-02-11

Radiomics and an Erosion Model to Predict Post-Neoadjuvant Therapy Tumor Characteristics for Personalized Breast Cancer Treatment

Presenting Author(s) and Co-Author(s):

B. Feiger. SimBioSys, Inc., United States

J. Pfeiffer. SimBioSys, Inc., Chicago, Illinois, United States

J. Cole. SimBioSys, Inc., Chicago, Illinois, United States

A. Antony. SimBioSys, Inc., Chicago, Illinois, United States

J. Peterson. SimBioSys, Inc., Chicago, Illinois, United States

Background:

Neoadjuvant therapy (NAT) has become a standard-of-care (SOC) for patients diagnosed with locally advanced or early-stage breast cancer. A critical step towards optimizing treatment selection and coordinating surgical care is to estimate the tumor's response to NAT. While pathological complete response (pCR) is commonly used to measure NAT effectiveness, patients who do not achieve pCR still benefit from NAT depending on the tumor's response. A reduction in tumor extent could alter the surgical approach from mastectomy to breast conserving therapy and improve recurrence and overall survival. In this study we used pre-treatment imaging data to provide a comprehensive prediction of clinically relevant metrics including tumor volume, tumor convex hull volume, and spatially derived metrics; this research represents an important advancement in predicting NAT effectiveness.

Methods:

262 breast cancer patients from 5 institutions who underwent NAT with pre- and post-NAT dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) were included in this study. Each MRI was automatically segmented using a convolutional neural network with manual edits and verification. Radiomic features were extracted from the pre-NAT MRI and tumor segmentation. Significant radiomic features were selected based on their correlation with post-NAT volume, feature-to-feature correlation, and LASSO regression. Altogether, 12 and 17 radiomic features were selected for volume and convex hull volume prediction, respectively. The selected features were inputted into a Huber loss regression model to predict either the post-NAT tumor volume or the convex hull volume (surgical excision volume). To enable spatial and morphological comparison between the predicted and post-NAT tumor, an erosion model was developed in which the pre-NAT and post-NAT MRIs were co-registered, and the pre-NAT tumor was symmetrically eroded until its volume matched the predicted volume. Clinically relevant metrics such as the distance from the tumor to the nipple, skin, and chest were computed to assess the morphological and spatial prediction capabilities of the model. All models were tested on patients from cohort holdout sets (n=110) unseen during training.

Results:

The volume prediction analysis yielded promising results, with an R^2 value of 0.62 for post-NAT tumor volume prediction and an R^2 value of 0.56 for post-NAT tumor convex hull volume prediction. The mean volume and convex hull volume error was 1.1 cc and 1.3 cc, respectively. Table 1 provides an overview of the morphological and spatial comparisons between the predicted and post-NAT tumors. Overall, the predicted tumors demonstrated close agreement with their post-NAT counterparts.

Conclusion:

This study demonstrates a successful approach towards estimating post-NAT tumor volume, convex hull volume, and morphological and spatial characteristics. By providing reliable estimates of post-NAT tumor characteristics using SOC pre-NAT data, our predictive models enable personalized treatment planning and patient stratification to optimize patient care.

Table 1. Predicted vs. post-NAT tumor comparison.

Metric	Tumor to nipple - predicted	Tumor to nipple - actual	Tumor to nipple - error	Tumor to Skin - predicted	Tumor to skin - actual	Tumor to skin - error	Tumor to chest - predicted	Tumor to chest - actual	Tumor to chest - error
Mean ± Std (mm)	51.2 ± 26.0	50.3 ± 22.9	10.9 ± 11.6	12.7 ± 6.4	13.8 ± 7.5	4.7 ± 4.4	31.5 ± 21.9	35.2 ± 23.8	10.4 ± 10.8

Results demonstrate accurate predictions for clinically relevant distance metrics.

PO2-02-13

A Mechanical Conditioning gene expression (MeCo) score detects the patients that benefit from neoadjuvant anti-fibrotic therapy in early HER2-negative breast cancer (HER2negBC).

Presenting Author(s) and Co-Author(s):

M. Quintela-Fandino. CNIO - Spanish National Cancer Research Center, Madrid, Spain

A. Watson. MeCo Diagnostics, California, United States

A. Grant. UGenome Biotech, United States

G. Mouneimne. MeCo Diagnostics, United States

M. Bueno. CNIO - Spanish National Cancer Research Center, United States

S. Mouron. CNIO - Spanish National Cancer Research Center, United States

Background: Extracellular matrix (ECM) stiffness in the tumor microenvironment is associated with aggressive features that lead to adverse clinical outcomes, including metastasis. Mechanical conditioning (MC) is the phenomenon whereby cancer cells that have grown in a fibrotic-like stiff ECM acquire aggressive features which can be maintained after metastasis in distant sites (Cell Rep.; 35:109293). MeCo Score is a gene expression signature that measures the response to ECM stiffness in early tumors which is associated with subsequent metastasis. We sought to study whether MeCo Score is associated with pathologic complete response (pCR) in early HER2negBC, and whether anti-fibrotic treatment with nintedanib (a multikinase VEGFR1-3, FGFR1-3 and PDGFRA/B inhibitor approved for idiopathic lung fibrosis) is able to mitigate the impact of MC. Methods: Baseline tumor samples from patients (N=130) from a randomized phase II clinical trial (Clin Cancer Res 23: 1432-42) in early HER2negBC trial comparing weekly paclitaxel monotherapy (85 mg/m² x 12 courses; N=65; Arm A) versus the same treatment plus nintedanib (150 mg p.o. bid, continuous schedule; Arm B) were analyzed by RNAseq. MeCo Score was computed as previous described (Cell Rep.; 35:109293), and intrinsic PAM50 subtypes were determined using the R package geneFu. Clinical, demographic and pathologic variables were gathered for all patients; pCR was graded according to the Residual Cancer Burden (RCB) score, RCB=0. Regression models were built using the variables RCB, T, N, G, age, intrinsic subtype, Ki67, MeCo Score and treatment arm. Bi-variate correlations were analyzed with the Pearson coefficient. All statistic tests were two-sided. Results: MeCo Score was successfully determined in 76 women (50% from each arm); the average score was 0.34 (range: 0.052 – 0.617). Of them, 48.6% were Luminal A, 34.2% Luminal B, 14.5% Basal-like, and 2.7% Normal according to PAM50. Median age was 49 y.o. (range: 30.6 – 79.2); tumor size distribution was T1:3.0%; T2:68.2%; T3:24.3%; T4: 4.5%; 47% of the patients were N0, 47% were N1 and 6% were N2. Most patients (85%) were ER and/or PR positive; 15% were “triple-negative”. Histological grade distribution was G1/G2/G3: 15%/62%/23%. The average Ki67 was 28.7% (range: 1%-98%). pCR was 10.8% and 4.5% in arms A and B. The average MeCo Score by intrinsic subtype was 0.26 (LumA); 0.43 (LumB) and 0.38 (Basal), LumB vs LumA P< 0.001; LumB vs Basal: P=0.037. We did not find correlation between MeCo Score and G, T, N, age or Ki67, neither in the Luminal subgroup or the whole cohort. In Arm A, patients with high MeCo Score (i.e., above median) had a 0% pCR rate compared to 10.5% pCR rate for those with low MeCo Score (P=0.035); however, in the nintedanib arm (Arm B) no differences were found: 10.5% versus 11.1% pCR rate in high versus low MeCo Score (P=0.4). Conclusions: Among early HER2negBC, Luminal B cases display the highest MeCo Scores. MeCo Score was independent of all classic prognostic variables. High MeCo Score is associated with lack of pCR to neoadjuvant paclitaxel

monotherapy, but concurrent administration of the anti-fibrotic agent nintedanib rescues this association.

PO2-02-14

Development of a multi-institutional, photograph-rich clinical dataset to test and validate a novel inflammatory breast cancer (IBC) scoring system

Presenting Author(s) and Co-Author(s):

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Niman. Dana Farber Cancer Institute, United States

M. Kai. MD Anderson Cancer Center, United States

S. Ryan. DFCI, United States

E. Troll. DFCI, United States

L. Li. UT MD Anderson Cancer Center, United States

K. Miller. Indiana University, United States

R. Jagsi. Emory University, Ann Arbor, Michigan, United States

G. Mason. IBC Research Foundation, United States

B. Overmoyer. DFCI, United States

H. Le-Petross. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

F. Nakhlis. Dana-Farber Cancer Institute, United States

S. Krishnamurthy. MD Anderson cancer center, United States

B. Harrison. BWH, United States

S. Sun. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

E. Yeh. DFCI/BWH, United States

J. Bellon. Dana Farber Cancer Institute, United States

L. Warren. DFCI/BWH, United States

M. Stauder. UT MD Anderson Cancer Center, United States

M. Regan. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

W. Woodward. UT MD Anderson Cancer Center, Houston, Texas, United States

Purpose: Susan G. Komen, The Inflammatory Breast Cancer (IBC) Research Foundation, and the Milburn Foundation convened a collaborative of patient advocates, clinicians, and researchers and proposed a novel quantitative scoring system for IBC diagnosis. The score includes timing of symptoms, extent of skin edema and erythema/other discoloration, breast and nipple asymmetry, lympho-vascular space invasion, nodal stage, and diffuse extent disease in the breast on breast imaging. Total scores were categorized (< 14 Not IBC, 14-24 Weak Possibility of IBC, 25-41 Strong Possibility of IBC, > 41 Definitely IBC). Herein, we developed a multi-institutional clinical dataset to retrospectively test and validate the proposed scoring system. Methods: IBC (N= 988) and non-IBC (N=322) cases were identified at two institutions with dedicated multi-disciplinary IBC programs, UT MD Anderson Cancer Center (MDA) and Dana-Farber Cancer Institute (DFCI). The DFCI cohort was diagnosed from 1986-2021 and the MDA cohort was diagnosed from 2010-2020. The non-IBC cohorts were identified as consecutive T4b and T4c cases in existing retrospective databases. Photographs were reviewed for available cases. All scoring variables were reviewed with data extractors and standard operating procedures (SOPs) developed for all ambiguous findings and language. A subset of scores were reviewed by IBC clinicians (FL, WW) and discrepancies discussed to

inform the SOPs. Missing data imputation using three methods was examined. Area under the curve (AUC) - Receiver operator characteristic (ROC) curves and values, and sensitivity and specificity for the proposed score cut offs were examined. Results: Of 1320 patients currently in the analysis, 421 (31.9%) have missing data on > 1 characteristics and 47 (3.6%) are missing data on > 4. The rubric characteristic most commonly missing was "nipple abnormalities" accounting for 21.0% and 19.3% for IBC and non-IBC cohorts respectively. Unavailable bilateral breast photograph was the primary source of missing data. The highest scoring finding was present in the following percentage of IBC and non-IBC cases, respectively: timing of symptom onset < 3 months (74.1% vs 38.6%), any peau d'orange (61.2% vs 30.1%), clinically apparent enlargement or new asymmetry of breast size (87.8% vs 90.1%), complete or near complete involvement of the breast skin by erythema or discoloration (55.6% vs 25.6%), new nipple inversion (24.6% vs 9.0%), dermal lymphovascular emboli present (17.9% vs 1.8%), diffuse involvement of the breast parenchyma by imaging (72% vs 77.7%). True IBC cases were categorized as Definitely IBC, Strong Possibility, Weak Possibility, not IBC and unknown 19.7%, 49.1%, 0.4%, 0.1%, and 30.7%. True non-IBC were 0.6%, 51.8%, 9.9%, 2.1%, and 35.5%. Random imputation, lowest value imputation, and median value imputation were compared to impute missing data. AUC-ROC values for each method were similar, 0.80 - 0.84. Conclusion: We describe the development of the largest multi-institutional IBC clinical database to date. SOPs for the rubric characteristics were developed. The importance of bilateral photography to assess the score retrospectively is highlighted. The score is associated with a good AUC-ROC but still leaves much overlap among cases between 25 and 42. Further optimization of the current scoring system and association with outcomes are in progress.

PO2-03-01

Personalized 3D tumor models drive shared decision-making in early breast cancer

Presenting Author(s) and Co-Author(s):

D. Collyar. Patient Advocates in Research, United States

M. Biancalana. SimBioSys, Inc., Chicago, Illinois, United States

A. Antony. SimBioSys, Inc., Chicago, Illinois, United States

N. Liadis. SimBioSys, Inc., Chicago, Illinois, United States

J. Palaniappan. SimBioSys, Inc., United States

R. Seago-Coyle. SimBioSys, Inc., United States

Background:

Decision-making for early (Stages 1-3) breast cancer (eBC) care is complex and highly personal, requiring discussions between patients and multiple physicians. Shared decision-making (SDM) is an accepted process that combines input from both patients and physicians, although its overall use is low due to a lack of time and incentives, complicated application techniques, and few communication tools. Reviews show that SDM results in “improved affective-cognitive outcomes” but evidence linking to patient outcomes is sparse. Consequently, patients often receive mixed messages and feel anxious when making treatment decisions.

SimBioSys (SBS) developed the TumorSight(TM) platform for individualized treatment planning, coordinated care, and SDM. The first application on this platform, TumorSight Viz, rapidly builds 3D computational models from standard breast MRI data, and further integrates deep learning, genomic/genetic testing, metabolomics, and clinical and demographic data to tailor these models for each individual diagnosed with eBC. The platform can also transform acquired data (e.g., prone) to surgical position (e.g., supine) to create realistic images for precision surgical planning and tools for better SDM with eBC patients. We are assessing how surgeons and patient advocates (PA) perceive TumorSight, and how it may support better SDM and treatment implementation. Methods:

SBS conducted an exploratory survey with 31 eBC surgeons to assess the utility of TumorSight Viz visualizations across a range of didactic and planning applications and to query preferences for future components like predicted response to chemotherapy and immunotherapy. Questions were developed with input from breast surgeon advisors.

More exploration on TumorSight Viz utility is planned with semi-structured qualitative interviews to assess patient advocates’ perceptions of 3D visualizations, surgical planning, and ability to support decision making. PAs will represent geographic, experience, and race/ethnicity diversity. Questions to elicit patient needs, perception of SBS tools, and quality-of-life are being finalized with academic advisors. These will also be used to develop a future eBC patient survey. Results:

The SBS surgeon survey revealed that 96% of breast surgeons find visualization important to surgical planning, and these depictions were considered to be critical by a third of breast surgeons surveyed. 96% also listed the conversion of prone to supine visualizations as important (45% critical, 35% valuable, 16% nice to have, 0% not important) for surgical planning value. Surgeons also assigned strong utility for:

- Graphical 3D rotation to determine tumor shape, size, location, positioning, and landmarks relative to other breast structures – 100%

- Ability to instantly provide tumor-to-breast volume determination with high accuracy – 96%
- Ability to instantly provide anticipated tumor extirpation volume to breast volume with high accuracy – 96%
- Automatic tumor-to-landmark structures measurements (nipple, chest, skin) – 96%
- Visualization of tumor in the context of other anatomical structures (e.g., skin, blood vessels, chest, heart) – 87%

Initial PA discussions (n=3) listed the importance of individualized treatment based on evidence instead of hunches; reasons to avoid prophylactic mastectomies; and ways to lower patient anxiety. Conclusions:

Survey-based feedback shows value to eBC surgeons and patients to coordinate care and personalize approaches for optimal outcomes. Computational tools can facilitate patient understanding and patient-tailored treatment. Additional surveys are planned with patients and eBC patient advocacy groups to assess the utility and potential expansion of patient-specific 3D tumor visualizations, both of which will be further discussed.

PO2-03-02

Technology-enabled identification of low-risk breast cancer survivors for personalized survivorship care

Presenting Author(s) and Co-Author(s):

- F. Brasfield. Kaiser Permanente Southern California, Anaheim, United States
- A. Chen. Kaiser Permanente Southern California, Pasadena, California, United States
- E. Haupt. Kaiser Permanente Southern California, Pasadena, California, United States
- L. Lyons. Kaiser Permanente Southern California, Pasadena, California, United States
- T. Habeshian. Kaiser Permanente Southern California, Pasadena, California, United States
- C. Munoz-Plaza. Kaiser Permanente Southern California, Pasadena, California, United States
- E. Shen. Kaiser Permanente Southern California, Pasadena, California, United States
- H. Nguyen. Kaiser Permanente Southern California, Pasadena, California, United States
- M. Gould. Kaiser Permanente, United States
- A. Ferreira. Kaiser Permanente Southern California, United States
- A. Joo. Kaiser Permanente Southern California, United States
- S. Monemian. Kaiser Permanente Southern California, United States
- C. Lai. Kaiser Permanente Southern California, United States
- Y. Park. Kaiser Permanente Southern California, United States
- H. Lee. Kaiser Permanente Southern California, United States
- S. Steinberg. Kaiser Permanente Southern California, United States
- P. Ganz. UCLA Jonsson Comprehensive Cancer Center, and UCLA Fielding School of Public Health, Los Angeles, California, United States
- E. Hahn. Kaiser Permanente Southern California, Pasadena, California, United States

Background. Advancements in cancer medicine have resulted in prolonged survival for the majority of patients. Personalized care pathways which account for clinical needs of this growing population of cancer survivors—and which address oncology workforce shortages—are urgently needed. Rapid identification of low-risk cancer survivors who could be cared for in other settings is a critical element of personalized care. Here we present final algorithm performance on risk-stratification from an ongoing clinical trial evaluating a primary care physician-led cancer survivorship clinic for breast cancer survivors. We captured data on real-time clinical risk stratification of early-stage patients between 6-36 months post-treatment. **Methods.** With oncology stakeholder input, we developed a screening algorithm to identify low-risk breast cancer survivors from the electronic medical record based on data from pathology, treatment, and utilization records. The algorithm identified patients meeting study eligibility: adult stage 0-IIb breast cancer patients diagnosed with first primary cancer, excluding those with treatments indicative of high-risk or metastatic disease, ongoing ovarian suppression, neoadjuvant therapy, or enrollment in other cancer clinical trials. Next, the treating oncologist was asked to confirm or deny patient eligibility; if denied, we tracked and categorized the reason provided for ineligibility. We describe: 1) characteristics and proportions of patients identified by the algorithm; 2) a breakdown of patients confirmed or denied eligibility; and 3) oncologists' reasons for ineligibility. **Results.** The algorithm identified 1186 patients. Of those, 91 were flagged by oncology as not followed (e.g., consult only), and 204 were not categorized. Of the remaining 890 patients, 716 (81%) were categorized as eligible. Mean age was 62 years

(SD: 11.4, Table 1). There were significant differences by stage, with a higher proportion of stage 0 in the eligible group (24% vs. 18%) and a lower proportion of stage II (24% vs. 35%). There was also a significant difference by HER2 status, with a greater proportion of HER2+ patients categorized as eligible (21% vs. 16%). There were significant differences by race/ethnicity, with a higher proportion of Asian and Black patients categorized eligible (14% vs. 8%, and 28% vs. 17%, respectively) and fewer Hispanic and White patients categorized eligible (26% vs. 36%, and 30% vs. 37%, respectively). There were not significant differences by ER/PR, surgery, or endocrine therapy. Reasons for ineligibility included: suspicious for recurrence (6%), new primary disease (3%), considered high-risk based on genetic/tumor factors (9%), co-occurring heme/oncology disorder (9%), treatment-related concerns (e.g., patient declined chemotherapy) (7%), complex case/condition (11%), patient preference per conversation with oncologist (32%), other (19%), and lost to follow-up (4%). Conclusions. Leveraging technology to support survivorship in the primary care setting is critical. Our findings demonstrate that consensus-based risk algorithms with oncologist review can effectively perform identification of low-risk patients who may be appropriately transitioned to other settings for survivorship care. These patients may benefit from primary care-led survivorship with a focus on healthy lifestyle, managing comorbid conditions, and psychosocial care.

Eligible/Ineligible per oncologist by patient demographics and cancer characteristics

Table 1.

	Eligible per oncologist (N=716)	Ineligible per oncologist (N=174)	Total (N=890)	P-value
Age				0.003 ¹
N	716	174	890	
Mean (SD)	62.3 (11.2)	59.4 (11.9)	61.7 (11.4)	
Range	30.0, 95.0	23.0, 88.0	23.0, 95.0	
Gender, N (%)				0.12 ²
Female	714 (99.7%)	172 (98.9%)	886 (99.6%)	
Male	2 (0.3%)	2 (1.1%)	4 (0.4%)	
Race/Ethnicity, N (%)				0.001 ²
Asian/Pacific Islander	99 (13.8%)	14 (8.0%)	113 (12.7%)	
Black	204 (28.5%)	29 (16.7%)	233 (26.2%)	
Hispanic	190 (26.5%)	62 (35.6%)	252 (28.3%)	
Other/Unknown	12 (1.7%)	4 (2.3%)	16 (1.8%)	
White	211 (29.5%)	65 (37.4%)	276 (31.0%)	
Cancer Stage, N (%)				0.009 ²
0 (DCIS)	174 (24.3%)	31 (17.8%)	205 (23.0%)	
1	369 (51.5%)	82 (47.1%)	451 (50.7%)	
2	173 (24.2%)	61 (35.1%)	234 (26.3%)	
Primary Surgery Type, N (%)				0.08 ²
Mastectomy	349 (48.7%)	96 (55.2%)	445 (50.0%)	
Lumpectomy	340 (47.5%)	72 (41.4%)	412 (46.3%)	
Excisional Biopsy Only	27 (3.8%)	5 (2.9%)	32 (3.6%)	
ER/PR Status, N (%)				0.78 ²
Missing	7 (1.0%)	2 (1.1%)	9 (1.0%)	
ER/PR negative	51 (7.1%)	15 (8.6%)	66 (7.4%)	
ER/PR positive	658 (91.9%)	157 (90.2%)	815 (91.6%)	
HER2 Status, N (%)				0.03 ²
Missing	227 (31.7%)	44 (25.3%)	271 (30.4%)	
HER2 negative	336 (46.9%)	101 (58.0%)	437 (49.1%)	
HER2 positive	153 (21.4%)	29 (16.7%)	182 (20.4%)	
Endocrine Therapy, N (%)				0.24 ²
	514 (71.8%)	117 (67.2%)	631 (70.9%)	

¹Kruskal-Wallis p-value; ²Chi-Square p-value

PO2-03-03

The Significance of Cavity Shave Margins in Breast Carcinoma on Margin Status and Re-excision Rates

Presenting Author(s) and Co-Author(s):

f. Zaiem. Wayne State University, United States

A. Numi. Wayne State University, United States

M. Kheil. Wayne State University, United States

A. AbuJamea. Wayne State University, United States

D. Jain. Departments of Pathology, School of Medicine and Surgery, Wayne State University, United States

O. Abbas. Wayne State University, United States

L. Larson. School of Medicine and Surgery, Wayne State University, United States

N. Suleiman. School of Medicine and Surgery, Wayne State University, United States

S. Al-Juburi. School of Medicine and Surgery, Wayne State University, United States

S. Awada. School of Medicine and Surgery, Wayne State University, United States

R. Almsaddi. School of Medicine and Surgery, Wayne State University, United States

H. Jang. Biostatistics and Bioinformatics Core, Karmanos Cancer Institute Department of Oncology, School of Medicine, Wayne State University, United States

S. Kim. Biostatistics and Bioinformatics Core, Karmanos Cancer Institute Department of Oncology, School of Medicine, Wayne State University, United States

N. Salem. Ascension St. John Hospital, United States

L. Choi. Department of Surgery, Wayne State University, United States

S. Bandyopadhyay. Departments of Pathology, School of Medicine and Surgery, Wayne State University, United States

S. Jaiman. Departments of Pathology, School of Medicine and Surgery, Wayne State University, United States

R. Ali-Fehmi. Department of Pathology , University of Michigan, United States

Abstract:

Context: The comparative outcomes of breast conserving surgery (BCS) with and without cavity shave margins are not well established. We aim to evaluate the impact of each procedure on final margin status and rate of re-excision.

Design: A total of 529 breast cancer cases from our institution between 2013-2015 were included. Demographic and clinicopathological data including procedure type, tumor type, grade, margins status, and re-excision rates were collected. H&E slides of positive margins (tumor on ink) were reviewed by two pathologists. Appropriate statistical analysis was performed.

Results: Out of 529 breast cancer cases, 125 were Ductal Carcinoma in situ (DCIS), 152 were Invasive Ductal Carcinoma (IDC) and 252 had both pathologies. The median age of patients was 59 years (range: 24-90). Patients who underwent excision with shave margins were 162 (35 DCIS, 56 IDC, 71 both) while excision without shave margins were 367 (90 DCIS, 96 IDC, 181 both). Re-excision rates were significantly lower 1) in patients who underwent BCS with

cavity shave margins compared to those without (OR 0.32, $p < 0.001$) and 2) in patients who did not require lymph node excision compared to those who did (OR 4.26, $p < 0.001$). Additionally, patients who had DCIS had a higher rate of re-excision than those with invasive cancer only (OR 5.17, $P < .001$). After adjusting for type of tumor, patients who underwent cavity shaving compared to those who did not, no significant difference was seen in tumor at margins (OR 0.73, $p = 0.282$) or tumor within 2mm (OR 1.14, $p = 0.512$) from margins. However, patients with IDC who underwent cavity shave had a higher proportion of negative tumor at the margins (76.5% vs. 67.0%; $p = 0.051$). We found that patients who had an invasive carcinoma (IC) had a lower risk of having tumor at the margin or within 2 mm from the margin than those with DCIS or DCIS+IC, ($p < .05$).

Conclusions: Our data shows that BCS with cavity shave margins is superior with regards to negative margin and re-excision rates when compared to without cavity shave margins.

PO2-03-05

Neoadjuvant anthracycline followed by Toripalimab combined with nab-paclitaxel in patients with stage IIA-IIIC triple negative breast cancer (NeoTENNIS): efficacy and safety results of a phase II study

Presenting Author(s) and Co-Author(s):

M. He. Fudan University Shanghai Cancer Center, United States

L. Ma. Fudan University Shanghai Cancer Center, Shanghai, China, United States

S. Hao. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China, United States

B. Yang. Fudan University Shanghai Cancer Center, Shanghai, China, Shanghai, China (People's Republic)

B. Xiu. Fudan University Shanghai Cancer Center, Boston, Massachusetts, United States

Y. Chi. Fudan University Shanghai Cancer Center, United States

R. Shui. Fudan University Shanghai Cancer Center, United States

Z. Wang. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, United States

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Background: Immune checkpoint inhibitors (ICIs) have shown promising antitumor activity in triple negative breast cancer (TNBC) patients. Toripalimab, a novel PD-1 antibody, has been approved for the treatment in multiple solid tumors. However, the neoadjuvant use of toripalimab with chemotherapy has not been evaluated in TNBC patients. In addition, whether chemotherapy could sensitize the ICI treatment has not drawn conclusion yet. In this phase II trial, a sequential use of chemotherapy and anti-PD1 therapy was given in a neoadjuvant setting. The efficacy and safety of toripalimab were evaluated. Patients and methods: Female patients with histologically confirmed stage IIA to IIIC TNBC were included. Eligible patients received neoadjuvant therapy with four cycles of epirubicin-cyclophosphamide every 2 weeks followed by toripalimab (240 mg) every 3 weeks plus nab-paclitaxel weekly for 12 weeks. The primary endpoint was pathologic complete response (tpCR; ypT0/is ypN0) rate. Key secondary endpoints were breast pCR (bpCR; ypT0/is) rate, biomarker analysis, and safety. Results: Among 70 enrolled patients (median age, 51 years; 62.9% stage III), 66 patients completed study treatment without progression and received surgery after study treatment. Overall, the percentages of patients with a tpCR and bpCR were 55.7% (39 of 70 patients) and 58.6% (41 of 70 patients), respectively. For women with CD8-positive and negative tumors, the tpCR rates were 66.0% and 30.0% (P = 0.006), respectively. Significant upregulation of CD8 positive cells after 4 cycles of epirubicin-cyclophosphamide induction chemotherapy (P = 0.011) were shown in sequential biopsy samples. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 30 patients (42.9%), the most common of which were neutropenia (15.7%), leukopenia (14.3%) and alanine aminotransferase increase (4.3%). Most common immune-related AEs were hepatobiliary disorders (Grade 3, 7.2%), creatinine increase (all Grade 1-2,

2.8%) and hypothyroidism (all Grade 1-2, 2.8%). Conclusions: The addition of toripalimab to neoadjuvant chemotherapy is efficacious and safe in patients with locally advanced TNBC. Anthracycline-based chemotherapy could sensitize the ICI treatment with upregulated tumor immune response. The event-free survival results are expected with further follow up. Mechanisms of chemotherapy sensitization are still under investigation (ClinicalTrials.gov number: NCT04418154).

PO2-03-06

Pathological complete response with chemotherapy and immune checkpoint inhibition in triple negative inflammatory breast cancer (TN-IBC)

Presenting Author(s) and Co-Author(s):

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
S. Niman. Dana Farber Cancer Institute, United States
A. Gonçalves. Institut Paoli-Calmettes, France
M. Kai. MD Anderson Cancer Center, United States
S. Ryan. DFCI, United States
E. Troll. DFCI, United States
R. Layman. The University of Texas MD Anderson Cancer Center, United States
A. Giordano. Dana Farber Cancer Institute, Harvard University, Boston, MA, United States
A. Nasrazadani. Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
F. Nakhlis. Dana-Farber Cancer Institute, United States
J. Bellon. DFCI/BWH, Boston, Massachusetts, United States
L. Warren. DFCI/BWH, United States
C. Block. Dana-Farber Cancer Institute, United States
S. Schumer. Dana-Farber Cancer Institute, United States
A. Lucci. MD Anderson Cancer Center, Houston, Texas, United States
S. Krishnamurthy. MD Anderson cancer center, United States
F. Lerebours. Institut Curie, United States
F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France
C. Levy. Centre François Baclesse, Caen, Basse-Normandie, France
T. Petit. Centre Paul Stauss, Strasbourg, France
M. Leheurteur. Department of medical oncology, Henri Becquerel Cancer Center, United States
T. Bachelot. Medical Oncology, Centre Léon Bérard, Lyon, France
O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France
S. Ladoire. Centre Georges François Leclerc, France
L. Lopez Almeida. Paoli-Calmettes Institute, Marseille (France), United States
C. Zemmour. Institut Paoli-Calmettes, United States
S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
V. Valero. Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Bellaire, Texas, United States
F. BERTUCCI. Predictive Oncology Laboratory, Inserm Umr1068, Aix Marseille University, France
M. Regan. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
W. Woodward. UT MD Anderson Cancer Center, Houston, Texas, United States

BACKGROUND: Patients with stage III inflammatory breast cancer (IBC) are treated with tri-modality therapy consisting of neoadjuvant systemic therapy followed by modified radical mastectomy and post-mastectomy radiation therapy. Triple negative IBC (TN-IBC) is the subtype of IBC associated with the worst survival outcomes. Pathological complete response (pCR) rates after neoadjuvant chemotherapy have been historically low, with reports ranging between 13% and 42%. It is unknown if the addition of immune checkpoint inhibition to chemotherapy leads to improved pCR rate in TN-IBC as these patients were underrepresented in the seminal studies that led to the approval of chemoimmunotherapy for high-risk early-stage triple negative breast cancer (TNBC).

METHODS: We conducted a retrospective analysis of patients with stage III TN-IBC who underwent breast surgery after receiving neoadjuvant chemoimmunotherapy. Patients were seen at Dana-Farber Cancer Institute (DFCI) or MD Anderson Cancer Center (MDACC). The analysis population consisted of all patients that were seen at either institution no more than 30 days after starting immunotherapy. The primary objective was the estimation of the pCR rate. An additional cohort of patients with TN-IBC treated with neoadjuvant chemotherapy and pembrolizumab while participating in the multi-institutional PELICAN trial (NCT03515798) will be added to the analysis at the time of the meeting.

RESULTS: Thirty-seven patients (16 DFCI, 21 MDACC) were identified as having stage III TN-IBC and having received neoadjuvant chemoimmunotherapy. Twenty-five patients met criteria for inclusion in the analysis population. Patients in the DFCI cohort initiated treatment with chemoimmunotherapy between May 2021 and June 2022, and in the MDACC cohort between June 2021 and October 2022. Most patients were White (N=20, 80%), premenopausal (N=15, 60%) and overweight/obese (N=19, 76%). All patients received pembrolizumab-based therapy (Table 1). Among the 25 patients in the analysis population, 10 (40%) (95% CI: 21% to 61%) achieved a pCR, 6 patients experienced RCB-II and 9 RCB-III. At the time of last follow up, 84% of patients were alive. The results will be updated at the time of the meeting to include an additional cohort of 17 patients from the PELICAN trial.

CONCLUSIONS: The addition of immune checkpoint inhibition to neoadjuvant chemotherapy led to a higher pCR rate in TN-IBC than most historical estimates. However this is still lower than what has been reported in TNBC in general. The investigation of novel systemic therapies is warranted in TN-IBC.

Table 1. Patient characteristics and treatment received (analysis population)

	Institute				Total	
	DFCI		MDA		N	%
	N	%	N	%		
Patients (analysis population)	8	100.0	17	100.0	25	100.0
Age at diagnosis						
30-39	2	25.0	4	23.5	6	24.0
40-49	4	50.0	7	41.2	11	44.0
50-59	1	12.5	3	17.6	4	16.0
60+	1	12.5	3	17.7	4	16.0
Menopausal status						
Pre-menopause	6	75.0	9	52.9	15	60.0
Peri-menopause	.	.	1	5.9	1	4.0
Post-menopause	2	25.0	7	41.2	9	36.0
Race						
White	6	75.0	14	82.4	20	80.0
Black or African American	.	.	1	5.9	1	4.0
Asian	1	12.5	1	5.9	2	8.0
Other	.	.	1	5.9	1	4.0
Unknown	1	12.5	.	.	1	4.0
Ethnicity						
Hispanic	1	12.5	3	17.6	4	16.0
Not Hispanic	7	87.5	14	82.4	21	84.0
BMI						
< 25	1	12.5	4	23.5	5	20.0
25-30	3	37.5	6	35.3	9	36.0
30+	3	37.5	7	41.2	10	40.0
Unknown	1	12.5	.	.	1	4.0
Neoadjuvant treatment						
Carboplatin, paclitaxel, doxorubicin, cyclophosphamide, pembrolizumab	6	75.0	17	100.0	23	92.0
Carboplatin, paclitaxel and pembrolizumab	2	25.0	.	.	2	8.0

PO2-03-07

Immune Landscape in PD-L1-positive and TROP2-positive Triple-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

B. Gyorffy. RCNS, United States

L. Santarpi. Seagen Inc., Bothell, WA, USA, United States

Background: Triple-negative breast cancer (TNBC) tends to be more aggressive, and more likely to recur than other subtypes of breast cancer, and patients with metastatic TNBC have a poor prognosis. The recent approvals and data of pembrolizumab (anti-PD-1 inhibitor) in combination with chemotherapy in advanced-metastatic and early high-risk TNBC, and sacituzumab govitecan (an ADC that targets the tumor cell surface antigen TROP2 coupled with the irinotecan metabolite SN-38) in metastatic TNBC, has shed light on some of the immune and cancer signaling associated with TNBC. Although exciting progress has been made in the treatment of TNBC, there are still important gaps to fill to understand the biology of TNBC and identify additional therapies.

Materials and Methods: We identified a total of 1500 patients whose tumors were negative for the expression of ER and HER2 receptors by gene array. PD-L1 and TROP2 expression data were available for 802 early TNBC patients, of whom 657 were treated with adjuvant chemotherapy. A comprehensive identification and analysis of immune-related genes (n= 1169) was conducted. Mann-Whitney test comparing the gene expression for all immune related-genes was evaluated in patients expressing PD-L1 and TROP2 at low and high expression levels. Immune gene modules resembling key immune gene signaling were analyzed in all subgroups identified. Fold changes and Mann-Whitney P values were calculated in each subgroup.

Results: Patients were stratified based on high and low expression levels of PD-L1 and TROP2 mRNA. PD-L1 highly expressing (PD-L1+) tumors showed a marked difference in immune-related genes as compared to PD-L1 low-level tumors (PD-L1-) with PD-L1+ tumors demonstrating a significantly higher proportion of correlated immune genes (CXCL9/10/11, IFN- γ , CCL5 and STAT1). TROP2 highly and low expressing tumors (TROP2+ and TROP2-, respectively) showed a relatively limited difference in terms of immune-related gene expression with key immune-related genes having statistical differential expression in the two subgroups. TROP2+ tumors showed a high presence of several Mucin family gene members (MUC1, -5AC, -4). In addition, CLDN 4, VTCN1, and MET were among the key immune genes significantly expressed in TROP2+ tumors (P = 5.73E-20; P = 6.2E-13, P = 2.1E-11). Overall, PD-L1+ tumors and TROP2+ tumors showed an immune suppressive genomic landscape but were potentially regulated by different signaling. Of note, tumors with very high expression of PD-L1 showed an inverse correlation with VTCN1 gene expression.

Conclusions: This preliminary analysis confirmed that only a limited number of early TNBC highly expressed PD-L1 and that a different immune suppressive landscape for PD-L1 \pm and TROP2 \pm tumors exists. In addition, our data suggest that early TNBC cases lacking PD-L1 might escape immune surveillance by virtue of the upregulation of key alternate signaling. Ongoing efforts investigating the expression of such markers on stroma/epithelial tumor components will help to clarify their biological, clinical, and potential therapeutic role in TNBC.

PO2-03-08

Uncovering Novel Potential Prognostic Biomarkers in Basal-Like Breast Cancer using Transcriptomic Data of 1,899 Patients

Presenting Author(s) and Co-Author(s):

B. Györffy. RCNS, United States

L. Santarpia. Seagen Inc., Bothell, WA, USA, United States

Introduction: Patients with basal-like breast cancer (BLBC) predominantly represented by triple-negative breast cancer have shown a high recurrence rate and are characterized by poor prognosis. There is an urgent need to uncover reliable prognostic biomarkers that can help in the clinical management of such patients and identify additional therapeutic targets. The objective of this study was to create a comprehensive transcriptomic database on a large scale and leverage it to identify and prioritize cancer-related genes associated with BLBC patients' outcomes.

Methods: We identified breast cancer cohorts from public repositories that contained gene expression data at the transcriptome level, along with clinical follow-up information. BLBC were identified using the PAM50 signature. All samples were standardized using a standard array normalization coupled with scaling to have a mean expression across all genes of 1000 in each sample and incorporated into a unified database. Redundant samples were removed. For each gene, Cox univariate survival analysis was conducted, to account for multiple hypothesis testing, the false discovery rate was computed, and a significant cutoff of 1% was employed to determine the highest statistical significance. Association with RFS and OS was performed. Multivariate analysis was performed for selected genes involving clinical and pathological variables. To uncover higher-level functions related to altered RFS, gene ontology analysis was performed using the enrichGO function in the TNM plotter (<http://www.tnmplot.com>).

Results: The complete integrated database comprises 1,899 samples from 52 breast cancer datasets. Altogether, 2,342 genes were correlated with relapse-free survival (RFS), and 1,149 genes were correlated with overall survival (OS). 619 genes were statistically significant for both RFS and OS. The most significant genes were ANGPTL4 ($p=4.25E-08$, HR=2.02), NHP2 ($p=5.98E-10$, HR=1.93), STK3 ($p=4.86E-10$, HR=1.93), GBE1 ($p=2.77E-09$, HR=1.86), and PMVK ($p=3.65E-09$, HR=1.85) for RFS and PINK1 ($p=1.64E-05$, HR=3.31), CAMK2N1 ($p=1.06E-07$, HR=2.93), CACFD1 ($p=4.79E-04$, HR=2.61), SCAP ($p=3.29E-04$, HR=2.6), SDC1 ($p=2.81E-04$, HR=2.57), for OS. The most significant gene ontology biological processes upregulated in tumors with a worse prognosis include GO:0000184, nuclear-transcribed mRNA catabolic process, nonsense-mediated decay ($p=6.64E-18$); GO:0045047, protein targeting to ER ($p=6.64E-18$); GO:0006614, SRP-dependent cotranslational protein targeting to membrane ($p=9.08E-18$); GO:0072599, establishment of protein localization to endoplasmic reticulum ($p=1.30E-17$); and GO:0006613, cotranslational protein targeting to membrane ($p=1.90E-17$).

Conclusions: Our results help to prioritize genes and to neglect those which are most likely to fail in studies aiming to establish new clinically useful biomarkers and therapeutic targets in BLBC.

PO2-03-09

Cost-effectiveness analysis of RAD51 functional biomarker for platinum sensitivity in the GeparSixto trial

Presenting Author(s) and Co-Author(s):

I. Pimentel. Hospital Universitari Vall D'Hebron, Barcelona, Spain, Catalonia, Spain

C. Forné. Department of Basic Medical Sciences, University of Lleida, Lleida, Spain, United States

A. Llop-Guevara. Vall d'Hebron Institute of Oncology, Spain

M. Carles-Lavila. Department of Economics, Rovira I Virgili University, Tarragona, Spain, United States

V. Serra. Vall d'Hebron Institute of Oncology, Spain

M. Rué. Department of Basic Medical Sciences, Lleida Biomedical Research Institute (IRBLleida), University of Lleida, Lleida, Spain, United States

J. Balmaña. Vall d'Hebron University Hospital, Barcelona, Spain

Background: Homologous recombination repair deficiency (HRD) has long been recognized as a predictive biomarker for platinum sensitivity and is present in up to 60% of early triple negative breast cancers (TNBC). Different commercial and lab-developed assays to measure HRD are available, but they do not necessarily reflect homologous recombination functionality. Functional HRD, defined by a low score in RAD51 foci, is emerging as an accurate and dynamic biomarker to predict DNA damaging agents' response. We performed a cost-effectiveness evaluation of the RAD51 test compared to tumor BRCA1/2 mutation (tBRCA1/2) or genomic HRD by Myriad Mychoice® to identify patients sensitive to platinum-based chemotherapy within the GeparSixto trial. Methods: The effectiveness measure was the primary outcome of the GeparSixto study: rate of pathological complete response (pCR), defined as ypT0 ypN0. The pharmacological costs were calculated following treatment protocol of GeparSixto where TNBC patients received neoadjuvant paclitaxel plus Myocet®-nonpegylated liposomal doxorubicin (PM) or PM plus carboplatin (PMCb), both arms including bevacizumab. Bevacizumab was excluded from the cost analysis as it is not administered by standard practice. The cost of a session/stay at the day hospital was added, as well as the cost of the test used, comparing 4 scenarios: All comers (assuming all patients receiving PMcB); RAD51 test (assuming RAD51 $\leq 10\%$ received PMcB and RAD51 $> 10\%$ received PM); tBRCA1/2 test (assuming tBRCA1/2 mutated received PMcB and tBRCA1/2 non-mutated received PM) and genomic HRD by Myriad Mychoice® (HRD score ≥ 42 received PMcB, and HRD score < 42 received PM). The available commercial costs were considered for tBRCA1/2 and Myriad Mychoice®, and the VHIO performance cost was considered for the RAD51 test. Parameter uncertainties were assessed by means of one-way and probabilistic sensitivity analyses. Results: All comers total cost was 20,530€ per patient, with associated pCR rate of 54.5%. Functional RAD51 test was associated with a pCR probability of 55.1% with a Δ cost of 198€, as opposed to tBRCA1/2 which presented a pCR rate of 40.1% with a Δ cost of 814€, and genomic HRD with 47% pCR rate and the higher Δ cost of 1,023€ per patient, when compared to all comers. The incremental cost-effectiveness ratio (Δ cost / Δ pCR) was 33,000 for RAD51 test and dominated in both tBRCA1/2 and genomic HRD tests. These results were robust on one way and probabilistic sensitivity analyses. Conclusion: The most efficient scenarios are the functional RAD51 test and all comers. Both tBRCA1/2 and genomic HRD by Myriad Mychoice® scenarios provide worse health outcomes at a higher cost, based on the data of the GeparSixto trial. This study highlights the potential overall benefit of functional HRD biomarkers to predict

PARPi sensitivity.

PO2-03-10

Association of pathologic complete response with the 27-gene IO score and week 3 IOpath response following neoadjuvant pembrolizumab +/- intralymphatic cytokines in the neoIRX trial

Presenting Author(s) and Co-Author(s):

D. Page. Robert W. Franz Cancer Research Center and Alliance, Portland, Oregon, United States

A. Su. Earle A. Chiles Research Institute, United States

N. Moxon. Providence Cancer Institute, Portland, Oregon, United States

S. Mellinger. Providence Cancer Institute, Portland, Oregon, United States

T. Kelly. Providence Cancer Institute, Portland, Oregon, United States

N. Fredrich. Providence, United States

A. Seino. Earle A. Chiles Research Institute, United States

Z. Topp. Earle A. Chiles Research Institute, United States

P. Newell. Earle A. Chiles Research Institute, United States

K. Massimino. Earle A. Chiles Research Institute, United States

S. Aliabadi. Oregon Clinic, United States

Y. Wu. Earle A. Chiles Research Institute, United States

M. Martel. Earle A. Chiles Research Institute, United States

W. Redmond. Earle A. Chiles Research Institute, United States

Y. Kogushi. Earle A. Chiles Research Institute, United States

G. Mcgee. Earle A. Chiles Research Institute, United States

A. Mendez-Torres. Earle A. Chiles Research Institute, United States

Z. Sun. Earle A. Chiles Research Institute, United States

J. Imatani. Earle A. Chiles Research Institute, United States

A. Conlin. Providence Cancer Institute, United States

K. Perlewitz. Earle A. Chiles Research Institute, United States

T. Nielsen. Oncocyte, United States

S. Stanton. Earle Chiles Research Institute, Portland, Oregon, United States

Introduction: Novel biomarker strategies are needed to identify immunotherapy (IO)-sensitive early-stage triple-negative breast cancers (TNBC). We recently reported a phase II trial (neoIRX, NCT04373031) evaluating induction IO (pembrolizumab +/- intralymphatic cytokines, IRX-2, comprised of physiologic doses of IL-2, IFN γ , and other cytokines derived from activated donor lymphocytes) preceding de-escalated neoadjuvant chemotherapy (NAC). Here, we report associations of response with the 27-gene IO score (DetermaIO), a commercially available RT-qPCR assay shown to predict IO response in the neoPACT, I-SPY2, and neoTRIP trials. We also propose a novel surrogate endpoint, entitled "IOpath" response, that characterizes radiographic and pathologic response following single-cycle IO and may be useful for guiding NAC de-escalation or omission. Methods: Subjects with stage II-III TNBC were randomized 1:1 (n=12) to receive induction pembrolizumab (200mg IV) +/- peri-areolar IRX-2 (IRX-2 arm: 1 ml SQ x2 daily for 10 days + cyclophosphamide 300 mg/m² IV x 1) preceding initiation of

pembrolizumab + NAC. The primary endpoint was pathologic complete response (pCR) rate. Post-induction IO response (IOpath) was assessed by week 3 ultrasound (US) and biopsy. IOpath response was designated as IOpath-NR (non-response: radiographic progression and/or biopsy non-response [neither treatment effect nor TILs expansion]), IOpath-PR (partial response: viable tumor with either treatment effect or TILs expansion), IOpath-CR (complete response: treatment effect with no viable tumor), or IOpath-NE (not evaluable). Results: The IRX-2 arm achieved 83% pCR (n=5/6, CI 36-100%) compared to 33% pCR with pembrolizumab alone (n=2/6, CI 4-78%) and was well tolerated (67% grade I skin bruise). Baseline 27-gene IO score predicted pCR (AUC 0.77, IO+: 5/6 pCR; IO-: 2/6 pCR) and week 3 IOpath response (AUC 0.85, IO+: 3/5 IOpath-CR/PR; IO-: 1/4 IOpath-PR), and outperformed TILs (AUC for pCR: 0.66; AUC for IOpath: 0.68) and CPS score (AUC for pCR: 0.63, AUC for IOpath: 0.58). Week 3 IOpath response was associated with 100% pCR (IOpath+: 4/4 pCR; IOpath-: 2/5 pCR). Conclusion: A subset of TNBCs experience brisk IO response following single-cycle IO (IOpath response), which is associated with 100% pCR in this preliminary dataset, highlighting IOpath as a potential surrogate biomarker to guide NAC de-escalation or omission in early-stage TNBC. Baseline 27-gene IO score predicts pCR and week 3 IOpath response. A future study is planned (neoINBRX) to evaluate the feasibility of combining baseline IO score with week 3 IOpath response to identify and treat IO-sensitive tumors with chemotherapy-sparing IO combination therapy. Acknowledgements: The study was funded in part by Merck, Sharpe, & Dohme as part of the Merck Investigator Studies Program, and by BrooklynImmunotherapeutics.

PO2-03-11

A novel peripheral CD4+ T cell immune network associated with response to PD-1 inhibitor in early-stage triple negative breast cancer

Presenting Author(s) and Co-Author(s):

Z. Wang. Fudan University Shanghai Cancer Center, United States

Z. Shao. Fudan University Shanghai Cancer Center, United States

B. Xiu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

A novel peripheral CD4+ T cell immune network associated with response to PD-1 inhibitor in early-stage triple negative breast cancer Background: Immunotherapy has showed benefits in early-stage triple-negative breast cancer (eTNBC). However, there is an urgent need to identify novel biomarkers that can guide stratification for immunotherapy in eTNBC. Anti-tumor immunity is a systemic response that encompasses the mobilization of dendritic cells, lymphocytes, and myeloid cells involving the tumor, blood, and lymph nodes. The activation of anti-tumor immune responses via immunotherapy is expected to reflect in the subset change of circulation. Combined with advantage of dynamic monitoring by liquid biopsy, we detected peripheral blood in the eTNBC patients under immunotherapy to explore potential immune therapeutic predictive subsets. Methods: Single-cell (sc) RNA sequencing was utilized to determine the transcriptomics of immune cells in the peripheral blood. Meanwhile scTCR sequencing was used to trace the dynamic changes of clonotypes under multi-therapy. Nanostring analysis of primary tumor and in vivo models were used to validate the mechanism of immune crosstalk. Prediction index was built based on the proportion of immune subsets at each time point and change of tumor size in each patient. Results: 12 eTNBC patients who participated in neoadjuvant chemotherapy in combination with PD-1 inhibitor (Toripalimab) clinical trial were included in this study. The clinical trial consists of two stages. All eligible patients received four cycles of EC (cyclophosphamide plus epirubicin) regimen and followed four cycles of nab-paclitaxel plus PD-1 inhibitor. Among the 12 patients, 5 patients achieved pCR, while the remaining 7 patients were non-pCR. Peripheral blood samples were collected at baseline, after chemotherapy induction, and on PD-1 inhibitor treatment for scRNA- and scTCR-sequencing. Through prediction index, a novel predictive pattern based on ratio of memory T cells (central memory T and resident memory T) to effective T cells in the peripheral was vividly defined, by which the patients could be classified into C-type (memory T cells dominated) and E-type (effective T cells dominated). The C-type indicated better efficacy of immunotherapy combination therapy, while the E-type suggested better efficacy of chemotherapy alone. Meanwhile, a novel peripheral CD4+Trm (resident-memory-like) subset that possessed both strong differentiation potential and memory function was higher in pCR group at baseline. TCR-tracing analysis revealed that the new clones induced by chemotherapy mainly belong to the CD4+ Trm and CD8+ CD161+ Tcm (central memory) subsets, and the upregulation of CD8+ CD161+ Tcm during therapy was a dynamic predictor for immunotherapy benefits. Besides, most of CD4+Trm transitioned into CD4+Th1-like cells as an activated status, which considered CD4+Trm as a group of reservoirs with polyclonality and differentiation potential for tumor-killing. Meanwhile, the increase in CD5+ cDC2 (type 2 conventional dendritic cell) after chemotherapy was associated with enhanced antigen-

presenting function and cell communication and co-stimulation with CD4⁺ Trm cells which helped the activated transition from CD4⁺Trm into CD4⁺Th1-like cells in lymph nodes. Moreover, CD4⁺Th1-like cells increased secretion of Th1 cytokines thus leading to promote CD8⁺CD161⁺ Tcm upregulation and tumor-infiltration after immunotherapy. Conclusions: A novel peripheral pattern based on subsets of T cells as C-type and E-type was established as potential predictors for immunotherapy stratification in eTNBC patients. Meanwhile, a novel peripheral CD4⁺Trm immune network was identified, in which CD5⁺cDC2 activated the transition of CD4⁺Trm into CD4⁺Th1-like subset leading to activation and tumor-infiltration of CD8⁺CD161⁺Tcm. All the above provided potential therapeutic targets for enhancing immunotherapy.

PO2-03-12

Dose-Dense Doxorubicin plus Cyclophosphamide (ddAC) and Impact of Chemotherapy Sequence in a Modified KEYNOTE-522 Regimen for Neoadjuvant Treatment of Triple Negative Breast Cancer: Real World Experience

Presenting Author(s) and Co-Author(s):

N. Mai. Memorial Sloan Kettering Cancer Center, United States

S. Myers. Memorial Sloan Kettering Cancer Center, United States

S. Shen. Memorial Sloan Kettering Cancer Center, United States

S. Downs-Canner. Memorial Sloan Kettering Cancer Center, United States

Y. Chen. Memorial Sloan Kettering Cancer Center, United States

T. Traina. Memorial Sloan Kettering Cancer Center, United States

N. Abuhadra. Memorial Sloan Kettering Cancer Center, United States

Background:

Standard of care systemic treatment for early stage triple negative breast cancer (TNBC) consists of neoadjuvant chemoimmunotherapy based upon the results of KEYNOTE 522 (KN-522). The KN522 regimen utilized q3week dosing for doxorubicin plus cyclophosphamide (AC); however, dose-dense AC (ddAC) has shown superior OS compared to q3week AC in anthracycline and taxane-based regimens (per CALGB 9741 and EBCTCG analyses). We now present a retrospective study of patients treated with ddAC in a modified KN-522 regimen and report real world feasibility, safety, and efficacy endpoints, including exploration of whether sequencing ddAC before or after carboplatin/paclitaxel (CbT) plus pembrolizumab impacts outcome.

Methods:

Patients with TNBC treated at MSK from August 2021 to September 2022 with a preoperative KN-522 regimen were eligible for inclusion. Clinicopathological and demographic data were obtained from chart review. The primary goal of this study was to describe pathologic complete response (PCR) rate, incidence of treatment-related toxicities resulting in treatment delays, and type of toxicity. Treatment delays for toxicity were defined as a >1 week delay in treatment or discontinuation of a treatment regimen component due to a medical reason. Exploratory analysis was conducted to assess efficacy and toxicity of ddAC before or after CbT as well as rate of GCSF usage with CbT. Baseline characteristics, incidence and type of delays, and treatment outcomes were compared between ddAC first and CbT first using two sample non-parametric tests.

Results:

129 TNBC patients met eligibility as defined above. Median age of diagnosis was 50. Clinical stage at diagnosis: Stage I 6%, Stage II 83%, and Stage III 11%. 128 patients received ddAC and 1 patient received AC q3week. Of the 128 patients, 54% received ddAC first while 46% received CbT first. Overall PCR rate of 56%. Treatment-related toxicity leading to chemotherapy delays was 61% and immunotherapy delays was 30%. Most chemotherapy delays were due to cytopenias (79%), with neutropenia (66%) most common. Adrenal insufficiency (4%) and hepatitis (5%) were the most common immune-related toxicities leading to delays. Overall, PCR rate was not affected by chemotherapy delays (No Delay 50% vs. Delay 60%, RR 0.83, 95%CI 0.60-1.15, p=0.25) or immunotherapy delays (No Delay 56% vs. Delay 58%, RR 0.96, 95%CI 0.69-1.33, p=0.81). Exploratory analysis comparing sequencing of

ddAC vs CbT first showed incidence of CbT delays was 58% in patients treated with ddAC first and 27% in CbT first. Incidence of ddAC delays was 3% in patients treated with ddAC first and 7% in CbT first. Incidence of delays in both ddAC and CbT was 9% in ddAC first and 10% in CbT first. There was no difference in PCR rate (ddAC 55% vs. CbT 58%, RR 0.96, 95%CI 0.70-1.30, p=0.77) or rate of immunotherapy delays (ddAC 32% vs. CbT 34%, RR 0.93, 95%CI 0.55-1.57, p=0.79) based on sequence of chemotherapy. However, ddAC first compared to CbT first correlated with a significant increase in the incidence of overall treatment delays (ddAC 70% vs. CbT 51%, RR 1.37, 95%CI 1.02-1.84, p=0.03), use of GCSF during CbT (ddAC 55% vs. CbT 34%, RR 1.60, 95%CI 1.06-2.45, p=0.02), and treatment-limiting cytopenias at any time point before surgery (ddAC 59% vs. CbT 31%, RR 1.95, 95%CI 1.26-3.00, p=0.001).

Conclusions:

These real world data support the feasibility and tolerability of ddAC in a modified KN522 regimen. Exploratory analysis on sequencing of ddAC vs. CbT first in this regimen suggests that efficacy is comparable, yet ddAC first is significantly associated with higher rates of treatment delays and cytopenias. Overall, our experience suggests ddAC is a safe and viable modification to KN-522, and sequencing ddAC after CbT may reduce the risk of treatment induced cytopenias.

PO2-04-01

Predictors of exceptional response to first line HER2-targeted therapy for metastatic breast cancer

Presenting Author(s) and Co-Author(s):

S. Morganti. Dana-Farber Cancer Institute; Harvard Medical School; Broad Institute of MIT and Harvard, United States

T. Li. Dana-Farber Cancer Institute, United States

K. Santos. Dana-Farber Cancer Institute, United States

M. Hughes. Dana Farber Cancer Institute, United States

N. Priedigkeit. Dana-Farber Cancer Institute / Broad Institute of MIT and Harvard, Boston, Massachusetts, United States

Y. Li. Medical Oncology, Dana-Farber Cancer Institute, United States

M. Lipsyc-Sharf. Dana-Farber Cancer Institute, United States

G. Kirkner. Medical Oncology, Dana-Farber Cancer Institute, United States

J. Files. Dana-Farber Cancer Institute, United States

J. Kasparian. Dana-Farber Cancer Institute, United States

E. Grant. Dana-Farber Cancer Institute, United States

G. Gupta. Dana-Farber Cancer Insitute, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Cherniack. Medical Oncology, Dana-Farber Cancer Institute; Genome Data Analysis Center, Broad Institute; Genomic Data Analysis Network, National Cancer Institute, United States

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

H. Parsons. Dana Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

Background

HER2-targeted therapies have transformed the trajectory of HER2-positive (HER2+) metastatic breast cancer (MBC), with a subgroup of responders remaining on first line (1L) therapy for many years (yrs). Despite these promising outcomes, the paradigm remains palliative, with some patients (pts) receiving therapy indefinitely. Opportunities to interrupt therapy are controversial and anecdotal in the setting of a limited understanding of long-term responders and lack of predictive biomarkers.

Methods

We identified prevalent pts with HER2+ MBC seen and consented at Dana-Farber Cancer Institute between 2010 and 2023, regardless of the original date of MBC diagnosis. Exceptional responders (ExRes) were pts without evidence of progressive disease (PD) 3 yrs from initiation of 1L therapy for MBC. Conventional responders (ConRes) were pts who experienced PD within 3 yrs of 1L treatment initiation. We compared clinicopathological characteristics and treatment patterns between ExRes and ConRes using Chi-square or Wilcoxon test. We analyzed median time to treatment switch due to PD (TTS-PD) – i.e., time from metastatic

diagnosis to 1L treatment end due to PD - and overall survival, via the Kaplan-Meier method and with a landmark analysis at year 3 (Y3). Our primary aim was to identify predictors of exceptional response to 1L anti-HER2 therapy.

Results

Of 635 pts with HER2+ MBC, we identified 147 ExRes and 370 ConRes and excluded 118 pts due to follow up \leq 3 yrs and no PD events. Median follow up was 7.1 yrs (IQR 5.5-11.0) for ExRes and 7.1 yrs (IQR 4.0-11.4) for ConRes. Median age at MBC diagnosis was 50.7 yrs (range 21.9-91.9) for ExRes and 49.8 yrs (26.9-82.3) for ConRes. ExRes presented more often with de novo MBC than ConRes (52.1 vs 30.6%, $p < 0.0001$). On metastatic samples, more ExRes than ConRes had HER2 3+ tumors by immunohistochemistry (IHC) (93.7 vs 81.0%, $p = 0.002$), whereas the proportion of ER-positive disease was similar between the two groups (45.6 vs 53.4%, $p = 0.1$). Most pts received (neo)adjuvant anti-HER2 agents in both groups (62.5 vs 72.7%, $p = 0.1$). More ExRes than ConRes (55.8 vs 42.7% $p = 0.007$) received 1L chemotherapy (CT) plus trastuzumab (H)/pertuzumab (P). Alternative 1L treatments were CT plus H (26.5 vs 25.7%), H +/- P +/- endocrine therapy (8.2 vs 10.5%), T-DM1 (2 vs 9.2%), tyrosine kinase inhibitors-based regimens (7.5 vs 10.8%). For pts with recurrent MBC, disease-free interval was longer for ExRes than ConRes (median 4.7 vs 3.4 yrs, $p = 0.01$). Visceral involvement at MBC relapse was similar for ExRes and ConRes (78.2 vs 77.8%, $p = 0.9$). Brain metastases at any timepoint were less frequent among ExRes than ConRes (42.9 vs 55.1%, $p = 0.01$).

Among ExRes, 70 (47.6%) pts experienced PD after Y3, with a median TTS-PD of 4.6 (4.1-5.1) yrs. In a landmark analysis at Y3, the 2-year TTS-PD was 68.5% (95% CI: 59.8%-75.7%) (5 yrs from treatment start), and 4-year overall survival was 86.5% (95% CI: 78.1%-91.9%) (7 yrs from treatment start). ConRes received a median of 5 (1-19) treatment regimens for MBC, with a median 1L TTS-PD of 12 (10.8-13) mo. A total of 89 (60.5%) ExRes and 214 (57.8%) ConRes underwent tumor sequencing. Data comparing genomic features between ExRes and ConRes will be presented.

Conclusions

In this prospective cohort, 28% of pts with HER2+ MBC had exceptional response to 1L anti-HER2 therapy. Consistent with prior data, ExRes present more frequently with de novo disease and HER2 IHC 3+ tumors. In our cohort, ExRes had a median follow-up of 7.1 years and 52.4% never experienced PD. Although a significant proportion of pts with HER2+ MBC derive long-term benefit from anti-HER2 therapy, the treatment paradigm remains palliative, and it is unknown whether biomarkers may reliably predict exceptional response and guide future treatment. Ongoing work will explore whether genomic features vary between ExRes and ConRes.

PO2-04-02

Trends in Disparities and Transitions of target therapy in Patients With ERBB2 Positive Early Breast Cancer in China and the US, 2011 to 2021

Presenting Author(s) and Co-Author(s):

J. Li. fifth medical center of PLA general hospital, United States

J. Zhou. China Pharmaceutical University, United States

H. Wang. Affiliated Hospital of Qingdao University, United States

Z. liu. Affiliated Cancer Hospital of Zhengzhou University, United States

Z. Fan. First Hospital of Jilin University, United States

Y. Liu. Peking University First Hospital,, United States

C. Geng. Breast Center, the Fourth Hospital of Hebei Medical University, China (People's Republic)

Z. Jiang. Medicine–Oncology, The Affiliated Hospital of Military Medical Sciences (The 307th Hospital of Chinese People's Liberation Army), Beijing, China, United States

Background. Diagnosis and treatment of breast cancer have been profoundly improved in China recently. However, trends in disparities and transitions of target treatment in early stage with ERBB2 positive between China and United States are not well known. **Methods.** This cross-sectional study used Chinese Society of clinical oncology breast cancer (CSCO BC) database from hospitals in 13 provinces of China and Flatiron database from more than 280 US community oncology clinics. Patients with ERBB2 positive and diagnosed as stage I to III breast cancer from 2011 to 2021 were collected. The distribution of target therapy was examined overall and by years. **Results.** A total of 10245 early-stage breast cancer with ERBB2 positive diagnosed from 2011 to 2021 were screened from the CSCO BC database(n=8446) and the Flatiron Database(n=1799). The median age at diagnosis for Chinese and US was 47 years old and 63 years old. For neoadjuvant therapy, the annual rate of trastuzumab-therapy increased from 0.4% in 2011 to 33% in 2021 in CSCO BC database, while rate of trastuzumab and pertuzumab therapy increased from 0.6% in 2016 to 42% in 2021. The proportion of trastuzumab therapy in Flatiron database decreased from 50% in 2011 to 23% in 2021, while the proportion of dual target therapy increased from 11% in 2013 to 67% in 2021. In adjuvant setting, the trastuzumab therapy increased from 6.8% in 2011 to 37% in 2021 in CSCO BC database, with highest proportion of 65% in 2018. Only 0.1% of patients received dual target therapy in 2018, the proportion increased to 32% in 2021. In Flatiron database, the trastuzumab therapy decreased from 60% in 2011 to 50% in 2021, while rate of trastuzumab and pertuzumab therapy increased from 5% in 2015 to 10% in 2021. Further follow-up is needed for survival data from two databases. **Conclusions.** Although significant differences were found between the China and US in target therapy, the disparities have been gradually narrowed. Use of trastuzumab in China has overtaken that in US since 2017 attributed to the effort of China's health reform in medical insurance and the promotion of guidelines.

PO2-04-03

BL-M07D1, an antibody-drug conjugate directed to HER2 in patients with locally advanced or metastatic Breast Cancer with HER2-positive/low-expression and other solid tumors: Results from a first-in-human phase 1 study

Presenting Author(s) and Co-Author(s):

E. Song. Breast Tumour Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

H. Yao. Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Breast Tumor Center, Department of Medical Oncology, Phase I Clinical Trial Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

M. Sun. Jinan Central Hospital, China (People's Republic)

H. Zong. The First Affiliated Hospital of Zhengzhou University, China (People's Republic)

R. Lin. Fu Jian Cancer Hospital, United States

W. Zou. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., United States

M. Ding. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., China (People's Republic)

J. Yu. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., China (People's Republic)

S. Xiao. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., China (People's Republic)

H. Wang. SystImmune Inc., United States

H. Zhu. SystImmune Inc., United States

M. Olivo. SystImmune Inc, Port Jefferson, New York, United States

Y. Zhu. SystImmune Inc., United States

Background: BL-M07D1 is an anti-HER2 antibody-drug conjugate (ADC) comprised of a humanized anti-HER2 antibody, a cathepsin B cleavable linker, and a novel topoisomerase I inhibitor (Ed-04).

Methods: This study included subjects with locally advanced or metastatic HER2 expressing (positive/low) breast cancer (BC) and other solid tumors. BL-M07D1 would be administered at doses of 1.0mg/kg Day 1 & Day 8 every 3 weeks (D1D8 Q3W) or 2.6, 3.2, 3.8, 4.4, 5.0, 5.6, 6.2, 6.8 and 7.4 mg/kg Day 1 every 3 weeks (D1Q3W) during dose escalation (D-ESC). A subset of patients (pts) will be enrolled in the dose-expansion phase (D-EXP) at D1 Q3W regimens.

Results: As of June 25, a total of 75 pts have been treated with at least one dose of BL-M07D1, with 22 pts in the D-ESC phase and 53 in the D-EXP phase. Among the 75 pts, 1 received 1.0 mg/kg D1D8Q3W and 74 were treated on the D1Q3W schedule. Dose-limiting toxicity (DLT) was observed at 6.2mg/kg (febrile neutropenia and G3 thrombocytopenia lasting >7 days in one patient). The maximum tolerated dose (MTD) has not been reached yet. D-EXP dose levels included 3.8, 4.4, 5.0 and 5.6mg/kg D1 Q3W. This study enrolled 62 patients with BC, 6 with gastric cancer, 4 with colorectal cancer and 3 with non-small cell lung cancer.

The most common TEAEs (>10%, all grade /≥G3) were leukopenia (79%/24%), neutropenia (69%/39%), anemia (63%/11%), nausea (47%/0%), thrombocytopenia (37%/9%), vomiting (37%/1%), decreased appetite (27%/0%), lymphopenia (24%/8%), alopecia (23%/0%), asthenia (19%/0), gamma-glutamyl transferase increased (17%/0%), aspartate aminotransferase

increased (17%/0%), constipation (13%/0%), diarrhea (12%/0%), hypertriglyceridemia (12%/0%), urinary tract infection (11%/1%), COVID-19 (11%/0%), occult blood positive (11%/0%), pyrexia (11%/0%). No ILD was observed. Forty-five pts with BC were evaluated for efficacy (i.e., had at least one post-baseline tumor assessment). Updated efficacy and pharmacokinetic (PK) results will be presented at the meeting.

Conclusions: BL-M07D1 demonstrated encouraging efficacy in heavily pretreated HER2 expressing cancers, especially in HER2+ BC. The safety profile showed adequate safety and tolerability.

Clinical trial identification: NCT05461768.

Efficacy in Patients with Breast Cancer

	HER2+BC (n=29)	HER2+BC Prior HER2-ADC ^a (n=9)	HER+HER2-Low BC (n=16)
Median prior treatment line (range)	3 (1-13)	4 (3-13)	3.5 (1-6)
Best overall response			
CR	1	0	0
PR	24	8	6
ORR	12	4	2
PR+on-going	9	3	5
PR+ORR	0	0	1
SD (n with shrinkage)	7 (7 ^b)	1 (1 ^b)	5 (3 ^b)
SD	0	0	0
ORR, %	75.5%	88.9%	100%
(95% CI)	(66.5-89.7)	(83.5-99.7)	(100.0-100.0)
DCR, %	100%	100%	100%
(95% CI)	(88.1-100)	(86.4-100)	(79.4-100)

- 8/9 pts received prior HER2-ADC with microtubule inhibitor. 1/9 pts received prior HER2-ADC with TOPI inhibitor.
- 6 pts with tumor shrinkage are still on-going.
- All pts with tumor shrinkage are still on-going.

PO2-04-04

Trastuzumab deruxtecan for the treatment of patients with HER2-positive breast cancer with brain and/or leptomeningeal metastases: an updated overall survival analysis using data from a multicenter retrospective study (ROSET-BM)

Presenting Author(s) and Co-Author(s):

T. Yamanaka. Department of Breast Surgery and Oncology Kanagawa Cancer Center, Japan

N. Niikura. Tokai University School of Medicine, Isehara-shi, Isehara, Kanagawa, Japan

T. Nakayama. Osaka International Cancer Institute, United States

M. Yamamoto. Department of Breast Surgery, Hokkaido Cancer Center, United States

K. Matsuura. Department of Breast Oncology, Saitama Medical University International Medical Center, United States

K. Inoue. Saitama Cancer Center, Saitama, Japan

S. Takahara. Tazuke Kofukai, Medical Research Institute, Kitano Hospital, Osaka, Osaka, Japan

H. Nomura. Department of Digestive and General Surgery, Graduate School of Medicine, University of the Ryukyus, United States

S. Kita. Department of Medical Oncology, National Cancer Center Hospital, United States

M. Yamaguchi. JCHO Kurume General Hospital, Kurume city, Fukuoka, Japan

T. Aruga. Department Breast Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, United States

N. Shibata. Cancer Treatment Center, Kansai Medical University Hospital, United States

A. Shimomura. Department of Breast and Medical Oncology, National Center For Global Health And Medicine, Tokyo, Japan

Y. Ozaki. Department of Breast Oncology, Aichi Cancer Center Hospital, United States

S. Sakai. Department of Imaging Diagnosis and Nuclear Medicine, Tokyo Women's Medical University, United States

D. Takiguchi. Daiichi Sankyo Co., Ltd., United States

T. Takata. Daiichi Sankyo Co., Ltd., United States

A. Bastanfard. Daiichi Sankyo Co., Ltd., United States

K. Shiosakai. Data Intelligence Department, Daiichi Sankyo Co., Ltd., United States

J. Tsurutani. Advanced Cancer Translational Research Institute at Showa University, Tokyo, Shinagawa, Japan

Background: ROSET-BM (UMIN000044995) was a multicenter, retrospective chart review study of patients (pts) who received trastuzumab deruxtecan (T-DXd) treatment for HER2-positive (HER2+) metastatic breast cancer (MBC) with brain metastases (BM) and/or leptomeningeal carcinomatosis (LMC). Primary results (data cutoff, October 31, 2021) were presented at SABCS2022 (median progression-free survival [PFS], 16.1 months; 1-year overall survival [OS] rate, 74.9%; and median follow-up duration, 11.2 months). To confirm the long-term effectiveness of T-DXd in HER2+ MBC pts with BM and/or LMC, we conducted an updated analysis using additional 1-year follow-up data. Methods: Pts who started T-DXd treatment between May 25, 2020, and April 30, 2021, were registered for ROSET-BM. For this updated OS analysis, the extended observation period ended on October 31, 2022. OS, PFS,

and time to treatment failure (TTF) were evaluated. Median survival times and 95% CIs were calculated using the Kaplan–Meier method. In addition, prespecified and exploratory subgroup analyses were performed based on patient background characteristics. Univariate and multivariate Cox proportional hazards regression models were used to evaluate baseline prognostic factors for OS. Results: 104 pts from 62 institutions were included in this updated OS analysis. Median duration of follow-up was 20.4 months. Median number of prior lines of therapy was 4 (range, 1–15). Median time from first diagnosis of MBC to first administration of T-DXd was 37.5 months. Median time from first diagnosis of BM to first administration of T-DXd was 18.9 months. The prevalence of active BM, stable BM, LMC, and unclassified (image not evaluated) was 64.4% (n=67), 11.5% (n=12), 18.3% (n=19), and 5.8% (n=6), respectively. Median OS was not reached (NR) among all pts (1-year OS rate, 74.8%; 2-year OS rate, 56.0%). Subgroup analyses showed that median OS in pts with active BM was 27.0 months (95% CI, 16.4 to NR) and that median OS was NR in pts with stable BM or LMC (2-year OS rate for pts with stable BM, 71.6%; 2-year OS rate for pts with LMC, 61.6%). The results of univariate and multivariate analyses for OS showed no relevant baseline prognostic factors. Among all pts, median PFS was 14.6 months (95% CI, 10.6–20.8). Subgroup analyses showed that in pts with active BM, stable BM, and LMC, median PFS was 13.2 months (95% CI, 10.0–20.3), NR (95% CI, 5.3 to NR), and 17.5 months (95% CI, 8.3–22.1), respectively. Among all pts, median TTF was 9.3 months (95% CI, 6.3–11.8). The most common event and adverse event leading to discontinuation of T-DXd was progressive disease (37 pts, 35.6%) and interstitial lung disease (ILD; 24 pts, 23.1%), respectively. Median time to onset of an ILD event was 5.3 months (range, 0.7–20.0). ILD was grade 1 in 14 pts (13.5%), grade 2 in 3 pts (2.9%), grade 3 in 5 pts (4.8%), grade 4 in 2 pts (1.9%), and grade 5 in 0 pts. The Table summarizes the primary and updated results of ROSET-BM. Conclusion: The updated OS results of this retrospective chart review show that T-DXd has promising effectiveness in HER2+ MBC pts with long-term and heavily pretreated BM and LMC. This study was funded by Daiichi Sankyo Co., Ltd.

Primary and updated results from the ROSET-BM study

Variable	Primary results (N=104)	Updated results (N=104)
Median follow-up duration, months (95% CI)	11.2 (10.2–12.5)	20.4 (16.4–22.5)
Median OS, months (95% CI)	NR (16.1 to NR)	NR (20.6 to NR)
1-year OS rate, %	74.9	74.8
2-year OS rate, %	Not applicable	56.0
Median PFS, months (95% CI)	16.1 (12.0 to NR)	14.6 (10.6–20.8)
Median TTF, months (95% CI)	9.7 (6.3–13.0)	9.3 (6.3–11.8)
Discontinued due to ILD, %	18.3	23.1

The updated results show that T-DXd has promising effectiveness in HER2+ MBC pts with long-term and heavily pretreated BM and LMC.

PO2-04-05

**FINAL OUTCOME ANALYSIS FROM THE PHASE II TUXEDO-1 TRIAL OF TRASTUZUMAB-
DERUXTECAN IN HER2-POSITIVE BREAST CANCER PATIENTS WITH ACTIVE BRAIN
METASTASES**

Presenting Author(s) and Co-Author(s):

R. Bartsch. Medical University of Vienna, Department of Medicine I, Division of Oncology, Vienna, Austria, Austria

A. Berghoff. Medical University of Vienna, United States

J. Furtner. Danube Private University, United States

M. Marhold. Medical University of Vienna, United States

E. Bergen. Medical University of Vienna, United States

S. Roider-Schur. St. Josef Krankenaus Wien, United States

A. Starzer. Medical University of Vienna, United States

M. Mair. Medical University of Vienna, United States

H. Forstner. Medical University of Vienna, United States

B. Rottenmanner. Medical University of Vienna, United States

M. Aretin. Medical University of Vienna - Vienna General Hospital, United States

K. Dieckmann. Medical University of Vienna, United States

Z. Bago-Horvath. Department of Pathology, Medical University Vienna, United States

H. Haslachner. Medical University of Vienna, United States

G. Widhalm. Medical University of Vienna, United States

A. Ilhan-Mutlu. Medical University of Vienna, United States

C. Minichsdorfer. Medical University of Vienna, United States

T. Fuereder. Medical University of Vienna, United States

T. Szekeres. Medical University of Vienna, United States

L. Oehler. Department of Internal Medicine/Oncology, St Joseph Hospital, Vienna,, Austria

B. Gruenberger. LKH Wiener Neustadt, United States

G. Pfeiler. Medical University of Vienna, Austria, Vienna, Austria

C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria

A. Weltermann. Ordensklinikum Linz, United States

L. Berchtold. Medical University of Vienna, United States

M. Preusser. Medical University of Vienna, United States

Background Brain metastases (BM) are a severe complication of HER2-positive metastatic breast cancer. In the absence of any immediate indication for local therapy, the tyrosine-kinase inhibitor tucatinib combined with trastuzumab and capecitabine (TTC) is regarded as the preferred systemic treatment option for active BM, while data on the activity of antibody-drug conjugates (ADC) is limited. In the primary outcome analysis of TUXEDO-1, an intracranial response rate (RR) of 73.3% was reported with the ADC trastuzumab-deruxtecan (T-DXd). Here, we report final progression-free survival (PFS) and overall survival (OS) results of this

study. Patients and Methods: TUXEDO-1 is a prospective, single-centre, single-arm phase 2 trial. Adult patients with HER2-positive BC and active BM (newly diagnosed untreated or progressing after prior local therapy), prior treatment with trastuzumab and pertuzumab, ECOG performance status 0 or 1 without indication for immediate local therapy were accrued and received T-DXd until progression, unacceptable toxicity, or withdrawal for any other reason. The primary endpoint was intracranial RR centrally assessed by Response Assessment in Neuro-Oncology (RANO)-BM criteria in the intention-to-treat population; secondary endpoints included PFS, OS, safety, quality-of-life (QoL), and neurocognitive function. PFS and OS were estimated with the Kaplan-Meier method and analysed in the per-protocol population (PPP). Results A total number of 15 patients were accrued; one patient was found to have dural metastases only upon restaging, resulting in a PPP of 14 patients. Patients had received a median number of two prior treatment lines (range, 1-5), 60% had progressive brain metastases and 60% had received prior T-DM1. At 26.5 months median follow-up, median PFS was 21 months (95% CI 13.3-n.r.) and median OS was not reached (95% CI 22.2-n.r.). A total of 238 cycles of T-DXd were administered (median 11.5 cycles; range 4-42). With longer follow-up, no new safety signals were observed. The most common grade 3 adverse event (AE) was fatigue (n=3; 20%). A total of 8 serious AEs were reported in 8 patients. Grade 2 interstitial lung disease and a grade 3 symptomatic drop of left-ventricular ejection fraction were observed in one patient each. QoL and neurocognitive functioning were maintained over the entire treatment duration and a significant deterioration of global QoL was observed upon progression (p=0.036). Most patients received TTC (n=5) or local therapy (n=4) as next subsequent treatment line. Ancillary biomarker studies are ongoing, and results will be presented at the meeting. Discussion In TUXEDO-1, T-DXd yielded prolonged intra- and extracranial disease control in patients with active HER2-positive breast cancer BM. The safety profile was consistent with previous reports. T-DXd did not impair QoL and neurocognitive functioning was maintained. Results therefore support the concept of ADCs as systemic therapy for active BM.

PO2-04-06

Investigation of the genomic evolution of HER2-positive breast cancer following progression on dual HER2-targeted therapy with Trastuzumab and Tucatinib.

Presenting Author(s) and Co-Author(s):

E. Blackley. Peter MacCallum Cancer Centre, Abbotsford, Victoria, Australia

C. van Geelen. Peter MacCallum Cancer Centre, Melbourne, Australia

Y. Ko. Peter MacCallum Cancer Centre, United States

S. Wong. Peter MacCallum Cancer Centre, United States

M. Yeung. Peter MacCallum Cancer Centre, United States

S. Luen. Peter MacCallum Cancer Centre, United States

S. Dawson. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Background: Advanced HER2-positive breast cancer remains an incurable and highly morbid condition. One of the key challenges has been treatment of central nervous system (CNS) metastases, commonly seen in those with HER2-positive disease. Tucatinib is a recently approved treatment HER2-targeting tyrosine kinase inhibitor with proven CNS activity. There has been little analysis of potential genomic mechanisms of drug resistance.

Method: We retrospectively identified patients that were treated with tucatinib, capecitabine and trastuzumab. We collated baseline clinical data and treatment history and all tumour and plasma samples available were obtained for testing. DNA was extracted from plasma samples using the QIAamp DNA Mini Kit (Qiagen) on 4ml plasma samples. Targeted next generation sequencing (NGS) of serial tumour and plasma samples was performed using a custom hybrid capture assay that covered 180 genes known to be recurrently mutated in breast cancer focusing on the known genomic landscape of metastatic disease as well as the inclusion of specific actionable targets. Survival analyses was performed using Cox regression models.

Results: We identified 11 patients at our institution. Plasma samples were available for all 11 patients with a total of 107 serial samples across multiple time points, with a median of 8 (range 2-19) samples per patient. All 11 patients had baseline and End of Treatment (EOT) samples. In addition, 6/11 (54%) patients had tumour sequenced on the same NGS platform prior to commencement of therapy, with 12 individual tumour samples tested. The median PFS of our cohort was 9.6 months (4.0 - NR) with a median OS of 36.2 months (10.4-NR). 7/11 (64%) patients had CNS disease at baseline with their median PFS being 13.5 months (3.9-24.4) and median OS of 36.2months (10.4-NR).

Overall, we observed an average of 18.4 (4-35) mutations per patient in tumour, 5.1 (1-15) in baseline plasma and 5.8 (2-14) in EOT plasma. The most frequent mutations seen in baseline tumour samples were ERBB2 (92%), KMT2C (67%) and NCOR1 (58%) compared with KMT2C (64%), NOTCH4 (36%) and PIK3CA (27%) in baseline plasma. Patients with a lower number of ctDNA mutations at baseline showed a trend towards improved survival (PFS 14 months vs 7.5 months).

In this small cohort of patients we identified a higher than expected rates of KMT2C mutations. A KMT2C mutation was identified in 67% of samples which is higher than previously described rates of 7-15% in TCGA and METABRIC cohorts respectively.

The presence of a concordant ctDNA KMT2C mutation in baseline and progression samples was a poor prognostic indicator (mPFS 7.5 months) when compared with no KMT2C mutation (mPFS 15.5 months) $p = 0.14$ suggesting a possible mechanism of resistance to tucatinib.

Conclusions: In this retrospective analysis of patients treated with Tucatinib, Trastuzumab and Capecitabine we established the genomic landscape of heavily pre-treated, advanced HER2-positive disease is complex. We observed there may be a correlation with KMT2C mutations and poorer clinical outcomes, however given the very small number of patients this data remains hypothesis generating, requiring validation with larger datasets.

PO2-04-07

Efficacy and Safety of First-line Therapy in Patients with HER-2 positive Advanced Breast Cancer : A network Meta-analysis of Randomized Controlled Trials

Presenting Author(s) and Co-Author(s):

j. wang. The Second Hospital of Sanming, China (People's Republic)

Y. Yu. Fujian Cancer Hospital, United States

J. Zhang. Fujian Medical University Union Hospital, United States

C. Song. Fujian Provincial Cancer Hospital, United States

Background: The numerous but conflicting first-line treatment regimens for Her-2 positive advanced breast cancer necessitate a comprehensive evaluation to inform clinical decision-making. In this study, we conducted a Bayesian network meta-analysis (NMA) to compare the efficacy and safety of different interventions.

Methods: We systematically searched for relevant randomized controlled trials (RCTs) in Pubmed, Embase, Cochrane Library and online abstracts published by ASCO, SABCS. NMA was performed using R software, STATA and Review Manager 5.4 to calculate and analyze the primary endpoint progression free survival (PFS), as well as the secondary endpoints of overall survival (OS), objective response rate (ORR) and adverse events (AE) higher than grade 3.

Results: Out of the 8,603 manuscripts retrieved, we included 30 RCTs involving 12,045 patients in our analysis. Regarding PFS, the combination of trastuzumab with TKI was more favorable than dual-target therapy (hazard ratio=0.54, 95% [CI]: 0.40–0.72), and combination chemotherapy was superior to monotherapy (HR=0.66, 0.53-0.83). It is important to note that the addition of anthracycline did not result in improved PFS (HR=1.27, 0.87-1.86). For the HR+HER2+ population, dual-target plus endocrine therapy was more effective than single-target plus endocrine therapy (HR=0.65, 0.53-0.80). Monotherapy combined with dual-target therapy significantly improved OS and ORR compared to monotherapy with single-target therapy (HR=0.69, 0.56-0.84; OR=1.89, 1.34-2.65). A comprehensive analysis of both PFS and AE higher than grade 3 indicated that monotherapy plus dual-target therapy struck a balanced approach between effectiveness and toxicity compared to other regimens.

Conclusions: Monotherapy plus dual-target therapy remains the optimal choice among all first-line treatment options for advanced breast cancer. The combination of trastuzumab with TKI demonstrated a significant improvement in PFS, but further data are warranted to confirm the survival benefit.

Figure 1. Network diagrams of PFS, OS, ORR and adverse events higher than grade 3 in eligible experimental arms.

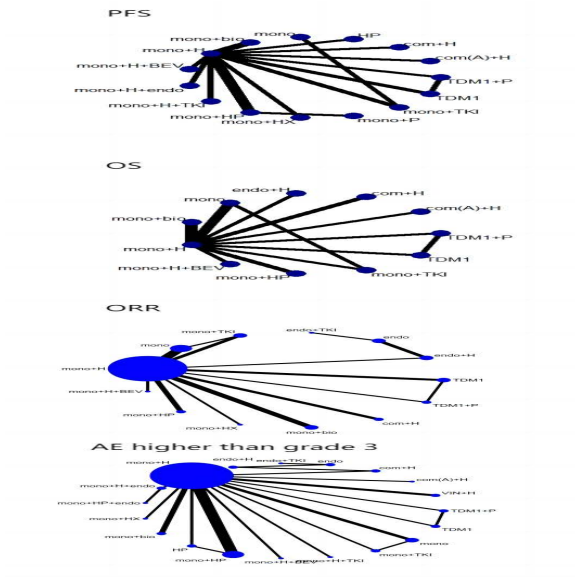
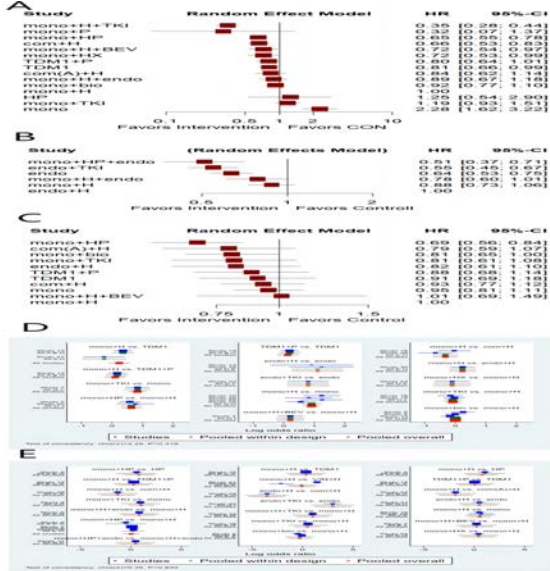
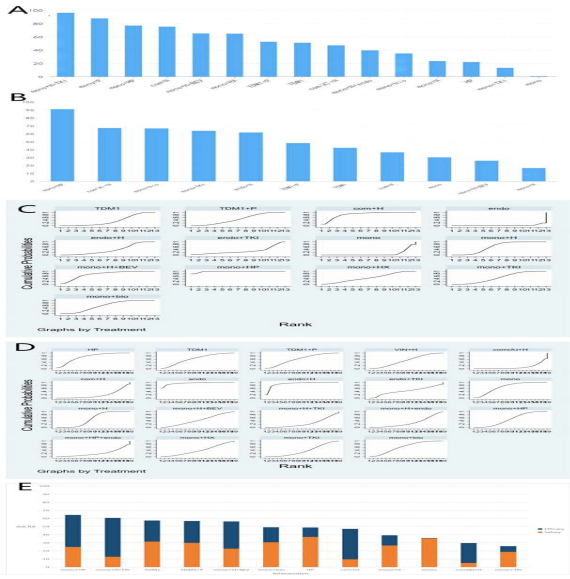


Figure 2. Forest plot of PFS, OS, ORR and adverse events higher than grade 3 in eligible experimental arms.



(A): PFS of HER2+ for experimental arms. (B): PFS of HR+ and HER2+ for experimental arms. (C): OS of HER2+ for experimental arms. (D): ORR of HER2+ for experimental arms. (E): Adverse events higher than grade 3 of HER2+ for experimental arms.

Figure 3. Each endpoint ranking for experimental arms. (SUCRA, surface under the cumulative ranking)



(A): PFS ranking for experimental arms. (B): OS ranking for experimental arms. (C): ORR ranking for experimental arms. (D): Adverse events higher than grade 3 ranking for experimental arms. (E): Experimental arms ordered by their overall probability as the best treatment in terms of both efficacy and safety

PO2-04-08

Translational insights from a phase 1, first-in-human (FIH) clinical trial of the anti-HER2 CAR macrophage CT-0508 in participants with HER2 positive metastatic breast cancer and other HER2 overexpressing solid tumors.

Presenting Author(s) and Co-Author(s):

Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States

J. Mortimer. City of Hope, Duarte, California, United States

P. Pohlmann. The University of Texas MD Anderson Cancer Center, United States

M. Johnson. Tennessee Oncology, Sarah Cannon Research Institute, Nashville, Tennessee, United States

R. Maziarz. OHSU Knight Cancer Institute, Portland, Oregon, United States

J. Specht. Fred Hutch Cancer Center, University of Washington, Seattle, WA, United States

C. Dees. University of North Carolina, Chapel Hill, North Carolina, United States

N. Ueno. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

Y. Yuan. Cedars-Sinai Cancer, Los Angeles, California, United States

M. Angelos. University of Pennsylvania Perelman Comprehensive Cancer Center, Philadelphia, Pennsylvania, United States

S. Gill. University of Pennsylvania Perelman Comprehensive Cancer Center, Philadelphia, Pennsylvania, United States

O. Shestova. University of Pennsylvania Perelman Comprehensive Cancer Center, Philadelphia, Pennsylvania, United States

J. Serody. University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

S. Priceman. City of Hope Cancer Center, Duarte, California, United States

R. Qureshi. Carisma Therapeutics, Philadelphia, Pennsylvania, United States

P. Sonawane. Carisma Therapeutics, Philadelphia, Pennsylvania, United States

S. Pierini. Carisma Therapeutics, Philadelphia, Pennsylvania, United States

M. Oliveira-Nunes. Carisma Therapeutics, Philadelphia, Pennsylvania, United States

D. Cushing. Carisma Therapeutics, Carisma Therapeutics, Pennsylvania, United States

M. Klichinsky. Carisma Therapeutics, Philadelphia, Pennsylvania, United States

T. Condamine. Carisma Therapeutics, Philadelphia, Pennsylvania, United States

R. Swaby. Carisma Therapeutics, Philadelphia, Pennsylvania, United States

K. Reiss. University of Pennsylvania Perelman Comprehensive Cancer Center, Philadelphia, Pennsylvania, United States

Background: In pre-clinical studies, CAR macrophages (CAR-M) phagocytose tumor cells, activate the tumor microenvironment (TME), recruit T cells, and induce anti-tumor T cell immunity. CT-0508 is a first-in-class CAR-M product comprised of autologous monocyte-derived macrophages expressing an anti-HER2 CAR. In pre-clinical models, anti-HER2 CAR-M was able to control the growth of syngeneic metastatic HER2+ breast cancer. Here we present preliminary clinical results and translational data from Group 1 of the CT-0508 Phase 1 FIH study.

Methods: This multi-center, open-label study is evaluating CT-0508's safety, tolerability, and manufacturing feasibility in 18 participants with advanced solid tumors overexpressing HER2 with progression on prior therapies. Monocytes are isolated from mobilized apheresis products, differentiated into macrophages, and engineered with an anti-HER2 CAR. Group 1 participants (n = 9) receive a fractionated dose on days 1, 3, 5 and Group 2 participants (n = 9) receive the full dose on day 1. CT-0508 is administered without preparative chemotherapy. Serial blood samples and biopsies (baseline and 2 post-treatment) are collected to investigate safety, pharmacokinetics, and mechanism of action. AU565 and 4T1-HER2 cell lines were utilized to model human and murine breast cancer, respectively, in vitro and in vivo.

Results: Nine participants (6F/3M) have been treated in Group 1, comprising breast (4), esophageal (2), cholangiocarcinoma, ovarian, and parotid gland cancers, with a median age of 58. Participants had received a median of 3 (range, 2-11) prior lines of therapy; 8 had received prior anti-HER2 therapy. CT-0508 was successfully manufactured and well tolerated with no dose-limiting toxicities. Three related SAEs occurred in 2 participants: grade 1 CRS with hospitalization for monitoring and grade 2 infusion reaction that resolved within 1 hour were reported in one participant. Grade 2 CRS with fever and hypoxia occurred in another participant and resolved within ~ 72 hours. Five additional participants experienced Grade 1-2 CRS and/or infusion reactions with rapid resolution. There were no cases of Grade 3 or 4 CRS. There were no major organ toxicities. Post-infusion cytokines were transiently elevated in most participants enrolled in group 1 and were self-limiting. Four of the 7 participants evaluated had stable disease. CT-0508 was transiently detectable in the blood and was detected in the TME of 8/9 participants. CT-0508 modulated the TME, leading to myeloid cell activation, effector T cell infiltration, activation, and proliferation. TCR sequencing demonstrated newly expanding T cell clones in the blood post-treatment that accumulated within the TME, suggesting expansion of tumor-reactive T cells upon CT-0508 infusion. Data from participants enrolled in Group 1 will be presented. Most of these patients were breast cancer patients with HER2 overexpressing metastatic disease.

Conclusions: CT-0508 was feasible to manufacture and had acceptable safety and tolerability. Early correlative data demonstrate trafficking, TME modulation, and induction of anti-tumor T cell immunity in participants with HER2 overexpressing solid tumors including metastatic breast cancer. The study is actively enrolling (NCT04660929).

PO2-04-09

Combination of the PLK1 Inhibitor Onvansertib and the PI3K α Inhibitor Alpelisib Overcomes Palbociclib Resistance in PIK3CA-mutated HR+ Breast Cancer.

Presenting Author(s) and Co-Author(s):

S. Sreekumar. Cardiff Oncology, United States

P. Painsec. Institut Curie, United States

D. Klein. Cardiff Oncology, United States

D. Gonzalez. Cardiff Oncology, United States

L. Sourd. Institut Curie, United States

E. Montaudon. Institut Curie, United States

T. Smeal. Cardiff Oncology, United States

E. Marangoni. Institute Curie, United States

M. Ridinger. Cardiff Oncology, United States

In the 1st line setting of hormone receptor-positive HER2 negative (HR+/HER2-) metastatic breast cancer, cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors (palbociclib, abemaciclib and ribociclib) are typically used in combination with endocrine therapy. Though initially effective, acquired resistance to either CDK4/6 inhibitors or endocrine therapy eventually leads to disease relapse in most patients. Activating mutations in PIK3CA, the gene encoding alpha catalytic subunit of phosphatidylinositol-4,5-bisphosphat 3-kinase (PI3K) are found in approximately 40% of HR+ breast cancer patients and have been implicated in mediating resistance to CDK4/6 inhibitors. The PI3K α inhibitor alpelisib is currently approved for PI3KCA-mutant HR+ breast cancer after progression on CDK4/6 inhibitors. However, drug-associated resistance mechanisms may limit its clinical benefit. Synergistic combination therapies have the potential to improve efficacy and overcome resistance mechanisms. Polo-like kinase 1 (PLK1) is a serine-threonine-protein kinase, key cell cycle regulator that controls G2/M entry and mitotic progression, and that has been shown to mediate resistance to palbociclib in HR+ breast cancer. Onvansertib is an oral and highly specific PLK1 inhibitor currently on clinical development in solid tumors and hematological malignancies. Here we evaluated the potential of onvansertib to increase the activity of alpelisib in PIK3CA-mutant HR+ breast cancer preclinical models.

The combination of onvansertib and alpelisib synergistically inhibited cell viability and/or colony formation in three PI3KCA-mutant HR+ breast cancer cell lines, MCF-7 (PIK3CA E545K), EFM-19 (PIK3CA H1047L), and T-47D (PIK3CA 1047R). A significant increase in apoptosis was observed in cells treated with the combination compared to either agent alone. We next tested the combination of onvansertib and alpelisib in patient-derived xenograft (PDX) models. For this purpose, palbociclib-resistant PIK3CA-mutant HR+ breast cancer PDXs were established from primary breast tumor (PDX HBCx-86, PIK3CA E545K) or from metastatic bone biopsies of patients who had progressed on endocrine therapy plus palbociclib (HBCx-180, PIK3CA H1047R) or on PI3K α inhibitor (HBCx-134palboR31, PIK3CA H1047R). PDX tumors were grafted subcutaneously in nude mice and mice were treated with vehicle, onvansertib (45 mg/kg, oral, 5 days a week), alpelisib (25mg/kg, oral, 5 days a week) or the combination. The combination was well tolerated and showed superior anti-tumor activity than the single agents in the 3 PDX models. In the HBCx-86 PDX, although none of the single agents showed activity, the combination induced potent tumor growth inhibition. In the metastasis-derived PDX HBCx-

134palboR31, the combination treatment induced pronounced tumor regression in 62% of mice (5/8), with complete response in 25% (2/8), while mice treated with the single agents showed tumor progression. Finally, in the HBCx-180 PDX, established from a patient with primary resistance to palbociclib, the efficacy of the combination was greater and more durable, with significant survival advantage, compared to the monotherapies.

Collectively, our preclinical findings suggest that co-targeting PLK1 and PI3K α with onvansertib and alpelisib respectively, may constitute a promising therapeutic combination strategy for patients with PIK3CA-mutant HR+ breast cancer failing to respond to first-line standard of care therapies.

PO2-04-10

Effect of Alpelisib Dose Modification for AE Management on Progression-Free Survival and Treatment Duration in SOLAR-1 and BYLieve Clinical Trials

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

A. Gennari. University of Piemonte Orientale, Italy

S. Chia. British Columbia Cancer Agency, Vancouver, British Columbia, Canada

D. Juric. Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

N. Vasan. Columbia University Irving Medical Center, New York, New York, United States

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

F. Lerebours. Institut Curie, United States

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

P. Razavi. Memorial Sloan Kettering Cancer Center, New York, New York, United States

J. Singh. Novartis Healthcare Private Limited, United States

Y. Chattar. Novartis, United States

M. Akdere. Novartis, United States

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

Background: Alpelisib (ALP) is an α -selective phosphatidylinositol 3-kinase (PI3K) inhibitor and degrader approved with fulvestrant (FUL) for patients (pts) with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)-mutated, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) following progression on/after endocrine therapy-based treatment (tx). Toxicity limited ALP exposure in some pts in the SOLAR-1 and BYLieve studies. On-target effects of PI3K inhibitors, including hyperglycemia, rash, and diarrhea, are among the most common adverse events (AEs) associated with ALP. During SOLAR-1, median onset times were 15 and 13 days for grade ≥ 3 hyperglycemia and rash and 46 days for grade 2/3 diarrhea. ALP dose modification can help manage AEs. We report efficacy of ALP + FUL as second-line (2L) tx in pts who underwent ALP dose reduction (DR).

Methods: Pts with PIK3CA mutations from SOLAR-1 and BYLieve, treated with ALP + FUL in 2L, were included. Landmark (LM) analyses were performed at 1, 2, 3, 4, 5, and 6 mo after tx initiation to evaluate the association between DR status (yes, no) with progression-free survival (PFS) and duration of tx (DoT), respectively. Pts with PFS or exposure time less than each LM time point were excluded from each LM analysis; pts were then grouped by DR (yes, no) before each LM time point. Median PFS and DoT were obtained using a modified Kaplan-Meier method. Alternatively, Cox regression analysis was used to assess the effect of DR on PFS and DoT, where 2 time-dependent variables were included separately in the model as a covariate: 1) DR status, and 2) DR groups (300 to 250 mg [1 DR] vs no DR, 300 to 250 to 200 mg [2 DR] vs no DR). Association between AEs and DR was evaluated descriptively. A matched analysis of AEs will be presented.

Results: In all, the analysis included 212 pts in 2L: 77 from SOLAR-1, and 95 and 40 from BYLieve Cohorts A and C, respectively. Of these pts, 92 (43.4%) had no DR and 120 (56.6%) had DRs: 70 (58.3%) had 1 DR, 43 (35.8%) had 2, and 7 (5.8%) had other types of DR. 25 of 92 pts (27.2%) with no DR and 40 of 120 pts (33.3%) with DR had ≥ 12 -mo exposure to ALP. Hazard ratios (HRs) for PFS and DoT in DR status for the LM analysis are shown (Table). HRs (95% CI) for PFS from the time-dependent covariate analyses were 1.28 (0.94-1.74) with DR status as the covariate, and 1.24 (0.88-1.76) and 1.21 (0.79-1.84) with DR group (1 DR vs no DR, 2 DR vs no DR) as the covariate, respectively; for DoT, these were 1.34 (1.00-1.79) for DR status, and 1.30 (0.93-1.80) and 1.30 (0.87-1.93) for DR group, respectively. During the treatment period, the incidence rate for grade ≥ 3 AEs was the highest for pts with 2 DR and lowest for those with no DR. Similarly, incidence of AEs leading to DR or tx discontinuation was higher in pts with 2 DR than 1 DR. The post-DR incidence rate for grade ≥ 3 AE was similar for pts with 2 DR or 1 DR. A matched analysis will assess the relationship between DR group and AE.

Conclusions: In this pooled analysis, regardless of if/when DR occurred, PFS was similar and DoT may be sustained with ALP + FUL. ALP DR can potentially reduce AEs, which may allow pts to remain on tx. Using DR as an AE management strategy may enable pts with PIK3CA-mutated, HR+, HER2- ABC to optimize tx duration and clinical benefit of ALP in the 2L.

Landmark Analyses of PFS and Tx Duration by DR Group (Yes vs No; Pooled FAS)

Table. Landmark Analyses of PFS and Tx Duration by DR Group (Yes vs No; Pooled FAS)

Landmark (month)	Patients remaining, ^a n (%) ^b	Dose reduction prior to landmark		Events, n	HR (95% CI) ^c
		Yes	n (%) ^d		
PFS					
1	189 (89.2)	Yes	57 (30.2)	48	1.15 (0.82-1.62)
		No	132 (69.8)	112	
2	162 (76.4)	Yes	65 (40.1)	55	1.08 (0.76-1.52)
		No	97 (59.9)	80	
3	150 (70.8)	Yes	63 (42.0)	52	1.05 (0.74-1.51)
		No	87 (58.0)	71	
4	132 (62.3)	Yes	62 (47.0)	51	1.02 (0.70-1.49)
		No	70 (53.0)	57	
5	122 (57.5)	Yes	57 (46.7)	46	0.97 (0.65-1.45)
		No	65 (53.3)	52	
6	103 (48.6)	Yes	48 (46.6)	37	0.96 (0.61-1.50)
		No	55 (53.4)	42	
Tx Duration					
1	193 (91.0)	Yes	59 (30.6)	58	1.34 (0.98-1.83)
		No	134 (69.4)	125	
2	165 (77.8)	Yes	67 (40.6)	65	1.22 (0.88-1.68)
		No	98 (59.4)	90	
3	154 (72.6)	Yes	65 (42.2)	62	1.09 (0.78-1.53)
		No	89 (57.8)	52	
4	136 (64.2)	Yes	65 (47.8)	60	1.02 (0.71-1.45)
		No	71 (52.2)	66	
5	123 (58.0)	Yes	57 (46.3)	52	0.92 (0.63-1.34)
		No	66 (53.7)	61	
6	109 (51.4)	Yes	50 (45.9)	45	0.89 (0.59-1.32)
		No	55 (54.1)	54	

Analysis is based on pooled data from Studies C2301 (PIK3CA mutants + 2L patients) and X2404 (2L patients).
^aPatients remaining are those with exposure duration > landmark and no PFS event before landmark. % = n/N * 100. % = n/n * 100. ^cCox model contains dose reduction status at landmark as covariate. HR is referenced with no dose reduction.
 2L, second-line; DR, dose reduction; FAS, Full Analysis Set; HR, hazard ratio; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; Tx, treatment.

PO2-04-12

From Clinical Trials to Clinical Practice; Real World Clinical Outcomes of Patients Treated with Ribociclib in Combination with Aromatase Inhibitors or Fulvestrant for HR-Positive, HER2- Negative Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

B. Sharaf. King Hussein Cancer Center, United States

F. Tamimi. King Hussien Cancer Center, Jordan

S. Edaily. King Hussien Cancer Center, Jordan

O. Salama. King Hussien Cancer Center, United States

H. Abdulelah. King Hussein Cancer Center, United States

A. Zayed. Khcc, Jordan

M. Abunasser. King Hussein Cancer Center, United States

H. Abu-Fares. King Hussein Cancer Center, Jordan

H. Abdel-Razeq. King Hussein Cancer Center, Amman, Jordan

Background: Cyclin-dependent kinase (CDK) 4/6 inhibitors have revolutionized the treatment landscape of hormone receptor-positive (HR+), human epidermal growth factor receptor-2 (HER2)-negative metastatic breast cancer (MBC), with an impressive efficacy and safety profile. Here we report real-world clinical outcomes and toxicity data in patients treated at a tertiary care cancer center.

Methods: The study is a retrospective analysis of individual patients' data. All consecutive patients with HR+ and HER2-negative MBC, treated at our institution with ribociclib plus aromatase inhibitors (AI) or fulvestrant, between June 2017 and May 2020 were reviewed. Data were collected from patients' electronic medical records. Progression free survival (PFS) was defined as the time from treatment initiation with CDK4/6i until the first documented progression, death from any cause or last follow-up, whichever occurred first. The Overall survival (OS) was defined as the time from treatment initiation with CDK4/6i until the date of death from any cause, or last follow-up.

Results: A total of 305 patients, median age 49 (22-87) years were enrolled. Although bone metastasis was reported in 241 (79.0%) patients, bone-only metastasis was identified in 64 (20.9%). Visceral metastasis in the liver and lungs were reported in 22.0% and 25.9 % of patients, respectively. CDK4/6i combined with AI were used in first-line setting in 195 (63.9%) patients and with fulvestrant as a second line (20.7%) or beyond (15.4%). Dose reduction was required in 44 (14.14%) patients, mostly because of neutropenia (n=38, 12.5%) and abnormal liver enzymes (n=12, 3.9%), while 11 (3.6%) discontinued treatment, mostly due cardiac toxicities. Nevertheless, there were no deaths due to toxicity.

Patients were followed up for a median of 31.1 months. Overall response rate (ORR) was 51.4% and median PFS, irrespective of the line of therapy, was 19.3 (17.6-23.3) months. PFS was longer in first-line setting; 23.1 (19.7-NR) months compared to 13.9 (10.2-17.6) months in second-line or beyond, $p < 0.0001$, and when combined with AI compared to fulvestrant; 28.6 (17.8-23.1) months versus 9.1 (4.4-NR) months, $p = 0.0001$, and in those with bone-only metastasis; 23.1 (19.5-NR) months versus 17.3 (12.2-18.9) months for patients with visceral metastasis, $p = 0.0008$. The median OS was not reached.

Conclusions: Despite enrolling sicker patients, and outside the stringent clinical trials settings, our treatment outcomes, in real world settings, are comparable to those reported in major clinical trials, including MONALEESA-2, MONALEESA-3 and MONALEESA-7.

PO2-04-13

TWT-203: PHASE 1b/2 STUDY OF CFI-402257 AS MONOTHERAPY IN ADVANCED SOLID TUMORS AND IN COMBINATION WITH FULVESTRANT IN PATIENTS WITH ER+/HER2- ADVANCED BREAST CANCER AFTER PROGRESSION ON PRIOR CDK4/6 INHIBITORS AND ENDOCRINE THERAPY

Presenting Author(s) and Co-Author(s):

J. Call. South Texas Accelerated Research Therapeutics Mountain Region, United States

M. Beeram. The START Center, United States

A. Spira. Virginia Cancer Specialists (VCS) Research Institute, Fairfax, VA, United States

M. Bray. Treadwell Therapeutics, United States

D. Chen. Treadwell Therapeutics, United States

L. Kwei. Treadwell Therapeutics, United States

E. Roberts-Thomson. Treadwell Therapeutics, United States

T. Denny. Treadwell Therapeutics, United States

R. Sidhu. Treadwell Therapeutics, United States

R. Wesolowski. James Cancer Hospital and the Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

Background:

TTK (Threonine Tyrosine Kinase also known as Monopolar spindle 1), is a dual-specificity serine-threonine kinase critical for anaphase promoting complex inhibition at the spindle assembly checkpoint and is required for chromosome alignment and error correction. TTK inhibition results in premature mitosis exiting with unattached chromosomes potentially leading to aneuploidy and cell death. High TTK tumor levels correlate with worse prognosis and contribute to the survival and proliferation of aneuploid cells.

CFI-402257, a potent and selective inhibitor of TTK, inhibits the growth of a variety of human cancer-derived cell lines.

A first-in-human phase 1 study of CFI-402257 ([NCT02792465](#)) demonstrated a tolerable safety profile when enrolled as a monotherapy in solid tumors, and in combination with fulvestrant in hormone receptor positive, HER2 negative (HR+/HER2-) breast cancer¹. The dose for expansion was 168 mg, dose limiting toxicity was dose-dependent neutropenia which was manageable and reversible. Investigator-confirmed partial responses (cPR) were observed in 5 pts (8%) with 32 (50.8%) exhibiting disease control. In the HR+/HER2- breast cancer population previously treated with cyclin dependent kinase 4/6 inhibitors (CDK4/6i) and aromatase inhibitors (N=25), there were 4 cPR's with a median duration of response of 223 days, with responses emerging after 2 cycles of therapy. Responses were observed with CFI-402257 as a single agent and in combination with fulvestrant.

Based on these data, study TWT-203 will focus on advanced solid tumors for dose confirmation then focus on advanced HR+/HER2- breast cancers in combination with an approved endocrine therapy. Methods:

In TWT-203 study, safety and clinical activity of CFI-402257 monotherapy will be evaluated in patients (pts) with advanced solid tumors (Part A) or in combination with fulvestrant in pts with HR+/HER2- advanced breast cancer (Part B). Part A will confirm the RP2D using a 3+3 design

with a starting dose of 126 mg daily. Part B evaluates CFI-402257 in combination with fulvestrant in pts with HR+/HER2- advanced breast cancer following progression on prior CDK4/6i and endocrine therapy. Efficacy endpoints include overall response rate and disease control rate. Safety endpoints include incidence of treatment emergent adverse events. Exploratory objectives include characterization of protein and molecular alterations relevant to the cell cycle and CFI-402257 response. Results:

At data cutoff of 11 May 2023, 14 pts were enrolled. All received monotherapy treatment. Median treatment duration was 2.1 months (range, 0.2-7.3+). Median age was 67 years (57-76). Median number of prior regimens was 3.5 (2-12). Tumor types enrolled were colorectal (n=6, 43%), breast (3, 21%), and endometrial, hepatocellular, leiomyosarcoma, pancreatic, and sarcoma (1 each, 7%). 4 dose levels, from 126 to 252 mg, were studied. Most pts (12, 86%) experienced ≥ 1 treatment emergent adverse event (TEAE). More than half of pts (8, 57%) experienced ≥ 1 treatment related TEAE. Most common TEAEs were fatigue (5, 36%) and nausea (4, 29%). 5 pts (36%) experienced TEAEs grade ≥ 3 , most common were fatigue, neutrophil count decrease, white blood cell count decrease (2 pts each, 14.3%). 1 pt (7%) experienced a serious adverse event (hematuria), not related to study therapy. No patients discontinued treatment due to TEAE. All pts who ended treatment were due to disease progression (8, 57%). No grade 5 TEAEs occurred. No dose limiting toxicities were reported. Disease control rate (CR, PR, or SD ≥ 6 weeks from baseline) was 54.5% (6 pts/11): all achieved SD. 3 of the 6 pts remain on study. Conclusion: CFI-402257 is a potent inhibitor of TTK. It is well tolerated with manageable TEAEs, no dose limiting or treatment limiting toxicities, and no treatment related deaths. Dose expansion in the patient population of interest will commence.

1. John Hilton et al. Cancer Res 2023;83(5 Suppl): P6-10-13.

PO2-04-14

Dual Inhibition of WEE1 and PKMYT1 Synergistically Overcomes CDK4/6 Inhibitor Resistance in Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Chen. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, United States

G. DeAlessandro. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, United States

T. Bui. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Keyomarsi. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are approved for the treatment of advanced estrogen receptor-positive, HER2-negative (ER+ve) breast cancer when combined with endocrine therapy. However, the emergence of resistance to CDK4/6 inhibitors poses a significant clinical challenge. This study investigates the mechanisms underlying CDK4/6 inhibitor resistance and identifies a common occurrence of high replication stress in triple-negative breast cancer (TNBC) and CDK4/6 inhibitor-resistant ER+ve breast cancers. While ER+ve breast cancer patients have benefited from targeted therapy, TNBC patients, particularly those without germline BRCA1/2 or PALB2 mutations, lack effective treatment options. TNBC and CDK4/6 inhibitor-resistant ER+ve breast cancer cells exhibit an increased dependence on cell cycle arrest to repair replication stress-induced DNA damage. Failure to exit the cell cycle results in excessive DNA damage, thereby limiting their proliferative potential.

Based on these findings, we hypothesize that dual inhibition of WEE1 and PKMYT1, two kinases involved in G2/M cell cycle transition and crucial for cell cycle arrest and DNA damage repair, could synergistically inhibit tumor growth. Although WEE1 and PKMYT1 share a common function in promoting G2/M cell cycle transition through CDK1 phosphorylation, their functions are not entirely redundant, suggesting that targeting both kinases may elicit a synergistic response. Recent clinical trials have shown resistance to WEE1-targeted monotherapies, emphasizing the need for combining WEE1 inhibitors with other agents, such as PKMYT1 inhibitors.

We demonstrate the synergistic effects of WEE1 inhibitor (MK1775/AZD1775) and PKMYT1 inhibitor (RP6306) in a panel of TNBC and ER+ve breast cancer cells with acquired palbociclib resistance (PalboR). Combination treatment with both inhibitors leads to excessive unrepaired DNA damage, as indicated by increased γ H2AX foci following 48 hours of combination treatment, whereas single-agent treatments induce significantly lower levels of DNA damage. Furthermore, we observed the AZD1775/RP6306 combination decreases the expression of the DNA repair protein Rad51 in PalboR cells.

To evaluate the clinical potential of dual WEE1 and PKMYT1 inhibition, we generated organoids from metastatic breast cancer lesions of patients who had progressed on CDK4/6 inhibitors for ex vivo studies. Our results demonstrate that dual inhibition of WEE1 and PKMYT1 is more effective than single-agent treatments in eliminating CDK4/6 inhibitor-resistant organoids. Additionally, using patient-derived xenograft mouse models from patients who had progressed on palbociclib and endocrine treatment, we show that the AZD1775/RP6306 combination exhibits superior tumor suppression effects compared to single agents.

Overall, this study highlights the potential therapeutic benefits of dual inhibition of WEE1 and PKMYT1 in overcoming CDK4/6 inhibitor resistance in TNBC and ER+ve breast cancer patients. These findings provide a rationale for future clinical trials aimed at exploring the clinical utility of this combination therapy.

PO2-05-01

Famitinib, a multi-targeted receptor tyrosine kinase inhibitor, combined with dalpiciclib and fulvestrant in advanced HR-positive and HER2-negative breast cancer

Presenting Author(s) and Co-Author(s):

M. Yan. Henan Cancer Hospital, Henan, China

M. Zhang. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China (People's Republic)

L. Niu. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China (People's Republic)

H. Lv. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China (People's Republic)

Z. Liu. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

H. zeng. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China (People's Republic)

S. Zhao. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China (People's Republic)

H. Sun. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

J. Wang. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China (People's Republic)

Y. Feng. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

H. Li. Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, Shanghai, China (People's Republic)

Background: CDK4/6 inhibitors combined with endocrinotherapy (ET) represent an essential part of the treatment for HR-positive and HER2-negative breast cancer (BC). However, the role of angiogenesis inhibitors, such as bevacizumab, in these patients (pts) is controversial. While it has been demonstrated to improve progression-free survival (PFS), it has failed to show a significant overall survival (OS) benefit in HER2-negative BC. Several preclinical studies have explored the combination of anti-angiogenesis multi-targeted receptor tyrosine kinase inhibitors (TKIs) and CDK4/6 inhibitors in other cancers, suggesting a synergistic effect. Our phase Ib/II trial (NCT05176080, ChiCTR2100053950) aims to evaluate the safety and efficacy of a novel anti-angiogenesis TKI famitinib (F) added to dalpiciclib (D) and ET in advanced HR-positive and HER2-negative BC. Here we report the results of Phase Ib. Methods: A 3+3 de-escalation design was used in this dose-exploring phase (phase Ib). Pts with HR-positive and HER2-negative BC, who had no more than two prior chemotherapies in the advanced setting, were enrolled and administered F (orally, at doses of 15 mg/d, 10 mg/d, or 15 mg qod), D (orally, at doses of 150, 125 or 100 mg/d, 21 days on and 7 days off) and fulvestrant (intramuscularly, at a

fixed dose of 500 mg every four weeks) until progression, unaccepted toxicities, or withdrawal. The initial dose level (Level 1) was set as F 15 mg daily and D 150 mg/d. The primary endpoints were recommended phase 2 dose (RP2D) and safety. Results: From December 2021 to June 2022, 18 pts were enrolled, and 3, 6, 3, and 6 pts were assigned to Level 1 (F 15 mg + D 150 mg), Level 2 (F 10 mg + D 125 mg), Level 3 (F 15 mg qod + D 125 mg), and Level 4 (F 10 mg + D 100 mg), respectively. 14 (77.8%) pts had visceral metastasis, and 7 (38.9%) had prior systemic therapies in the advanced setting. 13 (72.2%) pts had received ET, and 11 (61.1%) were resistant to ET before enrolled. A total of 6 dose-limiting toxicities (DLTs) were observed, including 3 Grade 4 thrombopenia (2 in Level 1, 1 in Level 2) and 3 Grade 4 neutropenia (2 in Level 3, 1 in Level 4), 4 of which were serious adverse events (AEs). The most common ($\geq 20\%$) treatment-related AEs of Grade 3 or above were neutropenia (100.0%), leukopenia (88.9%), thrombocytopenia (33.3%), anemia (27.8%), lymphopenia and hypertension (both 22.2%). No death was reported. Overall 10 pts (55.6%) achieved confirmed partial responses and 16 (88.9%) achieved clinical benefits. Confirmed objective response rates (ORRs), clinical benefit rates (CBRs), and DLTs in different dose levels were shown in Table 1. Considering the efficacy and safety profiles, Level 4 was selected as RP2D. Conclusion: The anti-angiogenesis multi-targeted receptor TKI famitinib combined with CDK4/6i and fulvestrant has shown antitumor effects in advanced HR-positive and HER2-negative BC, and no new safety signals were observed.

	Level 1 F 15 mg + D 150 mg	Level 2 F 10 mg + D 125 mg	Level 3 F 15 mg qod + D 125 mg	Level 4 F 10 mg + D 100 mg
ORR, n/N (%)	2/3 (66.7)	3/6 (50.0)	1/3 (33.3)	4/6 (66.7)
CBR, n/N (%)	2/3 (66.7)	5/6 (83.3)	3/3 (100.0)	6/6 (100.0)
DLT, n/N (%)	2/3 (66.7)	1/6 (16.7)	2/3 (66.7)	1/6 (16.7)

PO2-05-02

Real-world experience of patients receiving treatment for hormone receptor-positive /human epidermal growth factor receptor-2 negative metastatic breast cancer: A global analysis of symptoms and side effects

Presenting Author(s) and Co-Author(s):

M. Rehnquist. Gilead Sciences, Inc., United States

A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Lambert. Adelphi Real World, United States

A. Kurian. Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California, United States

N. Sadetsky. Gilead Sciences, Inc., United States

E. Freeman. Gilead Sciences Inc, United States

L. Carey. UNC-Lindberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

Background: Advances in treatment for patients (pts) with hormone receptor-positive (HR+)/human epidermal growth factor receptor-2 negative (HER2-) metastatic breast cancer (mBC) have improved overall survival, but treatment resistance is common and median survival remains only a few years. These pts usually need chronic therapy and often experience symptoms and side effects. There is limited knowledge on pts' experiences outside the clinical trial setting, largely because this information is not routinely reported. This analysis leverages a unique database of physician- and pt-reported data to describe symptoms and side effects among a real-world, geographically diverse population of pts receiving treatment for HR+/HER2- mBC. **Methods:** This retrospective cohort study used Adelphi Disease Specific Programme Real World Data, comprising validated, linked pt and physician questionnaire data from the US, France, Germany, Italy, Spain, and UK. Eligible pts were ≥ 18 y, currently receiving treatment for advanced BC and not enrolled in a clinical trial. Data were collected between August 2022 and February 2023. Physician surveys provided data on individual pt demographics and disease characteristics, comorbidities, treatment history, and treatment (including adherence). Physicians also reported presence or absence of symptoms and side effects after treatment initiation for each pt they considered. A subset of pts completed one-time validated quality of life (QOL) instruments, including the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC QLQ-breast (BR23). **Results:** Data from 1578 pts receiving treatment for HR+/HER2- mBC were analyzed. Mean age was 65-y, 91% were white, 71% had de novo mBC, and 82% had ECOG performance status 0-1 at the start of current treatment. Across all lines of therapy, 71% of pts were receiving endocrine-based therapy, 16% were receiving chemotherapy only, and 13% were receiving other therapies; 40% of all pts were receiving second or later lines of any systemic therapy (2L+). Among all pts, the most common physician-reported symptoms and side effects (in $\geq 10\%$ of pts) were bone pain (30%), change in appetite (13%), weight loss (12%), neutropenia (11%), and joint/muscle pain (11%). Pts on 2L+ therapy experienced a greater frequency of symptoms and side effects than those on first-line therapy (Table). Of 220 pts who completed QOL questionnaires, the most commonly reported symptoms and side effects (in $\geq 70\%$ of pts) were feeling tired (87%), worry about future health (80%), general worrying (79%), needing to rest during the day (74%), feeling weak (74%), having trouble doing strenuous activity (71%), and trouble taking a long walk (71%). These were common irrespective of pt age, disease state (recurrent vs de novo), current treatment regimen, and line

of therapy. Conclusions: This real-world analysis shows that both physicians and pts identified substantial symptoms and side effects during treatment. These were pervasive across the population and more common in those receiving 2L+ therapy, although it remains unclear which were due to treatment or disease. Thus, it is important to continue to develop treatments and supportive care to improve both clinical outcomes and pt QOL.

Table. Physician-reported symptoms and side effects affecting >5% of patients overall			
Symptom/side effects	Patients, n (%)		
	Overall N=1573*	1L n=951	2L+ n=622
Bone pain	475 (30)	258 (27)	217 (35)
Change in appetite	202 (13)	102 (11)	100 (16)
Weight loss	183 (12)	87 (9)	96 (15)
Neutropenia	175 (11)	127 (13)	48 (8)
Joint/muscle pain	169 (11)	92 (10)	77 (12)
Diarrhea	132 (8)	75 (8)	57 (9)
Anxiety	122 (8)	73 (8)	49 (8)
Cough	114 (7)	59 (6)	55 (9)
Difficulty sleeping	105 (7)	53 (6)	52 (8)
Fatigue/asthenia	111 (7)	56 (6)	55 (9)
Dyspnea on exertion	97 (6)	43 (5)	54 (9)
Shortness of breath	92 (6)	44 (5)	48 (8)
Nausea	90 (6)	44 (5)	46 (7)
Depression	85 (5)	41 (4)	44 (7)
Anemia	84 (5)	43 (5)	41 (7)

1L, first line; 2L+ second or later line.
*Unknown responses excluded.

PO2-05-03

Costs associated with adverse events in patients receiving treatment for hormone receptor positive/human epidermal growth factor receptor-2 negative metastatic breast cancer

Presenting Author(s) and Co-Author(s):

A. Shah. Department of Global Value and Access, Gilead Sciences, Inc., Foster City, CA, USA, United States

A. Sainski-Nguyen. Optum HEOR, United States

K. Moore. Optum HEOR, United States

M. Rehnquist. Gilead Sciences, Inc., United States

R. Nanda. University of Chicago Medicine, Chicago, Illinois, United States

Background: Adverse event (AE)-related health care resource utilization (HCRU) and costs are an important component in understanding the economic burden associated with managing patients (pts) with cancer and can inform treatment decision-making and access for pts, providers, and payers. At present, there are little data on AE-related HCRU and costs among pts receiving late-line treatment for hormone receptor positive (HR+)/human epidermal growth factor receptor-2 negative (HER2-) metastatic breast cancer (mBC). As such, the objective of this analysis was to describe the AE-related HCRU and costs among pts with HR+/HER2- mBC receiving chemotherapy (CT) who have received prior CT and endocrine-based therapies (ET). **Methods:** This retrospective study included pts who had at least 1 prior ET, had completed at least 2 CTs, had initiated their third (or greater) CT (post-ET) in the metastatic setting between Jan 2016 and Mar 2022, and were included in the Optum Research Database. The start date for the current line of CT was the index date. Pts were followed until disenrollment from health plan, study end date (Jun 2022), or death. AEs included in this study were based on clinical impact; these AEs were then organized into categories. AE-related HCRU and costs were reported as per pt per month (PPPM) and included outpatient visits, office visits, emergency room visits, inpatient stays, other medical costs (eg, laboratory/ancillary costs), and pharmacy costs. Costs were adjusted to 2021 US dollars using the Consumer Price Index. **Results:** A total of 769 pts were included with a mean age of 64 y (standard deviation: 13 y) and baseline National Cancer Institute comorbidity score of 0 (44%) or 1-2 (39%). 51% were commercially insured. A total of 715 (93%) pts had ≥ 1 AE during the follow-up period; the mean total PPPM cost associated with AEs was \$7421 (Table 1) and the majority of costs were driven by ambulatory visits (office and outpatient visits: \$3846 PPPM; Table 1) and inpatient stays (\$3042 PPPM; Table 1). Among pts who experienced AEs, AEs that were associated with the highest mean total PPPM costs included infections, hepatotoxicity, gastrointestinal toxicity and renal failure events. The costs associated with infections and renal failures were predominantly driven by inpatient stay costs (\$5540 and \$3298 PPPM, respectively; Table 1). **Conclusions:** This real-world analysis suggests that there is high prevalence of AEs associated with CTs in late-line (≥ 3 CTs) HR+/HER2- mBC, which may lead to a substantial economic burden and suboptimal treatment outcomes. Newer, effective therapies with manageable AE profiles may

offer a better benefit-to-risk profile and improve outcomes compared with chemotherapies.

Table 1. Adverse events and mean associated costs per patient per month									
AE category	N (n = 769) ^a	%	Total cost ^{b,c} (\$)	Medical costs ^{b,d} (\$)	Office ^e costs ^b (\$)	Outpatient ^f costs ^b (\$)	ER visit costs ^b (\$)	Inpatient stay costs ^b (\$)	Pharmacy claims cost ^b (\$)
At least 1 AE	715	93.0	7420.94	7195.42	879.02	2967.26	127.21	3041.96	225.52
Infections ^g	167	21.7	5997.33	5988.11	18.00	308.14	47.75	5539.61	9.22
Hepatotoxicity	100	13.0	5279.28	5272.44	367.96	2742.19	95.07	2038.25	6.84
Gastrointestinal ^h	421	54.7	3705.12	3683.24	649.05	1992.07	80.27	883.44	21.88
Renal failure	121	15.7	3564.35	3564.35	3.19	134.46	66.16	3297.76	0.00
Blood and lymphatic ⁱ	532	69.2	3445.02	3310.09	441.85	1595.57	49.24	1081.60	134.93
Thromboembolic ^j	191	24.8	3080.39	2896.06	87.60	759.14	44.13	1936.84	184.33
Respiratory ^k	67	8.7	3064.00	3060.74	441.97	1225.73	44.81	1295.43	3.27
Cardiovascular ^l	427	55.5	2741.82	2729.47	31.99	421.74	69.17	2176.67	12.35
Cutaneous	10	1.3	1928.09	1921.16	27.78	1746.71	71.42	0.00	6.93
Allergic reaction	12	1.6	1665.76	1663.35	48.37	1059.42	166.98	388.59	2.41
Peripheral neuropathy	226	29.4	709.35	694.73	47.55	540.72	5.32	79.28	14.62

^aFollow-up time was variable and these values do not account for censoring.
^bCost based on mean number of AEs among patients who had ≥ 1 AE (n = 715).
^cMedical and pharmacy costs.
^dOffice, outpatient, ER, inpatient, and other medical (eg, laboratory/ancillary) costs.
^ePhysician visits
^fHospital visits
^gOpportunistic infections, sepsis
^hColitis, diarrhea, nausea, stomatitis, vomiting
ⁱAnemia, leukocytosis, neutropenia, pancytopenia, thrombocytopenia, neutropenic fever.
^jCerebrovascular accident, pulmonary embolism, venous thromboembolism.
^kInterstitial lung disease, pneumonitis, pleural effusion.
^lCardiac arrhythmia, congestive heart failure, left ventricular dysfunction.
AE, adverse event; ER, emergency room.

PO2-05-04

ELEVATE: A phase 1b/2, open-label, umbrella study evaluating elacestrant in various combinations in patients (pts) with estrogen receptor-positive (ER+), HER2-negative (HER2-) locally advanced or metastatic breast cancer (mBC)

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

S. Hurvitz. Fred Hutchinson Cancer Center/University of Washington, Los Angeles, California, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

V. Kaklamani. UT Health San Antonio, San Antonio, Texas, United States

G. Tonini. Menarini Group, United States

S. Matheny. Stemline Therapeutics, United States

K. Theall. Stemline Therapeutics, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

Background: ER+/HER2- breast cancer (BC) is the most prevalent BC subtype. Endocrine therapy (ET) is the mainstay of treatment; however, development of resistance to this therapeutic approach is common in the metastatic setting. After progression on first-line treatment, both ET monotherapy and combination therapy options are available. Combinations such as everolimus + exemestane and alpelisib + fulvestrant can be associated with higher efficacy, but also significant toxicity with discontinuation rates around 25%. Also, for second-line treatment, pts who did not receive prior treatment with a CDK4/6i, the combination of fulvestrant with a CDK4/6i (palbociclib, abemaciclib, and ribociclib) are among the recommended treatment options for this pt population (NCCN, 2022). However, fulvestrant has low bioavailability and an IM injection burden. The crosstalk between the three pathways ER, PI3K/AKT/mTOR and cyclin-dependent kinases (CDK4/6) provide a rationale for the combination of elacestrant, a next-generation oral SERD, with inhibitors of these pathways that are natural targets to overcome endocrine resistance. The EMERALD trial reported significantly prolonged progression-free survival (PFS) with elacestrant vs SOC ET in pts with ER+/HER2-ESR1 mutated (ESR1-mut) mBC following disease progression on prior ET (Bidard, 2022). Elacestrant was well tolerated with a manageable safety profile. Most adverse events, including nausea, were low-grade and consistent with other endocrine therapies. The replacement of the fulvestrant backbone with elacestrant in combination with targeted agents enabling oral-oral combinations is of therapeutic interest.

Methods: ELEVATE (NCT05563220) is a phase 1b/2 clinical trial that will evaluate the safety and efficacy of elacestrant combined with alpelisib, everolimus, palbociclib, abemaciclib, and ribociclib. Eligible pts must be adults with confirmed ER+/HER2- advanced or mBC, > 1 measurable lesion as per RECIST v1.1, and adequate bone marrow or organ function. The main objectives for Phase 1b are to determine the RP2D of elacestrant combined with other targeted agents. The RP2D of elacestrant and abemaciclib will be determined in the ELECTRA study (NCT05386108). The Phase 2 portion will evaluate the efficacy of elacestrant combined with other study drugs for PFS; secondary objectives include PK of the various combinations, ORR, DoR, CBR, PFS, and OS. Here we report the initial dosing from the Phase 1b portion.

Results: As of June 2023, 11 pts were enrolled in the phase 1b portion of the trial, cohort 1 for all combinations: 5 pts in the elacestrant and everolimus (300 mg elacestrant QD/ everolimus 5 mg QD) and 3 pts in the elacestrant and alpelisib (300 mg elacestrant QD/ alpelisib 250 mg QD) and 2 patients for palbociclib and 1 patient in the ribociclib combinations. Further patient accrual is expected in phase 1b cohorts of various combinations during the second half of 2023; both safety and PK data will be provided.

Conclusion: In the Phase 1b portion of ELEVATE, elacestrant is being combined with various targeted agents enabling oral-oral combinations to determine a RP2D. Recruitment is actively ongoing; safety and PK results will be presented at the meeting from the completed phase 1b cohorts.

PO2-05-05

ELECTRA: An open-label, multicenter, phase 1b/2 study of elacestrant in combination with abemaciclib in patients with brain metastasis (mets) from estrogen receptor-positive (ER+), HER2-negative (HER2-) breast cancer (BC)

Presenting Author(s) and Co-Author(s):

N. Ibrahim. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Kim. Asan Medical Center, Seoul, Republic of Korea, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

A. Awada. Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, United States

E. Gil. Hospital Universitario 12 de octubre, United States

G. Tonini. Menarini Group, United States

B. Piza Vallespir. Clinical Sciences, Menarini Ricerche S.p.A., Firenze, Italy, United States

K. Theall. Stemline Therapeutics, United States

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

Background: Currently, there are no approved systemic treatment options specifically for patients with ER+/HER2- BC who have brain metastasis. The prevalence of brain metastases from ER+/HER2- BC is approximately 14% of women (Aversa, 2014). Elacestrant is a next-generation oral SERD that was evaluated in a pivotal phase 3 trial, EMERALD, as monotherapy vs. standard of care (SOC) endocrine therapy. The EMERALD trial reported significantly prolonged progression-free survival (PFS) with elacestrant vs SOC endocrine therapy in patients with ER+/HER2- ESR1 mutated (ESR1-mut) mBC following progression on prior endocrine therapy (Bidard, 2022). Elacestrant was well tolerated with a manageable safety profile. Most adverse events, including nausea, were low-grade and consistent with other endocrine therapies. A clinical study in healthy postmenopausal women demonstrated the ability of elacestrant to cross the blood-brain barrier (Conlan, 2020). Abemaciclib, a CDK4/6i, has been shown to achieve therapeutic concentrations in brain metastases tissue (Tolaney, 2020). Given the lack of current systemic treatments, elacestrant is now being evaluated with abemaciclib in patients with ER+/HER2- BC and brain metastasis (NCT05386108). Methods: ELECTRA (NCT05386108) is an open-label phase 1b/2, multicenter study evaluating elacestrant in combination with abemaciclib in patients with brain metastasis from ER+, HER2- BC. Eligibility are patients with ER+/HER2- locally advanced or mBC and measurable brain metastasis. For phase 1b, the presence of brain metastases is allowed but not required for eligibility. For phase 2, patients must have ≥ 1 active and measurable brain metastasis per RECIST v1.1. Patients must have received prior therapy in the metastatic setting, including ≥ 1 ET, ≤ 2 chemotherapy regimens, and 0-2 prior CDK4/6i (excluding abemaciclib). The primary objectives of Phase 1b are to determine the recommended Phase 2 dose (RP2D). Phase 1b secondary objectives include safety, PK, objective response rate (ORR), duration of response (DoR), clinical benefit rate (CBR), PFS, and overall survival (OS). Phase 2 primary objective is ORR per RECIST version 1.1. Phase 2 secondary objectives include intracranial response rate (RR), DoR, CBR, PFS, OS, PK, and quality of life (QoL). The phase 1b portion evaluated dose-limiting toxicities (DLTs) of the combination during the first cycle (28 days) of treatment in up to three 6-patient cohorts, starting at elacestrant 300 mg daily plus abemaciclib 100 mg twice daily. Here we report initial safety results from the phase 1b portion. Results: As of June 2023,

15 patients have been enrolled in the phase 1b portion of the trial. At dose level 1, elacestrant 300 mg QD + abemaciclib 100 mg BID, no patient experienced DLTs, and the combination was feasible. Dose level 2, elacestrant 400 mg QD + abemaciclib 100 mg BID has been completed, and no patients experienced DLTs. In dose level 1, 4/7 patients remain on treatment at cycle 5. Additional safety and PK data for the cohorts will be provided. Conclusion: In the phase 1b portion of ELECTRA, dose level 1 and dose level 2 have been completed. No patients experienced DLTs in either dose level 1 or dose level 2, and the combination was considered feasible in the respective dose levels. Dose level 3 (elacestrant 400 mg QD + abemaciclib 150 mg BID) is proceeding. Recruitment is actively ongoing, enabling oral-oral combinations to determine a RP2D.

PO2-05-06

Palbociclib in advanced hormone receptor positive breast cancer: A real world study in South America

Presenting Author(s) and Co-Author(s):

C. SÁNCHEZ. PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE, United States

S. Samtani. Hospital Félix Bulnes (Chile), United States

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

S. Falcon-Lizaraso. Aliada Cancer Center, Lima, Peru

R. Muñoz. LIFE and HOPE (Ecuador), United States

T. Soria. Hospital Metropolitano (Ecuador), United States

BACKGROUND: First-line combined endocrine therapy is the standard of care for hormone receptor-positive (HR+) human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC). Palbociclib, in combination with aromatase inhibitors or fulvestrant, is a treatment option for HR+/HER2-negative ABC patients. We aimed to analyze the real-world experience of palbociclib in this setting in South America.

METHODS: Real-world study collecting sociodemographic and clinical data from women with ABC treated with palbociclib in centers from Chile (n = 40), Perú (n = 61), and Ecuador (n = 10). Treatment efficacy and safety were analyzed.

RESULTS: The median age was 54 years (range: 28 – 83), and 81.1% of women had received previous treatment: adjuvant therapy (20.0%), ABC treatment (31.1%), or both (48.9%). The median duration of palbociclib treatment was 14 months (range: 1 – 57), with differences among countries (longer in Perú; p = 0.009). The dose was reduced in 28.2% of women and only 6.5% returned to the previous one. Most women (97.3%) received combined endocrine therapy, letrozole (48.1%) or fulvestrant (44.4%), with differences between countries (p < 0.001). Palbociclib was usually the first-line therapy in Ecuador (60.0%) and Perú (80.3%), and the third line in Chile (37.5%). Considering all women, it was the first- or second-line therapy for 52.3% and 20.7% of them, respectively. The overall response rate was 34.2% and progressive disease was significantly lower in patients receiving first-line palbociclib (25.9 vs. 66.0%, p < 0.001). The disease-free survival was longer than 12 months in 67.2% of patients treated with first-line palbociclib. Regarding safety, 38.7% of women had any relevant adverse event (AE) during the treatment, most frequently neutropenia (39.5%), diarrhea (9.3%), and elevated transaminase levels (4.7%). The number of patients who developed any relevant AE was lower among the first-line treated patients (19.0% vs. 60.4%, p < 0.001).

CONCLUSION: The study reflects differences among countries in routine palbociclib use. But considering all data, palbociclib has confirmed its efficacy and safety, supporting its use in HR+/HER2-negative patients, especially as a first-line therapy.

PO2-05-07

Which treatment is done in patients with metastatic breast cancer who received a prior treatment with CDK4/6 inhibitors? A real-world experience in a single Italian Institution

Presenting Author(s) and Co-Author(s):

S. Bravaccini. IRCCS Istituto Romagnolo Per lo Studio dei Tumori, Meldola, Italy, United States

W. Balzi. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

A. Roncadori. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

A. Virga. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

P. Ulivi. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

G. Martinelli. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

R. Maltoni. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

Patients with HR positive (HR+) and c-erb-b2 negative (HER2-) advanced breast cancer are treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in combination with hormone therapy (HT). At the time of disease progression with these treatments, no established guidelines are defined for the subsequent therapeutic options. Treatment options after progression can be different, in terms of use of chemotherapy or ET alone, or the combination of the two, or of other biological agents (such as everolimus) or the HT combined with other therapies.

We aimed to verify in our Institute (IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy) how HR+ mBC patients are treated after having received a treatment with HT plus CDK4/6 inhibitors (ribociclib, palbociclib, abemaciclib). 105 mBC patients, 32 of whom were treated with CD4/6 inhibitors plus letrozole and 73 treated with CDK4/6 inhibitors and fulvestrant were included in the study. 83 were treated with palbociclib, 16 with ribociclib and 6 with abemaciclib. The median age was 65 years (range 40-86), 58 were younger than 65 years. 90 were in postmenopausal status. On the total 105 patients, 46 (43.8%) were treated with a single chemotherapy regimen while 25 (23.8%) with a combined schedule of chemotherapies (Table 1). Only 9 (8.6%) have been treated with HT alone. 22 (20.95%) patients received combined treatments with ET or chemotherapy+targeted therapy or chemotherapy +immune checkpoint inhibitor. 1 (0.95%) patient was treated with a triplet chemotherapy regimen (cyclophosphamide+capecitabine +vinorelbine), 2 (1.9%) for whom the re-biopsy of the tumor resulted HER2+ and were treated with taxol +pertuzumab +trastuzumab. 82/105 (78%) patients performed more lines of therapies after CDK4/6 inhibitors.

In conclusion, patients with mBC were treated heterogeneously. The major part of them have been treated with chemotherapy alone or with combination of more chemotherapies. The evaluation of the patient response in relation to the different therapies is still ongoing as well as the effect of all the other therapies beyond the first line of treatment.

Table 1. Type of treatments done in mBC patients (N=105) after treatment with HT+ CDK4/6 inhibitors

Chemotherapy regimen	N	Type of treatment (N of patients)			
		Combination chemotherapy	Metronomic therapy	Double combination treatment	Triple combination treatment
epirubicin	13*	irinotecan+epirubicin	irinotecan	irinotecan+epirubicin	irinotecan+epirubicin+5-fluorouracil
taxol	12	irinotecan+cyclophosphamide	irinotecan	irinotecan+mitomycin	irinotecan+mitomycin+paclitaxel
irinotecan	9	irinotecan+epirubicin	irinotecan	irinotecan+epirubicin	irinotecan+epirubicin+5-fluorouracil
capecitabine	6	capecitabine	capecitabine	capecitabine+irinotecan	capecitabine+irinotecan+5-fluorouracil
irinotecan	3	irinotecan	irinotecan	irinotecan	irinotecan
epirubicin	1	irinotecan+epirubicin	irinotecan	irinotecan	irinotecan
irinotecan	1	irinotecan	irinotecan	irinotecan	irinotecan
irinotecan	1	irinotecan	irinotecan	irinotecan	irinotecan
total	46	28	9	22	3

*1 performed only 1 cycle

** 1 was treated also with a metronomic schedule of therapy

PO2-05-08

ISM5043, a novel, selective KAT6 inhibitor for the treatment of advanced and refractory ER+ breast cancer

Presenting Author(s) and Co-Author(s):

X. Cai. Insilico Medicine, United States

X. Cheng. Insilico Medicine, United States

L. Qin. Insilico Medicine, United States

M. Zhang. Insilico Medicine, United States

J. Qiao. Insilico Medicine, United States

S. Bavadekar. Insilico Medicine, United States

S. Rao. Insilico Medicine, United States

F. Ren. Insilico Medicine, United States

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer death among women in the US. Approximately 70% of human breast tumors are estrogen receptor positive (ER+), and endocrine therapy (ET), which inhibits the estrogen signaling pathway, remains the backbone of therapy for ER+ breast cancer. However, ET resistance often develops, and patients eventually experience disease progression. This is a significant clinical challenge and highlights the urgent need for novel therapies that may help overcome the resistance.

KAT6A is a histone (lysine) acetyltransferase (HAT) belonging to the MYST family. KAT6A and its paralog KAT6B play important roles in cell cycle progression, neuron stem cell maintenance and hematopoietic development via acetylation of H3K23. Molecular dysregulation of KAT6A, including amplification and fusion, has been reported in many cancers. In breast cancer, KAT6A is amplified as part of the 8p11 amplicon in about 10-15% of the ER+ breast cancer population, where it functions as an epigenetic modulator of ER expression, and is associated with a worse clinical outcome. Therefore, inhibition of KAT6A may be a promising therapy for ER+ breast cancer. Here, we evaluated ISM5043, a novel, small molecule KAT6 inhibitor for anti-tumor effects in ER+/HER2- breast cancer cell lines and animal models.

ISM5043 demonstrated potent inhibitory activity against KAT6A (IC₅₀, 8 nM) and KAT6B (IC₅₀, 16 nM) with selectivity over KAT7 (IC₅₀, 344 nM) and other HATs (IC₅₀ >2000 nM). The compound showed robust, dose-dependent, anti-proliferation activity (IC₅₀ < 10 nM) in multiple ER+/HER2- breast cancer cell lines with KAT6A amplification, in accordance with its suppression of H3K23 acetylation. Investigation of the mechanism of action revealed that treatment with ISM5043 resulted in the downregulation of the expression of ER α in these breast cancer cells.

In the ZR-75-1 (ER+, HER2-) xenograft model, ISM5043 demonstrated robust and dose-dependent anti-tumor activity, as monotherapy, with Tumor Growth Inhibition (TGI) between 80~110% at doses ranging from 0.3 to 10 mg/kg, QD. ISM5043 (0.3 mg/kg, QD), in combination with tamoxifen (20 mg/kg, QD) exhibited synergistic effect against tumor growth, with a Q value of 1.25 based on Jin's equation. Notably, ISM5043 displayed a strong anti-tumor effect (TGI of 67.7% and 83.6% at 3 and 10 mg/kg QD, respectively) as monotherapy, in a patient-derived ER+/HER2- breast cancer xenograft model representing disease progression following multiple prior lines of treatment (including palbociclib in combination with letrozole).

ISM5043 also showed favorable ADME properties as well as good pharmacokinetic and safety profiles.

Taken together, these data support the clinical evaluation of ISM5043 as a targeted therapy in patients with advanced and refractory ER+ breast cancer.

PO2-05-09

Beyond endocrine resistance: estrogen receptor (ESR1) activating mutations mediate chemotherapy resistance through the JNK/c-Jun MDR1 pathway in breast cancer

Presenting Author(s) and Co-Author(s):

M. Taya. Tel Aviv University, United States

K. Merenbakh-Lamin. Tel Aviv Sourasky Medical Center, United States

A. Zubkov. Tel Aviv Sourasky Medical Center, United States

Z. Honig. Tel Aviv Sourasky Medical Center, United States

O. Mayer. Tel Aviv University, United States

N. Shomron. Tel Aviv University, United States

W. Ido. Oncology Division, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, United States

T. Rubinek. Tel Aviv Sourasky Medical Center, United States

Purpose: All patients with metastatic breast cancer (MBC) expressing estrogen receptor- α (ESR1) will eventually develop resistance to endocrine therapies. In up to 40% of patients, this resistance is caused by activating mutations in the ligand-binding domain (LBD) of ESR1. Accumulating clinical evidence indicate adverse outcomes for these patients, beyond that expected by resistance to endocrine therapy. We hypothesized that ESR1 mutations may also confer resistance to chemotherapy. **Experimental Design:** MCF-7 cells harboring Y537S and D538G ESR1 mutations (mut-ER) were employed to study response to chemotherapy using viability and apoptotic assay in vitro, and tumor growth in vivo. JNK/c-Jun/MDR1 pathway was studied using qRT-PCR, western-blot, gene-reporter and CHIP assays. MDR1 expression was analyzed in clinical samples using IHC. **Results:** Cell harboring ESR1 mutations displayed relative chemoresistance, evidenced by higher viability and reduced apoptosis as well as resistance to paclitaxel in vivo. To elucidate the underlying mechanism, MDR1 expression was examined and elevated levels were observed in mut-ER cells, and in clinical BC samples. MDR1 is regulated by the JNK/cJun pathway, and indeed, we detected higher JNK/cJun expression and activity in mut-ER cells, as well as increased occupancy of c-Jun in MDR1 promoter. Importantly, JNK inhibition decreased MDR1 expression, particularly of D538G-cells, and reduced viability in response to chemotherapy. **Conclusions:** Taken together, these data indicate that ESR1 mutations confer chemoresistance in BC through activation of the JNK/MDR1 axis. Targeting this pathway may restore sensitivity to chemotherapy and serve as a novel treatment strategy for MBC patients carrying ESR1 mutations.

PO2-05-10

'I am Still Alive': An Interpretative Phenomenological Analysis of Older Women Living with Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Chidebe, Miami University, Ohio, USA, Project PINK BLUE - Health & Psychological Trust Centre, United States

K. Banwo-Fatai. Project PINK BLUE - Health & Psychological Trust Centre, Nigeria, United States

A. Agha. Department of Social Work, University of Nigeria Nsukka, United States

O. Nwakanma-Akanno. Smile With Me Foundation, Nigeria, United States

D. Narine. University of Maryland, Baltimore and Baltimore County, USA, United States

T. Yamashita. University of Maryland, Baltimore County (UMBC), United States

A. Platas. Breast Medical Oncology Department, Instituto Nacional de Cancerología, Mexico

J. Kinney. Miami University, Ohio, USA, United States

P. Cummins. Scripps Gerontology Center, Miami University, Ohio, USA., United States

F. Cardoso. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

Background: Metastatic breast cancer (mBC) is cancer that has spread from the primary organ (breast) to other distant organs such as bone, spine, lungs, brain, and liver. It is a treatable but incurable cancer. While the burden of mBC is devastating to all patients, older mBC patients have poorer prognoses, poor access to care and experience social isolation. This current study is aimed to explore the experiences of older women living with mBC and the impact of belonging to a peer support group (PSG) in Nigeria.

Method: Using interpretative phenomenological analysis (IPA), eight women living with mBC aged 50 and above participated in the semi-structured interview.

Results: Our findings showed that participants encountered psychological, physiological, and social challenges that are interrelated across four central themes: "Tormented by Pain," "I am the One that is Going to Die," "I am Not alone," and "Winning the 'war' against mBC." While the experiences of older women living with mBC were dominated by different levels of pain, death anxiety, stigma, and financial burden; belonging to a PSG brought participants hope, information, self-worth, and courage.

Conclusion: This study has shown PSG should be an important component of cancer control. Hence, healthcare leaders should support and fund the establishment of PSG across Nigeria. Whether mBC is curable or not, the last days of older women living with mBC should be filled with dignity, peer support, and the absence of pain.

PO2-05-11

Patient Perspectives on the Value of Stereotactic Body Radiotherapy (SBRT) in the Management of Breast Cancer: The PERSPECTIVE Study

Presenting Author(s) and Co-Author(s):

S. Nagpal. The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, United Kingdom

A. Kirby. The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, United States

G. Ross. The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, United Kingdom

S. Cruickshank. The Royal Marsden NHS Foundation Trust, United States

Background: Oligometastatic disease describes limited metastases amenable to local therapy such as stereotactic body radiotherapy (SBRT). Within the UK National Health Service (NHS), SBRT is a standard of care for up to 3 metachronous sites of oligometastatic breast cancer (OMBC), offering high local control rates with low toxicity. The SABR-COMET study demonstrated improved progression-free survival (PFS) and overall survival (OS) with SBRT compared to standard of care in a number of oligometastatic cancers, including breast cancer [1]. Conversely, the NRG-002 trial results suggest no PFS or OS improvement with the addition of SBRT to standard systemic therapy in OMBC [2]. The OS data for this study are yet to mature and in the meantime the results of other prospective studies are awaited. As patients' attitudes and perspectives govern their preferences around treatment decisions, it is vital to understand whether PFS and OS are the most important considerations for patients. This study aims to explore patients' perspective on the role of SBRT in breast cancer management. Their views will help inform future trial endpoints and support clinicians to support patients with their decision making and expectations.

Methods: We conducted an exploratory qualitative study with focus groups and individual interviews, to understand participants knowledge, views and opinions on SBRT in treating breast cancer. All patients were asked to watch an educational video about SBRT in advance of participating in the interviews. An interview guide with open-ended questions was developed. Breast cancer patients were recruited using a purposive sampling matrix based on the patients age, presence of metastatic disease and previous experience with radiotherapy. Each focus group had at least two moderators and all interviews were digitally recorded and then transcribed. The data were managed and coded using NVivo version 12 and analysed using a thematic analysis approach.

Results: A total of 18 breast cancer patients participated in this study, with 7 (39%) having primary disease and 11 (61%) with metastatic disease. The study included two focus groups (group one = 5 patients; group two = 9 patients) and four individual interviews conducted between May and June 2023. The participants had a median age of 54 years (range 38-74). The majority of participants (83%) had previous experience with radiotherapy, with 4 (27%) having received SBRT previously for their OMBC. Only 2 (2%) patients who had not previously received SBRT were aware of it before participating in this study. Most of the patients (78%) were Caucasian and 72% had attained at least an undergraduate degree level of education. Throughout the study, three main themes emerged: theme 1 - participants experience with radiotherapy; theme 2 - interests and considerations regarding SBRT (including desired treatment outcomes) and theme 3 - willingness to consider SBRT in absence of a survival

benefit. Extending their life was unanimously described as the most important desired outcome of SBRT, followed by quality of life. Other desired treatment outcomes expressed included reduction of tumour size, minimal collateral damage/side effects, relief of symptoms, avoidance of recurrence and increase in time to change of systemic therapy.

Conclusion: In our study, while extension of life was a desired treatment outcome of SBRT for OMBC, all participants expressed willingness to consider SBRT for its potential benefits in local control and durable pain control, even in absence of a survival benefit.

References: 1. Palma DA et al. *The Lancet*. 2019, 393:2051–8 2. Chmura SJ et al. *J Clin Oncol*. 2022, 40:1007–1007

PO2-05-12

Retrospective analysis on therapeutic efficacy and predictive indicators of eribulin plus anti-angiogenic drugs for metastatic breast cancer

Presenting Author(s) and Co-Author(s):

J. Zhang. Department of Medical Oncology, XI'AN International medical center hospital, United States

X. Wang. Mailman School of Public Health, Columbia University, United States

h. Du. Chongqing General Hospital, United States

Y. Xue. Department of Medical Oncology, XI'AN International medical center hospital, United States

Background:

Eribulin has been widely used for the treatment of metastatic breast cancer (MBC). It has been found that eribulin can work in synergy with Bevacizumab or Anlotinib to achieve anti-angiogenic effects and possible synergistic enhancement. To optimize the efficacy of eribulin usage in late-line MBC patients, it is essential to delve deeper into the effects of combined treatments and gather more real-world clinical outcomes. Therefore, we evaluated the efficacy and safety of eribulin plus the anti-angiogenic drugs in late-line MBC patients.

Objective:

This study aims to retrospectively analyze the therapeutic efficacy and safety of eribulin plus anti-angiogenic drugs in treating metastatic breast cancer and explore predictive indicators of the therapeutic efficacy of eribulin in treating MBC.

Methods:

A retrospective review study was performed. 40 Patients diagnosed with MBC and treated with eribulin in Xi'an international medical center hospital from May 2020 to May 2021 were enrolled in this study. Patients were evaluable for this study and divided into two groups based on whether they received eribulin monotherapy or combined therapy. 22 patients were treated with eribulin monotherapy, and 18 were treated with eribulin and anti-angiogenic drugs (Bevacizumab and Anlotinib). Patients' treatment parameters and characteristics were recorded. The Kaplan-Meier method was used to calculate the median PFS and corresponding 95% confidence interval (CI), and the Cox regression model was used for multivariate analysis of predictive indicators. The Fisher exact probability test was used to compare the difference in adverse reactions between the two groups, with a level of significance set at p -value < 0.05 .

Results:

All study patients have an average of 5 treatment lines and a median progression-free survival (mPFS) of 4.2 months. The eribulin plus anti-angiogenic drug treatment group had a significantly prolonged mPFS compared to the group without anti-angiogenic drug treatment (7.0 months vs 2.0 months, $p < 0.001$, log-rank). Multivariate analysis identified that the combination of anti-angiogenic therapy (HR = 0.043, $p = 0.004$) and the occurrence of grade 3-4 neutropenia after treatment were two predictive factors for longer PFS (HR = 0.322, $p = 0.009$). In contrast, prior resistance to taxanes was predictive of shorter PFS (HR = 4.583, $p = 0.019$). Other factors, including age, Eastern Cooperative Oncology Group (ECOG) performance status, hormone receptor (HR) type, expression status, human epidermal growth factor receptor-2 (HER-2) expression status, Ki-67 level, number of metastatic lesions, and number of prior lines of Eribulin therapy, were not significantly associated with PFS. The results

of Fisher's exact test show that there was no significant increase in treatment-related adverse events (all grades) after combination with anti-angiogenic drugs.

Conclusion:

A combination of eribulin and anti-angiogenic therapy has significantly prolonged mPFS in the treatment of MBC patients. Other factors such as prior non-taxane resistance, grade 3-4 neutropenia occurrence after treatment, and combined anti-angiogenic therapy can be used as biomarkers for predicting treatment efficacy. The adverse events are manageable and the safety of combined therapy can be guaranteed. Therefore, the eribulin plus anti-angiogenic combination may act as a potential therapy for late-line MBC patients with clinically beneficial therapeutic effects.

Keywords:

metastatic breast cancer, eribulin, anti-angiogenic therapy, retrospective analysis

PO2-05-13

HER2 status presented an unstable switching from primary to recurrent breast cancer

Presenting Author(s) and Co-Author(s):

A. Zhu. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital & Institute, Beijing, China, United States

H. Li. Department of Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, Beijing, China (People's Republic)

Background: Breast cancer patients with HER2-2+ expression had heterogeneous characteristic. Treatment decision is of great importance after progression. Objective: We explored patients with HER2-2+ in matched primary or recurrent/metastatic tumor samples from January 2010 to June 2022 in our institute were included to evaluate the evolution from or to HER2-2+ expression. Meanwhile, with an emerging of novel entity as HER2-low expression breast cancer, we included this category when analysis as well. Results: In the cohort of a total of 159 breast cancer patients with HER2-2+ expression in either primary tumor or locoregional/distant metastases samples, HER2-2+ breast cancer accounted for 44.0% in primary tumor and 88.8% in recurrent diseases. There were 18.5% and 15.2% patients with HER2 gene amplification on ISH assay among primary and recurrent/metastatic HER2-2+ breast cancers, respectively. The overall rate of HER2 IHC discordance was 67.1%. Among primary HER2-2+ cases, 74.6% maintained in HER2-2+ when disease relapsed. Discordance was mostly driven by cases switching from HER2-2+ to HER2-1+ (64.7%). In HER2-2+ recurrent/metastatic cases, discordance was mostly driven by cases switching from HER2-0 to HER2-2+ (47.1%). The proportion of HER2 discordant cases got a higher statistically trend among HR-positive patients in compared with HR-negative patients (44.1% vs. 21.7%, $p = 0.062$). There were 35.0% in primary HR-positive/HER2-negative patients and 11.8% in primary triple-negative patients switching from HER2-0 to HER2-low when disease progressed, respectively. Meanwhile, HER2 discordance rate had a significant difference across different metastatic sites ($p = 0.026$). All contralateral breast and skin metastasis presented with discordant HER2 results. While, all central nervous system metastasis maintained the same HER2-low expression. HER2-positive phenotype in primary breast cancer samples loss their positivity in 42.1% cases. There was a total of 6.6% cases gained HER2 positivity in recurrent breast cancer samples. Conclusion: HER2 expression from primary to relapse breast cancer samples were highly unstable. Biopsy of recurrent sites was necessary to find novel treatment.

PO2-05-14

Prognosis and clinicopathological characteristics of HER2-negative metastatic breast cancers with low expression of hormone receptors: real world evidence from the French ESME cohort.

Presenting Author(s) and Co-Author(s):

- M. Alexandre. Medical oncology department, Regional Cancer Institute, Montpellier, montpellier, France
- L. Gauthier. Biostatistics Unit, Regional Cancer Institute, Montpellier, montpellier, France
- A. Mailliez. Oscar LAMBRET Centre, LILLE, France
- t. DE LA MOTTE ROUGE. CENTRE EUGENE MARQUIS, Rennes, Bretagne, France
- T. Bachelot. Medical Oncology, Centre Léon Bérard, Lyon, France
- M. Arnedos. Department of Medical Oncology, Institute Bergonié, Bordeaux, France, United States
- F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France
- E. Brain. European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium, United States
- J. Ferrero. Centre Antoine Laccassagne, Nice, France
- V. Massard. Department of medical oncology, Lorraine Cancer Institute, United States
- I. Desmoulins. Centre Georges-François Leclerc, Dijon, France
- M. Mouret-Reynier. Centre Jean Perrin, United States
- C. Levy. Centre François Baclesse, Caen, Basse-Normandie, France
- A. Gonçalves. Institut Paoli-Calmettes, France
- M. Leheurteur. Department of medical oncology, Henri Becquerel Cancer Center, United States
- T. Petit. Centre Paul Stauss, Strasbourg, France
- J. frenel. Health Data and Partnership department, Unicancer, United States
- L. Bosquet. Department of Medical Oncology, ICO Cancer Center, United States
- S. Delaloge. Institut Gustave Roussy, Villejuif, Ile-de-France, France
- W. Jacot. Institut du Cancer de Montpellier, Université de Montpellier, INSERM U1194, Paris, Montpellier, Languedoc-Roussillon, France

Background: HER2-negative breast cancers expressing low (1-9 %) immunohistochemistry levels of hormone receptors (HR, estrogen and progesterone receptors), remain an uncertain category, being considered either as triple negative breast cancers (TNBC) or HR-positive (HR+) tumors across guidelines or approvals. The issues regarding this clinical subgroup are both prognostic, with the need of a better definition of their clinical outcome, as well as predictive. Methods: The ESME database is a French National cohort of all consecutive patients who initiated a first-line treatment for metastatic breast cancer (MBC) from 2008 on, in one of the 18 French Comprehensive Cancer Centers. Patients with HER2-negative (0 to 2+, ISH negative) MBC and known estrogen receptor (ER) and progesterone receptors (PR) expression levels were selected. Primary objective was to evaluate crude overall survival (OS) in HER2-/HR-low (ER and PR 0-9 and not TNBC) MBC pts compared with those with TNBC and HR+ disease defined by ER and PR < 1%, and ER ± PR ≥ 10%, respectively. In these 3 populations, predefined secondary objectives were to evaluate PFS under first line

chemotherapy (CT), to describe clinical characteristics and the distribution of genetic abnormalities identified at the time of MBC diagnosis. Results: Out of 30,459 patients in the ESME database initiating their MBC treatment between 01/2008 and 01/2021, 19109 patients (2113 TNBC; 228 HR-low; 16768 HR+) were eligible for this analysis. Median follow-up was 58.0 months (95%CI [56.6; 59.0]). Median OS were 15.7 months [15.0-16.8], 19.1 months [15.5-22.4] and 44.6 months [43.8-45.5] in the TNBC, HR-low and HR+ subgroups, respectively. The multivariable analysis adjusted on age at MBC diagnosis, pathological grade and subtype, metastatic-free interval, number and sites of metastases and HER2 status (0 vs. 1-2+), identified no significant OS difference between HR-low and TNBC subgroups (HR=0.95, 95%CI 0.79-1.14), while HR+ patients had a better OS than TNBC patients (reference) (HR=0.50, 95%CI 0.47-0.53). Of these 19109 pts, 8910 received first-line CT regimen (1960 TNBC; 195 HR-low; 6755 HR+): taxanes-based: 66.7%, anthracyclines-based: 32.9%, capecitabine: 18%. Median PFS under first line CT were 5.3 (5.1-5.6), 5.1 (4.1-6.2) and 10.2 months (9.9-10.6) for TNBC, HR-low and HR+ subgroups, respectively. In the multivariable analysis adjusted on the same variables, the HR-low subgroup had a statistically poorer PFS compared to TNBC (HR=1.24, 95% CI 1.04-1.49). On the other hand, the HR+ subgroup had a better PFS than the TNBC (HR=0.74, 95%CI [0.70; 0.78]). Baseline germline BRCA1 mutations (at MBC diagnosis) were present in 4.5% of the TNBC cases, 2.6% of the HR-low cases, and 0.4% of the HR+ cases. The distribution of germline BRCA2 mutations was more homogeneous between the three groups (0.9% of TNBC cases, 1.3% of HR-low cases and 1.1 % of HR+ cases). Conclusions: In this large cohort, patients with HER2-negative, HR-low MBC seem to share similar general prognosis, oncogenetic features and PFS under standard chemotherapy treatment with TNBC patients.

PO2-06-01

Validity of patient-reported data from long-term survivors of metastatic breast cancer

Presenting Author(s) and Co-Author(s):

M. Gallagher. University of Wisconsin School of Medicine and Public Health, Wisconsin, United States

M. Burkard. DEPARTMENT OF MEDICINE University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States

Background: Metastatic Breast Cancer is incurable, with 5-year survival of ~30%. The Outliers Study recruited participants with metastatic breast cancer to fill out an extensive survey to better elucidate how clinical, social, and genetic factors affect metastatic breast cancer survivorship. Patient-reported surveys can be a valuable source of data for research studies and cancer registries to further our understanding of disease, but concerns regarding the validity of patient reporting remain. Beatty et al. (2022) suggest that patients with early stage breast cancer are reliable reporters of disease recurrence (79% accuracy rate), but no study to our knowledge has evaluated the validity of reporting regarding metastases, or those who are long-term survivors. In this study, over 1000 women with metastatic breast cancer filled out an extensive survey. We compared the medical records with self-reported data on clinical history to assess concordance.

Objective: To determine the validity of patient-reported data pertaining to a wide variety of oncologic information, including but not limited to primary diagnosis date, stage, hormone status, metastatic date, site, and post-metastatic chemotherapy regimens, in long term survivors of metastatic breast cancer.

Methods: Patients with metastatic breast cancer were recruited for the nation-wide Outliers Study to fill out an extensive survey on their oncologic history. Of >1000 participants enrolled in the Outliers Study, we identified a subpopulation of those who had lived the longest with metastatic disease and named this cohort “Long Term Survivors” (LTS). We acquired either partial or complete oncologic medical records from 31 LTS in order to determine the validity of patient-reported survey responses. Table 1 describes the details of this LTS cohort (n=31). We then compared each LTS survey to the medical record to verify responses and identify any inaccuracies. We also assessed accuracy to compare those who did and did not consult their medical records while responding to the survey.

Results: Of the verifiable survey responses, we identified 592 accurate responses and 5 inaccuracies, yielding a 99.2% accuracy rate of patient-reported oncologic data. The identified errors included 2 minor discrepancies in clinical detail, 2 false-negative reports and 1 false-positive report. Specifically, there were minor discrepancies regarding biopsy type (i.e. core biopsy reported instead of fine needle) and site of radiation (e.g. “chest wall” instead of T12 vertebrae). The false-negative reporters failed to report 1) a positive history for surgery distant from breast for metastatic disease and 2) a positive history of biopsy for disease distant to the breast. The false positive error was a report of “surgery on distant metastasis” for a history of bone marrow biopsy. Each error identified was made by a separate participant and we found no association between patients who were reporting from memory and patients who reported an inaccurate response. Of note, there were no inaccurate responses identified pertaining to the topics of initial diagnosis date, stage, and histologic type, breast surgical history, hormone and HER2 receptor status of initial and metastatic disease, date and site of metastatic disease, BRCA mutation status, date and regimens of chemotherapy, and date of radiation history.

Conclusion: Long term survivors of metastatic breast cancer report clinical data spanning a wide range of oncologic topics with high accuracy. The majority of errors identified in patient reported survey responses were minor and suggested misunderstandings of medical nomenclature (surgery vs biopsy; core vs FNA) and anatomic specificity. The topic of biopsy was most prone to error. Notably, we found no association between errored responses and patients who reported from memory without referencing their medical records.

Table 1

Table 1: Characteristics of Long Term Survivors of Metastatic Breast Cancer (n=31)	
	Average in years (min-max)
Age at time of survey completion	67 (54-81)
Interval from primary diagnosis to survey completion	28 (9-42)
Diagnostic interval from primary malignancy to metastasis at time of survey completion	19.8 (4-38)
Average years living with metastatic disease*	8.11 (0.5-31)
	N (%)
Referenced medical records to fill out survey:	
No, reported from memory	6 (19.4%)
Yes, with access to partial medical records	13 (41.9%)
Yes, with access to complete medical records	12 (38.7%)
Cancer stage at primary diagnosis:	
Stage 0 (DCIS)	5 (16.1%)
Stage 1	10 (32.3%)
Stage 2	15 (48.4%)
Stage 3	1 (3.2%)
Histologic type of primary breast cancer:	
Ductal	19 (61.3%)
Lobular	4 (12.9%)
Other	6 (19.4%)
Unknown	2 (6.4%)

PO2-06-02

Characteristics and Treatment Patterns of de novo Oligometastatic Stage IV Breast Cancer: A Single-Center Retrospective Cohort Study.

Presenting Author(s) and Co-Author(s):

D. Blansky. Yale School of Medicine, United States

m. lustberg. Yale Cancer Center, New Haven, Connecticut, United States

L. puzstai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

M. Rozenblit. Yale Cancer Center, New Haven, Connecticut, United States

Background: Retrospective studies suggest that patients with oligometastatic breast cancer (≤ 5 metastatic lesions) have improved prognosis and may benefit from multimodality treatment. Randomized clinical trials, however, with mostly recurrent oligometastatic breast cancer have not shown improved prognosis with this approach. Real-world data on de novo oligometastatic stage IV (oligo-stage IV) disease are limited. We therefore investigated differences in 5-year mortality in patients with de novo oligo-stage IV vs de novo extensive-stage IV breast cancer who received curative vs palliative chemotherapy at our institution.

Methods: In a retrospective cohort design, using the Yale tumor registry, we identified de novo stage IV breast cancer (metastatic to distant sites at diagnosis), diagnosed 2012-2016. Clinical characteristics and treatment patterns were compared between oligo-stage IV vs extensive-stage IV. Curative regimens were defined as TCHP or AC-THP for HER2+, ddAC- >T or TC for ER+, and ddAC- >T for TNBC. Palliative regimens were defined as THP for HER2+ or single agent chemotherapy. 5-year mortality rates were calculated from date of diagnosis to date of death, with living patients censored at date of last contact. Kaplan-Meier curves were estimated and compared using log-rank tests. Multivariable Cox proportional hazards models assessed the association between oligo-stage IV vs extensive-stage IV breast cancer, curative vs palliative regimen, and 5-year mortality. Models were adjusted for receptor status, age at diagnosis, receipt of surgery, and radiation. Models were then stratified by receptor status.

Results: Of the 202 de novo stage IV cases, 140 (69.3%) were extensive-stage IV and 62 (30.4%) were oligo-stage IV. A larger proportion of oligo-stage IV vs extensive-stage IV was TNBC (19.4% vs 8.8%, $p=0.03$), lower proportion was ER+ (65.6% vs 81.5%, $p=0.01$), and no difference in HER2 (30.5% vs 29.0%, $p=0.83$). Higher proportion of oligo-stage IV vs extensive-stage IV received curative chemotherapy (24.2% vs 7.9%, $p < 0.001$) and breast surgery (25.0% vs 13.6%, $p < 0.001$). There was no difference in receipt of radiation to distant sites (25.0% vs 27.5%, $p=0.70$). Patients who received curative vs palliative chemotherapy were younger (55.3 vs 62.1yo, $p=0.02$). Oligo-stage IV had lower 5-year mortality (64.7%) vs extensive-stage IV (70.6%; HR=0.58, 95% CI 0.39-0.89), with no significant difference in 5-year mortality between curative vs palliative chemotherapy. When stratifying by receptor status, ER+ had the strongest association between oligo-stage IV and decreased 5-year mortality (HR=0.56, 95% CI 0.34 – 0.92). There was no significant association between surgery or radiation and 5-year mortality (HR = 0.62, 95% CI 0.38-0.99; HR= 1.33, 95% CI 0.91-1.95, respectively). Only a small number of patients received all 3 components; curative chemotherapy, surgery, and radiation (N=5; 18.5%). The dose of radiation (palliative vs ablative) is unknown.

Conclusions: Patients with oligo-stage IV breast cancer had lower 5-year mortality vs extensive-stage IV breast cancer. Neither curative intent chemotherapy, breast surgery nor radiation were

associated with lower 5-year mortality. However, very few patients received all 3 modalities with curative intent. These results are consistent with prior randomized clinical trials that showed no survival benefit to escalating therapy, but leave the question unanswered if combining all 3 modalities may improve overall survival in de novo oligometastatic stage IV breast cancer.

Multivariable-Adjusted Association Between Disease Status and 5-Year Mortality Among Patients with De Novo Stage IV Breast Cancer, Stratified by Receptor Status.

All Breast Cancer Cases (N = 201)*				
		Median Survival (years)	5-Year Mortality Rates, N (%)	
	Extensive Stage IV	2.7	108 (70.6)	
	Oligometastatic Stage IV	3.3	44 (64.7)	
Disease Status	Oligometastatic Stage IV	HR of 5-year mortality	95% CI	p-value
		0.62	0.40 - 0.94	0.02
Therapy Intent	Extensive Stage IV	Reference		
	Curative	1.67	0.96 - 2.90	0.07
	Palliative	Reference		
Receptor Status	Triple Negative	3.16	1.83 - 5.46	< 0.001
	Not Triple Negative	Reference		
Surgical Treatment	Received	0.62	0.38 - 0.99	0.04
	Did Not Receive	Reference		
Radiation Therapy	Received	1.33	0.91 - 1.95	0.14
	Did Not Receive	Reference		
Triple Negative Breast Cancer Cases (N = 21)*				
		Median Survival (years)	5-Year Mortality Rates, N (%)	
	Triple Negative	1.0	27 (93.3)	
Disease Status	Oligometastatic Stage IV	HR of 5-year mortality	95% CI	p-value
		0.40	0.12 - 1.43	0.16
Therapy Intent	Extensive Stage IV	Reference		
	Curative	2.48	0.44 - 13.81	0.31
	Palliative	Reference		
Surgical Treatment	Received	0.55	0.10 - 2.84	0.47
	Did Not Receive	Reference		
Radiation Therapy	Received	2.82	0.73 - 10.85	0.13
	Did Not Receive	Reference		
ER Positive Breast Cancer Cases (N = 156)*				
		Median Survival (years)	5-Year Mortality Rates, N (%)	
	ER Positive	3.0	122 (69.3)	
Disease Status	Oligometastatic Stage IV	HR of 5-year mortality	95% CI	p-value
		0.54	0.33 - 0.91	0.02
Therapy Intent	Extensive Stage IV	Reference		
	Curative	2.09	1.02 - 4.29	0.05
	Palliative	Reference		
Surgical Treatment	Received	0.61	0.33 - 1.12	0.11
	Did Not Receive	Reference		
Radiation Therapy	Received	1.41	0.91 - 2.20	0.13
	Did Not Receive	Reference		
HER-2 Positive Breast Cancer Cases (N = 59)*				
		Median Survival (years)	5-Year Mortality Rates, N (%)	
	HER-2 Positive	4.0	38 (56.7)	
Disease Status	Oligometastatic Stage IV	HR of 5-year mortality	95% CI	p-value
		1.08	0.48 - 2.45	0.85
Therapy Intent	Extensive Stage IV	Reference		
	Curative	0.86	0.28 - 2.58	0.78
	Palliative	Reference		
Surgical Treatment	Received	0.27	0.06 - 1.14	0.07
	Did Not Receive	Reference		
Radiation Therapy	Received	1.06	0.47 - 2.42	0.88
	Did Not Receive	Reference		

*Further adjusted for age at diagnosis; HR – hazard ratio, CI – confidence interval

PO2-06-03

Meta-Analysis of Clinical Characteristics and Outcomes in Breast Cancer Patients with Visceral Crisis

Presenting Author(s) and Co-Author(s):

M. Auster. UT Health San Antonio MD Anderson Cancer Center, United States

R. Benkhadra. UT Health San Antonio MD Anderson Cancer Center, United States

S. Lee. UT Health San Antonio MD Anderson Cancer Center, United States

T. Aldawoodi. UTHSCSA, United States

L. Prokop. Mayo Clinic Libraries, United States

T. Nayfeh. Evidence-Based Practice Research Program, Mayo Clinic, United States

P. Datta. Audie L. Murphy VA Hospital, United States

K. Lathrop. UT Health San Antonio, San Antonio, Texas, United States

Background: Recent advancements in novel therapeutics have resulted in improved survival over the last decade for patients with metastatic breast cancer, but there remain subsets of patients who experience disproportionately poor outcomes. Patients with visceral crisis (VC), defined by the 5th ESO ESMO as the presence of visceral metastasis with severe organ compromise and/or rapid progression, are often excluded from clinical trials of novel therapeutics. This is despite patients with VC having poorer clinical outcomes and a lack of guidelines consensus on best therapeutic practices. Thus, we sought to better characterize this patient cohort via a meta-analysis to elucidate clinical characteristics and treatment options. Methods: We searched MEDLINE, Embase, Cochrane, Scopus and other sources, from each database's inception to March 2023. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for patients with breast cancer in visceral crisis. Outcomes of interest included mortality and progression at different time points. Meta-analysis was conducted using the random-effects model. Results: The studies matching our initial inquiry was 154. After evaluation for patient number, and VC related outcomes, 16 studies (12 abstract only) met initial criteria. After data extraction, 12 studies were excluded due to insufficient outcomes delineated by VC. The treatment period was 01/2008 until 01/2022. The mean age at diagnosis of VC was 53.9 with a total of 6404 patients, 6259 were hormone positive, 41 Her2 positive and 87 triple negative. The type of VC included 212 liver dysfunction, 84 respiratory dysfunction, 40 with bone marrow dysfunction, 4 with SVC syndrome, and 43 with meningeal disease (VC type is not reported in every study). The treatments were varied and included multiple platinum doublets, CDK4/6 with endocrine therapy, platinum with bevacizumab, endocrine monotherapy and Her-2 targeted agents. Unfortunately, the number of patients per treatment group or VC type is not enough for targeted outcome analysis. The proportion of patients who progressed at 1, 6, 12 and 18 months were 0.17, 0.64, 0.95 and 0.91 respectively (2 studies Yang et al and Funasaka et al). Mortality assessed as proportion who expired at 1, 6, 12 and 18 months at 0.07, 0.44, 0.64 and 0.77 respectively (3 studies Yang et al, Funasaka et al and Franzoi et al) and at 24 months 0.89 in 4 studies (Yang et al, Funasaka et al, Dawood et al and Franzoi et al) (Table 1). Conclusions In this systematic review, we clearly demonstrate a lack of clinical trial data available to demonstrate specific outcomes based on chemotherapy, visceral crisis type or targeted treatment. The prognosis, however, is consistently poor with mortality at 64 percent by 12 months. Thus, further studies are needed to guide best treatment strategies that address both the poor clinical outcomes and therapeutic toxicities for patients with VC. Clinical trial groups and regulatory bodies overseeing new drug

development for breast cancer should consider specific arms for patients with VC, instead of targeted exclusion from trials, as this strategy has proven effective in expansion of therapeutics for other challenging breast cancer subtypes.

Table 1

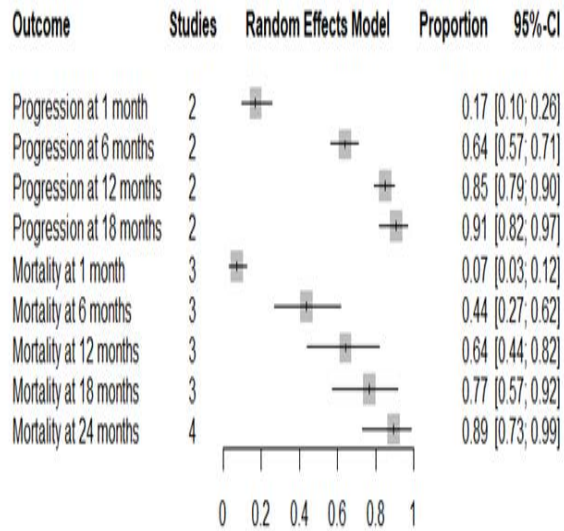


Table 1: Proportion of progression and mortality. Progression studies include Yang et al 2022, Funasaka et al 2021. Mortality studies at 1, 6 and 12 months Yang et al 2022, Funasaka et al 2021 and Franzoi et al 2021. Mortality studies at 24 months Yang et al 2022, Funasaka et al 2021, Franzoi et al 2021, Dawood et al 2021.

PO2-06-04

Prospective study on eribulin efficacy in advanced and metastatic breast cancer: changes in TGF- β compared to other standard chemotherapy agents (KBCSG-TR 2018, POTENTIAL)

Presenting Author(s) and Co-Author(s):

T. Nakayama. Department of Breast and Endocrine Surgery, Osaka International Cancer Institute, United States

T. Yoshinami. Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, United States

F. Fujisawa. Department of Medical Oncology, Osaka International Cancer Institute, Osaka-city, Osaka, Japan

M. Nishio. Department of Medical Oncology, Osaka International Cancer Institute, United States

T. Yamanaka. Department of Breast Surgery and Oncology Kanagawa Cancer Center, Japan

T. Yamashita. Kanagawa Cancer Center, Japan, Yokohama, Japan

C. Oshiro. Kaizuka City Hospital, United States

A. Izui. Department of Breast Surgery, Kaizuka City Hospital, United States

N. Tomioka. Department of Breast Surgery, National Hospital Organization Hokkaido Cancer Center, United States

H. Maeda. Department of Breast Surgery, National Hospital Organization Hokkaido Cancer Center, United States

M. Shimoda. Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, United States

K. Shimazu. Department of Breast and Endocrine Surgery, Graduate School of Medicine, Osaka University, United States

M. Tsuneizumi. Department of Breast Surgery, Shizuoka General Hospital, Japan

R. Matsunuma. Department of Breast Surgery, Shizuoka General Hospital, Shizuoka, Japan

H. Bando. University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan

A. Ueda. Department of Breast-Thyroid-Endocrine Surgery, University of Tsukuba Hospital, United States

H. Yasojima. Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

K. Okada. Department of Surgery, Breast Oncology, National Hospital Organization Osaka National Hospital, United States

K. Inoue. Saitama Cancer Center, Saitama, Japan

Y. Kai. Ueo Breast Cancer Hospital, Oita, Japan

K. Yoshidome. Breast and Endocrine Surgery, Osaka Police Hospital, United States

H. Kawaguchi. Matsuyama Red Cross Hospital, Matsuyama, Ehime, Japan

M. Nagahashi. Hyogo Medical University, United States

K. Oshima. Breast Surgery, Kansai Rosai Hospital, United States

S. Kashiwagi. Breast Surgical Oncology, Osaka Metropolitan University Graduate School of Medicine, United States
T. Iwasa. Kindai University Hospital, United States
K. Taruno. Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine, United States
S. Tsuyuki. Osaka Red Cross Hospital, United States
F. Tsukamoto. Department of Breast and Endocrine Surgery, Japan Community Health care Organization Osaka Hospital, United States
T. Morimoto. Department of Breast Surgery, Yao Municipal Hospital, United States
N. Kittaka. Department of Breast Surgery, Osaka Rosai Hospital, United States
T. Higuchi. Breast Unit, Japanese Red Cross Saitama Hospital, United States
Y. Naito. National Cancer Center Hospital East, Kashiwa, Chiba, Japan, United States
R. Saita. Department of Medical Innovation, Osaka University Hospital, United States
H. Nishikawa. Department of Immunology, Nagoya University Graduate School of Medicine, Division of Cancer Immunology, Research Institute/Exploratory Oncology Research & Clinical Trial Center (EPOC), National Cancer Center, United States
D. Sugiyama. Nagoya University Graduate School of Medicine, United States
Y. Miyoshi. Dept of Surgery, Division of Breast and Endocrine Surgery, Hyogo Medical University, Nishinomiya-hama, Hyogo, Japan
Y. Uchida. Eisai, United States
T. Yamada. Department of Medical Innovation, Osaka University Hospital, United States
N. Masuda. Nagoya University Graduate School of Medicine, Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

Title

Prospective study on eribulin efficacy in advanced and metastatic breast cancer: changes in TGF- β compared to other standard chemotherapy agents (KBCSG-TR 2018, POTENTIAL)

Introduction

Eribulin (E) has been demonstrated to improve overall survival (OS) compared to standard chemotherapies in pivotal phase III clinical trials (studies 301 and 305), although there was no difference in progression-free survival. These findings suggest that E might have a mechanism for OS improvement different from the common anti-tumor effect. Several studies reported that E inhibits epithelial-mesenchymal transition and the suppression of TGF- β plays a central role. Data on the relationship between the E-induced serial change in TGF- β and the improvement in OS remains insufficient. Therefore, we conducted this prospective observational study of patients treated with E while undergoing sequential TGF- β testing. This study also enrolled patients who received chemotherapy other than E as a control.

Methods

Patients with HER2-negative recurrent / metastatic breast cancer (MBC) were prospectively enrolled from 23 breast cancer centers in Japan, if they had not previously used E, had received two or fewer prior chemotherapy regimens, and were scheduled to start either E, capecitabine, S-1 or paclitaxel (\pm bevacizumab) between September 2020 and February 2022.

The target sample sizes were 150 and 50 patients scheduled to receive E (Cohort E) and other drugs (Cohort Others), respectively. We collected blood samples for TGF- β testing at baseline, at two or three weeks (week 2/3), and at four or five weeks (week 4/5) from the beginning. The observation period was until February 2023. The primary endpoint was to evaluate the relationship between changes in TGF- β and clinical response, including OS and time to treatment failure (TTF).

Results

A total of 202 of the 203 enrolled patients were included in the analysis (1 patient declined consent). The median age was 60.0 (interquartile range, 52.0-69.0) years and ECOG performance status was 0 or 1 in all patients. Among 152 patients in Cohort E and 50 patients in Cohort Others, 37 patients (24.3%) and 12 patients (24.0%) had hormonal receptor-negative breast cancer, and 29 patients (19.1%) and 30 patients (60.0%) had no prior chemotherapy for MBC, respectively. Visceral metastasis totaled 115 (75.7%) in Cohort E

and 46 (92.0%) in Cohort Others. In OS analysis of 199 patients, the median OS was 24.5 months (95% CI, 17.3-NA) for no prior chemotherapy, and 17.7 months for one or two prior chemotherapy (median follow-up 14.5 months). In Cohort E and Cohort Others, 139 and 45 patients, respectively, had paired samples for TGF- β testing at baseline and week 2/3. The proportion of patients with a percent change at week 2/3 from baseline in TGF- β (Δ TGF- β) of less than zero (decreased TGF- β) was 46.8% in Cohort E and 33.3% in Cohort Others, indicating a 13.4% (-2.6% – 29.5%) higher trend in Cohort E. Based on the time-dependent receiver operating characteristic (ROC) curves at 6 months for TTF, the threshold of Δ TGF- β was determined to be 27%. For the low Δ TGF- β group (< 27%) and the high Δ TGF- β group (\geq 27%), OS rates at median follow-up (14.5 months) were 70.6% and 54.3% ($p=0.085$) in Cohort E and 68.9% and 58.2% ($p=0.585$) in Cohort Others, respectively, suggesting a relationship between low Δ TGF- β and a favorable prognosis only in Cohort E.

Conclusions

The current study showed the trend in the higher frequency of decreased TGF- β , as well as the important relationship between decreased TGF- β and a favorable prognosis in patients treated with E compared with those receiving other chemotherapies. As the next step, further biomarker analyses including cytokines and chemokines, and immunological analyses are planned.

PO2-06-05

Neutrophil-to-lymphocyte ratio (NLR) Predict the Outcome Significance for Primary Tumor Surgery in Patients with De novo stage IV Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Sugihara. Department of Surgery, Kurume University School of Medicine, Kurume, Fukuoka, Japan

U. Toh. Department of Surgery, Kurume University School of Medicine, United States

H. Watanabe. Kurume University School of Medicine, Department of Surgery, Japan

Y. Katagiri. Department of Surgery, Kurume University School of Medicine, United States

S. Matsushima. Department of Breast Surgery, National Hospital Organization Kyushu Medical Center, United States

O. Mina. Department of Breast Surgery, National Hospital Organization Kyushu Medical Center, United States

Y. Takao. Department of Surgery, Kurume University School of Medicine, United States

N. Iwakuma. Department of Breast Surgery, National Hospital Organization Kyushu Medical Center, United States

F. Fujita. Department of Surgery, Kurume University School of Medicine, United States

[Background] Although several prospective randomized trials have not shown a statistically significant difference in overall survival(OS),and quality-of-life(QOL) for the primary tumor surgery(PTS) of De novo stageIV breast cancer(BC), but more recent studies showed that could prolong OS in selected cases. This study respectively evaluated the value of neutrophil-to-lymphocyte ratio(NLR) as a biomarker for predicting the benefit of PTS in patients(pts) with stageIV BC.

[Method] The clinical outcome and associated prognostic factors of pts with De novo stageIV BC were investigated. The decision of surgery option for primary tumor was shared with pts and determined by treating physicians according to the clinical symptoms. Laboratory blood examinations were performed before and after surgery or each treatment courses. The kinetics of peripheral blood lymph cell counts, NLR etc. were analyzed simultaneously.

[Result] A total of 141 pts with stageIV BC were treated and enrolled from January 2004 to December 2022. 61 pts (Surgery group: SG) received and 80 pts (Non surgery group: NSG) not received PTS. The biological subtypes of primary BC included that 76 HR+(Luminal), 13 HR+Her2+(Luminal Her2), 29 Her2+ and 21 triple negative, respectively. The median PFS of SG and NSG were 88 ms and 30.3 ms, the median OS were 100.1 ms and 31.8 ms, respectively. Pts of SG who had high NLR (>3) before the surgery showed a significant worse OS ($p < 0.0001$) (Fig.1). And pts who responded to the systemic therapies prior to PTS for longer than 8.1 months showed a better OS($p=0.044$). In contrast, pts of NSG who had a low ALC($\leq 1500/\mu\text{L}$) at 6 months($p=0.026$) and 1 year($p=0.007$) after systemic therapies, and high NLR (>3) at 1 year($p=0.001$) had worse prognosis.

[Summary] Our results suggested that pts with De novo stageIV BC who responded to the systemic therapies prior to PTS longer than 8.1 months, and who had a preoperative low NLR(≤ 3) might be benefit to PTS after the systemic therapies. And peripheral blood NLR before surgery may be a predictive marker for the indication of PTS in those pts. Further larger

scale prospective studies are warranted.

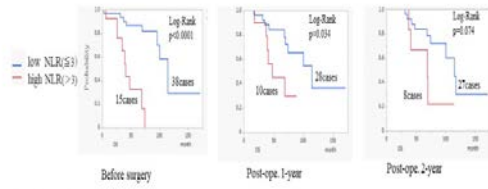


Fig.1 The association between NLR and OS

PO2-06-06

Effectiveness and prognostic predictors of primary systemic therapy for de-novo Stage IV breast cancer - Supplementary analysis of JCOG1017 PRIM-BC

Presenting Author(s) and Co-Author(s):

- T. Shien. Okayama University Hospital, Okayama-city, Okayama, United States
A. Shimomura. Department of Breast and Medical Oncology, National Center For Global Health And Medicine, Tokyo, Japan
M. Ishitobi. Mie University Hospital, United States
K. Tanaka. Toranomon Hospital, Japan
T. Tsukioki. Okayama University Hospital, United States
T. Yamanaka. Department of Breast Surgery and Oncology Kanagawa Cancer Center, Japan
F. Hara. Breast Medical Oncology, Cancer Institute Hospital of JFCR, United States
K. Aogi. Department of Breast Surgery, National Hospital Organization Shikoku Cancer Center, Matsuyama, Ehime, Japan
Y. Yanagita. Gunma Cancer Center, United States
M. Tsuneizumi. Department of Breast Surgery, Shizuoka General Hospital, Japan
N. Yamamoto. Division of Breast Surgery, Chiba Cancer Center, United States
H. Matsumoto. Saitama Cancer Center, United States
A. Suto. Department of Breast Surgery, National Cancer Center Hospital, Japan
K. Watanabe. NHO Hokkaido Cancer Center, Sapporo, Japan
M. Harao. Department of Breast Oncology, School of Medicine, Jichi Medical University, United States
C. Kanbayashi. Department of Breast Oncology, Niigata Cancer Center Hospital, United States
M. Ito. Hiroshima City Hiroshima Citizen's Hospital, United States
K. Anan. Kitakyushu Municipal Medical Center, kitakyushu, Japan
S. Maeda. National Hospital Organization Nagasaki Medical Center, United States
K. Sasaki. JCOG Data Center/Operations Office, National Cancer Center Hospital, tyuoukukiji, Tokyo, United States
G. Ogawa. JCOG data center, United States
H. Fukuda. JCOG Data Center/Operations Office, National Cancer Center Hospital, United States
H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Background The optimal choice of drug is important in treating metastatic breast cancer, and the efficacy of the drug should be determined early, especially in cases of progression. On the other hand, untreated de novo Stage IV (dnST-IV) patients are expected to be more sensitive to drugs, but no detailed data are available. In JCOG1017 (Randomized trial of primary tumor resection in dnST-IV), dnST-IV patients were treated with primary systemic therapy for 3 months according to breast cancer subtypes before randomization. We already presented the results of primary endpoint. Primary tumor resection (PTR) could not significantly prolong the overall survival of de-novo stage IV breast cancer patients with sensitivity to primary systemic therapy. We conducted the supplementary analysis of JCOG1017 to clarify the efficacy of

primary systemic therapy for dnST-IV and develop optimal treatment strategies for dnST-IV breast cancer. Methods In JCOG1017, systemic therapy was performed for each subtype/metastatic status as follows; 1) hormone therapy: ER+ HER2- and no life-threatening metastases, 2) weekly PTX therapy: life-threatening metastases, or ER-HER2-, 3) trastuzumab + pertuzumab + docetaxel (HPD) therapy OR trastuzumab + paclitaxel (HPTX) therapy: ER-HER2+. 4) hormone therapy: ER+HER2+ and no life-threatening metastases. The non-PD rate (no increase of more than 10% of the sum of the diameters of the target lesions compared before systemic therapy), the responses rate (cCR or cPR), and overall survival (OS) of responder (cCR or cPR)/non-responder (cSD or cPD) and PD/non-PD were examined. Results Among 569 patients who received primary systemic therapy in JCOG 1017, the non-PD rate was 77.2% and the response rate was 29.0% after 3 months of systemic therapy. By subtype, the non-PD rate was 78.2% for ER-HER2-, 75.4% for ER+HER2-, 92.9% for ER-HER2+, and 66.7% for ER+HER2+. The response rate was 36.4% for ER-HER2-, 13.4% for ER+HER2-, 81.0% for ER-HER2+, and 40.3% for ER+HER2+. In multivariable analysis, the non-PD rate was higher in postmenopausal (odds ratio [OR] 1.673, p=0.0240) and PgR-positive (OR 2.391, p= 0.0019) patients besides subtypes. Analysis results by drug were as follows; 1) hormone therapy (non-PD rate: 72.9%) was more effective for PgR-positive (OR 3.258, p< 0.0001), less effective for patients with visceral metastasis (OR 0.605, p=0.0334) and HER2-positive (OR 0.365, p=0.0016), 2) wPTX (non-PD rate: 76.1%) was no significant predictors of efficacy, 3) HPD/HPTX (non-PD rate: 92.7%) was more effective in patients with visceral metastasis (OR 15.818, p=0.0030). PD patients had much worse OS (hazard ratio [HR] 0.501, p< 0.0001) compared to non-PD, whereas responders had a little worse OS (HR 0.788, p=0.0538) compared to non-responders. Similar tendency was observed in any drug. Discussion Predictors of response to primary systemic therapy differed by subtype, with the need for treatment strategies tailored to PgR, HER2 expression, and the status of visceral metastasis. In the ER+HER2+ group, the efficacy of hormonal therapy alone was low, and combination therapy with molecular-targeted agents was considered necessary. The non-PD rate reflected prognosis in determining the efficacy of primary systemic therapy for dnST-IV.

PO2-06-07

A Randomized Phase II Comparison of Single-Agent Carboplatin versus the Combination of Carboplatin and Everolimus for the Treatment of Advanced Triple Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Patel. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

J. Fukui. University of Hawaii Cancer Center, United States

P. Klein. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

E. Moshier. Icahn School of Medicine at Mount Sinai, United States

C. Shapiro. Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

A. Goel. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

J. Fasano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

T. Shao. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

A. Bhardwaj. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

R. Vaccaro. Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, United States

G. Joshi. University of Vermont Cancer Center, United States

J. Sparano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

A. Tiersten. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

Background: Both TNBC and BRCA-1 associated breast cancers are sensitive to DNA cross-linking agents such as platinum compounds due to defective DNA repair by homologous recombination. TNBCs are also associated with a high frequency of PTEN loss, which can lead to activation of the mTOR pathway resulting in tumor cell growth and proliferation. mTOR activation can confer resistance to platinum agents, and this phenomenon may be reversible by the addition of an mTOR inhibitor, such as everolimus. A prior phase II single arm trial of carboplatin and everolimus in patients (pts) with advanced TNBC demonstrated good tolerability and preliminary efficacy. Methods: We conducted a phase II, multicenter, randomized trial in pts with advanced TNBC, who had received 0-3 prior lines of therapy. Pts were randomly assigned (in a 2:1 ratio) to carboplatin and everolimus or carboplatin alone. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR), and safety. We planned to enroll 72 pts which would provide > 80% power for a one-sided log-rank test at the 5% level of significance, to detect a 2.5 month improvement in median PFS between treatment groups, assuming a median PFS of 2.5 months in the control group. An interim analysis for futility was planned after 36 events with a stopping boundary of $P < 0.375$ for the comparison of PFS, using an O'Brien-Fleming spending function. Of note, the trial was stopped earlier than planned based on a sensitivity/tipping point analysis which indicated that terminating the trial 3 months ahead of schedule would have no substantial impact on the primary endpoint. Results: A total of 56 pts were randomized between 2015 and 2022, of whom 36 received carboplatin/everolimus and 20 carboplatin alone. The median age of the population was 62.8 years (range: 33-87) and about 20% of pts had BRCA-1 or BRCA-2 mutations. In the overall population, pts had received a

median of 1 (range 1-3) prior line of therapy in the metastatic setting, with 75% of pts receiving prior chemotherapy and 47% prior carboplatin. The median PFS was significantly improved in pts who received carboplatin and everolimus (4.7 months) versus those who received carboplatin alone (2.1 months; HR: 0.37; 95% CI: 0.19-0.72; p=0.0042). Overall survival was 22.1 months in pts on the combination versus 14.4 months on carboplatin alone (HR: 0.73; 95% CI: 0.30-1.72; p=0.3106). CBR was 61% with the combination vs 50% with carboplatin monotherapy, as shown in Table 1. Most common adverse events (AEs) on carboplatin and everolimus included thrombocytopenia (81%), anemia (69%), leukopenia (67%), fluid retention (64%), and neutropenia (61%). Overall, Grade 3/4 events occurred in 75% of pts (83% of pts on combination vs 60% on carboplatin alone) and were primarily anemia (40% vs 17%), thrombocytopenia (47% vs 0%), and neutropenia (20% vs 0%). Of note, there was an increase in thrombocytopenia with the addition of everolimus (All Grades: 81% vs 35%, Grade 3/4: 39% vs 0%). Conclusions: Treatment options for TNBC are limited due to a lack of targeted therapies. The combination of carboplatin and everolimus in this study was associated with a 63% reduction in risk of progression or death in pts with metastatic TNBC. The regimen was well tolerated and provides a promising treatment option for pts with advanced TNBC.

Table 1. Results in Patients on Carboplatin and Everolimus versus Carboplatin Alone

Outcome	Carboplatin and Everolimus 64.3% (N=36)	Carboplatin Alone 35.7% (N=20)	P-Value
Median PFS, months [95% CI]	4.7 [3.9-11.5] HR: 0.37 [0.19-0.72]	2.1 [1.9-7.9]	0.0042
Median OS, months [95% CI]	22.1 [14.3-1.8] HR: 0.73 [0.30-1.72]	14.4 [11.3-NE]	0.3106
Investigator-assessed response, % (N)			
Clinical benefit rate	61% (22)	50% (10)	0.4208
Overall response rate	22% (8)	10% (2)	0.2525
Complete Response	0% (0)	0% (0)	
Partial Response	22% (8)	10% (2)	
Stable Disease	39% (14)	40% (8)	
Progressive Disease	33% (12)	50% (10)	
Unevaluable ¹	6% (2)	0% (0)	

NE= Not Estimable; ¹Unevaluable patients treated as non-responders in CBR and ORR calculations.

NE= Not Estimable; ¹Unevaluable patients treated as non-responders in CBR and ORR calculations.

PO2-06-08

Suppression of GATA2/3-FOXA1-HER3 Axis by Histone Deacetylase (HDAC) Inhibitors shows Antitumor Activity in Basal-like Breast Cancer

Presenting Author(s) and Co-Author(s):

B. Liu. LSU Health New Orleans, Louisiana, United States

C. Tan. Louisiana State University Health Sciences Center-New Orleans, United States

H. Lyu. LSU Health New Orleans, United States

Introduction: Basal-like breast cancer (BLBC) represents an aggressive subtype of triple-negative breast cancer (TNBC) that exhibits a high risk of recurrence and resistance to treatment. Histone deacetylase (HDAC) inhibitors (HDACis), including panobinostat and romidepsin, have obtained approval for the treatment of hematopoietic malignancies and demonstrated effectiveness in TNBC cells. We recently found that panobinostat and romidepsin potently induced TNBC cell growth inhibition and apoptosis via downregulation of HER3 through suppression of forkhead box protein A1 (FOXA1), a pioneering transcription factor. Nonetheless, the underlying mechanism through which HDACis suppress FOXA1, thereby inhibiting HER3 expression and its downstream signaling in FOXA1/HER3 co-expressing TNBC remains elusive. Methods: Colony formation, MTS, and LIVE/DEAD cell staining assays were used to detect cell viability. Apoptosis was detected by flow cytometry assays. QRT-PCR, western blots, and immunohistochemistry were performed to determine the expression and activation of genes and/or proteins. Co-immunoprecipitation was performed to assess the interaction between proteins. Lentivirus vectors containing cDNA or shRNAs were used to overexpress or knockdown gene expression. Chromatin immunoprecipitation-quantitative PCR and dual luciferase reporter assays were performed to elucidate the regulatory role of gene transcription. Results: Elevated expression of FOXA1 was observed in BLBC specimens and cell lines tested. FOXA1 was co-expressed with HER3 and transcriptionally activated the HER3 expression in BLBC cells. HER3 formed heterodimers with epidermal growth factor receptor (EGFR), activating downstream signaling pathways in BLBC cells. Treatment with panobinostat and romidepsin resulted in growth inhibition and apoptosis in BLBC cells by downregulating FOXA1 expression and inhibiting HER3 signaling. Notably, the combination of HDACis with an EGFR inhibitor (gefitinib) or an anti-HER3 antibody synergistically enhanced the anti-survival effects on BLBC cells. Additionally, gene expression profiling datasets revealed a significant positive correlation between FOXA1 expression and the transcription factors GATA-Binding Protein 2/3 (GATA2/3). Patients with high GATA2/3-FOXA1 expression exhibited worse Relapse-Free Survival (RFS) compared to those with low expressions in BLBC via Kaplan-Meier analysis. Further investigations showed that GATA2/3 directly activated FOXA1 transcription by binding to its promoter. Moreover, ectopic expression of GATA2/3 not only restored FOXA1 expression downregulated by HDACis but also attenuated the anti-survival effects of HDACis on BLBC cells. Conclusion: HDACis exhibit potent inhibitory effects on BLBC cells via downregulation of GATA2/3-mediated repression of FOXA1 gene transcription, which in turn suppresses HER3 expression and signaling. Our findings indicate that epigenetic targeting of the GATA2/3-FOXA1-HER3 axis may be an effective therapeutic strategy for the eradication of BLBC tumors. Keywords: FOXA1, GATA2/3, HER3, HDAC inhibitors, Basal-like breast cancer

PO2-06-09

A prospective phase 2 study on efficacy and safety of AK105, anlotinib combined with nab-paclitaxel (nab-P) as a first-line therapy in patients(pts) with advanced triple-negative breast cancer(TNBC)

Presenting Author(s) and Co-Author(s):

L. Zhang. Department of Medical Oncology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Key Laboratory of Liaoning Breast Cancer Research, Shenyang, Liaoning, China (People's Republic)

T. Sun. Department of Medical Oncology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Key Laboratory of Liaoning Breast Cancer Research, Shenyang, United States

Background: PD-1/PD-L1 inhibitor plus chemotherapy have shown tolerability and significant clinical benefits in pts with advanced TNBC. Antiangiogenic agent could remodel tumor blood vessels and increase the response to immune-checkpoint inhibitors (ICIs). AK105, an anti-PD-1 antibody, can effectively prevents PD-1 from binding to PD-L1 and PD-L2, and avoid immune evasion of tumor cells. Anlotinib is a novel antiangiogenic, multi-target tyrosine kinase inhibitor which inhibits VEGFR, FGFR, PDGFR, c-KIT, c-RET and MET. This investigator initiated trial (IIT) (NCT05244993) aims to investigate the efficacy and safety of AK105, anlotinib combined with nab-P as a first-line therapy in pts with advanced TNBC. Methods: In this multicenter, prospective, single arm, phase 2 study, eligible pts were female aged 18-75 years, with ECOG PS 0-1, who had locally advanced or recurrent/metastatic triple-negative (estrogen receptor-, progesterone receptor- and HER2-) breast cancer. Eligible pts were treated with intravenous AK105 (200 mg on day 1), oral anlotinib (12 mg once daily on days 1-14) and intravenous nab-P (125 mg/m² on days 1 and 8) . The triplet combination regimen repeated every 21 days until disease progression, death or intolerable toxicity. The primary endpoint is overall response rate (ORR), and the secondary endpoints are disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety. Results: From July 2022 to July 2023, 19 patients were enrolled in this study. Median follow-up was 6.18 months (95% CI 1.29-11.06). Of all the patients whose efficacy could be evaluated (16/19), no patient achieved complete response (CR); 9(56.25%), 6(37.5%) and 1(6.25%) patients got partial response (PR), stable disease (SD) and progression disease (PD), respectively. ORR was 56.25 % (95% CI 30.55-79.25) and DCR was 93.75% (95% CI 67.71-99.67). mPFS and OS have not reached. The most common adverse events (AEs) were grade 1 or 2. The grade 3 AEs were neutropenia (15.79%), Leukopenia (10.52%), elevated ALT (5.26%), elevated AST (5.26%) and hypercholesteremia (5.26%). There were one case of grade 4 neutropenia and one case of grade 4 hypertriglyceridemia. No treatment-related death was observed. Conclusion: The combination of AK105, anlotinib and nab-P showed better treatment response and tolerable toxicity in the treatment of first-line patients with TNBC. Further studies enrolling more patients are still needed.

PO2-06-10

Prevalence of genomic alterations in Xerna tumor microenvironment subtypes in triple negative breast cancer patients

Presenting Author(s) and Co-Author(s):

G. Basu. Exact Sciences, United States

J. Lobello. Exact Sciences, United States

S. Thakkar. Exact Sciences, United States

J. Aldrich. Exact Sciences, United States

M. Halbert. Exact Sciences, United States

P. Eimerman. Exact Sciences, United States

C. Flannery. Exact Sciences, United States

N. Therala. Exact Sciences, United States

D. Hall. Exact Sciences, United States

D. Pointing. Genialis, United States

L. Vohar. Genialis, United States

R. Luštrik. Genialis, United States

L. Ausec. Genialis, United States

M. Uhlik. OncXerna Therapeutics, United States

S. Iyer. OncXerna Therapeutics, United States

L. Benjamin. OncXerna Therapeutics, United States

F. Baehner. Exact Sciences, SAN FRANCISCO, California, United States

Introduction: Immune checkpoint inhibitors (ICI) are an important therapeutic option for patients with triple negative breast cancer (TNBC). However, identification of patients most likely to respond is challenging. PD-L1 positivity by immunohistochemistry is the standard biomarker used for ICI therapy selection in TNBC. However, other biomarkers, such as analysis of the tumor microenvironment (TME) may be more accurate in predicting response. The Xerna™ TME Panel uses RNA sequencing data and machine learning to analyze the TME, utilizing the angiogenic and immunogenic biology of the TME to classify tumors into four TME subtypes. In this study, the distribution of Xerna TME subtypes and associated genomic alterations in TNBC were investigated for their potential use in therapy selection. Methods: A total of 203 TNBC patient samples underwent tumor-normal whole-exome, whole-transcriptome sequencing testing with the OncoExTra™ assay. The whole-transcriptome expression data were analyzed using the Xerna TME Panel to assign each sample to one of four subtypes: Immune Active (IA), Immune Suppressed (IS), Immune Desert (ID) and Angiogenic (A). The IA and IS subtypes both have high immune scores that may be particularly sensitive to ICI therapy. Actionable alterations, defined as those with FDA-approved matched therapies in any cancer, with matched clinical trials, or with evidence in cancer guidelines or the literature for possible matched therapies, were also identified and associations across Xerna subtypes were explored. Results: Approximately half (100 of 203; 49.3%) of the patient samples had high (IA+IS) immune subtypes (Table 1). Targetable alterations associated with an FDA-approved therapy were present in 114 (56.2%) patients. No biomarkers were significantly associated ($p < 0.05$) with high (IA+IS) versus low (ID+A) immune scores. Biomarkers associated with ICI response, namely mismatch repair gene alterations (MSH2/3/6, MLH1/3, PMS1/2), high tumor

mutational burden (TMB-high) and microsatellite instability were detected in only 6 (3.0%), 3 (1.5%) and 1 (0.5%) patient samples respectively, and all but 1, an MSH6 alteration, were in high immune subtype samples. Conclusions: The Xerna TME Panel classified 49.3% of TNBC patient tumors to IA or IS, suggesting they may respond to ICI therapy. Many (56.2%) patient tumors harbored alterations associated with FDA-approved therapies, providing the potential for novel combination therapies. These findings warrant further study and clinical validation in

Co-mutated Biomarker	Total (N=203)	A (N=48)	IA (N=51)	ID (N=55)	IS (N=49)
TP53	173 (85.2%)	36 (75.0%)	40 (78.4%)	49 (89.1%)	40 (81.6%)
PIK3CA	34 (16.7%)	8 (16.7%)	9 (17.6%)	9 (16.4%)	8 (16.3%)
PTEN	17 (8.4%)	5 (10.4%)	1 (2.0%)	5 (9.1%)	6 (12.2%)
BRCA1	16 (7.9%)	3 (6.2%)	4 (7.8%)	6 (10.9%)	3 (6.1%)
APC	12 (5.9%)	0 (0.0%)	4 (7.8%)	7 (12.7%)	1 (2.0%)
RBT	12 (5.9%)	5 (10.4%)	3 (5.9%)	1 (1.8%)	3 (6.1%)

TNBC patients treated with ICI therapy.

Table 1. Frequency of actionable biomarkers that were present in at least 10 (5%) TNBC patient samples.

PO2-06-11

A phase II randomized trial of gemcitabine plus cisplatin(GP) vs gemcitabine plus carboplatin (GC) as the first-line treatment for patients with metastatic triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

C. Gong. Fudan University Shanghai Cancer Center, United States

Y. Zhao. Fudan University Shanghai Cancer Center, United States

L. Wang. Fudan University Shanghai Cancer Center, United States

j. Cao. Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

Z. Tao. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

T. Li. Fudan University Shanghai Cancer Center, United States

M. Zhao. Fudan University Shanghai Cancer Center, United States

H. Miao. Fudan University Shanghai Cancer Center, United States

J. Jin. Fudan University Shanghai Cancer Center, United States

X. Hu. Shanghai Cancer Center, Fudan University, Shanghai, China

B. Wang. Fudan University Shanghai Cancer Center, United States

Background: Triple-negative breast cancer (TNBC) is an aggressive disease with limited treatment options and poor prognosis. Gemcitabine plus carboplatin (GC) is one of the classic chemotherapeutic regimens for patients with metastatic triple-negative breast cancer(mTNBC) and also a backbone regimen for chemoimmunotherapy, with a median progression-free survival (PFS) of 4.6 months in the first-line (O'Shaughnessy J, et al. J Clin Oncol 2014). Gemcitabine plus cisplatin (GP) has also demonstrated promising efficacy and safety in the first-line phase III trial of mTNBC, with a median PFS of 7.7 months (Hu XC, et al. Lancet Oncol 2015). To further investigate the superiority between carboplatin and cisplatin when combined with gemcitabine, a prospective phase II study was conducted to directly compare the efficacy and safety of GP with GC in the first-line treatment for patients with mTNBC (NCT02341911). **Methods:** Patients with untreated mTNBC were randomized 1:1 to receive gemcitabine (1250 mg/m², D1,8) plus cisplatin (75 mg/m², D1) or gemcitabine (1000mg/m², D1,8) plus carboplatin (area under the curve 2 mg × min/mL, D1,8) every 21 days until disease progression or intolerable toxicity. The stratification factors included visceral metastasis (yes or no) and the number of metastatic sites (1, 2, or ≥3). The primary endpoint was PFS and secondary endpoints included overall response rate (ORR), overall survival (OS), and safety. **Results** A total of 150 mTNBC patients were enrolled. After a median follow-up of 49.1 months (IQR 31.3-70.7), PFS events had been recorded in 55 (73.3%) of 75 patients in the GP group and 59 (78.7%) of 75 patients in the GC group. PFS was numerically longer in the GP group than in the GC group, though not significantly (median, 7.8 months [95% CI 7.2–8.4] vs. 6.9 months [95% CI 6.4–7.4]; HR, 0.93; 95% CI 0.64–1.34; P = 0.689; stratified HR, 0.84; 95% CI 0.58–1.23; P = 0.375). Median OS was 20.7 months (95%CI 17.9-23.5) in GP group and 20.9 months (95%CI 15.3-26.5) in GC group, HR, 1.13; 95% CI 0.77–1.67; P = 0.537; stratified HR, 1.03; 95% CI 0.70–1.52; P = 0.886). The ORR of GP and GC was 49.3% and 41.3% in the intent-to-treat population. Dose reduction occurred in 30(40.0%) patients in the GP group and 38 (50.7%) patients in the GC group. Grade 3 and 4 hematological AEs, including leucopenia, neutropenia, anemia, and thrombocytopenia were slightly higher in the GC group. Grade 3 and 4 non-hematological AEs, including nausea, vomiting, and hearing toxicity, were more common in the

GP group. No treatment-related deaths were reported. Conclusions

Cisplatin was not associated with a survival advantage over carboplatin when combined with gemcitabine as a first-line treatment for patients with mTNBC, though numerically longer PFS and higher ORR was observed. The safety profiles of the two combinations were different but the adverse events were manageable.

PO2-06-12

Patients with metastatic triple-negative breast cancer who receive trilaciclib prior to cytotoxic chemotherapy exhibit improved survival after receiving subsequent anticancer therapy

Presenting Author(s) and Co-Author(s):

S. Goel. The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

K. Lu. The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia, United States

A. Beelen. G1 Therapeutics Inc., Research Triangle Park, NC, USA, United States

S. Melemed. G1 Therapeutics, Inc., Research Triangle Park, NC, USA, United States

J. Yi. G1 Therapeutics, Inc., Research Triangle Park, NC, USA, United States

M. Danso. Virginia Oncology Associates, Norfolk and Virginia Beach, VA, USA, United States

A. Tan. Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, United States

Background

In an open-label, randomized, phase 2 trial in patients (pts) with metastatic triple-negative breast cancer (mTNBC; NCT02978716), administering trilaciclib prior to gemcitabine plus carboplatin (GCb) significantly prolonged overall survival (OS; a key secondary endpoint) versus administering GCb alone (median 19.8 vs 12.6 months; hazard ratio 0.37; $P < 0.0001$), with a nonsignificant trend toward improved progression-free survival (median 9.0 vs 5.7 months; hazard ratio 0.62; $P = 0.13$; Tan et al. Clin Cancer Res. 2022). Given murine data suggesting trilaciclib may preserve the long-term function of hematopoietic stem and progenitor cells (He et al. Sci Transl Med. 2017) and improve T-cell memory (Goel et al. Nature. 2017; Lelliott et al. Cancer Discov. 2021; Heckler et al. Cancer Discov. 2021), we examined survival of pts with mTNBC who received subsequent lines of therapy after receiving GCb with or without trilaciclib.

Methods

In the phase 2 trial, pts with ≤ 2 prior chemotherapy regimens for locally recurrent or metastatic TNBC were randomized 1:1:1 to receive GCb on days 1 and 8, trilaciclib prior to GCb on days 1 and 8, or trilaciclib alone on days 1 and 8 and prior to GCb on days 2 and 9. The 2 trilaciclib arms were combined for this analysis. To determine if trilaciclib improved outcomes in pts who received additional therapy after GCb, a post hoc survival analysis was performed using data from pts who received any subsequent anticancer therapy (SACT).

Results

In the subanalysis of data from pts with mTNBC who received any SACT after the phase 2 trial, clinical characteristics such as demographics, disease variables, duration from study treatment to first SACT, and type of SACT were balanced between the trilaciclib ($n = 43$) and placebo ($n = 20$) arms. The most common SACTs were gemcitabine, capecitabine, eribulin, taxanes, checkpoint inhibitors, carboplatin, and anthracyclines. Median OS in pts who had previously received trilaciclib was 32.7 months versus 12.8 months in those who had received placebo, with increasing separation of survival curves over time. Median OS from start of first SACT was 17.4 months in the trilaciclib arms vs 5.8 months in the placebo arm. Improved survival and

sustained separation of curves was also observed in pts unable to receive SACT (trilaciclib, n = 25; placebo, n = 14), although the magnitude of benefit was smaller (median 9.4 vs 5.4 months).

Mechanistic in vivo murine and in vitro human studies are underway to examine the effect of trilaciclib on the generation of memory T cells. These studies will assess the preferential differentiation of specific memory T-cell subsets along with in vivo assessment of memory T-cell responses following a rechallenge. Further data will be presented to evaluate whether the enhanced generation and preservation of a memory T-cell pool is supportive of improved outcomes in pts receiving SACT.

Conclusions

Data from the phase 2 study suggest that pts with mTNBC who received trilaciclib prior to cytotoxic chemotherapy have prolonged survival, which is notably improved for pts who are able to receive SACT following discontinuation of trilaciclib. The survival benefit from trilaciclib extends to pts who subsequently received immune checkpoint inhibitors and/or chemotherapy, and also to those who did not receive any SACT. Improved OS in pts receiving trilaciclib may be associated with protection of hematopoietic stem and progenitor cells and formation of a memory T-cell pool, which is critical for long-term immune surveillance and in eliciting rapid recall responses. OS will be evaluated in pts with mTNBC in the ongoing phase 3 trial of trilaciclib prior to GCb (PRESERVE 2; NCT04799249) and phase 2 trial of trilaciclib prior to sacituzumab govitecan (NCT05113966).

PO2-06-13

Promising clinical performance of ⁸⁹Zirconium-labelled Girentuximab PET-CT for imaging metastatic triple negative breast cancer patients (OPADESCENCE)

Presenting Author(s) and Co-Author(s):

C. Rousseau. Nantes Université, Univ Angers, ICO René Gauducheau, INSERM, CNRS, CRCI2NA, F-44000 Nantes, France, Saint Herblain, Pays de la Loire, France

M. Heymann. Institut de Cancérologie de l'Ouest site Saint-Herblain, Saint-Herblain, Pays de la Loire, France

J. FRENEL. ICO, United States

E. Picot-Dilly. ICO René Gauducheau, F-44800 Saint-Herblain, France, Saint Herblain, Pays de la Loire, France

M. Le Thiec. ICO René Gauducheau, F-44800 Saint-Herblain, France, Saint Herblain, Pays de la Loire, France

M. Taupin. ICO René Gauducheau, Research pathology platform, F-44800 Saint-Herblain, France, Saint Herblain, Pays de la Loire, France

A. Mouton. ICO René Gauducheau, F-44800 Saint-Herblain, France, Saint Herblain, Pays de la Loire, France

E. Bourbouloux. ICO René Gauducheau, F-44800 Saint-Herblain, France, Saint Herblain, Pays de la Loire, France

A. Morel. ICO René Gauducheau, F-44800 Saint-Herblain, France, Saint Herblain, Pays de la Loire, France

N. Allam. ICO René Gauducheau, F-44800 Saint-Herblain, France, Saint Herblain, Pays de la Loire, France

A. Mallet. ICO René Gauducheau, F-44800 Saint-Herblain, France, Saint Herblain, Pays de la Loire, France

M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France

L. Ferrer. Nantes Université, Univ Angers, ICO René Gauducheau, INSERM, CNRS, CRCI2NA, F-44000 Nantes, France, Saint Herblain, Pays de la Loire, France

F. Kraeber-Bodéré. Nantes Université, Univ Angers, CHU Nantes, INSERM, CNRS, CRCI2NA, F-44000 Nantes, France, Nantes, Pays de la Loire, France

Aim: Triple Negative Breast Cancer (TNBC) is aggressive, often with a metastatic evolution and drug-resistant with limited therapeutic options. Evaluating new markers is an unmet need. Recently, the combination of anti-angiogenic and targeted hypoxia effectors agents proved to enhance therapy response. Indeed, anhydrase Carbonic-IX (CA-IX), a hypoxia-mediated breast tumor growth regulator, is important for the BC stem cells maintenance within hypoxic region and is highly overexpressed in TNBC. This pilot prospective study "OPADESCENCE" (NCT04758780) aimed at assessing PET/CT with ⁸⁹Zr-labeled girentuximab (⁸⁹Zr-TLX250) targeting CA-IX in 12 metastatic TNBC patients. **Methods:** Patients underwent FDG and ⁸⁹Zr-TLX250 PET-CT and conventional imaging (CI) if needed (CT, US, mammography, brain MRI). Without any premedication or dietary preparation, patients received a single slow intravenous administration of 37±10% MBq ⁸⁹Zr-TLX250 (10 mg). Day 3 or 5 post injection, a skull to mid-thigh PET/CT was acquired with 10 minutes acquisition time per bed position. The gold standard was determined by FDG PET/CT, CI and follow-up; lesion detected at least by 2 modalities was considered as true positive. Immunohistochemistry (IHC) was performed with

Bond RX fully automated research stainer with CA-IX antibody (Leica, clone TH22). Staining was evaluated with semi-quantitative analysis (percentage and intensity of tumor cells expression). Human anti-chimeric antibody (HACA) were sampled but will be determined at study end. Results: Enrolment has been completed, a total of 273 lesions confirmed by gold standard as shown on table 1 were detected in 12 patients (231 by 89Zr-TLX250 and 264 by FDG PET/CT). Overall sensitivity of 89Zr-TLX250 PET/CT was 87.5%, with 100% sensitivity for breast, skin, adrenal gland and brain and 88.0%, 91.9% for nodes and bone respectively. Overall sensitivity for FDG-PET/CT was 96.7%. According to table 2, 6 patients had 100% of their lesions highlighted by 89Zr-TLX250 PET. In addition, for 2 other patients only one of the lesions was not detected by immunoPET. 89Zr-TLX250 PET therefore detected almost all of the metastatic lesions in 67% of the patients. For 8/12 patients, IHC was analysed and for 6 patients, CA-IX expression lesions was from 100% to 10% with an intensity from 3+ to 2+, whereas two patients presented no Ca-IX expression on tumour lesions. No 89Zr-TLX250 safety issue was reported. Conclusion: 89Zr-TLX250 PET/CT seems very promising because it allows the CA IX status lesions knowledge on whole body scale with a minimally invasive way, unlike the information provided by biopsies corresponding to only 1 or 2 lesions studied. Moreover, these results illustrated interest of 89Zr-TLX250 PET/CT as targeting agent for TNBC patients leading above all to a theranostic approach possibility. Study analysis (specially IHC, HACA and semi-quantitative PET/CT analysis) is ongoing and supplementary data will be presented during the congress. This is an investigator initiated trial. Investigational medicinal product was provided by Telix Pharmaceuticals.

Table 1: Sensitivity of 89Zr-TLX250 PET, FDG PET, and conventional imaging (US, brain MRI and Mammography).

Table 1

Location	89Zr-TLX250 PET	CT	FDG PET	Conventional Imaging
Overall	231/273	NA	264/273	NA
Lymph nodes	65/78	66/78	74/78	NA
Bone	102/112	NA	111/112	NA
Liver	12/19	19/19	19/19	19/19
Lung	17/27	27/27	27/27	NA
Breast	25/25	7/25	23/25	10/25
Cutaneous nodule	5/5	4/5	5/5	NA
Adrenal Gland	2/2	2/2	2/2	NA
muscle nodule	0/2	0/2	2/2	NA
Brain	3/3	NA	1/3	3/3

NA: Not Applicable

Table 2: Number of confirmed lesions according to Gold Standard detected by 89Zr-TLX250 PET/CT (iPET), FDG PET/CT and CI for each patients.

Table 2

Patients	No of confirmed lesions according to Gold Standard	No of lesions detected by 89Zr-TLX250	No of lesions detected by FDG	No of lesions detected by conventional imaging (CT, US, brain MRI and mammography)
1	11	11	11	10
2	12	9	12	12
3	12	12	12	10
4	9	9	9	5
5	73	51	73	23
6	93	82	90	27
7	14	10	14	11
8	8	7	8	2
9	14	13	14	13
10	5	5	3	5
11	16	16	16	14
12	6	6	6	6

PO2-06-14

Kynurenine induces senescence reprogramming to promote metastasis in young triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

C. Liu. Cancer Center and Cancer Institute, Shanghai Medical College, Fudan University, United States

K. Yu. Cancer Center and Cancer Institute, Shanghai Medical College, Fudan University, United States

Triple-negative breast cancer (TNBC), which has been associated with a high risk of relapse and poor prognosis, has an increasing incidence among young women and ongoing inferior long-term outcomes. Given TNBC arising at a young age are more likely to present at advanced stages and to have aggressive biology, it is necessary to investigate the underlying mechanism and develop multidisciplinary strategies for optimal therapy of young women with breast cancer. Here, we integrated the multiomics data of our large TNBC cohort (n=456) to investigate different molecular mechanism between younger and older patients in the context of genetic and transcriptional subtypes and immune cell infiltration. We discovered that young TNBC patients exhibited a poorer outcome of both 2-year relapse-free survival and 2-year distant disease-free survival. Multi-omics analysis revealed that kynurenine (KYN) was preferentially enriched in young TNBC and activated tumor cellular senescence pathway which was positively correlated with increased metastasis. Mechanistically, KYN activated the aryl hydrocarbon receptor (AHR) signaling pathway in an ARNT2-dependent manner which was critical for cellular senescence, to mediate senescence reprogramming and promote tumor metastasis in young TNBC. Our findings unveil a novel interplay between cancer cell metabolites and cell senescence, which provides valuable insights that can potentially enhance therapeutic strategies for young TNBC patients. Keywords: young TNBC, metastasis, kynurenine, cellular senescence, AHR pathway

PO2-07-01

Predicted Circadian-related Transcription Factors in Human Breast Cell Lines—A key to understanding breast cancer pathology?

Presenting Author(s) and Co-Author(s):

Y. Perfecto-Avalos. Tecnologico de Monterrey, Zapopan, Jalisco, Mexico

J. Yoo. University of Houston, Texas, United States

C. Saravia Heyman. University of Houston, Texas, United States

P. Deranmie. University of Houston, Texas, United States

J. Tran. University of Houston, Texas, United States

S. Scott. University of Houston, Texas, United States

Studies show that disrupted circadian clocks are associated with breast and other forms of cancer. However, the pathways and cell processes linking broken circadian clocks to breast cancer are still mostly unknown. In this study, we conducted a reanalysis of mRNA expression in breast cell lines, specifically MCF10a (a fibrocystic cell line) and MCF7 (a metastatic adenocarcinoma cell line). To achieve this, we utilized microarray data obtained from Gutierrez et al. in 2016, specifically the datasets GSE76370, GSE76368, and GSE76369. First, Metacycle, an R statistical package employing a cosine fitting algorithm, was used to identify circadian-oscillations in mRNA expression from both cell lines. MetaCycle (Wu et al., 2016) analysis produced an amplitude, phase, and period value for each circadian gene. Following the analysis, we conducted principal component analysis on the Metacycle output to identify any outlier genes. Subsequently, hierarchical clustering analysis was employed to group these outlier genes based on their oscillating expression levels, with the purpose of identifying clusters that exhibited similar period and phase patterns. We hypothesized that genes found in the same cluster would share common transcription factors that would drive and synchronize the expression of those genes. We tested this hypothesis and found that genes with the same circadian pattern did indeed share common transcription factor binding sites, using Ciider 3.0 (Gearing et al, 2019), an internet-based tool for predicting and analyzing transcription factor binding sites. We found 96 genes grouped into 6 clusters for MCF10a, and 92 genes grouped into 6 for MCF7 cell lines. Arid3A binding sites were highly enriched across MCF7 and MCF10a. In MCF10a, where circadian oscillations were more pronounced, Sox5 binding sites were highly enriched for cluster 1, Meis1 was enriched for cluster 2, and Arid3A was enriched in clusters 3-6, in combination with other transcription factors. In MCF7, a different set of genes showed circadian-like oscillating expression patterns. However, these different genes showed enrichment of Arid3A across all clusters. Since Arid3A binding sites were found in genes involved in all of the MCF7 clusters, and found in four of the six clusters in MCF10a, further work is needed in understanding the additional regulatory mechanisms that shift the phase and period of the oscillations of these groups of genes. In addition, more work needs to be done to study the role of these transcription factors in cancer progression and basic cell processes. Most of these transcription factors are known to be related to breast or other forms of cancer. Though this list is not complete, some of the more enriched transcription factor binding sites include Arid3A, Meis1, Znf354c, in MCF10a and in MCF7 they include Arid3A, Znf354c, Nfatc2, and Ahr:Arnt. The most enriched transcription factor amongst these circadian-like genes is Arid3A. Arid3A is an H3K9me3 demethylase and may impact regulation of other genes through demethylation. Suppression of Arid3A is associated with leukemia. Meis1 is also implicated in leukemia and tumor growth, as well as sleep disorders. Arnt splice variants are also associated with breast cancer. Future research is needed to determine if these transcription factors are

important for circadian-like control. Our in silico results suggest that genes found in the same clusters share their respective transcription factors that regulate the expression of these circadian-like genes.

PO2-07-03

Retrospective Validation Study of an Artificial Neural Network-Based Preoperative Decision-Support Tool for Noninvasive Lymph Node Staging (NILS) in Women with Primary Breast Cancer (ISRCTN14341750)

Presenting Author(s) and Co-Author(s):

I. Skarping. Faculty of Medicine, Lund University, Sweden, United States

J. Ellbrant. Region Skane, United States

L. Dihge. Region Skåne / Lund University, United States

M. Ohlsson. Centre for Environmental and Climate Science, Lund University, United States

L. Huss. Faculty of Medicine, Lund University, Sweden, United States

P. Bendahl. Lund University, United States

L. Rydén. Region Skane / Lund University, United States

Background

Surgical sentinel lymph node biopsy (SLNB) is routinely used to reliably stage axillary lymph nodes in early breast cancer (BC). However, SLNB may be associated with postoperative arm morbidities. For most patients with BC undergoing SLNB, the findings are benign, and the procedure is currently questioned. A decision-support tool for the prediction of benign sentinel lymph nodes based on preoperatively available data has been developed using artificial neural network modelling [1,2].

Methods

This was a retrospective geographical and temporal validation study of the noninvasive lymph node staging (NILS) model, based on preoperatively available data from 586 women consecutively diagnosed with primary BC at two sites. Ten preoperative clinicopathological characteristics from each patient were entered into the web-based calculator (Table 1), and the probability of benign lymph nodes was predicted. Vascular invasion, the tenth feature of the NILS model, was difficult to determine preoperatively. Therefore, a separate ANN model was developed to impute this feature, using the other nine features of the NILS model as predictors. A user-friendly web implementation of the NILS model was tested in this study. The performance of the NILS model was assessed in terms of discrimination with the area under the receiver operating characteristic curve (AUC). The primary endpoint was axillary nodal status (discrimination, benign [N0] vs. metastatic axillary nodal status [N+]) determined by the NILS model compared to nodal status by definitive pathology.

Results

The mean age of the women in the cohort was 65 years, and most of them (93%) had luminal cancers (Table 2). Approximately three-fourths of the patients had no metastases in SLNB (N0 74%). The AUC for the predicted probabilities for the whole cohort was 0.6741 (95% confidence interval: 0.6255–0.7227). More than one in four patients (n=151, 26%) were identified as candidates for SLNB omission when applying the predefined cut-off for lymph node negativity from the development cohort (Table 3).

Conclusion

The performance of the NILS model was satisfactory. In approximately every fourth patient, SLNB could potentially be omitted. Considering the shift from postoperatively to preoperatively available predictors in this validation study, we have demonstrated the robustness of the NILS

model. The clinical usability of the web interface will be evaluated before its clinical implementation.

Trial registration

Registered in the ISRCTN registry with study ID ISRCTN14341750.

References

1. Dihge L, et al. The implementation of NILS: A web-based artificial neural network decision support tool for noninvasive lymph node staging in breast cancer. *Front Oncol.* 2023;13:1102254. <https://doi.org/10.3389/fonc.2023.1102254>.

2. Skarping I, et al. The implementation of a noninvasive lymph node staging (NILS) preoperative prediction model is cost effective in primary breast cancer. *Breast Cancer Res Treat.* 2022;194:577–86. <https://doi.org/10.1007/s10549-022-06636-x>.

Table 1. The ten preoperatively available included variables in the noninvasive lymph node staging (NILS) model

	Variable
Clinical	Age
Mammography	Multifocality
	Tumor size
	Mode of detection
	Localization in the breast
Core needle biopsy	Estrogen receptor status
	Progesterone receptor status
	Histological subtype
	Proliferation (Ki67)
	Vascular invasion

Table 2. Patient and tumor characteristics at baseline

		Total N=588
		Count %
Age at diagnosis, years	Mean (range)	65 (29-91)
Screening detected	No	240 41.0%
	Yes	346 59.0%
Bilateral cancer	No	553 94.4%
	Yes	33 5.6%
Multifocal cancer (mammography)	No	531 91.1%
	Yes	52 8.9%
	Missing*	3
Largest tumor (long axis, mm, mammography)	Mean (range)	19 (3-110)
	Missing**	55
Centrally positioned tumor (mammography, subareolar or within 2 cm of the mamilla)	No	383 67.4%
	Yes	55 12.6%
	Missing*	148
Estrogen receptor status CNB	Negative (<1%)	24 7.3%
	Positive (>1%)	305 92.7%
	Missing	257
Progesterone receptor status CNB	Negative (<1%)	57 18.0%
	Positive (>1%)	259 82.0%
	Missing	270
HER2 status CNB	Negative	295 95.2%
	Positive	15 4.8%
	Missing	275
Proliferation index Ki67 (% CNB)	Mean (range)	26.6 (1.0-95.0)
	Missing	324
Histopathological type CNB	NST (No specific type, ductal)	445 75.9%
	Lobular	105 17.9%
	Other	36 6.2%

*When missing data on mammography, features from ultrasound was entered into the NILS web interface.

Abbreviations: CNB: core needle biopsy; HER2: human epidermal receptor 2

Table 3. Performance measures of the noninvasive lymph node staging (NILS) model, including potential sentinel lymph node biopsy (SLNB) reduction rate for the current model.

NILS	TP	TN	FP	FN	Sensitivity	Specificity	FNR**	SLNB reduction rate**
	136	133	259	18	88%	31%	12%	26%

*Equivalent to the maximum FNR of 10% reflecting accepted FNR of the SLNB procedure

**The SLNB reduction rate was calculated as follows = (TN + FN)/(TN + FN + TP + FP).

Abbreviations: TP: true positive; TN: true negative; FP: false positive; FN: false negative; FNR: false negative rate; SLNB: sentinel lymph node biopsy

PO2-07-04

Applying the Alliance Trial Guidelines in Multi-focal Breast Disease Using an Artificial Intelligence Computational Platform: Economic Analysis and Cosmetic Sensitivity

Presenting Author(s) and Co-Author(s):

J. Pfeiffer. SimBioSys, Inc., Chicago, Illinois, United States

M. Biancalana. SimBioSys, Inc., Chicago, Illinois, United States

D. Lopez-Ramos. SimBioSys, Inc., Chicago, Illinois, United States

B. Feiger. SimBioSys, Inc., United States

A. Antony. SimBioSys, Inc., Chicago, Illinois, United States

Background: Traditionally, multi-focal breast cancer results in mastectomy. The Alliance Trial offers a paradigm shift in surgical options available for multi-focal breast cancer patients in the context of adjuvant chemotherapy. In the trial, patients with multi-focal disease (< 3 tumors) who underwent breast conservation surgery (BCS) were found to have similar outcomes to patients undergoing mastectomy. BCS for large volume tumors (>30%) has been cited as having a high potential for cosmetic defect, and hence represents a typical upper limit for potential tissue removal in BCS. Here, we evaluated a patient cohort to better understand the economic impact of the Alliance trial and further categorize patients that would most benefit without suffering cosmetic impact. We employed a novel computational technology to quantify the ratio of tumor size to breast tissue volume. Methods: Using a publicly available, single site cohort (n=243, DUMC) of breast cancer patients that underwent mastectomy, we segmented the tumors using our TumorSight Viz software platform. This platform uses artificial intelligence to segment the tumor and surrounding tissues and allows for a volumetric and morphologic assessment in 3D space. We then applied relevant inclusion/exclusion criteria from the Alliance Trial to the cohort (Saha et al, 2018). In trial eligible patients, we used TumorSight Viz to create a convex hull (CH) around the multi-focal disease using dilations of 1 cm and 2 cm. The volume of the CH, corresponding to proposed surgical extirpation, and the overall breast volume (BV) were then computationally assessed in 3D. The ratio of CH to BV (CH:BV) was calculated and a cutoff of 30% (high potential for cosmetic deformity) was applied. A cost analysis was then carried out. We determined the aggregate per annum savings that could potentially be realized by transforming a subset of mastectomies to BCS by tabulating total costs of mastectomy+reconstruction vs. BCS+WBI (whole-breast irradiation), as well as adjusted for relative rates of adjuvant therapy (~80%) across the nationwide patient population. Results: We found that 19.3% of adjuvant mastectomy patients were eligible for BCS based on Alliance Trial criteria. Of those, 68% had tumor CH:BV < 30% when using a 1 cm dilation around the tumor. When using a 2 cm dilation, 56% had tumor CH:BV < 30%. Together, these results indicate that of all adjuvant mastectomy patients, an estimated 10.8-13.1% are eligible for BCS based on volumetric measures of cosmetically acceptable breast tissue removal. Our economic analysis of BCS vs. mastectomy revealed an estimated \$28,500 cost savings for patients with private insurance, suggesting that both decreased costs and improved quality-of-life (QOL) can be mutually aligned. By assessing the nationwide number of patients receiving adjuvant therapy for breast cancer, alongside the percentage potentially eligible for BCS using the above cosmetic defect analysis, we estimate that BCS conversion from mastectomy offers to provide a net savings of \$300-350 million annually. Conclusion: The Alliance Trial guidelines unveiled the potential option of BCS in ~20% of patients with multi-focal disease in our cohort, demonstrating considerable cost-savings. Computational tools can further differentiate individuals who may not be best candidates for BCS in this setting, ensuring high QOL and

informed decision-making.

PO2-07-05

Deep learning model for automated quantification of HER2 expression in invasive breast cancers from immunohistochemical whole slide images

Presenting Author(s) and Co-Author(s):

P. Bannier. Owkin France, Paris, France, United States

L. Herpin. Owkin France, Paris, France, United States

R. Dubois. Owkin France, Paris, France, United States

L. Van Praet. Owkin France, Paris, France, United States

C. Maussion. Owkin France, Paris, France, United States

E. Amonoo. Cancer & Pharmaceutical Sciences, King's College London, United States

A. Mera. School of Cancer and Pharmaceutical Sciences, Faculty of Life Sciences and Medicine, Guy's Cancer Centre, King's College London, London, UK, United States

J. Timbres. School of Cancer and Pharmaceutical Sciences, Faculty of Life Sciences and Medicine, Guy's Cancer Centre, King's College London, London, UK, United States

C. Gillett. King's Health Partners Cancer Biobank, King's College London, United States

E. Sawyer. Guy's and St.Thomas' NHS Foundation Trust/King's College London, United States

P. Gazinska. Breast Cancer Now Toby Robinsons Research Centre, The Institute of Cancer Research, London; Biobank Research Group, Lukasiewicz Research Network – PORT Polish Center for Technology Development, Wroclaw, Poland, United States

P. Ziolkowski. Department of Clinical and Experimental Pathology, Wroclaw Medical University, 50-368 Wroclaw, Poland, United States

R. Salgado. GZA-ZNA-Hospitals, Antwerp, Belgium; Peter Mac Callum Cancer Centre, Temse, Belgium

S. Irshad. King's College London, United States

Introduction Human epidermal growth factor receptor 2 (HER2) protein overexpression and/or HER2 gene amplification is found in about 20% of invasive breast cancers. Considering the results of the DESTINY-Breast trials confirming the remarkable efficacy of anti-HER2 antibody drug-conjugate (T-DXd) in both HER2-overexpressed and HER2-low tumors, it is necessary to identify not only HER2 (immunohistochemistry (IHC) score 3+) overexpressing tumors, but also HER2-low tumors. The latter category, defined as IHC1+ or IHC2+ but non-amplified, has proven to be challenging even for experienced pathologists, with high inter-observer variability. Here, we validate the performance of a deep learning (DL) model at: 1) predicting the IHC score from IHC histological features and 2) identifying HER2-low tumors with high sensitivity.

Methods 675 HER2 stained IHC slides from primary breast cancer patients were selected based on pathology reports across three different cohorts (KCL_GSTT_1 n=369; Cypath_Breast n=214; KCL_GSTT_2 n=92). The slides were digitized and reviewed by expert breast pathologists. Specifically, Cypath_Breast and KCL_GSTT_2 were each annotated by one expert pathologist, while KCL_GSTT_1 was annotated by 5 expert pathologists with the ground truth defined as a majority vote between the 5 annotators. Cypath_Breast was assigned as the “discovery” set; while KCL_GSTT_1 and KCL_GSTT_2 were used as two independent validation cohorts. The model was specifically trained to extract features from IHC tiles to ensure they would capture both the staining intensity and the staining location on the cells (membrane, cytoplasmic or nuclei). The one-vs-one (OVO) and one-vs-rest (OVR) AUC as well as sensitivity and specificity to HER2-low and positive tumors were used as metrics to assess

the performance of our model. An expert pathologist reviewed the most predictive regions of HER2 expression. Results After review by expert pathologists, 59 slides from KCL_GSTT_1 were removed either because of folded tissue, blurriness or because there was too little tissue. The IHC scores (0 / 1+ / 2+ / 3+) for the 3 cohorts were distributed as follows; Cypath_Breast: 42 / 120 / 36 / 16; KCL_GSTT_1: 120 / 90 / 52 / 48; KCL_GSTT_2: 54 / 22 / 15 / 1. For KCL_GSTT_1, the average agreement between the 5 expert pathologists amounted to a Cohen's Kappa score of 0.63. Following training on Cypath_Breast, the performance of the model are presented in Table 1.

Cohorts	OVO AUC	OVR AUC IHC 0	OVR AUC IHC 1+	OVR AUC IHC 2+	OVR AUC IHC 3+
KCL_GSTT_1	0.95 [0.93 - 0.96]	0.95 [0.94 - 0.95]	0.80 [0.79 - 0.82]	0.91 [0.90 - 0.92]	0.99 [0.99 - 1.00]
KCL_GSTT_2	0.92 [0.90 - 0.93]	0.97 [0.96 - 0.98]	0.78 [0.76 - 0.81]	0.84 [0.80 - 0.88]	N/A

An ablation study proved that a feature extractor trained on IHC tiles outperformed an in-house extractor solely trained on H&E tiles (OVO AUC 0.95 vs 0.93 on KCL_GSTT_1; DeLong p< 0.001). Specifically, the model performed best at distinguishing HER2-negative (HER2 IHC 0) from HER2-low and HER2-positive tumors with a sensitivity (0 vs 1+/2+/3+) of 0.95 [0.93 - 0.98] and a specificity (0 vs 1+/2+/3+) of 0.78 [0.72 - 0.84] on KCL_GSTT_1. We observed the same tendency on KCL_GSTT_2 with a sensitivity (0 vs 1+/2+/3+) of 0.97 [0.91 - 1.00] and a specificity of 0.91 [0.83 - 0.98]. More importantly, the DL model reached a Cohen's Kappa score of 0.72 [0.67 - 0.77] with the ground truth on KCL_GSTT_1, surpassing the average agreement Kappa score between expert pathologists (0.63). The most predictive regions showed cytoplasmic staining in tumor regions. Conclusion Our model provides a path towards a fully automated workflow for identifying up to 95% of breast cancer patients who could potentially benefit from anti-HER2 targeted therapies. Additionally, we show the utility of AI-based tools to minimize discrepancies among pathologists and assist in the diagnostic patient pathway.

Table 1: Results of external validation on KCL_GSTT_1 and KCL_GSTT_2

Cohorts	OVO AUC	OVR AUC			
		0	1+	2+	3+
KCL_GSTT_1	0.95 [0.93 - 0.96]	0.95 [0.94 - 0.95]	0.80 [0.79 - 0.82]	0.91 [0.90 - 0.92]	0.99 [0.99 - 1.00]
KCL_GSTT_2	0.92 [0.90 - 0.93]	0.97 [0.96 - 0.98]	0.78 [0.76 - 0.81]	0.84 [0.80 - 0.88]	N/A

PO2-07-06

Multimodal learning predictor of HER2-positive breast cancer therapy response in the randomized PREDIX HER2 trial

Presenting Author(s) and Co-Author(s):

K. Wang. Department of Oncology-Pathology, Karolinska Institutet Stockholm, Stockholms län, Stockholms Lan, Sweden

Y. Zhu. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden, United States

I. Zerdes. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Breast Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden, United States

E. Sifakis. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden, United States

G. Manikis. Karolinska Institutet, United States

D. Salgkamis. Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, United States

N. Tsiknakis. Karolinska Institutet, United States

L. Harbers. Karolinska Institutet, United States

N. Crosetto. Karolinska Institutet, United States

J. Bergh. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Breast Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden

A. Matikas. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Breast Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden

T. Hatschek. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Breast Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden, United States

T. Foukakis. Karolinska Institutet, Solna, Stockholms Lan, Sweden

Background: The PREDIX HER2 trial, compared six courses of docetaxel, trastuzumab, and pertuzumab (DTP) vs. trastuzumab emtansine (T-DM1) as neoadjuvant treatment for HER2-positive breast cancer (BC). Similar rates of pathologic complete response (pCR) were seen.

Methods: Clinicopathological, shallow whole-genome sequencing (CUTseq, n=176), whole exome sequencing (WES, n=192), and RNA-sequencing (RNA-seq, n=187) data were generated using fresh-frozen baseline core biopsies. Potential tumor intrinsic resistance factors and microenvironment components were quantified by multi-omics analysis, including BC-specific somatic mutations and copy number alterations (CNA), COSMIC mutational signatures, CNA-based chromosomal instability signatures (CIN), subclone percentage, PAM50 subtype, GGI/PIK3CA score, HER2DX score, immune profiles (Danaher signature score, TIDE score and immune repertoires). We assessed the association of biomarkers with pCR in each treatment arm using logistic regression adjusting for hormone receptor (HR) status, and evaluated their predictive value by adding the interaction term (biomarker x treatment arm). In addition, a machine learning (ML) analysis was conducted from different classifiers, comprising unimodal ML-based models from clinical, RNA and DNA information, respectively. Model performance was assessed using the mean and standard deviation (mean \pm std) of the area

under receiver operator characteristic curve (AUC), positive predictive value (PPV) and negative predictive value (NPV) using a nested stratified cross-validation (CV) schema of 200 outer shuffle splits and 100 inner 5-fold CV to mitigate potential risk of overfitting.

Results: In DTP arm, patients with higher ERBB2 copy ratio ($OR_{adj}=1.98$, $p=0.004$) or mRNA ($OR_{adj}=3.08$, $p<0.001$) or HER2-enriched subtype (PAM50) ($OR_{adj}=1.78$, $p=0.02$) had higher pCR rates, while ESR1 gene expression ($OR_{adj}=0.59$, $p=0.07$) predicted treatment resistance despite adjustment for HR status. Conversely, response to T-DM1 was less likely to depend on ERBB2 profiles and only PAM50 HER2 enriched subtype ($OR_{adj}=1.53$, $p=0.1$) showed higher pCR rate (52% vs. 25%) than other subtypes. Both ESR1 ($OR_{adj}=0.4$, $p=0.008$) and PGR ($OR_{adj}=0.5$, $p=0.03$) gene expression were independent predictors of T-DM1 resistance. Pre-treatment immune exclusion metrics could predict resistance to DTP (endothelial cell, $OR_{adj}=0.67$, $p=0.07$) and T-DM1 (neutrophils, $OR_{adj}=0.54$, $p=0.02$; mast cells, $OR_{adj}=0.57$, $p=0.02$; cancer-associated fibroblasts, $OR_{adj}=0.67$, $p=0.09$), respectively. Predefined metrics such as PIK3CA signature score ($OR_{adj}=1.67$, $p=0.04$) and Taxane response score ($OR_{adj}=1.64$, $p=0.03$) were positively related to pCR in DTP arm. Genome instability, involving CIN CX2 signature (impaired homologous recombination) ($OR_{adj}=1.71$, $p=0.05$), COSMIC signature6 ($OR_{adj}=1.53$, $p=0.07$) and signature13 ($OR_{adj}=1.57$, $p=0.05$), predicted benefit from DTP. The biomarker-treatment interaction tests were significant for HER2DX ($p_{interaction}=0.004$) and COSMIC signature15 (defective DNA mismatch repair) ($p_{interaction}=0.007$): lower HERDX score ($OR_{adj}=0.73$, $p=0.14$) or higher COSMIC signature15 score ($OR_{adj}=1.51$, $p=0.1$) could identify patients benefiting from T-DM1, while being resistant to DTP (HERDX: $OR_{adj}=1.46$, $p=0.13$; signature15: $OR_{adj}=0.70$, $p=0.1$). In the ML models, clinical information yielded an $AUC=0.62\pm0.07$, $PPV=0.64\pm0.12$ and $NPV=0.64\pm0.06$; for DNA data, AUC was equal to 0.70 ± 0.08 , $PPV=0.72\pm0.09$ and $NPV=0.71\pm0.07$; an adaptive boosting ensemble learning on RNA reported slightly increased pCR prediction performance ($AUC=0.72\pm0.06$, $PPV=0.64\pm0.06$, $NPV=0.80\pm0.09$).

Conclusion: This study demonstrates that antibody–drug conjugates and standard treatment harbor strikingly distinctive biomarkers across tumor ecosystem. Further external validation and integrated ML model comprising all unimodal models are ongoing.

PO2-07-07

The role of PET imaging with [18F]16 α -fluoro-17 β -fluoroestradiol in predicting response to endocrine therapies in patients with breast cancer

Presenting Author(s) and Co-Author(s):

N. DiGregorio. GE Healthcare, Pharmaceutical Diagnostics, United States

C. Brand. GE HealthCare, United States

D. Dunham. GE HealthCare, United States

E. McManus. Cogora, United Kingdom

Background

Fluoroestradiol F18 is a radioactive diagnostic agent (^{18}F -FES) used with positron emission tomography (PET) imaging to detect estrogen-receptor (ER)-positive lesions in patients with breast cancer. Convened by the Society of Nuclear Medicine and Molecular Imaging (SNMMI), an expert working group published appropriate use criteria (AUC) for ^{18}F -FES PET including, but not limited to, use of ^{18}F -FES for selection of endocrine therapies.

Quantitative determination of ER status, and thus treatment response, has the potential to prevent ineffective courses of endocrine therapies and associated therapeutic / financial burden. This meta-analysis reviewed the AUC-cited studies to assess the utility of ^{18}F -FES in predicting treatment response to endocrine therapies.

Methods

Eight studies cited in the AUC were selected based on having comparable ^{18}F -FES PET standardized uptake values (SUV) and progression-free survival (PFS) measures, and one additional study was included upon further systematic search of the same selected parameters defined in the AUC.

With the nine studies ($n = 327$), we conducted three investigations to explore the association between: (1) the patient baseline ^{18}F -FES PET SUVmean, across all lesions or across up to seven of the most intense lesions, and patient response to endocrine therapy (response / no response); (2) in the same population as investigation 1, the change (%) in ^{18}F -FES PET SUV from baseline to at 7 to 10 days post-treatment; (3) the ^{18}F -FES interlesional heterogeneity and PFS (months). Interlesional heterogeneity was qualitatively defined as patients displaying both ^{18}F -FES positive and negative lesions versus those with all FES-positive lesions.

Results

A fixed effects model was used to analyze three studies ($n = 102$). Findings reveal that patients who responded to endocrine therapy had a significantly higher baseline SUVmean versus non-responders (mean difference 0.91; CI 95% 0.49 to 1.34; $P < 0.001$); a sensitivity analysis was conducted via random effects modelling and revealed similar results (mean difference 0.92; CI 95% 0.48 to 1.36; $P < 0.001$). This was consistent with findings from an additional analysis performed on two papers ($n = 62$), whereby odds ratio estimates indicated that a response to therapy is 89% less likely to occur when baseline ^{18}F -FES SUVmax is < 1.5 (OR 0.11; CI 95% 0.02 to 0.72 $P = 0.02$).

Findings from the analysis of mean percentage change in ¹⁸F-FES SUV from baseline to 7-10 days post-treatment initiation showed no significant difference in the percentage change of SUV observed between responders and non-responders (mean difference -0.22; 95% CI -0.69 to 0.26; P = 0.37).

The final heterogeneity analysis revealed higher median PFS in all FES-positive cohort, suggesting that this group may respond better to endocrine therapy (Table 1).

Conclusion

The AUC states that the presence of ER by immunohistochemistry may not be the optimal predictive biomarker for the success of endocrine therapies. Our findings support this statement, as a significantly higher baseline SUVmean of ¹⁸F-FES may serve as a predictive biomarker for endocrine therapy response. Patients with a ¹⁸F-FES lesion SUVmax < 1.5 are 89% less likely to respond to endocrine therapies; patients demonstrating heterogeneity (FES+/FES- lesions) have a lower median PFS, reinforcing the predictive value of ¹⁸F-FES.

Table 1. Median PFS scores from FES heterogeneity analysis

¹⁸ F-FES parameters		Liu [1] (n=12)*	He (n=10)	Boers (n=20)	Liu [2] (n=10)
Heterogeneity	Median PFS	5.50	7.20	6.75	2.40
(FES+ /FES- lesions)	95% CI	2.30, 8.70	3.00, 11.40	3.50, 12.25	1.10, 3.70
All FES positive	Median PFS	14.70	14.60	18.25	23.60
(FES+ lesions)	95% CI	10.90, 18.50	8.40, 20.80	5.25, ∞	15.80, 31.40

*Patients with all FES positive lesions were categorised by the median ratio of FES/FDG SUVmax into low FES/FDG (<0.96), and high FES/FDG (>0.96); only patients with FES/FDG of >0.96 were included in the positive lesions arm.

PO2-07-08

The efficacy of an MRI/US fusion technique for MRI-detected lesions previously undetected by conventional B-mode second-look US

Presenting Author(s) and Co-Author(s):

M. Saito. Aichi Medical University, United States

H. Banno. Aichi Medical University, United States

Y. Ito. Aichi Medical University, United States

M. Ido. Aichi Medical University, United States

M. Goto. Aichi Medical University, United States

T. Ando. Aichi Medical University, United States

Y. Mouri. Aichi Medical University, United States

J. Kousaka. Aichi Medical University, United States

K. Fujii. Aichi Medical University, United States

T. Imai. Aichi Medical University, United States

S. Nakano. Aichi Medical University Hospital, Aichi, Japan, Japan

Introduction

Breast magnetic resonance imaging (MRI) is performed for preoperative screening of breast cancer and surveillance of BRCA gene carriers, and some lesions, called MRI-detected lesions, can only be detected by MRI. When MRI-detected lesions are found, second-look ultrasound (US) is recommended as the first choice for confirmation. However, the detection of MRI-detected lesions by conventional B-mode (cB-mode) second-look US varies from institution to institution, and it is often difficult to ensure objectivity and reproducibility. We use an MRI/US fusion technique called real-time virtual sonography (RVS) for the detection of MRI-detected lesions. RVS uses a magnetic position tracking system to display real-time US images on the same monitor as MRI images. Few reports on second-look US using RVS have examined its detection rate of MRI-detected lesions and the histopathological results of these lesions. In this study, we retrospectively reviewed MRI-detected lesions identified by second-look US using RVS but not by cB-mode second-look US from January 2018 to December 2022, with the goal of evaluating these lesions' pathological characteristics.

Materials and methods

Consecutive patients who had one or more MRI-detected lesions not detected by cB-mode second-look US were enrolled in this study between January 2018 and December 2021. Second-look US using RVS was conducted after an additional supine MRI with a body surface coil was performed.

Results

A total of 36 patients with 38 lesions were included in this study. The mean age was 54 years old (range: 31–76). We were able to detect 31 (82%) of the 39 MRI-detected lesions by second-look US using RVS. These lesions were characterized as follows: mass, 14; non-mass-enhancement (NME), 13; and focal, 4. US-guided biopsy or excisional biopsy was performed on all lesions, and 11 (35%) of 31 lesions were malignant.

We were able to detect 14 (74%) of the 19 mass lesions, and 3 were malignant (invasive ductal carcinoma (IDC) [luminal A type] in all 3 cases). We detected 13 (93%) of the 14 NME lesions, and 7 were malignant: 6 were ductal carcinoma in situ (DCIS) (high grade, 3; intermediate

grade, 2; and low grade, 1), and 1 was IDC (luminal A type). Finally, we were able to detect 4 (80%) of the 5 focal lesions, 1 of which was malignant (DCIS [low grade]).

Of 22 patients aged 55 years or younger, 3 had malignant lesions (IDC [luminal A type] in 2, DCIS [high grade] in 1). Of 15 patients aged 56 years or older, 8 had malignant lesions (DCIS in 7 [high grade, 2; intermediate grade, 2; low grade, 1] and IDC [luminal A type] in 1).

Conclusions

In this study, second-look US using RVS identified 82% of MRI-detected lesions that were not identified with cB-mode second-look US. Of these MRI-detected lesions, 35% were malignant. These results suggest that second-look US using RVS is useful for identifying MRI-detected lesions that are not detected by cB-mode second-look US.

PO2-07-09

Early stage invasive lobular breast cancer is underestimated on conventional imaging including MRI

Presenting Author(s) and Co-Author(s):

K. Van Herck. KU Leuven, United States

K. Van Baelen. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, Leuven, Vlaams-Brabant, Belgium

C. Van Ongeval. UZ Leuven, United States

V. Celis. UZ Leuven, United States

H. De Boodt. UZ Leuven, United States

M. Keupers. UZ Leuven, United States

R. Prevos. UZ Leuven, United States

G. Floris. University Hospitals Leuven, United States

I. Nevelsteen. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, Leuven, Belgium

A. Smeets. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, United States

T. Baert. UZ Leuven, United States

S. Han. University Hospitals Leuven, Leuven, Vlaams-Brabant, Belgium

H. Wildiers. University Hospitals Leuven, United States

A. Laenen. KU Leuven, United States

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

Background: Invasive lobular carcinoma (ILC), representing 15% of all invasive breast cancers, is characterized by loss or dysfunction of the adhesion molecule E-cadherin. This leads to an infiltrative growth pattern that is unlikely to disrupt the normal architecture of breast tissue. As a result, ILC is often non-mass forming and imaging is limited in correctly diagnosing stage I-III ILC. Mammography is believed to underestimate ILC, while MRI tends to overestimate the extent of ILC. The aim of this retrospective study was to correlate radiological with pathological findings.

Methods: All patients diagnosed with stage I-III pure (i.e. not mixed) ILC between January 2000 and December 2020 who underwent primary surgery in University Hospitals Leuven, were included. Data on patient characteristics, preoperative imaging and pathology were collected from the patient files. Imaging and pathology measurements were compared by use of Pearson correlation coefficient, Whitney U test or Chi-square test. Weighted kappa statistics were used to assess agreement. Since the techniques of mammography and ultrasound have evolved in the past 20 years, different time periods were considered in sub-analyses (2000-2004, 2005-2009, 2010-2014, 2015-2020).

Results: In total 1029 patients were included. Median age at diagnosis was 61.0 years (range 32.0 – 95.0 years). The breast density score determined on mammogram was Bi-RADS type A

for 52 (5.1%) patients, B for 238 (23.1%) patients, C for 235 (22.8%) patients and D for 141 (13.7%) patients. Density score was missing from the reports of the remaining patients (n=363, 35.3%). Contrast enhanced breast magnetic resonance imaging (MRI) was performed in 709 (68.9%) patients. An increase in preoperative use of MRI was seen over the years. In comparison to tumor size reported by pathology, all imaging techniques underestimated the tumor size. The mean difference in largest tumor size compared to pathology was 14.64 ± 21.15 mm for mammography, 18.19 ± 21.66 mm for ultrasound and 9.93 ± 20.63 mm for MRI. A higher breast density level and a larger tumor size were significantly associated with a larger difference between diameter on pathology versus mammography ($\rho=0.102$, p-value 0.025 and $\rho=0.530$, p-value < 0.001 respectively). Changes over different time periods are shown in Table 1 for mammography and ultrasound. There was an agreement on unifocality versus multifocality between pathology and mammography for 81.2% of the patients. In 52.1% of the 236 cases where multifocality was reported on MRI, only 1 lesion was reported by the pathologist. Multifocality was seen on pathology in 12.0% of the 460 cases that were seen as unifocal lesions on MRI. Considering adenopathies, the false positive rate of ultrasound was 3.0%. However, the false negative rate was 68.3%.

Conclusions: The local extent of ILC is underestimated by conventional imaging techniques. Unlike previous reports, our results suggest that tumor size of ILC is also underestimated by MRI. Ultrasound was inferior to mammography and MRI in estimating tumor size in our series. It was confirmed that MRI tends to overestimate the number of foci which might lead to unnecessary secondary ultrasounds and biopsies. The presurgical underestimation of lymph node involvement might increase the need of secondary surgeries. It is crucial to address these limitations in imaging of ILC and to prioritize the development of enhanced imaging techniques to improve diagnostic accuracy for these patients.

Table 1: difference between imaging techniques and pathology by year of diagnosis

Variable	Statistic	2000-2004	2005-2009	2010-2014	2015-2020	P-value
Diameter						
Diameter difference (mm) pathology - mammography	N	96	144	194	232	0.333
	Mean	15.52	12.90	16.32	13.95	
	Std	20.786	21.445	21.354	20.950	
	Median	10.50	7.00	9.00	9.00	
	IQR	(1.00; 25.00)	(1.00; 20.00)	(3.00; 23.00)	(1.00; 23.00)	
	Range	(-39.00; 90.00)	(-31.00; 132.00)	(-15.00; 108.00)	(-35.00; 118.00)	
Diameter difference (mm) pathology - ultrasound	N	156	195	227	265	0.811
	Mean	20.03	18.96	16.91	17.62	
	Std	25.266	23.657	20.226	18.672	
	Median	14.00	11.00	11.00	13.00	
	IQR	(3.00; 26.50)	(4.00; 25.00)	(4.00; 25.00)	(4.00; 27.00)	
	Range	(-19.00; 133.00)	(-34.00; 133.00)	(-29.00; 103.00)	(-31.00; 111.00)	
Number of foci						
N foci Pathology - mammography	N	222	199	238	262	0.006
	Mean	-0.09	0.04	0.13	0.12	
	Std	0.702	0.787	0.851	0.904	
	Median	0.00	0.00	0.00	0.00	
	IQR	(0.00; 0.00)	(0.00; 0.00)	(0.00; 0.00)	(0.00; 0.00)	
	Range	(-3.00; 3.00)	(-3.00; 3.00)	(-3.00; 3.00)	(-3.00; 3.00)	
Number of adenopathies						
Adenopathies pathology - ultrasound	N	213	222	263	281	0.117
	Mean	0.80	0.83	0.62	0.52	
	Std	1.448	1.419	1.142	1.066	
	Median	0.00	0.00	0.00	0.00	
	IQR	(0.00; 1.00)	(0.00; 2.00)	(0.00; 1.00)	(0.00; 1.00)	
	Range	(-4.00; 4.00)	(-4.00; 4.00)	(-1.00; 4.00)	(-2.00; 4.00)	

Variables presented with percentages are analyzed using a Chi-square test. Variables summarized by means, medians, etc. are analyzed using a Kruskal-Wallis test. All reported p-values are two-sided
IQR = interquartile range, N = number of patients, Std = standard deviation

PO2-07-12

Analysis Of Malignity Rates Of Percutaneous Biopsy In Lymph Nodes Of Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

M. Diogenes. HOSPITAL PEROLA BYINGTON, SÃO PAULO, Sao Paulo, Brazil

A. Amorim. Perola Byington Hospital, United States

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

M. ANTONINI. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, Sao Paulo, Sao Paulo, Brazil

L. Gebrim. Perola Byington Hospital, United States

R. COELHO LOPES. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

L. Damous. Hospital do Servidor Público Estadual – Francisco Morato de Oliveira, São Paulo, Brazil., United States

BACKGROUND: The evaluation of regional lymph nodes in patients with breast cancer is one of the main predictive and prognostic factors for treatment. The methods of percutaneous biopsies of suspicious lymph nodes frequently used are fine-needle aspiration cytology (FNA) and core needle biopsy (CORE). According to the international literature, CORE and FNA are considered diagnostic methods with high specificity (98% vs. 99%), however, the FNA may present up to 21% of inconclusive results by insufficient material. Although CORE is well established as a percutaneous method for diagnostic evaluation of suspected breast lesions, the literature is scarce on the use of this technique for the evaluation of suspicious lymph nodes in breast cancer patients. **OBJECTIVE:** Analyze the positivity of FNA and CORE performed in suspicious lymph nodes for breast cancer metastasis according to the anatomical location of biopsies and the type of needle used, verifying which technique was preferred. **METHODS:** A retrospective study was conducted by evaluating the database of patients treated in a public hospital in São Paulo, Brazil. Women submitted to ultrasound-guided percutaneous biopsy of lymph nodes from May 2015 to November 2019 were included in the study. The data were analyzed using IBM-SPSS version 27 and Microsoft EXCEL version 2010. **RESULTS:** A total of 499 biopsies were performed and the mean age of the women was 54.2 years (SD± 11.9) in the CORE group and 53.4 years (SD± 11.8) in the FNA group (p=0.619). According to the anatomical location, 385 were axillary (77.2%), 62 supraclavicular (12.4%), 48 cervical (9.6%) and 4 infraclavicular (0.8%). Regarding the type of needle, 393 were CORE (78.8%) and 106 were FNA (21.2%). When analyzing the results of the FNA, 38 (35.8%) did not present enough material, 31 (29.2%) were positive, 32 (30.2%) were negative and 5 (4.8%) showed atypical cells. Among the 393 CORE performed, 255 (64.9%) were positive, 132 (33.6%) were negative, 1 (0.3%) showed atypical cells and 5 (1.3%) had no representative material. No complications were reported after the procedures. **CONCLUSION:** CORE was the preferred diagnostic technique in our center, being considered a feasible procedure to evaluate lymph nodes in different sites and with low rates of inconclusive results by insufficient material. In the future, studies evaluating indirect costs may confirm the feasibility of CORE in patients with suspicious lymph nodes in terms of obtaining greater agility and resolute conducts in the public healthcare system.

PO2-08-01

Universal Multi-Gene Panel Testing of Newly Diagnosed Breast Cancer Patients in a Community Healthcare System

Presenting Author(s) and Co-Author(s):

N. Johns. St. Elizabeth Healthcare, United States

J. Wallace. St. Elizabeth Healthcare, Edgwood, Kentucky, United States

D. Raible. St. Elizabeth Healthcare, United States

J. Brady. St. Elizabeth Healthcare, United States

G. Miller. St. Elizabeth Healthcare, United States

B. Phillips. St. Elizabeth Healthcare, United States

Introduction

Multi-gene panel, germline genetic testing has emerged over the last decade as a useful tool in the assessment of hereditary cancer syndromes. As barriers to genetic testing are reduced, offering universal genetic testing to all cancer patients is a practice gaining traction. We present outcomes data specific to the offering of universal, multi-gene panel testing to newly diagnosed breast cancer patients in a community hospital setting.

Methods

A retrospective chart review was performed for all newly diagnosed breast cancer patients (n=1005) at a community hospital between 8/5/2019 and 8/5/2022. Uptake and outcomes of genetic counseling and genetic testing were assessed. All patients were offered genetic counseling, and those who consented to genetic testing were offered a multi-gene panel (37-93 genes). The National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (2020) guidelines were utilized to distinguish which patients met traditional genetic testing criteria.

Results

Of all newly diagnosed breast cancer patients, 915 (91.1%) patients underwent genetic counseling and 871 (86.7%) patients elected for genetic testing. Of those who declined genetic testing (n=134), 39 (29.1%) reported previous genetic testing. Of patients tested, 489 (56.1%) met NCCN criteria. Overall, 114 (13.1%) of tested patients received results with likely pathogenic/pathogenic (LP/P) variants. Of those, 86 (75.4%) had a clinically significant variant, a high-risk, moderate-risk or another dominantly inherited gene variant, while 28 (24.6%) were identified as genetic carriers; Table 1 summarizes genes with LP/P variants in this cohort, with 10 patients receiving results for 2 variants. Of the patients with clinically significant genetic results, 58 (67.4%) met NCCN criteria. Furthermore, 65 patients (75.6%) reported a family history of cancer relevant to the identified LP/P variant. The average age of the total population, and of those with a positive result, was 62 years. While nearly 19% of all patients tested were under age 50, patients under 50 comprised only 14.0% (n=12) of patients with a clinically significant result. Breast cancer management changes, including addition of a PARP inhibitor to chemotherapy regimen and/or elected bilateral mastectomies in the setting of unilateral disease, were noted in 71.4% (n=20) of patients with high-risk genetic findings and 20.6% (n=7) of patients with moderate-risk genetic findings.

Conclusion

The 86.7% uptake of genetic testing suggests implementation of universal testing in a

community setting is feasible and favored by patients. Clinically significant genetic results would have gone undetected in 32.6% of patients if NCCN criteria was strictly utilized to offer testing. In addition to the 62 patients with high and moderate risk genetic results, utilization of expanded panel testing provided benefit for an additional 24 patients found to have an actionable variant in a gene that would not have been detected on traditional breast cancer panels. Our data supports the offering of genetic testing to all newly diagnosed breast cancer patients, regardless of age, family history, or other criterion, to inform precise breast cancer management and overall, lifetime cancer risks.

Genetic Findings of Universal Multi-Gene Panels in a Community Setting

Table 1. Genetic findings of universal multi-gene panels in a community setting

Gene Category	Gene # of pathogenic/likely pathogenic variants identified	Percentage of total variants identified (n=124)
High risk genes	BRCA1 (7), BRCA2 (9), PALB2 (9), TP53 (3)	22.6% (n=28)
Moderate risk genes	ATM (10), BARD1 (1), CHEK2 (2), NF1 (3)	29.0% (n=36)
Carrier genes	MUTYH (20), NTHL1 (4), BLM (2), MSH3 (2), BRCC4 (1), NBN (1), RAD50 (2)	25.8% (n=32)
Others	PMS2 (2), MSH6 (3), BRIP1 (2), CDKN2A (2), EGFR (1), FH (3), HNR1B (5), MTF (2), RAD51 (1), RET (1), RUNX1 (1), SOX1 (3), TSC2 (1), **FRANC (1)	22.6% (n=28)

*Some patients tested positive for multiple gene mutations.
**FRANC was added to the expanded panel for one patient with a known family history.

PO2-08-02

Evaluation of predictive and prognostic value of androgen receptorexpression in breast cancer subtypes treated with neoadjuvantchemotherapy

Presenting Author(s) and Co-Author(s):

J. Zhang. The 3rd Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin 300060, China, Tianjin, China (People's Republic)

Background Neoadjuvant chemotherapy is the standard treatment for local advanced breast cancer administered to shrink tumors and destroy undetected metastatic cells, thereby facilitating subsequent surgery. Previous studies have shown that AR may be used as a prognostic predictor in breast cancers, but its role in neoadjuvant therapy and the relationship with prognosis of different molecular subtypes of breast cancer need to be further explored. **Methods** We retrospectively evaluated 1231 breast cancer patients with complete medical records at Tianjin Medical University Cancer Institute and Hospital who were treated with neoadjuvant chemotherapy between January 2018 to December 2021. All the patients were selected for prognostic analysis. The follow-up time ranged from 12 to 60 months. We first analyzed the AR expression in different subtypes of breast cancer and its correlation with clinicopathological features. Meanwhile, the association of AR expression and pCR of different breast cancer subtypes was investigated. Finally, the effect of AR status on the prognosis of different subtypes of breast cancer after neoadjuvant therapy was analyzed. **Results** The positive rates of AR expression in HR + /HER2-, HR + /HER2 +, HR-/HER2 + and TNBC subtypes were 82.5%, 86.9%, 72.2% and 34.6%, respectively. Histological grade III (P = 0.014, OR = 1.862, 95% CI 1.137 to 2.562), ER positive expression (P = 0.002, OR = 0.381, 95% CI 0.102 to 0.754) and HER2 positive expression (P = 0.006, OR = 0.542, 95% CI 0.227 to 0.836) were independent related factors for AR positive expression. AR expression status was associated with pCR rate after neoadjuvant therapy only in subtype of TNBC. AR positive expression was independent protective factor for recurrence and metastasis in HR + /HER2- (P = 0.033, HR = 0.653, 95% CI 0.237 to 0.986) and HR + /HER2 + breast cancer (P = 0.012, HR = 0.803, 95% CI 0.167 to 0.959), but was independent risk factors for recurrence and metastasis in TNBC (P = 0.015, HR = 4.551, 95% CI 2.668 to 8.063). AR positive expression is not an independent predictor of HR-/HER2 + breast cancer. **Conclusions** AR expressed the lowest in TNBC, but it could be a potential marker for the prediction of pCR in neoadjuvant therapy. AR negative patients had a higher pCR rate. AR positive expression was an independent risk factor for pCR in TNBC after neoadjuvant therapy (P = 0.017, OR = 2.758, 95% CI 1.564 to 4.013). In HR + /HER2- subtype and in HR + /HER2 + subtype, the DFS rate in AR positive patients and AR negative patients was 96.2% vs 89.0% (P = 0.001, HR = 0.330, 95% CI 0.106 to 1.034) and was 96.0% vs 85.7% (P = 0.002, HR = 0.278, 95% CI 0.082 to 0.940), respectively. However, in HR-/HER2 + and TNBC subtypes, the DFS rate in AR positive patients and AR negative patients was 89.0% vs 95.9% (P = 0.102, HR = 3.211, 95% CI 1.117 to 9.224) and 75.0% vs 93.4% (P < 0.001, HR = 3.706, 95% CI 1.681 to 8.171), respectively. In HR + /HER2- and HR + /HER2 + breast cancer, AR positive patients had a better prognosis, however in TNBC, AR-positive patients have a poor prognosis

PO2-08-03

Developing a polygenic risk score for precision prevention of estrogen receptor-positive (ER+)/HER2- breast cancer in Brazilian women

Presenting Author(s) and Co-Author(s):

M. Candido Visontai Cormedi. University of Sao Paulo, United States

□. Eburnêo Pereira. University of Sao Paulo, United States

F. Borchers Coeli-Lacchini. University of Sao Paulo, United States

S. Baroni. University of Sao Paulo, United States

L. Torres Bueno. University of Sao Paulo, United States

E. Ayumi Onga. University of Sao Paulo, United States

V. Girelli Piloto De Oliveira. University of Sao Paulo, United States

F. De Oliveira Bueno. University of Sao Paulo, United States

A. Fares. Hospital de Base, United States

T. Strava Correa. Hospital Sírio-Libanês, United States

I. Alves Chirichela. DASA Oncologia/Hospital Brasilia, Brasília, DF, Brazil, United States

F. Peria. University of São Paulo, United States

R. Barroso-Sousa. DASA Oncologia/Hospital Brasilia, Brasília, DF, Brazil, United States

R. Santa Cruz Guindalini. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

T. Manuela Bonfim Machado Lopes. Universidade Federal da Bahia, United States

R. Roela. University of Sao Paulo, United States

M. Azevedo Koike Folgueira. University of Sao Paulo, United States

D. Guimarães Tiezzi. University of Sao Paulo, United States

L. Machado Colli. University of Sao Paulo, United States

L. Rapatoni. University of São Paulo, United States

Polygenic risk scores (PRS) quantify the genetic risk of diseases based on risk alleles in genomic loci identified in genome-wide association studies (GWAS). As individuals of European ancestry are overrepresented in GWAS, PRS performance may vary in individuals of different ancestries. Brazil is the largest and most populated country in Latin America, with around 43% of admixed individuals, and data on breast cancer PRS performance for this population is lacking. We aimed to evaluate the performance of a breast cancer PRS with 313 SNPs generated with Europeans in Brazilian population. In this case-control study, we expect to include 1000 women age ≥ 18 years old with current or previous diagnosis of ER+/HER2- breast cancer. Germline DNA samples are genotyped with Illumina Infinium Global Screening Array-24 v3.0 chip. Controls are healthy woman previously genotyped with Global Screening Array-24 v1.0 chip. We selected the 313 SNPs PRS for ER+/HER2- breast cancer from PGS Catalog for evaluation. Quality control, imputation, PRS calculation and statistical analysis were performed in PLINK v2.0, Michigan server, PGS Catalog and R, respectively. We present the preliminary results for 1347 women (504 cases and 843 controls) included until March of 2023. After quality control and imputation, we calculated PRS for 1212 subjects (475 cases and 737 controls). Out of 313 SNPs, 211 were validated in our samples. For ER+/HER2- breast cancer, the odds ratio per SD of the 211-variant PRS (PRS211) was 1.363 (95% confidence interval [CI]: 1.211 to 1.537). Compared with women with average risk (40th-60th PRS percentile),

women in the top 10% of PRS211 had a 1.623-fold increased risk (95% CI: 1.047 to 2.522). The area under the receiver operating characteristic curve of 0.581. Our preliminary results indicate that a PRS derived from European-ancestry population correlates with ER+/HER2-breast cancer in admixed Brazilian population, although with attenuated performance. Further work is needed to better characterize PRS risk stratification in admixed populations.

PO2-08-04

Unraveling alterations in the pre-neoplastic breast microenvironment of BRCA1/2 mutation carriers using spatial transcriptomics

Presenting Author(s) and Co-Author(s):

M. Karaayvaz. Genomic Medicine Institute, Cleveland Clinic, Ohio, United States

A. Caputo. Genomic Medicine Institute, Cleveland Clinic, United States

K. Vipparthi. Genomic Medicine Institute, Cleveland Clinic, United States

P. Bazeley. Department of Quantitative Health Sciences, Cleveland Clinic, United States

E. Downs-Kelly. Department of Laboratory Medicine and Pathology, Mayo Clinic, United States

P. McIntire. Pathology & Laboratory Medicine Institute, Cleveland Clinic, United States

Y. Ni. Center for Immunotherapy & Precision Oncology, Cleveland Clinic, United States

B. Hu. Department of Quantitative Health Sciences, Cleveland Clinic, United States

R. Keri. Cleveland Clinic, United States

Breast cancer is the most common cancer in females, affecting one in every eight women and accounting for the majority of cancer-related deaths in women worldwide. Germline mutations in the BRCA1 and BRCA2 genes are significant risk factors for specific subtypes of breast cancer. BRCA1 mutations are associated with basal-like breast cancers, whereas BRCA2 mutations are associated with luminal-like disease. There are currently few chemoprevention strategies available for BRCA1/2 mutation carriers, and irreversible prophylactic mastectomy is the primary option. Designing chemo-preventive strategies requires an in-depth understanding of the physiological processes underlying tumor initiation. Here, we employ spatial transcriptomics to investigate defects in mammary epithelial cell differentiation accompanied by distinct microenvironmental alterations in preneoplastic breast tissues from BRCA1/2 mutation carriers and normal breast tissues from non-carrier controls. We uncovered spatially defined receptor-ligand interactions in these tissues for the investigation of autocrine and paracrine signaling. We discovered that β 1-integrin-mediated autocrine signaling in BRCA2-deficient mammary epithelial cells differs from BRCA1-deficient mammary epithelial cells. In addition, we found that the epithelial-to-stromal paracrine signaling in the breast tissues of BRCA1/2 mutation carriers is greater than in control tissues. More integrin-ligand pairs were differentially correlated in BRCA1/2-mutant breast tissues than non-carrier breast tissues with more integrin receptor-expressing stromal cells. These results reveal alterations in the communication between mammary epithelial cells and the microenvironment in BRCA1 and BRCA2 mutation carriers, laying the foundation for designing innovative breast cancer chemo-prevention strategies for high-risk patients.

PO2-08-05

ERBB2 mutated breast cancer detected by next generation sequencing: integrated analysis based on real-world data and The Cancer Genome Atlas

Presenting Author(s) and Co-Author(s):

J. Kim. Gangnam Severance Hospital, South Korea

Y. Kook. Gangnam Severance Hospital, South Korea

S. Baek. Gangnam Severance Hospital, South Korea

M. Kim. Gangnam Severance Hospital, Seoul, Seoul-t'ukpyolsi, Republic of Korea

S. Moon. Gangnam Severance Hospital, South Korea

S. Lee. Gangnam Severance Hospital, South Korea

J. Kim. Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Background ERBB2 mutation has been recognized as an actionable target for pan-HER tyrosine kinase inhibitors in the era of precision medicine for solid tumors. In our real-world cohort utilizing next-generation sequencing (NGS), we successfully identified cases of ERBB2-mutated breast cancer. Furthermore, we investigated the clinical and pathological characteristics of these cases by integrating our data with The Cancer Genome Atlas (TCGA). Methods Our real-world cohort with NGS included 423 breast cancer patients treated at Gangnam Severance Hospital in Seoul, Republic of Korea, between April 2017 and January 2023. Among these patients, 13 were confirmed to have ERBB2 mutation through NGS analysis. We also incorporated data from TCGA database, which included 818 cases with ERBB2 sequencing. We compared the clinical characteristics (age, sex, stage, and ER, PR, and HER2 status) between the two groups. Furthermore, we examined the frequency of two of the most common mutations, PIK3CA and TP53, in both groups. Additionally, we investigated the distribution of PAM50 subtypes in the TCGA cohort. Results This study analyzed a total of 1,244 cases with NGS data. Among these cases, 31 (2.5%) exhibited ERBB2 mutation, with 13 patients identified in our dataset and 18 in the TCGA data. Among the 31 cases with ERBB2 mutation, 21 (67.7%) had HER2-negative disease. No significant differences were observed in other clinical characteristics based on ERBB2 status. Within the group of 31 ERBB2-mutated cases, TP53 mutations were found in 12 cases (38.7%), while PIK3CA mutations were found in 12 cases (38.7%). In the TCGA dataset, 4 cases (22.2%) with ERBB2 mutation were classified as HER2-E subtype, and the rate of HER2-E subtype was significantly higher in the ERBB2-mutated group compared to the ERBB2-wild group (22.2% vs. 7.6%, $p=0.024$). Conversely, 14 cases (77.8%) with ERBB2 mutation exhibited a non-HER2 enriched subtype. Conclusions Consistent with previous knowledge, ERBB2 mutations can be detected in HER2-negative breast cancer, despite their rarity. Furthermore, a considerable proportion of ERBB2-mutated breast cancer may depend on various oncogenic signaling pathways other than the HER2 pathway. Further studies are warranted to optimize therapeutic strategies for ERBB2-mutated

breast cancer.

PO2-08-06

Metformin may improve the outcome of patients with breast cancer and type 2 diabetes mellitus through the effect of tumor immune microenvironment.

Presenting Author(s) and Co-Author(s):

S. Shiba. Jichi medical university, United States

M. Harao. Department of Breast Oncology, School of Medicine, Jichi Medical University, United States

K. Ogihara. Jichi medical university, United States

T. Fukuda. Jichi medical university, United States

M. Sakuragi. Jichi medical university, United States

K. Joji. Jichi medical university, United States

N. Sata. Jichi medical university, United States

Metformin, an anti-diabetic drug, is known to have anti-tumor effects. We examined the outcome of 177 patients with type 2 diabetes mellitus (T2DM) who received surgery for breast cancer. Among them, 49 patients were treated with drugs including metformin. In those patients, recurrence in distant organs was less frequent and postoperative disease-free survival (DFS) tended to be better than those without metformin intake. In patients who received preoperative systemic therapy (PST), rate of pathological complete response (pCR) was significantly more frequent in patients with metformin treatment ($p < 0.05$). Multiplex immunohistochemical staining of resected tumors revealed that the density of tumor associated macrophages (TAM), especially of CD68(+)CD163(+) M2-type TAM, was significantly lower in tumors with metformin treatment. In contrast, the rate of CD8(+) phenotype in CD3(+) tumor infiltrating lymphocytes (TILs) was significantly higher in metformin group. The results suggest that metformin can change the immune microenvironment from pro-tumorigenic to anti-tumorigenic status, which leads to the favorable outcome of the patients with breast cancer and T2DM.

PO2-08-07

Evaluating chemotherapy receipt and candidacy for PARP inhibitors in germline BRCA1/2 carriers with early and locally advanced breast cancer

Presenting Author(s) and Co-Author(s):

S. Wong. Segal cancer centre, Jewish General Hospital, Lady Davis institute, United States

C. Apostolova. McGill University Medical School, United States

A. Ferroum. McGill University Medical School, United States

B. Alhassan. McGill University Medical School, Department of Surgery and Oncology, United States

I. Prakash. McGill University Medical School, Department of Surgery and Oncology, United States

M. Basik. Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada, United States

K. Martel. McGill University Medical School, Department of Surgery, United States

S. Meterissian. McGill University Medical School, Department of Surgery and Oncology, United States

D. Fleiszer. McGill University Medical School, Department of Surgery, United States

N. Wong. McGill University Medical School, Department of Human Genetics, United States

T. Malagon. McGill University Medical School, Department of Oncology, United States

W. Foulkes. McGill University Medical School, Department of Human Genetics, Canada

J. Boileau. Jewish General Hospital Segal Cancer Centre, McGill University, Montréal, Quebec, Canada

Introduction: While enhanced breast screening of germline BRCA1/2 carriers results in earlier stage at diagnosis, the impact of tumour biology and BRCA mutation on chemotherapy receipt in early stage disease remains understudied. **Methods:** We retrospectively reviewed treatment administered following a first diagnosis of BRCA1/2-associated breast cancer between 2003-2023 at our institution. Chemotherapy receipt (neoadjuvant or adjuvant) was evaluated according to tumor size, biologic subtype, and BRCA mutation. Current guidelines for PARP inhibitor use were applied to estimate the proportion of affected BRCA1/2 carriers that would be deemed eligible for targeted therapy in the future. **Results:** Overall, 251 affected BRCA1/2 carriers were included; 137 (54.6%) BRCA1 (median age 40 years, range 19-72) and 114 (45.4%) BRCA2 (median age 43, range, 24-80 years). Chemotherapy was administered in 70.1% of index breast cancer cases and was significantly associated with clinical tumor size (36.7% T1a-T1b, 90.9% T1c, 95.2% T2, 95.3% T3-T4, $p < 0.001$), nodal status (71.8% cN0 vs. 100% cN1-2, $p=0.004$), and biologic subtype (90.0% TNBC vs. 75.0% ER+HER2-, $p=0.02$). BRCA1-associated breast cancers were less likely to present with DCIS or T1 tumours (%Tis/T1; 46.7% BRCA1 vs. 70.8% BRCA2, $p < 0.001$) and more likely to present with triple negative disease (71.4% BRCA1 vs. 24.6% BRCA2, $p < 0.001$). BRCA1 carriers were more likely to require chemotherapy for index breast cancer (81.8% BRCA1 vs. 56.1% BRCA2, $p < 0.001$). In subgroup analysis of early stage, T1N0 disease, chemotherapy was administered in 79.0% BRCA1 and 52.2% BRCA2 patients ($p=0.03$). If recent guidelines incorporating biologic subtype, nodal involvement, and response to neoadjuvant chemotherapy were retrospectively applied to the cohort, 33.6% would be deemed eligible for PARP inhibitors in the adjuvant setting, including 40.9% BRCA1 and 17.5% BRCA2 affected carriers ($p < 0.001$). **Conclusion:**

Chemotherapy receipt is high in BRCA-associated breast cancers including in early stage, node-negative disease. Overall, one third of affected carriers are expected to be eligible for PARP inhibitors in the adjuvant setting. Future studies exploring how this information may impact decisions around risk-reducing mastectomy are warranted.

PO2-08-09

Prevalence of germline genetic variants in breast cancer susceptibility genes among patients with metaplastic breast cancer

Presenting Author(s) and Co-Author(s):

K. Demarest. Hospital of the University of Pennsylvania, United States

A. Nayak. University of Pennsylvania, United States

P. Shah. Penn Medicine, Philadelphia, Pennsylvania, United States

Background: Pathogenic or likely pathogenic variants (PV) in breast cancer (BC) susceptibility genes are present in approximately 5-10% of individuals with breast cancer and approximately 13-15% of those with triple-negative breast cancer (TNBC). Identifying patients with PV in BRCA1 and BRCA2 can inform selection of appropriate candidates for poly(ADP-ribose) polymerase inhibitors (PARPi), which have improved progression-free and overall survival in the metastatic and adjuvant settings, respectively. Metaplastic breast cancer (MpBC) is a rare, aggressive subtype of breast cancer that is often triple-negative and refractory to chemotherapy. To date, limited data describe germline genetic findings in patients with MpBC. Methods: We conducted a retrospective chart review including patients with pathology results at the Hospital of the University of Pennsylvania from 2021 through May 2023 demonstrating MpBC. Germline genetic test results and tumor histopathologic characteristics including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status were evaluated. Descriptive statistics as well as two-tailed t tests were used for data analysis. Results: Of 89 patients identified with MpBC, 51 had germline genetic testing results available for review. Nine patients (17.6%) had MpBC with PV in BC predisposition genes (PV-MpBC) and 42 (82.4%) had PV-negative MpBC (PVneg-MpBC). Seven patients (13.7%) had a PV in BRCA1, 1 (2.0%) in BRCA2, and 1 (2.0%) in CHEK2. Median age at diagnosis was 45 years for patients with PV-MpBC and 56.5 years for those with PVneg-MpBC ($p=0.005$). Among patients with PV-MpBC, 6 (66.7%) had ER and PR negative disease by ASCO-CAP guidelines and 3 (33.3%) had ER and/or PR positive disease. Among patients with PVneg-MpBC, 31 (73.8%) had ER and PR negative disease and 11 (26.2%) had ER and/or PR positive disease. All 9 patients with PV-MpBC had HER2-negative disease, one (11.1%) of whom had HER2-low disease. Among patients with PVneg-MpBC, 40 (95.2%) had HER2-negative disease, two (4.8%) of whom had HER2-low disease, and 2 (4.8%) had HER2-positive BC. Conclusions: The frequency of PV in breast cancer susceptibility genes among patients with MpBC is comparable to, and possibly higher than, the reported rates of such PV in patients with TNBC, for whom genetic testing is recommended. If confirmed in a larger dataset, germline testing should be considered for all patients with MpBC regardless of ER, PR, and HER2 status, as findings may help identify candidates for PARPi therapy and genetically-directed clinical trials.

PO2-08-10

Effect of 6 months of bazedoxifene + conjugated estrogens on body composition and insulin resistance.

Presenting Author(s) and Co-Author(s):

- C. Fabian. University of Kansas Cancer Center, Kansas City, Kansas, United States
- A. Zelenchuk. University of Kansas Medical Center, Kansas City, Kansas, United States
- K. Powers. University of Kansas Medical Center, Kansas City, Kansas, United States
- A. Kreutzjans. University of Kansas Medical Center, Kansas City, Kansas, United States
- K. Pittman. University of Kansas Medical Center, Kansas City, Kansas, United States
- B. Hendry. University of Kansas Medical Center, Kansas City, Kansas, United States
- C. Altman. University of Kansas Medical Center, Kansas City, Kansas, United States
- E. Giles. University of Michigan, Ann Arbor, Michigan, United States
- K. Cook. Wake Forest University School of Medicine, United States
- S. Hursting. University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States
- B. Kimler. University of Kansas Medical Center, Kansas City, Kansas, United States

Menopause transition is often marked by an acceleration of visceral fat accumulation. Excess visceral fat is associated with insulin resistance and increased risk for breast cancer as well as heart disease and diabetes. We measured change in body composition (via iDXA), fasting insulin and glucose as part of an ongoing, Phase IIB trial (NCT04821141) of 6 months of bazedoxifene (BZA) + conjugated estrogen (CE) vs control with primary endpoints of change in mammographic density and breast tissue Ki-67. Participants are women ages 45-60 with vasomotor symptoms at increased risk for development of breast cancer. Methods: Visceral and total fat, lean, and total mass, were measured with iDXA (GE CoreScan™). Fasting plasma was assayed same day as drawn for total insulin using a chemiluminescence assay and glucose using a hexokinase method. Values generated were used to calculate HOMA IR (as a measure of insulin resistance) using the formula $\text{insulin } \mu\text{l/ml} \times \text{glucose mg/dl}/405$. HOMA %S was calculated as $1/\text{HOMA IR} \times 100$ as a measure of insulin sensitivity. Optimal HOMA IR is considered as ≤ 1 ; HOMA IR > 1.5 is considered abnormal with > 2.0 as evidence of insulin resistance. Optimal HOMA %S is 100%. Results: 24 women (12 BZA+CE, 12 Control) have completed baseline and 6-month body composition and insulin resistance assessments. Women randomized to BZA+CE were more likely to experience reduction in insulin resistance and improved insulin sensitivity despite a small weight gain over the initial 6 months. 7/12 randomized to BZA+CE had $\geq 15\%$ reduction in HOMA IR vs only 2/12 controls. Three participants had HOMA IR > 2 at baseline. Of these, one was randomized to BZA+CE and had a normal HOMA IR value at 6 months. The remaining two women were in the control group and saw no improvement in HOMA IR at 6 months. In addition, one woman randomized to control with normal HOMA-IR at baseline had HOMA IR > 2 at 6 months. Next Steps: The improvements in insulin resistance parameters with BZA+CE are similar to those observed in our rodent studies, supporting this combination as promising for use in breast cancer risk

reduction in women with vasomotor symptoms at high-risk for metabolic disease.

	Baseline	BZA + CE	Control	BZA+ CE	Control
Parameter	Median	Absolute ▲	Absolute ▲	Relative ▲	Relative ▲
BMI	25.4 kg/m ²	+ 0.3 kg/m ²	+ 0.2 kg/m ²	+ 1%	+ 1%
Total Mass	70.5 kg	+ 1.4 kg	- 0.4 kg	+ 2%	- 0.5%
Total Fat	30.5 kg	+ 1.3 kg	- 0.8 kg	+ 5%	- 3%
Visceral Fat	0.57 kg	+ 0.03 kg	- 0.05 kg	+ 14%	- 11%
Lean Mass	41.5 kg	+ 0.33 kg	+ 0.2 kg	+ 1%	+ 0.4%
Insulin	4.0 µIU/ml	- 0.7 µIU/ml	+ 0.2 µIU/ml	- 17%	+ 7%
Glucose	88.0 mg/dl	- 2.5 mg/dl	- 1.5 mg/dl	- 3%	- 2%
HOMA IR	0.9	- 0.2	- 0.01	- 17%	- 2%
HOMA %S	113.6	+ 21.6	+ 1.5	+ 21%	+ 2%

PO2-08-11

The MAGIC study: Universal whole genome tumour and germline sequencing of newly diagnosed breast cancer identifies a high proportion of ER+ BRCA-like tumours

Presenting Author(s) and Co-Author(s):

I. Campbell. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, United States

L. Devereux. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, United States

K. Hogg. Murdoch Children's research Institute, United States

I. Lal. Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia, United States

M. Sinclair. Royal Women's Hospital, Melbourne, VIC, Australia

L. Stafford. Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia, United States

M. Zethoven. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, United States

A. Skandarajah. The Royal Melbourne Hospital, United States

P. James. Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia, United States

G. Lindeman. Walter & Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

D. De Silva. Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia, United States

Background: Identification of germline mutations in hereditary breast cancer (HBC) genes can have profound benefits in the treatment of breast cancer (BC) and managing risk for patient and the family. In addition, sequencing of the tumours can reveal clinically relevant somatic features, such as homologous recombination deficiency (HRD) and mutational signatures, that can guide treatment which are not discernible by germline sequencing alone. We hypothesised that current standard of care where women diagnosed with BC are not routinely offered tumour sequencing is suboptimal as fails to exploit all therapeutic vulnerabilities which can be exploited in the treatment of BC. The MAGIC study is the first prospective trial in Australia of unselected invasive BCs in general oncology practice combining both germline and tumour sequencing.

Methods: The MAGIC study included a total of 651 consecutive consented patients presenting with non-metastatic BC between June 2020 to March 2023. It included invasive BC, high-grade DCIS and pleomorphic LCIS. The sequencing was conducted in two phases; for phase one, 157 cases underwent whole genome sequencing (WGS) on both germline and matched BC DNA while for phase two, 494 cases underwent only germline whole exome sequencing.

Germline variants were interrogated for pathogenic variants in BRCA1, BRCA2, PALB2, ATM, CHEK2, BARD1, BRIP1, RAD51B, RAD51C, RAD51D, MLH1, MSH2, MSH6, PMS2, CDH1, PTEN, STK11, TP53 and NTHL1. Tumour homologous recombination (HR) repair deficiency was calculated using HRDetect (Nat Med 2017;23:517). For BCs showing a high HRDetect score (>0.75) all HBC gene promoter CpG islands were assessed for hypermethylation using the Twist NGS Methylation system. Mutational signatures were calculated from somatic mutations identified from whole genome sequenced BCs using the DeconstructSig package in R (Genome Biol. 2016;17:31) and referenced against the COSMIC v2 signature catalogue.

Results: Actionable germline variants in any HBC gene were identified in 7.7% of cases (7.8% of invasive and 6.1% of in situ BC) with 5.2% having an actionable mutation in an HR pathway gene (BRCA1, BRCA2, PALB2 and RAD51C). Most cases with pathogenic variants showed bi-allelic inactivation in the tumour. All BRCA1, BRCA2 and PALB2 tumours showed high HRDetect and/or HRD scores consistent with loss of HR repair function, indicating them to be the underlying hereditary driver of the BC. One BC with a pathogenic PMS2 variant showed retention of the wild-type allele with no evidence of a mismatch repair mutational signature suggesting PMS2 was not the driver of this BC.

Of the 157 BC in phase one that underwent WGS and did not have a germline pathogenic HBC gene variant, 16% (18/117 invasive and 3/13 DCIS) had an HRDetect score of >0.7 indicative of a homologous recombination repair defect and therefore biologically a "BRCA-like" tumour. Of these 21 BRCA-like cases, only 3 invasive BCs had clear somatic bi-allelic inactivation of an HBC gene that could explain the high HRDetect score (2 BRCA1 and 1 BRCA2). One of the 21 BRCA-like cases had a germline variant of unknown significance (VUS) in an HBC gene (a BRCA2 missense variant in an ER+ tumour. The tumour showed loss of the wild-type allele). Of the BRCA-like cases, 71% were ER positive which included 3 invasive lobular cancers.

Conclusion: Tumour sequencing identified three times as many cases that might be eligible for HR repair defect targeted therapy than germline testing alone (16% versus 5.2%). Unlike a previous study (Ann Oncol., 2019 30:1071-1079), the majority of the BRCA-like BCs were ER+ with no evidence of a VUS in a known HBC gene suggesting these are driven by novel germline or somatic mutations in genes involved in DNA HR repair.

PO2-09-03

Twenty-one gene recurrence scores in individuals with breast cancer associated with PALB2 germline pathogenic variants

Presenting Author(s) and Co-Author(s):

P. Shah. Penn Medicine, Philadelphia, Pennsylvania, United States

S. Yadav. Mayo Clinic, Rochester, Minnesota, United States

J. Brower. Bassett Center for BRCA, Abramson Cancer Center, University of Pennsylvania, United States

J. Hamilton. Memorial Sloan Kettering Cancer Center, United States

E. Simmons. Bassett Center for BRCA, Abramson Cancer Center, University of Pennsylvania, United States

J. Garber. Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Division of Cancer Genetics and Prevention, Dana-Farber Cancer Institute, United States

K. Offit. Memorial Sloan Kettering Cancer Center, United States

M. Robson. Memorial Sloan Kettering Cancer Center, New York, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

S. Domchek. University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, United States

Background: The 21-gene recurrence score assay (Oncotype DX, Genomic Health Inc., CA) is prognostic, quantifies predicted benefit of adjuvant chemotherapy, and informs clinical decisions for patients with early-stage, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer (BC). Differences in Oncotype recurrence scores (RS) in individuals with and without BRCA1 and BRCA2 (BRCA1/2) pathogenic variants (PV) have been demonstrated, but the results of this assay in patients with BC and germline PALB2 PV have not previously been described. This is of particular relevance as PALB2 BC has demonstrated biologic features similar to BRCA1/2 BC such as poly(adenosine diphosphate ribose) polymerase inhibitor (PARPi) sensitivity. Methods: Patients with early-stage, HR+, HER2-, invasive breast cancer and a germline PALB2 PV were ascertained from academic cancer center databases and the Prospective Registry of MultiPlex Testing (PROMPT), an online research registry for individuals who have had multigene panel testing for inherited cancer susceptibility. Study participants (pts) were categorized by age < 50 and ≥50. Oncotype DX RS were retrospectively reviewed and categorized as those that would and would not warrant consideration of chemotherapy (≥16 and < 16, respectively, for pts < 50; ≥26 and < 26, respectively, for pts ≥50). Yates corrected Chi-square tests were used to compare RS distributions between carriers and a previously published genetically unselected reference population. Results: Oncotype DX reports were reviewed for 20 pts with BC and germline PALB2 PV. Median RS was 19 (range 6-41) overall. Four patients were diagnosed under the age of 50 (range 33-48); median RS for these individuals was 19 (range 12-41). Sixteen patients were diagnosed at age 50 or greater (median 59, range 50-70); median RS for these individuals was also 19 (range 6-31). Compared to the genetically unselected reference population, Oncotype DX RS in pts with PALB2-associated BC demonstrated a numerical but not statistically significant shift in distribution towards categories in which chemotherapy would be considered. Among pts under the age of 50, 75% had Oncotype DX RS for which chemotherapy would be considered and 25% had Oncotype DX RS for which endocrine

therapy alone would likely be recommended (p=0.726 compared to reference). Among pts aged 50 and older, 25% had Oncotype DX RS for which chemotherapy would be considered and 75% had Oncotype DX RS for which endocrine therapy alone would likely be recommended (p=0.579 compared to reference). Conclusions: Compared to data from the published genetically unselected commercial database, BC associated with PALB2 PV may have higher Oncotype DX RS reflective of intrinsically less favorable biology and greater therapeutic sensitivity. Larger datasets are forthcoming to confirm presence of significant differences in Oncotype DX RS distributions between BC with and without PALB2 PV.

Table 1. Oncotype DX RS distribution by age among pts with gPALB2 PV and genetically unselected reference

Genetic group	PALB2 (n=20)		Genetically unselected reference* (n=799,986)	
	<50 (n=4)	≥50 (n=16)	<50 (n=163,912)	≥50 (n=636,074)
RS, median (range)	19 (12-41)	19 (6-31)	n/a	n/a
RS < 16 (n,%)	1 (25)	-	75,727 (46.2)	-
RS ≥ 16 (n,%)	3 (75)	-	88,020 (53.7)	-
RS < 26 (n,%)	-	12 (75)	-	529,850 (83.3)
RS ≥ 26 (n,%)	-	4 (25)	-	106,224 (16.7)

*Jakubowski et al., J Surg Oncol 2020. PMID 3249731

PO2-09-04

Changes in an artificial intelligence model score for breast cancer detection (Transpara) with tamoxifen and aromatase inhibitor treatment

Presenting Author(s) and Co-Author(s):

Y. Wang. Mayo Clinic, United States

C. Scott. Mayo Clinic, United States

M. Jensen. Mayo Clinic, United States

D. Hursh. Mayo Clinic, United States

K. Brandt. Mayo Clinic, United States

A. Norman. Mayo Clinic, Rochester, Minnesota, United States

F. Wu. Mayo Clinic, United States

S. Winham. Mayo Clinic, United States

K. Kerlikowske. University of California, San Francisco, United States

C. Vachon. Mayo Clinic, Rochester, Minnesota, United States

Artificial intelligence (AI) models applied to mammography have been shown to improve breast cancer (BC) detection and risk estimation. The Transpara AI detection system has been associated with short and longer-term risk of invasive BC. Whether Transpara can identify changes in the breast associated with tamoxifen (TAM) and aromatase inhibitor (AIs) treatment is unknown. We compare changes in the Transpara malignancy score in the unaffected breast of BC cases using TAM or AIs to those of untreated women without cancer.

Cases and controls were sampled from the Mayo Clinic Rochester Breast Screening Practice. Eligible cases were women with breast cancer treated with TAM and/or AIs for at least 8 months who had full field digital (FFDM) mammograms within two years prior to start of treatment (pretreatment mammogram). Controls did not have BC, were not using TAM, AIs, or postmenopausal hormones, and had at least two FFDM screening mammograms. Transpara scores (1-10) were calculated for the contralateral breast in cases and a randomly selected side for controls. Two controls were matched to each case on menopausal status at both mammograms, time between mammograms (< 6 months) and baseline Transpara score (± 2 units).

Conditional logistic regression was used to assess the association of treatment (case (TAM/AIs) vs. control) with change in Transpara score between the pretreatment mammogram and the mammogram taken closest to 13 months later. Change was classified as having a decrease in Transpara score between the two mammograms vs. no change or an increase. Models were adjusted for age and Transpara score at pretreatment mammogram, and time between the two mammograms. We performed analyses on all women combined and stratified by time on treatment, menopausal status, and treatment type (TAM vs. AIs).

A total of 134 cases were identified, with 53 on TAM (21 premenopausal and 32 postmenopausal) and 81 on AIs (postmenopausal); 268 controls were matched to the cases. Characteristics of the study population are summarized (Table). Most case mammograms were obtained within six months prior to treatment start [median 2.63 months (interquartile range (IQR), 1.62, 5.72)] and median time on TAM/AIs was 10.9 months (IQR, 8.03, 16.6) at time of second mammogram. The median absolute change in Transpara score between the two

mammograms was similar in cases [0 (IQR, -2, 1)] vs. controls [0 (IQR, -1.25, 1)]; 40.3% of cases and 39.2% of controls had any decrease. Conditional logistic models found no evidence for an association between TAM/AIs and decrease in Transpara score [odds ratio (OR) = 1.07; 95% confidence interval (CI), 0.65, 1.78]. When stratified by median time on treatment (10.9 months), there was suggestion of a stronger association for those on treatment for a longer duration (OR = 1.21; 95% CI, 0.61, 2.40 for >10.9 months vs. OR = 0.96; 95% CI, 0.43, 2.13 for < 10.9 months) but these results were not statistically significant. Similarly, odds ratios were stronger in postmenopausal (OR = 1.18; 95% CI, 0.67, 2.07) compared to premenopausal (OR = 0.91; 95% CI, 0.24, 3.45) women, and for AIs (OR = 1.21, 95% CI, 0.64, 2.29) vs. TAM (OR = 0.93; 95% CI, 0.39, 2.22) but none of these results reached statistical significance.

In summary, we found no association between treatment with TAM/AIs and change in Transpara score. However, our study had limited power. Also, longer time on treatment as well as investigation of AI-based scores trained directly to assess BC risk may be necessary to identify relevant changes.

		Treatment (n = 134)	Control (n = 268)
		median (Q1, Q3)	median (Q1, Q3)
Age at index mammogram (years)		63.5 (55, 70)	62.5 (54, 70)
Age at diagnosis (years)		63.8 (55, 70)	N/A
Months between two mammograms		13.3 (12.2, 21.4)	13.3 (12.2, 21.9)
Months between pretreatment mammogram and start of treatment		2.63 (1.62, 5.72)	N/A
Months between pretreatment mammogram and diagnosis		0.10 (0.03, 0.26)	N/A
Months on treatment at second mammogram		10.9 (8.03, 16.6)	N/A
Transpara score at pretreatment mammogram		5 (2, 7.75)	5 (2, 7)
mean (SD)		4.87 (3.02)	4.84 (3.01)
Transpara score at second mammogram		4 (2, 7)	4 (2, 7)
mean (SD)		4.60 (2.99)	4.49 (2.91)
Change in Transpara score		0 (-2, 1)	0 (-1.25, 1)
mean (SD)		-0.26 (2.92)	-0.35 (2.82)
		n (%)	n (%)
Treatment type	TAM	53 (39.6%)	N/A
	AIs	81 (60.4%)	N/A
Menopausal status	Premenopausal	21 (15.7%)	42 (15.7%)
	Postmenopausal	113 (84.3%)	226 (84.3%)
Change in Transpara score	Decrease	54 (40.3%)	105 (39.2%)
	No change	36 (26.9%)	71 (26.5%)
	Increase	44 (32.8%)	92 (34.3%)

PO2-09-05

Building genomic and transcriptomic data among African American and Black patients with triple-negative inflammatory breast cancer

Presenting Author(s) and Co-Author(s):

W. Ma. The University of Texas MD Anderson Cancer Center, United States

L. Zhao. UT MD Anderson Cancer Center, United States

G. Devi. Duke University, United States

S. Krishnamurthy. MD Anderson cancer center, United States

L. Coffey. UT MD Anderson Cancer Center, United States

A. Alexander. UT MD Anderson Cancer Center, United States

M. Kai. UT MD Anderson Cancer Center, United States

X. Wang. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

H. Le-Petross. UT MD Anderson Cancer Center, United States

M. Patel. UT MD Anderson Cancer Center, United States

B. Debeb. UT MD Anderson Cancer Center, United States

C. Bartholomeusz. UT MD Anderson Cancer Center, United States

J. Zhang. UT MD Anderson Cancer Center, United States

X. Song. UT MD Anderson Cancer Center, United States

A. Futreal. UT MD Anderson Cancer Center, United States

N. Ueno. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

R. Layman. UT MD Anderson Cancer Center, United States

A. Lucci. UT MD Anderson Cancer Center, United States

J. Wang. UT MD Anderson Cancer Center, United States

W. Woodward. UT MD Anderson Cancer Center, Houston, Texas, United States

Background: Inflammatory breast cancer (IBC) is an aggressive breast cancer associated with poor response and early metastases. It represents a health disparity, with higher incidence and worse outcomes in Black compared to White patients. Further, IBC is enriched for the more aggressive triple-negative receptor subtype, TN-IBC, and this subtype is more prevalent among Black IBC patients. It is critical to identify genetic and molecular features that may guide better treatments for these aggressive cancers across races, and thus imperative to identify and increase racial representation among bioinformatics datasets. We previously performed comprehensive genomic and transcriptomic analyses for TN-IBC patient samples and here examine the differences among self-identified African American or Black (AA/B) and other races among IBC patients. Methods: As previously described, we collected matched blood and baseline tumor samples before treatment from 19 patients with primary TN-IBC. We performed whole exome and RNA sequencing (RNA-Seq) on these samples and compared mutations and differentially expressed genes (DEGs). Results were compared between 3 AA/B patient tissues vs the remaining 16 (Other) cases. Results: Mutations shared by all AA/B patients included amplification of the five most commonly mutated hallmark genes in the complete cohort, ARNT, BCL9, DDR2, FCGR2B and LMNA (all 100% in AA/B patients versus all 50% in the Other cohort). All AA/B patients had a Notch1 mutation (two deletions and one missense mutation, 100% AA/B vs 6% Other (one deletion)). Comparing differentially expressed genes and gene

set enrichment analyses of the Broad molecular signatures database (MSigDB) demonstrates the majority of DEGs are downregulated in these AA/B patients. Six of the top 20 downregulated gene sets from the MSigDB C2 group relate to breast cancer subtype and among this TNIBC cohort AA/B tumor expression was downregulated for luminal and normal subtype related genes in multiple gene sets and enriched in the Linn metaplastic related genes. In the MSigDB C5 sets, over half of the top 20 enriched gene ontology sets among AA/B patients related to chromosomes, chromatin, spindle assembly or histone binding, while 16 of the top 20 downregulated enriched sets related to immune function. Multiple KEGG pathways enriched in AA/B cases related to RNA processing and expression and DNA replication and repair. Lastly, hallmark gene sets enriched in AA/B patients were cell cycle related, and targets of Myc, Hedgehog, B-catenin, TGF β , and TNF α via NF κ B, while top significantly downregulated sets related to metabolism and immune response. Conclusion: While findings from a small sample size can only be considered hypothesis generating, some patterns emerge from the data among this rare cohort of AA/B TN IBC patients. These tumors appear to be devoid of luminal signals, characterized by cell cycle and chromatin remodeling signals, enriched for signaling typical of stem cell self-renewal, and perhaps more immune-deprived than other TN-IBC. Additional work to build racially diverse IBC transcriptomic data are needed to develop strategies to understand and improve outcomes for these patients.

PO2-09-06

Interaction of racial disparities on outcomes and toxicities associated with treatment of HER2+Breast Cancer- a TrinetX Database study

Presenting Author(s) and Co-Author(s):

M. Vasekar. Penn State Cancer Institute, United States

J. Petucci. Institute for computer and data science and CTSI, United States

A. Katoch. Clinical and Translational Sciences Institute, United States

V. Honavar. Institute for computational and data sciences, United States

Objective: Investigate the interaction of racial disparities on outcomes and toxicities associated with treatment of HER2+BrCa (Breast Cancer)- a TrinetX Database study Background: HER2+BrCa is an aggressive subtype accounting for about 1/3rd of all BrCa, for which Trastuzumab based therapy remains the mainstay of treatment. While we are starting to understand the breadth of racial disparities in BrCa, the knowledge about outcomes and toxicities in relation to treatment of HER2+ BrCa is still limited. Design/Methods: In this propensity score-matched cohort study we used the TriNetX Research Network, a multi-health care organization de-identified electronic health record (EHR) database, to compare the 1-, 3-, and 5-year mortality of HER2+BrCa non-Hispanic African American (NHAA) women to a corresponding non-Hispanic White cohort (NHW). Qualification into the two race based HER2+BrCa cohorts required the presence of a C50 ICD-10-CM diagnosis code and at least one proxy for HER2 positivity such as Trastuzumab administration (index event). Cohorts were matched for age, BMI, comorbidities (HTN, DM), and lab values using 1:1 matching with a greedy nearest neighbor search. Toxicity outcomes of interest such as cardiomyopathy, neuropathy, diarrhea, rashes, leg swelling/edema, and fatigue as well as the frequency of emergency room visits were also compared between the cohorts. The associations of observed outcome frequencies in the two cohorts were tested for significance using the chi-square test. The odds ratios and p-values, corrected for multiple hypothesis testing using the Benjamini-Hochberg procedure, are reported as an effect size and significance estimation. Results: 15983 patients met the inclusion criteria for HER2+BrCa (13611-NHW and 2372-NHAA). The mean age at the index event was 55.6 ± 12.6 years for NHAA and 57.2 ± 13.3 years for NHW. After matching the two sub-cohorts, 2303 patients remained in each. NHAA women were found to have significantly increased odds of neuropathy and cardiomyopathy for 1, 3, and 5-year time intervals after the HER2+BrCa index date, as compared to the reference NHW women (abbreviated results given in Table 1). In addition, the odds of an emergency room visit (for any reason) was found to be increased by as much as 79% in NHAA women as compared to the NHW women. The odds of experiencing fatigue/malaise, diarrhea/nausea, and rash, were reduced for NHAA women across all time intervals investigated. Odds ratios for mortality and leg swelling did not meet the significance threshold (p -value < 0.05). Conclusion: This study, which examined racial disparities in outcomes and toxicities associated with HER2+BrCa, revealed significant findings. NHAA women with HER2+BrCa treated with Trastuzumab based therapy demonstrated increased odds of experiencing neuropathy and cardiomyopathy compared to their NHW counterparts. Additionally, NHAA women had a higher likelihood of emergency room visits for any reason. Conversely, NHAA women exhibited decreased odds of fatigue/malaise, diarrhea/nausea, and rash. These findings underscore the importance of considering the impact of race on HER2+BrCa outcomes and treatment toxicities and suggest the need for further research and targeted interventions to address disparities and thus enhance treatment outcomes in diverse populations.

Table 1: Representative significant Odds ratios and corrected p-values for outcomes comparing the NHAA and NHW cohorts.

Outcome	Odds Ratio		
	95% CI	1%	5%
Depression	-	1.25 (0.000)	1.07 (0.000)
Substance Use	-	1.08 (0.000)	1.04 (0.000)
SAHSA	1.07 (0.000)	1.06 (0.000)	-
Algebra	1.06 (0.000)	1.06 (0.000)	-
Reading/Writing	1.05 (0.000)	1.05 (0.000)	-
Math	1.05 (0.000)	1.05 (0.000)	-

PO2-09-07

Neighborhood Disadvantage and Social Adversity in Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

A. Hernandez. Sylvester Comprehensive Cancer Center, University of Miami Health System, United States

M. Lubarsky. University of Miami Miller School of Medicine, United States

S. Kesmodel. University of Miami DeWitt Daughtry Dept. Surgery, United States

M. Antoni. University of Miami, United States

N. Goel. University of Miami Department of Surgery, United States

Introduction: Neighborhood disadvantage has been shown to independently predict breast cancer specific survival even after considering access to care barriers. This effect may be explained in part by biologic influences of the neighborhood environment on breast tumors. Social genomics literatures posits that this relationship is mediated by chronic stress in the form of social adversity, i.e. disadvantaged neighborhoods may be leading to increased stress for patients which in turn may effect tumor biology. Our objective in this study was to link a measure of patient-reported neighborhood specific stress with an objective and widely used measure of neighborhood disadvantage, the Area Deprivation Index (ADI). Methods: In this prospective cohort study patients with stage I-IV breast cancer completed survey questions from a validated Neighborhood Social Environment Adversity Survey (NSEAS) to measure perceived stress caused by their environment. Questions included both 5-item and 4-item Likert scale answer choices with higher scores indicating higher stress. Responses were standardized into Z-scores and composite and subscale scores were calculated by summation. Subscales included threat to safety, social cohesion, and aesthetic quality. Survey questions demonstrated good reliability with a Cronbach's α of 0.72. Cohort addresses were used to determine the ADI, a continuous measure from 1-10 with higher scores indicating more disadvantage. Hierarchical linear regression was used to assess the relationship between ADI and NSEAS composite and subscale scores while controlling for covariates. Results: 380 breast cancer patients completed the NSEAS 61.6% were Hispanic, 17.0% were Non-Hispanic White, and 21.4% were Non-Hispanic Black. Mean age (SD) was 56 (12) years. Mean (SD) ADI was 4 (3). On univariate analysis, we found that ADI significantly predicts NSEAS composite and subscale scores (Composite $\beta = 0.63$, $t=5.68$, $p < 0.001$; Threat to Safety $\beta = 0.18$, $t=5.07$, $p < 0.001$; Social Cohesion $\beta = 0.19$, $t=3.35$, $p < 0.001$; Aesthetic Quality $\beta = 0.15$, $t=4.20$, $p < 0.001$). After controlling for age, race, ethnicity, highest education level, patient insurance, and annual household income, we found that ADI continued to significantly predict levels of NSEAS (Composite $\beta = 0.48$, $t=4.02$, $p < 0.001$; Threat to Safety $\beta = 0.14$, $t=3.57$, $p < 0.001$; Social Cohesion $\beta = 0.14$, $t=2.34$, $p=0.02$; Aesthetic Quality $\beta = 0.12$, $t=3.09$, $p=0.002$). Conclusion: In our novel study, we found that higher levels of neighborhood disadvantage independently predict higher levels of perceived neighborhood stress in breast cancer patients. Because of the known detrimental effects of both chronic stress and neighborhood disadvantage on health, understanding the specific factors of stress caused by neighborhood-level social adversity can help define targetable areas of intervention for future studies. These findings contribute to current literature on how and why neighborhood disadvantage leads to worse breast cancer outcomes.

Table 1. Hierarchical Regression Illustrating Relationship between Neighborhood Disadvantage and Patient-Reported Neighborhood Social Environment Adversity Survey Scores

Table 1. Hierarchical Regression Illustrating Relationship between Neighborhood Disadvantage and Patient-Reported Neighborhood Social Environment Adversity Survey Scores

	Neighborhood Social Environment Adversity Survey Scores				
	Unstandardized			Standardized	
	β	SE	B [95% CI]	Beta	p
Composite					
ADI	0.48	0.12	[0.25, 0.72]	0.23	<0.001
Age at Diagnosis	-0.01	0.03	[-0.05, 0.04]	-0.01	0.82
Race/Ethnicity	0.86	0.38	[0.12, 1.60]	0.12	0.02
Insurance Status	-0.38	0.29	[-0.96, 0.20]	-0.07	0.19
Highest Education	-0.62	0.29	[-1.19, -0.05]	-0.12	0.03
Household Income	-0.63	0.21	[-1.05, -0.22]	-0.17	0.003
Threat to Safety					
ADI	0.14	0.04	[0.06, 0.21]	0.21	<0.001
Age at Diagnosis	-0.01	0.01	[-0.02, 0.01]	-0.04	0.43
Race/Ethnicity	0.12	0.12	[-0.12, 0.35]	0.05	0.33
Insurance Status	-0.10	0.09	[-0.29, 0.08]	-0.06	0.26
Highest Education	-0.05	0.09	[-0.23, 0.13]	-0.03	0.61
Household Income	-0.24	0.07	[-0.37, -0.11]	-0.21	<0.001
Social Cohesion					
ADI	0.14	0.06	[0.02, 0.26]	0.14	0.02
Age at Diagnosis	0.00	0.01	[-0.02, 0.03]	0.01	0.83
Race/Ethnicity	0.50	0.19	[0.11, 0.88]	0.14	0.01
Insurance Status	-0.12	0.15	[-0.41, 0.18]	-0.05	0.44
Highest Education	-0.20	0.15	[-0.49, 0.09]	-0.08	0.18
Household Income	-0.21	0.11	[-0.43, 0.00]	-0.12	0.05
Aesthetic Quality					
ADI	0.12	0.04	[0.04, 0.19]	0.18	0.002
Age at Diagnosis	0.00	0.01	[-0.02, 0.01]	-0.02	0.70
Race/Ethnicity	0.05	0.12	[-0.19, 0.29]	0.02	0.70
Insurance Status	-0.01	0.09	[-0.19, 0.18]	-0.01	0.94
Highest Education	-0.18	0.09	[-0.36, 0.00]	-0.11	0.06
Household Income	-0.04	0.07	[-0.17, 0.09]	-0.04	0.55

Composite: Total Model $R^2 = 0.14$, $F(6, 323) = 8.96$, $p < 0.001$; adjusted $R^2 = 0.13$
 Threat to Safety: Total Model $R^2 = 0.12$, $F(6, 323) = 6.98$, $p < 0.001$; adjusted $R^2 = 0.10$
 Social Cohesion: Total Model $R^2 = 0.07$, $F(6, 326) = 4.08$, $p < 0.001$; adjusted $R^2 = 0.05$
 Aesthetic Quality: Total Model $R^2 = 0.06$, $F(6, 326) = 3.72$, $p < 0.001$; adjusted $R^2 = 0.05$

Note: SE = Standard Error; CI = Confidence Interval; ADI = Area Deprivation Index

PO2-09-08

Biological and non-biological predictors of breast cancer disease-free survival among young Black females

Presenting Author(s) and Co-Author(s):

S. Reid. Vanderbilt-Ingram Cancer Center, United States

R. Fan. Vanderbilt University Medical Center, United States

L. Venton. Vanderbilt University Medical Center, United States

A. Weidner. Vanderbilt University Medical Center, United States

A. Tezak. Vanderbilt University Medical Center, United States

M. Roberson. University of North Carolina, United States

S. Vadaparampil. Moffitt Cancer Center, Tampa, Florida, United States

X. Wang. Moffitt Cancer Center, United States

S. Yoder. Moffitt Cancer Center, United States

M. Rosa. Moffitt Cancer Center, United States

J. Hirbo. Vanderbilt University Medical Center, United States

J. Whisenant. Vanderbilt University Medical Center, United States

J. Pietenpol.

S. Rajagopal. Cancer Data Sciences Laboratory, Center for Cancer Research, National Cancer Institute, Bethesda, MD, United States

B. Lehmann. Vanderbilt University Medical Center, Nashville, Tennessee, United States

F. Ye. Vanderbilt University Medical Center, United States

T. Pal. Vanderbilt University Medical Center, United States

Introduction: Young Black females bear a disproportionate burden of breast cancer (BC) deaths compared to White females yet remain underrepresented in clinical studies. We sought to discover predictors of disease-free survival (DFS) in a cohort of young Black females with BC.

Methods: Black females diagnosed with invasive BC \leq age 50 from 2005 to 2016 were recruited through the Florida and Tennessee state cancer registries. Participants were asked to complete a questionnaire, medical records release, and tissue/tumor release. Saliva was also requested for germline DNA extraction. For the primary outcome of BC DFS, univariate analyses were conducted using the following variables: proportion of West African ancestry, RNA expression based on PAM50 analyses, body mass index (BMI), social determinants of health (i.e., employment and insurance), immunohistochemistry (IHC) subtype, treatment category (i.e., chemotherapy, radiation, and surgery), and BC family history. Multivariate analyses were conducted using backward selection among these variables to analyze in the reduced model.

Results: Of 701 consented, 687 participants with early-stage disease were included in the analysis; 14 participants with stage 4 disease at diagnosis were excluded. Among the 687 participants, the median age at diagnosis was 44, 28% had triple-negative breast cancer (TNBC), 13% were deceased, and 5% had recurrent disease. Clinically, participants with TNBC and lymph node involvement had worse BC DFS ($p=0.001$ and $p=0.0002$, respectively). Socio-economically, full-time employment was associated with higher BC DFS ($p=0.0003$). Among those for whom global ancestry data were available ($n=551$), multivariate analysis showed an

association between increased percent of West African ancestry and worse BC DFS with HRIQR=1.23*, which approached significance ($p=0.085$). Additional subgroup analyses among those with hormone receptor-positive (HR+) (estrogen and/or progesterone receptor positive) BC ($n=431$) showed that participants with private insurance had better BC DFS (HR=0.45; $p=0.05$), while those with lymph node involvement had worse BC DFS (HR=2.07; $p=0.001$). Among HR+ participants with available ancestry data ($n=349$), worse BC DFS was associated with increased West African ancestry ($p=0.05$) and lymph node involvement ($p=0.08$). When ancestry was included in the model, private insurance was no longer associated with BC DFS in this HR+ subgroup ($p=0.31$). Other predictors analyzed did not reach statistical significance.

Conclusion: Our findings confirm prior established adverse predictors of BC DFS, such as TNBC with lymph node involvement and the protective effect of full-time employment. We also found a novel association with West African ancestry among patients with HR+ breast cancer. Although further large-scale studies are needed, results from this cohort of young Black females with BC and highlight the critical need to support research to understand biological and non-biological factors contributing to BC DFS and develop targeted strategies to improve survival outcomes.

* HRIQR is the ratio of hazard rates corresponding to upper and lower quartiles of percent West African (interquartile range (IQR): 70.0%-80.8%).

PO2-09-09

Racial/Ethnic Differences in Survival of Male Patients with Stage I-III Breast Cancer by Hormone Receptor Status Using Real-World Data

Presenting Author(s) and Co-Author(s):

J. Freeman. Department of Public Health Sciences, University of Chicago, Chicago, Illinois, United States

J. Hara. The University of Hawai'i Cancer Center, Honolulu,, Hawaii, United States

O. Omoleye. Center for Clinical Cancer Genetics and Global Health, The University of Chicago, Chicago, Illinois, United States

J. Li. Department of Public Health Sciences, University of Chicago, United States

W. Guo. Department of Medicine, The University of Chicago, Chicago, Illinois, United States

Background: Male breast cancer (BC) is rare and accounts for < 1.0% of all BCs in the US. Given its rarity and limited data, racial/ethnic differences in survival outcomes among men with early-stage BC (EBC) at the national level have not been well studied. In this study, we sought to estimate 5-year survival rates and assess how overall survival (OS) in male patients (pts) with EBC differed by race/ethnicity and by hormone receptor (HR) status.

Methods: Data were obtained from male pts with stage I-III BC in the 2004-2019 National Cancer Database (NCDB). Racial/ethnic groups included Asian or Pacific Islander (API), Black, Hispanic, and White. HR status was dichotomized as "negative/positive." The Kaplan-Meier method was used to estimate 5-year OS by race/ethnicity and comparisons were made using log-rank tests. OS, defined as death or censored from the date of diagnosis to the date of death or last contact, was modeled using a multivariable Cox regression, as well as stratified by HR status. Cox models were adjusted for sociodemographic and clinicopathologic factors.

Results: Of 22,340 pts, 56.4% were aged ≥ 65 years; 81.7% were White, 12.4% Black, 3.7% Hispanic, and 2.3% API; 94.3% had HR-positive tumors. 5-year OS rates were greater in API (84.5%) and Hispanic (84.2%) pts as compared with 5-year OS of White pts (77.2%); however, Black pts had a lower rate of 5-year OS (73.4%) ($p < .001$). Similar findings of estimated 5-year OS rates were observed across racial/ethnic groups stratified by HR status (Table). After adjusting for clinicopathologic factors, Black pts had a higher mortality risk than White pts (adjusted hazard ratio [aHR]=1.13, 95% CI: 1.01-1.25), while Hispanic (aHR=0.65, 95% CI: 0.51-0.85) and API (aHR=0.62, 95% CI: 0.45-0.86) pts had a lower risk of death than white pts. After further adjusting for sociodemographics, there was no significant OS difference between Black and White pts (aHR=0.98, 95% CI: 0.87-1.11); OS rates remained significantly higher in API (aHR=0.69, 95% CI: 0.50-0.96) and Hispanic (aHR=0.60, 95% CI: 0.46-0.79) pts than in White pts. Additionally, pts with a median household income of \$50,354-63,332 (aHR=0.86, 95% CI: 0.75-0.99) or of \geq \$63,333 (aHR=0.74, 95% CI: 0.64-0.86) had a lower risk of dying than those of < \$40,227. Uninsured pts (aHR=1.54, 95% CI: 1.12-2.12) or pts with public insurance (Medicare: aHR=1.54, 95% CI: 1.36-1.75; Medicaid: aHR=1.41, 95% CI: 1.13-1.77) had a higher risk of dying than privately insured pts. In the HR-positive cohort, similar mortality risks between racial/ethnic minoritized and White pts were observed (Table). However, in the HR-negative cohort, after adjusting for sociodemographic and clinicopathologic factors, API pts had a greater risk of death than White pts (aHR=2.75, 95% CI: 1.25-6.03); Black pts also had a higher mortality risk than White pts, though it was not statistically significant (aHR=1.37, 95% CI: 0.87-2.14).

Conclusions: In this large retrospective cohort of male EBC pts, API and Hispanic pts had higher OS than White pts. Higher income and private health insurance were associated with greater OS. Black pts had lower OS than their White counterparts when controlling for clinicopathologic factors; however, the difference was not significant after further controlling for sociodemographics. Addressing socioeconomic disparities and inequities that impact access to health care and services may help improve survival outcomes across racial/ethnic groups of male EBC pts.

Table. Racial and ethnic differences in overall survival of male patients with stage I-III breast cancer

Table. Racial and ethnic differences in overall survival of male patients with stage I-III breast cancer					
Race/Ethnicity	5-Year OS, % (95% CI)	aHR (95% CI)	P value	aHR (95% CI)	P value
All patients					
NH White	77.2 (76.6-77.9)	1.0 (reference)		1.0 (reference)	
NH Black	73.4 (71.5-75.2)	1.13 (1.01-1.25)^a	0.031	0.98 (0.87-1.11) ^b	0.766
NH Asian or Pacific Islander	84.5 (80.5-87.7)	0.62 (0.45-0.86)^a	0.004	0.69 (0.50-0.96)^b	0.028
Hispanic	84.2 (81.1-86.8)	0.65 (0.51-0.85)^a	0.001	0.60 (0.46-0.79)^b	<0.001
HR-positive					
NH White	77.8 (77.0-78.4)	1.0 (reference)		1.0 (reference)	
NH Black	74.2 (72.2-76.1)	1.12 (1.00-1.25)^a	0.046	0.96 (0.85-1.09) ^b	0.566
NH Asian or Pacific Islander	86.5 (82.3-89.7)	0.52 (0.36-0.74)^a	<0.001	0.59 (0.41-0.85)^b	0.004
Hispanic	85.3 (82.1-88.0)	0.68 (0.52-0.88)^a	0.003	0.60 (0.46-0.80)^b	<0.001
HR-negative					
NH White	74.3 (71.1-77.2)	1.0 (reference)		1.0 (reference)	
NH Black	66.5 (59.3-72.7)	1.37 (0.92-2.02) ^a	0.118	1.37 (0.87-2.14) ^b	0.171
NH Asian or Pacific Islander	64.8 (46.8-78.1)	2.14 (1.06-4.29)^a	0.033	2.75 (1.25-6.03)^b	0.012
Hispanic	81.8 (67.5-90.2)	0.60 (0.22-1.65) ^a	0.325	0.65 (0.23-1.88) ^b	0.429

Abbreviations: HR, hormone receptor; NH, non-Hispanic; aHR, adjusted hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; HER2, human epidermal growth factor receptor 2.

^a Adjusted for age, Charlson-Deyo comorbidity score, histologic type, molecular subtype, AJCC clinical TN stage, and tumor grade.

^b Adjusted for age, percent no high school degree quartile, median household income quartile, type of health insurance, distance from residence to hospital, Charlson-Deyo comorbidity score, histologic type, molecular subtype, AJCC clinical TN stage, and tumor grade.

^c Adjusted for age, Charlson-Deyo comorbidity score, histologic type, HER2 status, AJCC clinical TN stage, and tumor grade.

^d Adjusted for age, percent no high school degree quartile, median household income quartile, type of health insurance, distance from residence to hospital, Charlson-Deyo comorbidity score, HER2 status, histologic type, AJCC clinical TN stage, and tumor grade.

PO2-09-10

Addressing Breast Cancer Disparities: Co-Creating Digital Interventions with Patients, Navigators & the Community to Address Social Determinants of Health in the Memphis Statistical Area

Presenting Author(s) and Co-Author(s):

G. Vidal. The West Clinic, Germantown, United States, United States

S. Tinianov. Advocates for Collaborative Education, Santa Cruz, California, United States

A. Kelly. Rabble Health, United States

A. Curry. West Cancer Center, United States

C. Baker. UHESS, United States

Abstract Background: The Memphis Statistical Area, which covers counties in Arkansas, Mississippi, and Tennessee, leads in disparities in mortality rates between Black breast cancer patients compared to White counterparts¹. Urban Health Education & Support Services (UHESS), in partnership with RabbleHealth, and West Cancer Center & Research Institute (WCCRI), initiated a solutions-oriented, community-based scalable initiative in January 2023 to measurably address social determinants of health (SDOH), which often drive cancer inequities that disproportionately impact individuals of marginalized communities. By leveraging a community-driven, co-creation sustainable approach, the team sought to measurably improve breast cancer equality utilizing digital enablement and the knowledge of local breast cancer survivors and leading healthcare professionals, including navigators. **Methods:** A four-phase approach was leveraged to 1. improve access to locally available breast cancer services in communities that are traditionally underserved and 2. measure the public health impact against root causes of breast inequities (i.e., care pathway metrics), and 3. create a repeatable, scalable model to expand to other underserved communities. In Phase 1, UHESS leveraged the Mid-South Regional Breast Cancer Coalition, which convenes ten local breast cancer patient advocacy organizations, to recruit focus groups for co-creation throughout all phases of the initiative. The working group consisted of eight representatives from a variety of Memphis-based cancer organizations, faith-based organizations, navigator programs, and WCCRI. This phase centered around establishing trust with the local patient advocacy community. In Phase 2, an initial patient survey was circulated to identify key resources that reduce health inequities and barriers to access. Human-centered design facilitators supported a series of Listen & Learn workshops with patients to convey root causes of gaps in access to relevant services and with navigators to understand professional needs of navigators and scale the ability improve patient access to resources. To co-create a solution, facilitated patient and navigator workshops were held in Phase 3 to gather patient-centric user experience and design enhancements for a digital patient engagement app. These requirements as well as navigator-defined metrics needs were digitized and organized by SDoH. Phase 4, the Deploy & Measure phase, will begin in September of 2023 and the community-based deployment model focuses on three drivers including: (a) embedding within navigator workflow, (b) activating faith-based organizations, and (c) leveraging societies. Health equity performance data will be analyzed weekly to rapidly target those ZIP codes with the greatest need. **Results:** Co-design efforts included over 50 members of the Greater Memphis community and final initiative results will be presented at the meeting. Planning for further research regarding community impact and model scalability is already underway. **Conclusion:** By leveraging a community-driven, co-creation sustainable approach, this model enables a better way to measurably improve breast cancer equality utilizing digital enablement and the knowledge of local breast cancer survivors and leading healthcare professionals, including navigators. **Initiative Funding Acknowledgements:** Gilead

Life Sciences & Blue Cross Blue Shield of Tennessee Foundation 1. Vidal G, Bursac Z, Miranda-Carboni G, White-Means S, Starlard-Davenport A. Racial disparities in survival outcomes by breast tumor subtype among African American women in Memphis, Tennessee. *Cancer Med.* 2017 Jul;6(7):1776-1786. doi: 10.1002/cam4.1117. Epub 2017 Jun 14. PMID: 28612435; PMCID: PMC5504313.

PO2-09-11

Breast Cancer Care Disparities in Sexual Minority Women: An Analysis of the National Institutes of Health All of Us Research Program

Presenting Author(s) and Co-Author(s):

L. Houser. College of Medicine, University of Nebraska Medical Center, United States

C. Dougherty. Division of Surgical Oncology, Department of Surgery, University of Nebraska Medical Center, United States

S. Figy. Division of Plastic Surgery, Department of Surgery, University of Nebraska Medical Center, United States

J. Maxwell. Division of Surgical Oncology, Department of Surgery, University of Nebraska Medical Center, United States

J. Santamaria-Barria. Division of Surgical Oncology, Department of Surgery, University of Nebraska Medical Center, United States

Title. Breast Cancer Care Disparities in Sexual Minority Women: An Analysis of the National Institutes of Health All of Us Research Program **Background.** Currently, sexual orientation data is not collected, nor is the language to study sexual orientation data defined by any national cancer database. Due to this limitation, little is known about breast cancer (BC) disparities in sexual minority women (SMW) despite several studies showing increased lifestyle risk factors. Our objective was to study this question in the All of Us database. **Methods.** We analyzed data from the All of Us research program, a national open enrollment database that registers diverse subjects through associated healthcare electronic medical records and collects survey data. We aimed to compare risk factors, as well as preventative and procedural healthcare utilization differences between SMW and straight women (StW) as they relate to BC care. Results were expressed as odds ratios (OR) with a 95% confidence interval [CI]. **Results.** Of 229,917 cisgender women who answered the sexual orientation question, 27,302 (11.9%) selected “non-straight orientation, prefer not to answer, or skipped” and thus were defined as SMW. In total, 6,905 (3.0%) women had received a BC diagnosis, including 423 (6.1%) SMW. SMW were less likely to have a BC diagnosis than StW (OR 0.48 [0.43-0.53]). Among all women, there were significant differences in frequency and types of visits and procedures performed. SMW women were less likely to undergo annual history and physical examination (0.79 [0.73-0.85]), mammography (0.61 [0.53-0.69]), and breast biopsy (0.55 [0.41-0.72]), as well as being less likely to undergo breast surgeries (mastectomy 0.53 [0.30-0.93]; lumpectomy 0.53 [0.38-0.74]). Survey data revealed differences in several lifestyle factors that relate to BC risk development. While StW were more likely to answer yes to being an “alcohol participant” (0.79 [0.77-0.82]), SMW reported higher rates of alcohol intake on a daily, weekly, and monthly basis, as well as being more likely to consume 6 or more drinks in one sitting. SMW also showed significantly increased history of smoking/nicotine usage. There were also significant differences in healthcare access and utilization: StW were more likely to receive health advice from a primary care provider (0.65 [0.65-0.69]), while SMW were more likely to utilize urgent and emergency care (1.44 [1.34-1.54]). SMW were also more likely to report being unable to afford care (1.82 [1.72-1.93]), medication (1.69 [1.61-1.76]), specialty care (1.98 [1.89-2.08]), and follow-up care (1.85 [1.75-1.95]), as well as to delay care due to cost concerns about the copay (2.13 [2.02-2.23]), deductible (1.64 [1.56-1.73]), paying out of pocket (1.70 [1.63-1.77]) or because they were nervous (2.80 [2.69-2.91]). SMW reported being more likely to experience healthcare discrimination based on questions about healthcare provider interactions (Table 1). **Conclusions.** Although likelihood of a breast cancer diagnosis in the All of Us database is significantly higher in StW than SMW, discrimination, lack of access, and underutilization of

preventative and screening services by SMW likely creates an underrepresentation of the true number of SMW with BC. Further studies on characteristics at diagnosis, treatments, and survival are needed to address how these disparities affect BC outcomes in SMW.

Table 1: Survey answers among sexual minority women (SMW) compared to straight women (StW) reporting on discrimination from healthcare provider interactions in the All of Us database.

Table 1: Survey answers among sexual minority women (SMW) compared to straight women (StW) reporting on discrimination from healthcare provider interactions in the All of Us database.

Question	Answer	SMW	StW	OR	Lower 95 CI	Upper 95 CI	Sig.
How often are you treated with less respect than other people when you go to a doctor's office or other health care provider?	Always	110	607	1.36	1.11	1.67	*
	Most of the time	254	645	2.97	2.57	3.44	*
	Sometimes	1730	7055	1.88	1.78	1.98	*
	Rarely	2700	19579	1.04	1.00	1.08	*
	Never	3524	36245	0.69	0.67	0.72	*
How often are you treated with less courtesy than other people when you go to a doctor's office or other health care provider?	Always	102	741	1.03	0.84	1.27	*
	Most of the time	238	641	2.80	2.41	3.25	*
	Sometimes	1649	6823	1.86	1.76	1.97	*
	Rarely	2652	19708	1.52	1.48	1.57	*
	Never	3691	36961	0.72	0.69	0.75	*
How often do you feel like a doctor or nurse is not listening to what you were saying when you go to a doctor's office or other health care provider?	Always	302	889	2.57	2.25	2.93	*
	Most of the time	937	2670	2.69	2.49	2.90	*
	Sometimes	3081	16964	1.41	1.36	1.47	*
	Rarely	2122	20651	0.76	0.72	0.79	*
	Never	1896	23189	0.59	0.56	0.62	*
How often do you receive poorer service than others when you go to a doctor's office or other health care provider?	Always	106	583	1.37	1.11	1.68	*
	Most of the time	257	578	3.36	2.90	3.89	*
	Sometimes	1484	6205	1.84	1.73	1.95	*
	Rarely	2657	18822	1.07	1.02	1.11	*
	Never	3769	37624	0.71	0.69	0.74	*
How often does a doctor or nurse act as if he or she is afraid of you when you go to a doctor's office or other health care provider?	Always	57	494	0.87	0.66	1.14	*
	Most of the time	21	97	1.63	1.01	2.61	*
	Sometimes	217	709	2.31	1.98	2.69	*
	Rarely	886	4119	1.63	1.52	1.76	*
	Never	6944	56128	0.91	0.88	0.93	*
How often does a doctor or nurse act as if he or she is better than you when you go to a doctor's office or other health care provider?	Always	168	533	2.37	1.99	2.82	*
	Most of the time	514	1341	2.91	2.63	3.22	*
	Sometimes	1997	9205	1.66	1.58	1.75	*
	Rarely	2247	17486	0.96	0.92	1.01	*
	Never	3429	35759	0.68	0.66	0.71	*
How often does a doctor or nurse act as if he or she thinks you are not smart when you go to a doctor's office or other health care provider?	Always	173	708	1.84	1.56	2.18	*
	Most of the time	406	1024	3.00	2.68	3.37	*
	Sometimes	1805	7362	1.90	1.80	2.00	*
	Rarely	2094	15036	1.01	0.97	1.06	*
	Never	3772	38764	0.69	0.67	0.71	*

SMW: sexual minority women; StW: straight women; OR: odds ratio; Lower 95 CI: lower 95% confidence interval; Upper 95 CI: upper 95% confidence interval; Sig. *: statistically significant with p < 0.05; OR>1: SMW most likely to answer; OR<1 StW most likely to answer.

SMW: sexual minority women; StW: straight women; OR: odds ratio; Lower 95 CI: lower 95% confidence interval; Upper 95 CI: upper 95% confidence interval; Sig. *: statistically significant with p < 0.05; OR>1: SMW most likely to answer; OR <1 StW most likely to answer.

PO2-09-12

The magnitude and temporal variations of socioeconomic inequalities in quality of life after early breast cancer: results from the multicentric French CANTO cohort

Presenting Author(s) and Co-Author(s):

J. Sandoval. Geneva University Hospitals, Geneva, Switzerland
A. Di Meglio. Gustave Roussy, Villejuif, France, Paris, France
A. Ferreira. Universidade Católica Portuguesa, United States
M. Franzoi. Gustave Roussy, Villejuif, France, France
F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France
B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France
C. Jouannaud. Institut Godinot, Reims, France
M. Fournier. institut Bergonié, Bordeaux, France
P. Rouanet. L'Institut du Cancer de Montpellier, Montpellier, France
A. Dhaini Mermeche. Institut de cancérologie de Lorraine - Alexis Vautrin, United States
P. Cottu. Institut Curie, Paris, Paris, Ile-de-France, France
S. Everhard. Unicancer, Paris, France, United States
A. Martin. Unicancer, Paris, France, United States
S. Stringhini. Geneva University Hospitals, Geneva, Switzerland
I. Guessous. Geneva University Hospitals, United States
I. Vaz Luis. Gustave Roussy, Villejuif, France
G. Menvielle. INSERM Unit 981—Molecular Predictors and New Targets in Oncology, Institut Gustave Roussy, Paris Saclay University, United States

Objective

Previous studies showed that various outcomes in patients with early breast cancer (EBC), from incidence to survival, were influenced by social factors. However, there is limited research on the socioeconomic inequalities in quality of life (QoL) after treatment for EBC, and the magnitude and changes over time of these inequalities have not been quantified. This study examines the socioeconomic inequalities in QoL and their time trends among a large cohort of patients with EBC.

Methods

We conducted a comprehensive longitudinal analysis using data from the prospective multicentric CANTO study (CANcer TOxicity, NCT01993498), which included participants with EBC enrolled between 2012 and 2018. QoL was assessed using the summary score of the EORTC QLQ-C30 questionnaire at the time of diagnosis and 1 and 2 years post-diagnosis. We included patients with complete QoL data at diagnosis and 2 years post-diagnosis.

Analyses were conducted for three indicators of socioeconomic status separately: self-reported financial difficulties, household income and educational level. We first analyzed trajectories of QoL by socioeconomic status from diagnosis to Year 1 and Year 2. Then, social inequalities in QoL were estimated using the regression-based slope indexes of inequality (SII) and compared across the follow-up periods. The SII represents the absolute change in the QLQ-C30 summary score along the two extremes of the socioeconomic gradient, taking into account the

intermediate groups and their relative sizes.

The analyses were adjusted for age at diagnosis, Charlson comorbidity index, disease stage, use and type of endocrine therapy, use and type of chemotherapy, breast surgery, radiotherapy use, and lymph node management.

Results

In the 5915 analyzed patients, compared to those with higher socioeconomic status, those reporting a high level of financial difficulty, lower income, or lower education were younger, most often premenopausal, with comorbidities, diagnosed with stage III BC, and treated with mastectomy and axillary lymph node dissection. There were no differences between socioeconomically-defined groups concerning BC histology, grade and IHC-defined subtype.

Social inequalities in QoL at baseline were statistically significant for all socioeconomic status indicators ($SII_{\text{financial difficulties}} = -7.6 [-8.9;-6.2]$, $SII_{\text{income}} = -4.0 [-5.2;-2.8]$) and $SII_{\text{education}} = -1.9 [-3.1;-0.7]$).

In multivariable analyses, social inequalities significantly increased (interaction $p < 0.05$) in Year 1 ($SII_{\text{financial difficulties}} = -11.1 [-12.8;-9.4]$, $SII_{\text{income}} = -6.5 [-8.0;-5.0]$ and $SII_{\text{education}} = -5.0 [-6.6;-3.5]$) and Year 2 ($SII_{\text{financial difficulties}} = -10.7 [-12.2;-9.1]$, $SII_{\text{income}} = -6.7 [-8.0;-5.3]$ and $SII_{\text{education}} = -4.7 [-6.1;-3.3]$) suggesting a widening socioeconomic gap in QoL outcomes irrespective of pre-diagnosis health, tumor characteristics and treatment.

Similar results were observed in subgroups defined by menopausal status (pre/postmenopausal) and type of systemic treatment (chemotherapy, endocrine therapy).

Conclusion

Our study highlights and quantifies the association of several individual socioeconomic indicators with the QoL of patients with EBC in France. The magnitude of socioeconomic inequalities in QoL increased over time after EBC diagnosis in a country with a strong welfare system and universal healthcare coverage. In the era of precision medicine, these results underscore the importance of developing interventions to improve precision care, considering the conditions in which people are born, grow, work, live and age and the wider set of forces and systems shaping the conditions of daily life.

PO2-10-01

Discrimination, Trust, and Pain Outcomes Among Black Women with Early-Stage Breast Cancer After Mastectomy

Presenting Author(s) and Co-Author(s):

D. Smith-Graziani. Emory University Winship Cancer Institute, Atlanta, Georgia, United States

Y. Cao. Winship Cancer Institute of Emory University, United States

J. Switchenko. Winship Cancer Institute of Emory University, United States

M. Rimawi. Baylor College of Medicine, Houston, Texas, United States

A. Brewster. University of MD Anderson Cancer Center, Houston, Texas, United States

BACKGROUND Differences in perception, assessment, communication, and management of pain contribute to racial/ethnic pain disparities in breast cancer (BC). We previously found that Black women (BW) reported higher pain severity and interference with life after breast surgery compared to White women after adjusting for type of surgery and other potential confounders. Racial/ethnic inequities persist despite prior trials to improve disparate pain outcomes. This is likely because multiple factors contribute to pain expression, and structural factors affect the ability to control pain adequately. Perceived discrimination is associated with mistrust of medical providers. These factors are known to affect clinical outcomes, but their impact on pain has been understudied. In this preliminary analysis, we examine medical discrimination, trust in physician, and pain outcomes among BW with early-stage breast cancer after mastectomy.

METHODS We surveyed BW with stage 0-III breast cancer who had mastectomy < 2 years of study enrollment at Baylor St. Luke's Medical Center or Harris Health Smith Clinic in Houston, TX. Participants completed a demographic survey as well as the Brief Pain Inventory (BPI), Discrimination in Medical Settings Scale (DMS), and Trust in Physician Scale (TPS). In the BPI, participants reported their pain severity (PS) on a 0-10 scale at its worst, least, and on average. They reported pain interference with life (PI) from 0-10, types of pain treatments, and % relief from pain treatments. DMS and TPS questions were assessed on 5-point Likert scale. We performed chart review to obtain baseline clinical data related to BC diagnosis and treatment and comorbidities. We summarized patients' baseline demographic and clinical information using descriptive statistics. PI and DMS were scored as a mean of the total items of each survey. We created mean Trust and Mistrust scores using means of the TPS questions related to each category.

RESULTS Of the 37 BW surveyed, 36 (97.3%) were non-Hispanic. 23 (62.2%) had HR+ BC, and 2 (6.7%) had HER2+ disease. 26 (70.3%) women received chemotherapy, 10 (27%) received radiation therapy, and 17 (45.9%) received endocrine therapy. 26 (70.3%) women had > 1 comorbidity; the mean (SD) number reported was 1.3 (1.1). Mean BMI was 30.9 (6.6). 10 (29.4%) women completed high school, and 8 (23.5%) completed some college. 19 (55.9%) had a household income < \$25,000, and 11 (32.4%) had private health insurance. Mean worst PS was 4.2 (3.1), and mean average PS was 3.6 (2.9). Mean composite PI score was 2.7 (2.7). 11 (29.7%) women were taking opioids for pain, 17 (45.9%) were taking non-opioid analgesics, and 3 (8.1%) were receiving non-medication treatments. Mean % pain relief with treatment was 52.3% (38.3). Mean DMS score was 1.2 (0.6). Mean composite TPS Trust and Mistrust scores were 4.4 (0.7) and 1.8 (1.0), respectively.

CONCLUSION BW may continue to experience pain requiring opioid and/or non-opioid analgesics up to 2 years following mastectomy. Study participants reported relatively low levels of discrimination and high levels of trust on average. We are currently enrolling additional participants in the Emory Healthcare System and Grady Memorial Hospital in Atlanta, GA. After enrolling at least 80 total patients, we will determine the association between DMS and pain outcomes among participants adjusting for demographic, socioeconomic, and clinical factors as

well as assess TPS as a potential mediator in the causal pathway between DMS and PS.

PO2-10-02

'Sharing Our Own Experience': A Qualitative Study of Black Women Diagnosed with Triple-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

T. Felder. University of South Carolina, United States

L. Ingram. University of Georgia, United States

M. Austin. University of South Carolina, United States

V. Burke. SHARE Cancer Support, United States

S. Poland. SHARE Cancer Support, United States

M. Chase. SHARE Cancer Support, United States

C. Benjamin. SHARE Cancer Support, United States

Introduction: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer that is disproportionately prevalent among U.S. Black women. Black women diagnosed with TNBC are less likely to receive the primary treatment options for TNBC, and more likely to die from the disease compared to white patients with the same diagnosis. Given TNBC's impact on Black women, there is an urgent need to better understand their needs for information and support and any unique barriers to care they may face. Thus, this study explored the perspectives, needs, and lived experiences of Black women diagnosed with TNBC.

Methods: Our study was guided by the transformative paradigm and used a multi-method approach. Study-eligible participants self-identified as: a) Black or African American; b) 18 years or older; c) being diagnosed with TNBC within the previous 5-7 years; d) receiving TNBC treatment in the U.S.; and e) English-speaking. From August-October 2022, SHARE Cancer Support (a national nonprofit focused on cancer) and 15 partner organizations used social media and listservs to recruit potential participants from their constituencies to complete a quantitative survey (n=49). From the survey participants, a stratified, purposeful sample of 20 Black women diagnosed with TNBC completed in-depth interviews from November 2022-February 2023. Two Black women researchers conducted virtual interviews with the participants via Zoom. The research team performed thematic analysis on the professionally transcribed data using NVivo 12. A Black Feminist lens was used to analyze codes and interpret emerging themes present across the interviews. The University of South Carolina's Institutional Review Board approved this study.

Results: About half of those interviewed were between 35 and 44 years old, had a bachelor's degree or higher, and their annual household income ranged from less than \$25,000 to \$175,000. Eight major themes emerged from the personal stories of Black women diagnosed with TNBC. From diagnosis to survivorship, Black women discussed the importance of advocacy, including self-advocacy, others advocating on their behalf, and being motivated to become an advocate for others. The participants shared the significance of their identity as Black women and desired that cancer care team members acknowledge their identity and subsequently culturally tailor their care needs. Some participants also noted instances of racism and discrimination that occurred during their TNBC diagnosis or treatment experience. Participants overwhelmingly stressed the vital nature of having "someone who looks like me" to inform them about treatment options and existing resources, as well as to provide emotional support through their shared lived experiences with TNBC. Additionally, participants recognized the importance of embracing the uncertain yet inevitable future. They also emphasized that

mental health support is not uniformly provided in care settings but should be an essential component of the TNBC treatment plan. Having support was essential to all the women, but they noted that support can look different for everyone and many existing support resources need to be improved. The themes were adapted into a list of recommended action steps for support organizations, clinical care team members, and TNBC patients to help improve the quality of life for Black women diagnosed with TNBC.

Conclusions: The lived experiences of Black women diagnosed with TNBC can serve as a meaningful source of data and provide solutions to addressing persistent health disparities these women face. Findings from this study can inform future research and clinical practice about how to support the holistic needs of Black women diagnosed with TNBC.

Recommendations for improving the quality of life for Black women diagnosed with triple-negative breast cancer.

Recommendations	Black Women Diagnosed with TNBC	Care Teams	Support Organizations
1. Increase awareness about TNBC, especially in Black spaces.		✓	✓
2. Diversify the oncology care team.		✓	
3. Avoid color blindness.		✓	✓
4. Strive for equity, rather than equality, in treatment and care.		✓	
5. Black women should be treated with tenderness.		✓	
6. It is okay not to be okay.	✓		
7. Clinicians need to be better educated about TNBC in Black women.		✓	✓
8. Black women want tailored support groups.		✓	✓
9. Conversations about the future are necessary.	✓	✓	✓
10. Acknowledge the mental exhaustion of structural racism and its potential additional impact on Black women.	✓	✓	✓
11. Don't forget the caregivers.	✓	✓	✓
12. Surround yourself with positive others.	✓		
13. Formally integrate pathways for support.		✓	✓
14. Increase awareness about instrumental support resources.		✓	✓
15. Advocate for more research with Black women about TNBC.	✓		✓

The 8 major themes that emerged in the qualitative study were adapted into a list of actionable recommendations for key interest groups to improve the lives of Black women diagnosed with triple-negative breast cancer.

PO2-10-03

Clinical characteristics and survival trends of male breast cancer in the United States: A propensity score matched analysis

Presenting Author(s) and Co-Author(s):

A. Roy. Roswell Park Comprehensive Cancer Center, Amherst, New York, United States

A. George. Roswell Park Comprehensive Cancer Center, United States

A. Patel. Roswell Park Comprehensive Cancer Center, United States

M. Alharbi. Roswell Park Comprehensive Cancer Center, United States

K. Attwood. Roswell Park Comprehensive Cancer Center, United States

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

Introduction Male breast cancer (MBC) is extremely rare and represents less than 1% of breast cancer (BC). There are limited studies investigating clinical outcomes of MBC. Although the survival of female breast cancer (FBC) has increased over the years; there is a substantial knowledge gap regarding survival trends of MBC. Given the rarity of MBC, recommendations on the treatment of MBC are scarce and mainly extrapolated from the data from FBC. We aim to analyze the clinical characteristics and annual trend in the survival of MBC compared to FBC. **Methods** We queried the National Cancer Database for BC patients (pts) diagnosed during 2004-2020. The demographic, clinicopathological and treatment characteristics were summarized by sex. An inverse-propensity weighted cox regression model was used to assess the association between sex and overall survival. Propensity weights were based on age, race, insurance, T, N, M-stages, subtype, grade, chemotherapy (CT), radiation (RT), hormone therapy (HT), and time to definitive treatment. To compare survival trends over time, year of diagnosis and its interaction with sex were included in the model. All analyses were performed at a significance level of 0.05. **Results** A total of 24, 055 MBC and 2,532,470 FBC pts were identified. MBC pts were older (mean age: 65.6 vs 61.4 years), Blacks (12.8 vs 11.2%) and had more government insurance (55.7% vs 45.8%) compared to FBC (all $p < 0.001$). Compared with FBC, more MBC pts had stage IV (7% vs 4.7%), fewer pts had stage I (33.4% vs 44.8%), more pts had larger tumors (cT4: 6% vs 3.7%), and node positive disease (18.5% vs 15.5%) (all $p < 0.001$). MBC were more likely estrogen (ER) (88.5% vs 78.5%) and progesterone receptor (PR) (79.6% vs 68%) positive and less likely HER2 receptor positive (7.9% vs 9.3%) or triple negative (2.8% vs 7.6%) compared to FBC (all $p < 0.001$). Male pts with BC received less CT (38.7% vs 41.2%), RT (32% vs 52.6%), HT (59.8% vs 62.5%) compared to females with BC ($p < 0.001$). The overall survival (OS) rates were lower in MBC compared to FBC (5-year: 73% vs 83%; 10-year: 54% vs 70%, $p < 0.001$). In the propensity weighted cox-regression model, males had higher mortality compared to females with BC (HR 2.8, 95% CI 2.88 - 2.9, $p < 0.001$). This difference in OS was observed in TNBC (HR 1.2, 95% CI 1.21 - 1.24) and HER2+ (HR 2, 95% CI 1.9 - 2.0), but not in ER/PR+ HER2- BC (HR 0.78, 95% CI 0.78 - 0.79), all $p < 0.001$. The 5-year and 10-year OS of early-stage MBC and advanced MBC was lower compared to FBC (Early-stage: - 5-year: 77% vs 86%, 10-year: 57% vs 72%, HR 2.9, 95% CI 2.9-2.92; Advanced: 5-year: 23% vs 28%, 10-year: 8% vs 13%, HR 1.14, 95% CI 1.14 - 1.2, both $p < 0.001$) The 5-year OS rates increased steadily for FBC from 2004-2015; however, the survival rates were not improved for MBC (Table 1) (p -value for interaction of sex and year of diagnosis was 0.02). **Conclusion** MBC pts have higher mortality rates and poor clinical outcomes compared to FBC pts. We demonstrate that the survival of MBC pts has not improved over the last decade, even after adjusting for clinicopathological and treatment characteristics. These findings suggest the need to investigate personalized treatment

interventions for male breast cancer pts, especially given the disparate trends in survival among male and female BC over a period of time.

Table 1: Survival trend by sex - overall BC cohort

Year of Diagnosis	MBC 5-Year Survival Rate (95% CI)	FBC 5-Year Survival Rate (95% CI)
2004	0.75 (0.72, 0.77)	0.81 (0.81, 0.81)
2005	0.70 (0.68, 0.73)	0.81 (0.81, 0.82)
2006	0.72 (0.70, 0.75)	0.82 (0.82, 0.82)
2007	0.74 (0.71, 0.76)	0.82 (0.82, 0.82)
2008	0.71 (0.68, 0.73)	0.82 (0.82, 0.82)
2009	0.71 (0.69, 0.73)	0.83 (0.82, 0.83)
2010	0.72 (0.70, 0.74)	0.83 (0.83, 0.83)
2011	0.74 (0.72, 0.77)	0.83 (0.83, 0.83)
2012	0.72 (0.70, 0.74)	0.84 (0.83, 0.84)
2013	0.73 (0.71, 0.76)	0.84 (0.84, 0.84)
2014	0.76 (0.73, 0.78)	0.84 (0.84, 0.84)
2015	0.72 (0.70, 0.74)	0.85 (0.85, 0.85)

PO2-10-04

Clinicopathological Characteristics and Factors Associated With Screening and Late-Stage Diagnosis in Patients With Breast Cancer in Latin America: The LATINA Study (LACOG 0615/MO39485)

Presenting Author(s) and Co-Author(s):

G. Werutsky. Hospital São Lucas, PUCRS University, Porto Alegre, Rio Grande do Sul, Brazil

C. Villarreal-Garza. Tecnológico de Monterrey, Nuevo Leon, Mexico

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

J. Manuel Donaire. Clínica Las Condes, Santiago, Chile, United States

J. Bines. Instituto Nacional de Câncer (INCA), Brazil

L. Fein. Instituto de Oncología de Rosario, Rosario, Argentina, United States

M. Horsburgh. Roche Argentina, Buenos Aires, Argentina, United States

P. Cabrera-Galeana. Instituto Nacional de Cancerología, CDMX, Distrito Federal, Mexico

H. Resende. Hospital Jardim Amália, United States

R. Vasallo Veras. Instituto Oncológico Dr. Heriberto Pieter, Santo Domingo, República Dominicana, United States

M. Raimondo. Sanatorio de la Mujer, Rosario, Argentina, United States

R. Brugés Maya. Instituto Nacional de Cancerología, Bogotá, Colombia; Hospital Universitario San Ignacio, Bogotá, Colombia, United States

V. Del Rosario. Hospital de Morón, Buenos Aires, Argentina, United States

Y. Nerón. Centro de Pesquisas Oncológicas (CEPON), United States

A. Donoso. Hospital Hernán Henríquez Aravena, Villa Rica, Chile, United States

F. B. Damian. Hospital Fêmina, Porto Alegre, Brazil; Centro de Pesquisa em Oncologia (CPO) - PUCRS, Porto Alegre, Brazil, United States

J. D'Oliveira Couto Filho. Hospital do Câncer de Londrina, Londrina, Brazil, United States

M. Alonso. Sanatorio CASMU - Oncología, Montevideo, Uruguay, United States

V. Costanzo. Instituto Alexander Fleming, Buenos Aires, Argentina, United States

T. Reinert. Oncoclínicas, Porto Alegre, Brazil

A. Borello. Hospital Privado Universitario de Córdoba, Córdoba, Argentina, United States

E. Cronenberger. CRIO, Fortaleza, Brazil, United States

L. Fein. Instituto de Oncología de Rosario, Rosario, Argentina, United States

M. Urrego. Centro Medico Imbanaco de Cali, Cali, Colombia, United States

E. Alanya. Aliada Cancer Center, Lima, Lima, Peru

J. Soriano García. Department of Medical Oncology, Hospital Hermanos Ameijeiras, Havana, Cuba, United States

S. Campos-Gomez. Centro Oncológico Estatal Issemym, Toluca de Lerdo, Mexico, United States

E. Richardet. Instituto Oncológico de Córdoba, Córdoba, Argentina, United States

H. Castro-Salguero. Grupo Medico Angeles, Guatemala, United States

F. Cruz. São Camilo Oncologia, São Paulo, Brazil, United States

D. Gómez. Fundación Cardiovascular de Colombia, Santander/Bucaramanga, Colombia, United States

A. Hernández. Organización Clínica Bonnadona, Cali, Colombia, United States

C. Farfan Tello. Clínica Internacional SA, Lima, Peru, United States

R. Rodríguez. Instituto Nacional del Cancer, Chile, Chile, United States

R. Jesus. Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Rio Grande do Sul, Brazil

G. Gösling. Latin American Cooperative Oncology Group (LACOG), United States

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

Background: Breast cancer (BC) is the most common malignancy and one of the leading causes of cancer death in women in Latin America (LATAM). However, the region lacks a unified multinational initiative to investigate BC and to further understand regional disparities. **Methods:** LATINA (LACOG 0615/MO39485) is the first multinational prospective cohort study designed to describe clinicopathological characteristics, treatment patterns, and outcomes of patients with BC in LATAM. Patients aged ≥ 18 years diagnosed with primary or recurrent BC in the 12 months preceding site activation were included. Data were collected at enrollment and every 6 months for up to 5 years. We present here the results for clinicopathological and demographic characteristics at BC diagnosis. Multivariable logistic regression was performed to investigate characteristics associated with later diagnosis (stage II/III vs. stage I) and detection method (symptomatic vs. screening). Causal mediation analysis was performed to investigate the detection method as a mediator of the effect of health care provision (public or private) on stage at diagnosis. **Results:** Between February 2020 and August 2022, 3276 patients from 31 research sites in 10 LATAM countries were included. Most patients in this cohort (72.1%, N=2362) were treated in the public health system. Regarding ethnicity, most patients (91.8%, N=3008) self-identified as Latinos and were White (47.3%, N=1549), American Indian (21.0%, N=689), and Black or Brown (16.6%, N=544). The median age at diagnosis was 54 years (range 23–95), 41.8% (N=1368) were < 50 years of age at BC diagnosis, and 54.1% (N=375) of the American Indian patients were ≤ 50 years of age. BC subtype distribution was: 43.2% (N=1336) luminal A, 14.3% (N=433) luminal B, 22.9% (N=709) human epidermal growth factor receptor 2-positive (HER2+), and 15.4% (N=477) triple negative. In patients older than 50 years old, most cases were detected with symptoms, particularly in the public health system (63.2%, N=836) vs. 50.5% (N=232) in the private health system, $p < 0.0001$). This was also the case in Black/Brown (61.6%, N=178) and American Indian patients (89.5%, N=281) vs. White patients (45.6%, N=413) ($p < 0.0001$). In the public system, 37.7% (N=890) and 31.7% (N=748) of cases were diagnosed at stage II and III vs. 37.6% (N=343) and 26.6% (N=243) of cases in the private system, respectively ($p < 0.0001$). Users of the public health system had a significantly higher risk of being diagnosed with symptoms vs. screening (adjusted odds ratio [aOR] 3.54, 95% CI 2.17–5.76). Causal mediation analysis showed that the detection method (screening vs. symptomatic) mediated 21.8% (95% CI 1.7%–41.9%, $p = 0.034$) of the effect of health care provision (public or private) on stage at diagnosis. Self-identifying as Black (aOR 2.11, 95% CI 1.29–3.45), age < 40 years (aOR 1.97, 95% CI 1.20–3.23), public health care provision (aOR 2.18, 95% CI 1.32–3.59), and a diagnosis of HER2+ (aOR 1.74, 95% CI 1.20–2.52) or triple-negative BC (aOR 2.34, 95% CI 1.47–3.71) were associated with an increased risk of being diagnosed at a later stage. **Conclusions:** A significant proportion of new BC diagnoses in LATAM is observed in patients < 50 years of age. Reflecting the low screening coverage throughout the region, most patients detect the disease with symptoms. Stage III BC accounted for 30.3% of new cases, being more common among users of the public health system.

Differences in the stage at diagnosis related to health care provision (public or private), ethnicity, and country underscore significant disparities that need to be addressed. Further analyses of these data will help identify factors associated with late diagnosis and support the development of regional corrective health policies.

PO2-10-05

The Impact of Socioeconomic Factors on Breast Cancer Diagnosis in Latin America: The LATINA study (LACOG 0615/MO39485)

Presenting Author(s) and Co-Author(s):

G. Werutsky. Hospital São Lucas, PUCRS University, Porto Alegre, Rio Grande do Sul, Brazil

C. Villarreal-Garza. Tecnológico de Monterrey, Nuevo Leon, Mexico

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

J. Manuel Donaire. Clínica Las Condes, Santiago, Chile, United States

J. Bines. Instituto Nacional de Câncer (INCA), Brazil

L. Fein. Instituto de Oncología de Rosario, Rosario, Argentina, United States

M. Horsburgh. Roche Argentina, Buenos Aires, Argentina, United States

P. Cabrera-Galeana. Instituto Nacional de Cancerologia, CDMX, Distrito Federal, Mexico

H. Resende. Hospital Jardim Amália, United States

R. Vasallo Veras. Instituto Oncológico Dr. Heriberto Pieter, Santo Domingo, República Dominicana, United States

M. Raimondo. Sanatorio de la Mujer, Rosario, Argentina, United States

R. Brugés Maya. Instituto Nacional de Cancerología, Bogotá, Colombia; Hospital Universitario San Ignacio, Bogotá, Colombia, United States

V. Del Rosario. Hospital de Morón, Buenos Aires, Argentina, United States

Y. Nerón. Centro de Pesquisas Oncológicas (CEPON), United States

A. Donoso. Hospital Hernán Henríquez Aravena, Villa Rica, Chile, United States

F. B. Damian. Hospital Fêmina, Porto Alegre, Brazil; Centro de Pesquisa em Oncologia (CPO) - PUCRS, Porto Alegre, Brazil, United States

J. D'Oliveira Couto Filho. Hospital do Câncer de Londrina, Londrina, Brazil, United States

M. Alonso. Sanatorio CASMU - Oncología, Montevideo, Uruguay, United States

V. Costanzo. Instituto Alexander Fleming, Buenos Aires, Argentina, United States

T. Reinert. Oncoclínicas, Porto Alegre, Brazil

A. Borello. Hospital Privado Universitario de Córdoba, Córdoba, Argentina, United States

E. Cronenberger. CRIO, Fortaleza, Brazil, United States

L. Fein. Instituto de Oncologia de Rosario, Rosario, Argentina, United States

M. Urrego. Centro Medico Imbanaco de Cali, Cali, Colombia, United States

E. Alanya. Aliada Cancer Center, Lima, Lima, Peru

J. Soriano García. Department of Medical Oncology, Hospital Hermanos Ameijeiras, Havana, Cuba, United States

S. Campos-Gomez. Centro Ocológico Estatal Issemym, Toluca de Lerdo, Mexico, United States

E. Richardet. Instituto Oncológico de Córdoba, Córdoba, Argentina, United States

H. Castro-Salguero. Grupo Medico Angeles, Guatemala, United States

F. Cruz. São Camilo Oncologia, São Paulo, Brazil, United States

D. Gómez. Fundación Cardiovascular de Colombia, Santander/Bucaramanga, Colombia, United States
A. Hernández. Organización Clínica Bonnadona, Cali, Colombia, United States
C. Farfan Tello. Clínica Internacional SA, Lima, Peru, United States
R. Rodríguez. Instituto Nacional del Cancer, Chile, Chile, United States
R. Jesus. Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Rio Grande do Sul, Brazil
G. Gössling. Latin American Cooperative Oncology Group (LACOG), United States
C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

Background: Breast cancer (BC) is the most common malignancy and one of the leading causes of cancer death in women in Latin America (LATAM). Studies have highlighted the importance of understanding contextual characteristics of each patient population to inform health policy-making. However, few data are available on women from LATAM, a region with marked inequalities.

Methods: LATINA (LACOG 0615 / MO39485) is a multicenter prospective cohort study designed to describe sociodemographic characteristics, diagnosis, treatment, and outcomes of patients with BC in LATAM. Female and male patients aged ≥ 18 years newly diagnosed (i.e., < 12 months from research site activation) histologically confirmed clinical stage I-IV BC were enrolled. Eligible patients provided informed consent and had data collected from medical records at diagnosis and every 6 months up to 5 years.

Results: Between February 2020 and August 2022, 3276 patients with BC from 31 research sites in 10 LATAM countries were included. Median age was 54 years (range 23–95), 91.8% (N=3008) were Hispanic or Latinos, the majority (68%, N=2224) were diagnosed with stage II or III BC, and 73% (N=2362) were treated in the public health system. Age, stage and detection method stratified by education level, marital status and employment status are shown in Table 1. Overall, 38.8% (N=1149) of patients had not completed high school. These patients were more frequently diagnosed by symptoms and diagnosed at later stages than those who had completed high school or college. Half of the patients were married/in a civil partnership at BC diagnosis (50.5%, N=1497). Unmarried patients were more commonly diagnosed by symptoms (71.7%, N=835 vs. 64%, N=916, $p < 0.001$) and with stage II/III BC (71.4%, N=868 vs. 67.6%, N=1038, $p < 0.001$) than married patients. Most patients (54.1%, N=1603) were not employed at BC diagnosis. Patients not employed were more frequently diagnosed by symptoms (68.8%, N=1044) than employees/self-employed (61.6%, N=675). After adjusting for age, country, health care provision (public or private), stage, and BC subtype, being diagnosed by symptoms was associated with not being married (adjusted odds ratio [aOR] 1.41, 95% CI 1.11–1.82, $p = 0.004$), being not employed (aOR 1.41, 95% CI 1.08–1.84, $p = 0.011$), and not having completed high school (aOR 1.46, 95% CI 1.00–2.13, $p = 0.031$).

Conclusions: Patients with a lower level of education, unmarried and not employed, are more likely not to perform BC screening and to be diagnosed by symptoms. Socioeconomic characteristics impact the method of detection of BC in LATAM and are associated with diagnosis at later stages. Further analyses of the LATINA study will provide invaluable data for

informing regional health policy-making in LATAM.

	Education Level			Marital Status		Employment Status		
	Total	Completed college (N = 583)	Completed high school (N = 1065)	Incomplete high school (N = 1149)	Married (N = 1497)	Unmarried (N = 1216)	Employed (N = 1141)	Not employed (N = 1603)
Age - median (range)	54 (23 - 95)	48 (26 - 81)	53 (23 - 90)	57 (23 - 95)	52 (24 - 88)	54 (23 - 95)	49 (23 - 90)	58 (23 - 95)
Age - N (%)								
<40 years	461 (14.1)	128 (22.0)	156 (14.6)	120 (10.4)	222 (14.8)	183 (15.0)	215 (18.8)	163 (10.2)
40-50 years	907 (27.7)	209 (35.8)	311 (29.2)	259 (22.5)	442 (29.5)	331 (27.2)	421 (36.9)	336 (21.0)
>50 years	1908 (58.2)	246 (42.2)	598 (56.2)	770 (67.0)	833 (55.6)	702 (57.7)	505 (44.3)	1104 (68.9)
Stage - N (%)								
Missing	3 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
I	559 (17.1)	130 (22.3)	182 (17.1)	151 (13.1)	260 (17.4)	163 (13.4)	193 (16.9)	280 (17.5)
II	1233 (37.7)	234 (40.1)	386 (36.3)	402 (35.0)	558 (37.3)	438 (36.0)	477 (41.8)	538 (33.6)
III	991 (30.3)	156 (26.8)	326 (30.6)	419 (36.5)	453 (30.3)	430 (35.4)	322 (28.2)	528 (32.9)
IV	331 (10.1)	38 (6.5)	115 (10.8)	144 (12.5)	142 (9.5)	141 (11.6)	88 (7.7)	198 (12.4)
Unknown	159 (4.8)	25 (4.3)	55 (5.2)	33 (2.9)	84 (5.6)	44 (3.6)	61 (5.3)	59 (3.7)
Detection method - N (%)								
Missing	198 (6.0)	17 (2.9)	71 (6.7)	45 (3.9)	65 (4.3)	51 (4.2)	45 (3.9)	86 (5.4)
Other	186 (6.0)	14 (2.5)	70 (7.0)	46 (4.2)	71 (5.0)	39 (3.3)	48 (4.4)	79 (5.2)
Screening	914 (29.7)	180 (31.8)	322 (32.4)	262 (23.7)	445 (31.1)	291 (25.0)	373 (34.0)	394 (26.0)
Symptomatic	1978 (64.3)	372 (65.7)	602 (60.6)	796 (72.1)	916 (64.0)	835 (71.7)	675 (61.6)	1044 (68.8)

Education level, marital status, and employment status were not available for 479, 563, and 532 patients, respectively.

PO2-10-06

The Rising Burden of Contraception Requirements in Breast Cancer Clinical Trials: Time for Change?

Presenting Author(s) and Co-Author(s):

C. Chiodi. Gustave Roussy, Villejuif, France

M. Hamid. Department of Medical Oncology, Cork University Hospital, Cork Ireland, Ireland

C. Weadick. Department of Medical Oncology, Cork University Hospital, Cork Ireland, Ireland

M. Hennessy. Department of Medical Oncology, Cork University Hospital, Cork Ireland, Ireland

A. Martin-Quesada. Department of Medical Oncology, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain, Spain

L. Kenny. University of Liverpool, Liverpool, United Kingdom, Ireland

M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy

I. Vaz Luis. Gustave Roussy, Villejuif, France

S. O'Reilly. Department of Medical Oncology, Cork University Hospital, Cork, Ireland, Cork, Cork, Ireland

Background: Breast cancer clinical trials often involve therapies with potentially deleterious effects on the fetus and the baby in the event of pregnancy or breastfeeding. Consequently, eligibility criteria include contraceptive requirements for both the patient and their partner. Patient feedback on the burden of requirements in clinical trials prompted an evaluation of changes in contraceptive requirements in breast cancer clinical trials over the past two decades.

Methods: Breast cancer ClinicalTrials.gov trials protocols over three periods of enrollment were reviewed: 01/01/2001 - 01/01/2002, 01/01/2011 - 01/01/2012, and 01/01/2021 - 01/01/2022.

Inclusion criteria: 1. Interventional studies including (neo)adjuvant or palliative systemic therapy, 2. Premenopausal female patients. Data, including the required number, types, and duration of contraceptive strategies, treatment regimen, and study design, were collated. A descriptive analysis by time period was performed.

Results: 305 studies were included from the three periods: 63 (2001), 127 (2011), and 115 (2021). Of these, contraception requirements were specified in ClinicalTrial.gov protocol information in 4, 61, and 71 CT for 2001, 2011, and 2021, respectively, limiting our analyses in the two later periods. Complete data is available in Table 1.

Conclusions: Our data demonstrates a time trend towards more stringent contraception requirements in breast cancer clinical trials inclusion criteria. The impact of contraception

burden on enrollment, patient compliance, and investigator insight warrants further assessment.

Year (of registration)	2001	2011	2021
	n (%)	n (%)	n (%)
No. of trials	63	127	115
Contraception requirements specified	4 (6.35)	61(48.03)	71 (61.74)
Abstinence/sterilization or two contraception methods*	-	3 (4.92)	13 (18.31)
Two contraception methods or more*	-	5 (8.20)	10 (14.08)
Contraception duration \geq 6 months after study drug end*	-	10 (16.39)	31 (43.66)

Table 1. Summary of contraceptive requirements in interventional breast cancer clinical trials registered on ClinicalTrial.gov across the three time periods studied.

*% from the trials with the contraception requirements specified in ClinicalTrial.gov.

PO2-10-07

Patterns of presentation, treatment and survival for older patients with metastatic breast cancer (MBC): results from a large prospective registry

Presenting Author(s) and Co-Author(s):

M. Hughes. Dana Farber Cancer Institute, United States

A. Patterson. Dana-Farber Cancer Institute, United States

A. Newman. Brigham and Women's Hospital Boston/Harvard Medical School, United States

A. Higgins. Brigham and Women's Hospital Boston, United States

G. Kirkner. Medical Oncology, Dana-Farber Cancer Institute, United States

J. Files. Dana-Farber Cancer Institute, United States

M. Skeffington. Dana-Farber Cancer Institute, United States

M. Moore. Dana-Farber Cancer Institute, United States

S. Strauss. Dana-Farber Cancer Institute, United States

N. Kuhnly. Memorial Sloan Kettering Cancer Center, United States

L. Crowley. Beth Israel Deaconess Medical Center, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

R. Freedman. Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: The median age of breast cancer diagnosis in the U.S. is 62 years; however, older pts with breast cancer are consistently underrepresented in clinical research. In population-based studies, older pts, particularly those aged 70+, do worse than their younger counterparts at every stage of disease, including stage IV. However, our understanding of patterns of recurrence, treatment patterns, and outcomes for older pts with MBC is limited by a lack of available data.

Methods: We identified pts age >60 years seen at least once at a single, NCI-designated cancer center for a diagnosis of MBC between 1999-2022 with 1+ years of follow-up from the time of their metastatic diagnosis. We categorized pts into 5-year age groups (60-65; 66-70; 71-75; 76-80; >80) and two groups of 60-70 and >70. Clinicopathologic characteristics, treatment patterns, reason for treatment discontinuation, and the proportion enrolling on clinical trials were compared by tumor subtype and age group using Chi-Square testing. Median overall survival using Kaplan-Meier method was calculated from the date of initial MBC diagnosis to date of death or last follow-up, examined by tumor subtype and age.

Results: The final analytic cohort included 1,115 patients diagnosed with MBC with median follow-up of 2.9 years (1.0-18.5). Median age at MBC diagnosis was 66.3 years (60.0-95.4) and 10% were non-White; disease subtype distribution was the following: 70.7% HR+HER2-, 11.9% HER2+, 17.4% TN. Overall, 22.2 presented with de novo MBC. Presentation of MBC did not vary by ages 60-70 vs. 70+, with no differences in disease characteristics such as grade and disease sites at MBC diagnosis (except for bone). However, the proportion of pts with HR+HER2- disease increased with age, from 69% of MBC in ages 60-70 and 76% in ages >70 (p=.02). In pts with this subtype receiving first-line (1L) therapy (n=783), use of endocrine

therapy as 1L (with or without a CDK4/6 inhibitor) increased by age (77.8% in ages 60-65 v. 94.7% in ages >80); use of 1L chemotherapy also varied by age (22.2% in ages 60-65 v. 5.3% in >80). Among pts with HER2+ BC, 89% received a trastuzumab-containing regimen in the 1L setting; in pts with TN MBC, 94% received at least 1L line of chemotherapy. Overall, most pts discontinued 1L therapy for progression, not toxicity, and there was no variation in rates of discontinuation due to toxicity by age with 10.4% noted in both age groups, 60-70 and >70. The proportion of patients receiving 3+ lines of chemotherapy across disease subtype decreased with increasing age (e.g., 54% in ages 60-65 v. 25% in ages >80 among HR+HER2-; 69% in ages 60-65 and 33% in ages >80 among TN MBC). Overall, enrollment on a clinical trial in the MBC setting steadily decreased with older age from 40% in ages 60-65 to 13% in ages >80 (p=.0004). Overall median overall survival differed with increasing age from 4.4 yrs in ages 60-65 to 2.7 yrs in ages >80 (p< 0.005). In descriptive analyses, the proportion of pts alive at 2 yrs was variable. For those ages 60-65, 37.8%, 17.1%, and 42.9% of pts with HR+HER2, TN, and HR-HER2+, respectively were alive at 2 yrs. For those ages >80, 23.7%, 0%, and 0% of pts with HR+HER2-, TN, and, HR-HER2+ disease were alive at 2 yrs. Median survival times were < 2 years for pts with TN regardless of age.

Conclusions. In a unique, large prospective cohort of older pts with MBC, we examined detailed information on disease presentation, treatments, and outcomes, lending new information on patterns of care and experiences for older pts with MBC in a modern real-world experience. Limitations include a single center experience and small numbers of older pts with HER2+ and TN disease. Although the oldest pts with MBC had similar disease characteristics as younger pts in our dataset, survival outcomes were poor, particularly for those ages 80+. Therapeutic approaches, likely including improved supportive care, are urgently needed to optimize outcomes in the oldest pts with MBC.

Table 1. Outcomes for older pts with MBC

Table 1. Outcomes for older pts with MBC

Outcome	Age Group (yrs)				
	60-65	66-70	71-75	76-80	>80
HR+HER2- (n = 788)					
Time (yrs) from MBC diagnosis to death or last f/up median (min-max)	3.3 (2-18.5)	3.3 (5-14.9)	3.3 (0.2-15.7)	2.7 (0.3-13.2)	1.7 (0.2, 5.9)
% alive at 2 yrs from met diagnosis (%)	37.8%	28.2%	30.5%	37.8%	23.7%
HR+HER2+ (n = 77) or HR-HER2+ (n=56)					
Time from met diagnosis to death or last f/up median (min-max)	3.9 (4-16.8)	3.0 (6-12.1)	2.9 (7-18.1)	2.3 (5-7.4)	2.4 (1.4-5.6)
% alive at 2 yrs from met diagnosis (%)	40.3%	56.4%	40.0%	25.0%	33.3%
TNBC (n = 194)					
Time from met diagnosis to death or last f/up median (min-max)	1.6 (1-12.5)	1.3 (1-9.6)	1.8 (2-5.5)	1.0 (3-2.9)	1.1 (0.4-2.5)
% alive at 2 yrs from met diagnosis (%)	17.1%	8.9%	23.3%	0.0%	0.0%

PO2-10-08

Contemporary HER2-Positive MBC Treatment Recommendations Among Community Healthcare Professionals: Analysis of an Online Interactive Decision Support Tool

Presenting Author(s) and Co-Author(s):

K. Rosenthal. Clinical Care Options, United States

S. Hurvitz. Fred Hutchinson Cancer Center, Seattle, Washington, United States

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

H. McArthur. UT Southwestern, Dallas, Texas, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

T. Quill. Clinical Care Options, United States

Background: The management of HER2-positive (HER2+) metastatic breast cancer (MBC) has continued to evolve, with multiple FDA approvals of novel HER2-targeted agents since late 2019. Considering the growing HER2+ MBC treatment armamentarium, we sought to identify current practice patterns among community healthcare professionals (HCPs) for HER2+ MBC by comparing HCP and key opinion leader (KOL) treatment recommendations using an online decision support tool.

Methods: An online decision support tool was developed with input from 5 KOLs to provide therapy recommendations for 630 HER2+ MBC patient case scenarios based on conventional considerations including distribution of metastatic disease, treatment history, duration of response, and specific comorbidities. HCP tool users entered specific patient criteria to define a case along with their intended management for each case. The tool then showed 5 KOL recommendations for the user-entered patient case, and the users were asked to indicate if the expert recommendations confirmed or changed their intended approach. An analysis of expert recommendations and user-selected therapy was performed.

Results: Between November 2022 and July 2023, 313 patient cases were entered by 242 participating HCPs. HCP and KOL treatment recommendations were frequently discordant (Table). For patients with de novo HER2+ MBC (n = 55), there was strong concordance (63%; P = .0001) between HCP and KOL recommendations. However, weak treatment selection concordance (53%; P < .0001) was observed for patients with disease progression after standard neoadjuvant/adjuvant therapy with chemotherapy plus HER2-targeted agents (n = 57). In the second-line setting, 43% concordance was observed for patients with non-central nervous system (CNS) disease progression without CNS progression after first-line therapy with THP (n = 67; P < .0001), whereas 61% concordance was observed for patients with non-CNS and CNS disease progression after first-line therapy with THP (n = 61; P < .0001). In the third-line setting, 31% concordance was observed for patients with non-CNS disease progression without CNS progression (n = 32; P < .0001), and 47% concordance was observed for patients with non-CNS and CNS disease progression (n = 19; P = .0009).

For HCPs whose treatment plan did not match KOL recommendations in these scenarios, 62% indicated that KOL recommendations confirmed or changed their intended therapy, but 19% indicated that there were barriers to implementing those recommendations.

Conclusions: These data suggest ongoing challenges to optimally incorporate novel HER2-targeted therapies in the care of patients with HER2+ MBC, particularly in the second line and

beyond, but an online tool providing KOL advice on specific patient scenarios confirmed or changed the clinical approach for a majority of HCPs. Thus, continued development of resources for HCPs, including online decision support tools, may be increasingly important given the rapidly evolving treatment landscape.

Table. Summary of Treatment Choices by KOLs or HCPs for Select Patient Scenarios

Table. Summary of Treatment Choices by KOLs or HCPs for Select Patient Scenarios		
3L de novo MBC (n = 55), %		
Discordant treatment selection	KOL	HCPs
A lapatinib + trastuzumab + pertuzumab	90	27
T DM1	8	67
Trastuzumab + trastuzumab + capecitabine	0	4
T DM1	0	0
Other	2	11
Uncertain	--	11
PD after resective/adjuv CT + HER2-targeted agents (n = 97), %		
Discordant treatment selection	KOL	HCPs
T DM1	64	19
A lapatinib + trastuzumab + pertuzumab	24	33
Trastuzumab + trastuzumab + capecitabine	10	5
T DM1	0	5
Other	3	23
Uncertain	--	14
PD, no CNS progression after 3L MBC with THP (n = 67), %		
Discordant treatment selection	KOL	HCPs
T DM1	96	37
Trastuzumab + trastuzumab + capecitabine	4	3
A lapatinib + trastuzumab + pertuzumab	0	3
T DM1	0	24
Other	0	18
Uncertain	--	9
PD with progressive CNS mets after 3L MBC with THP (n = 61), %		
Discordant treatment selection	KOL	HCPs
Trastuzumab + trastuzumab + capecitabine	39	16
T DM1	25	41
A lapatinib + trastuzumab + pertuzumab	20*	8
T DM1	<1	8
Other	0	13
Uncertain	--	13
PD, no CNS progression after 2 lines of tx (n = 32), %		
Discordant treatment selection	KOL	HCPs
T DM1	59	28
Trastuzumab + trastuzumab + capecitabine	39	13
T DM1	1	6
Other	0	31
Uncertain	--	22
PD with progressive CNS mets after 2 lines of tx (n = 19), %		
Discordant treatment selection	KOL	HCPs
Trastuzumab + trastuzumab + capecitabine	53	21
T DM1	33	26
T DM1	13	5
Other	0	21
Uncertain	--	26

*For patients with progressive CNS mets and no other mets, some KOLs recommended local therapy for CNS mets and continuation of first-line systemic progression.

PO2-10-09

Professional Support for Eating and Nutrition among Women Living with Breast Cancer: Implications for Mental Health and Quality of Life

Presenting Author(s) and Co-Author(s):

V. Morris. Cancer Support Community, Palmer, Massachusetts, United States

M. Miller. Cancer Support Community, Washington, DC, District of Columbia, United States

S. Weldon. Unite for HER, West Chester, Pennsylvania, United States

G. Kelly. Unite for Her, West Chester, Pennsylvania, United States

Background: Within oncology, nutrition and eating behaviors are often tied to cancer prevention, incidence rates, progression, and healthy survivorship, as well as symptom and side effect management. While many nutrition-related resources and guidelines focus on physical health outcomes, support around nutrition and eating behaviors can have critical implications for mental health and quality of life outcomes among breast cancer patients and survivors.

Methods: 232 women with breast cancer enrolled in the online Cancer Experience Registry and provided sociodemographic and clinical characteristics, answered questions about their eating and nutrition experiences, including utilization of a Registered Dietitian for professional eating and nutrition support since being diagnosed with cancer, and completed the Patient-Reported Outcomes Measurement Information System (PROMIS-29v2.0 + 2-item Cognitive Function Short Form). Frequencies were calculated and group differences among those who wanted professional support for eating and nutrition but either did or did not receive it were assessed using independent-samples t-tests.

Results: The sample was 81% Non-Hispanic (NH) White, 9% NH Black. Participants varied in age (mean=61 yrs; SD=9.2), time since diagnosis (median=7 yrs, range: < 1-39) and socioeconomic status (16% household income < \$40K; 32% employer-provided insurance coverage). 44% were currently receiving treatment, with 70% in remission, 12% with metastatic disease, and 21% with history of recurrence. Over one-third (36%) received professional support for eating and nutrition from a Registered Dietitian since being diagnosed with cancer, including 12% receiving that support in the last 6 months. Participants wanted professional support for eating and nutrition during active treatment (51%), after treatment (44%), at initial diagnosis (23%), before treatment (18%), before being diagnosed with cancer (11%). The most commonly reported eating and nutrition needs driving the desire for professional support included weight-related support (54%; maintenance, gain, or loss), achieving healthy eating patterns (52%), increasing energy level (46%) and physical fitness/strength (45%). However, experiences with professional support for eating and nutrition varied: 54% wanted eating and nutrition support since being diagnosed with cancer, but only 68% of those who wanted this support were able to access care. Irrespective of access to professional eating and nutrition support, participants report changing their eating patterns to manage SSEs (50%) or improve long-term health (57%).

Among those who desired professional support for eating and nutrition since being diagnosed with cancer (n=102), those who did not get the desired support (n=34) compared to those who did (n=68) reported higher levels of anxiety, depression, sleep disturbance, and pain, as well as lower levels of physical and cognitive function (all ps < .05). Levels of fatigue and social function were not significantly different between groups.

Conclusion: While there is a strong desire for professional support surrounding eating and nutrition among women with breast cancer, when that support is needed and what it aims to address varies greatly. Among those interested in receiving professional support for eating and nutrition, those who accessed professional support reported greater mental health and quality of life. Further research is needed to understand barriers to accessing eating and nutrition support among those who are not able to obtain it. Community-based advocacy organizations that offer access to professional support services for eating and nutrition are critical for addressing unmet needs in this area to improve health and well-being among women with breast cancer.

PO2-10-10

Developing a Continuum of Care Model to Address Healthcare Disparities in Breast and Cervical Cancer: The Promise Fund's Approach

Presenting Author(s) and Co-Author(s):

N. Brinker. Promise Fund of Florida, United States

D. Shalala. Promise Fund of Florida, United States

E. Mitchell. Thomas Jefferson University, Philadelphia, Pennsylvania, United States

H. Brown. Promise Fund of Florida, United States

W. Frederick. Howard University, United States

J. Mendez. Promise Fund of Florida, United States

D. Jain. Promise Fund of Florida, United States

D. Dodson. Promise Fund of Florida, United States

D. Brodsky. Promise Fund of Florida, United States

L. Shockney. Promise Fund of Florida, United States

The Promise Fund is creating a systemic change in healthcare service delivery through its Continuum of Care model in which patients are provided health education, navigation for breast and cervical health, affordable early detection screenings, diagnostics, treatment, and/or support services through an established network of providers, reducing healthcare costs, alleviating the burden of our complex healthcare system, and improving patient outcomes. This model, established in Palm Beach County, has potential to be scaled across Florida and beyond. The Promise Fund's primary focus is to eliminate preventable deaths and stop the progression of breast and cervical cancer among women in South Florida. The region faces significant healthcare disparities, with over 80,000 uninsured women in Palm Beach County alone. Disproportionately affecting minority groups, these women often experience delayed diagnoses and higher mortality rates compared to White women. Barriers such as transportation, translation, education, and childcare further contribute to suboptimal survival rates, despite high cure rates exceeding 95% for breast and cervical cancer. Through public and private partnerships, the Promise Fund established a Women's Health Center co-located at a Palm Beach County Federally Qualified Health Center (FQHC). FQHCs are community-based facilities that provide comprehensive primary care services to uninsured or low-income individuals in areas of high need. At this strategically selected FQHC, the Promise Fund supplies state-of-the-art equipment for breast and cervical cancer screenings, such as a 3D Genius Mammography Machine, donated by Hologic, Inc., ultrasounds, LEEP, and colposcopy. To facilitate access, the Promise Fund employs over 20 patient navigators positioned in FQHCs, free clinics, and community-based organizations across South Florida. These navigators connect women to resources, engage in outreach, and enroll at-risk individuals into the program. The impact of the navigators is significant, with over 20,000 women engaged, over 80 cancers treated, more than 5,000 women finding medical homes, and over 19,000 women receiving education and outreach. Additionally, the program has facilitated over 4,000 mammograms and 2,000 pap tests, all provided at little to no cost to the patients. Promise Fund Patient Navigators are well-trained, culturally competent, and bilingual. They help patients overcome barriers to care, arranging transportation, childcare, and translation services. Our navigators are carefully selected from the community and undergo rigorous training in breast and cervical health, navigation, and reporting. Moreover, the Promise Fund supports patients throughout their cancer journey by brokering low-cost or free treatment from private hospitals.

Despite the prevailing healthcare disparities, the Promise Fund's patient-centered approach has yielded positive outcomes. Over 98% of women navigated by the organization comply with receiving their screening mammogram, drastically surpassing the national average. Research has consistently demonstrated that patient navigators significantly improve patient outcomes by facilitating early screening and timely access to treatment, thus reducing disease progression and healthcare costs. Additionally, the Promise Fund's expansive Continuum of Care model effectively decreases the time patients have to wait between diagnosis and starting treatment, as well as decreases the overall treatment time for patients. The success of the Promise Fund's inaugural Women's Health Center has led to the replication of this model in three additional FQHCs in Palm Beach and Broward County, ensuring that no woman in these areas should go without essential breast and cervical cancer resources.

PO2-10-11

Impact of COVID-19 Pandemic on the Disease Volume, Severity and Clinical Complications at Diagnosis and During First Year of Advanced Breast Cancer: COVID19-ABC Quasi-Experimental Study

Presenting Author(s) and Co-Author(s):

D. Martins-Branco. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Academic Trials Promoting Team (ATPT), Brussels, Belgium

V. Debien. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Academic Trials Promoting Team (ATPT), Brussels, Belgium, United States

M. Moreau. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Data Center, Brussels, Belgium, United States

G. Pinna. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Medical Oncology Department, Brussels, Belgium, United States

O. Amato. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Medical Oncology Department, Brussels, Belgium, United States

F. Cherifi. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Medical Oncology Department, Brussels, Belgium, United States

G. Nader-Marta. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Academic Trials Promoting Team (ATPT), Brussels, Belgium, United States

M. Paesmans. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Data Center, Brussels, Belgium, United States

E. de Azambuja. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Brussels Hoofdstedelijk Gewest, Belgium

Background: The COVID-19 pandemic affected healthcare systems, tumbling cancer screening programs and increasing fear of infection among medical facilities users. We hypothesized that the pandemic negatively impacted the clinical outcomes of patients (pts) with advanced breast cancer (ABC). The COVID19-ABC study aims to assess the influence of the pandemic on disease volume, severity, and clinical complications at diagnosis and during 1st year of ABC.

Methods: Single-center, retrospective, quasi-experimental study with historical control. We included women treated for unresectable/metastatic recurrent or stage IV de novo ABC in a Belgian cancer center. Pts were eligible if ABC was diagnosed between 1/Jan/2020-30/Nov/2021 - pandemic exposure (Exp) cohort - or between 1/Jan/2017-30/Nov/2018 - historical (Hist) cohort. We collected data from medical records for baseline characteristics and study outcomes: proportion of oligometastatic disease (OMD) at ABC diagnosis, and proportion of visceral crisis and disease-related serious clinical events during the 1st month and between 1-12 months after ABC diagnosis. We compared baseline variables between the two cohorts using χ^2 test for frequencies and Wilcoxon rank-sum test for continuous variables. We performed a pre-planned subgroup analysis by year of pandemic, immunohistochemistry (IHC) subtype, and recurrent vs de novo ABC. Univariate and multivariate backward stepwise logistic regressions were used to determine the odds ratio (OR) and the 95% confidence interval (CI) of the association of exposure to the pandemic with study outcomes, controlling for confounders.

Results: We included 150 pts, 74 in Exp and 76 in Hist cohort. Age and proportion of de novo ABC and triple-negative breast cancer (TNBC) were numerically higher, while comorbidities and Ki67 index were significantly higher among patients in the Exp cohort (Table 1). Pts in the Exp cohort had a significantly higher risk of visceral crisis during the 1st month of ABC (28.4% vs 15.8%; OR 4.24, 95% CI, 1.45-12.39, adjusted for histology grade and recurrent vs de novo), with similar trend between 1-12 months of ABC (19.4% vs 12.7%, OR 1.66, 95% CI, 0.67-4.13). Visceral crisis tended to be more common in patients diagnosed in the 2nd vs 1st year of the pandemic (35.7% vs 26.7%, p=0.50). We observed higher proportions of visceral crisis in the Exp cohort for pts with recurrent ABC (36.5% vs 17.7%, p=0.02), HER2+ (66.7% vs 10.0%, p=0.01), and TNBC (40.0% vs 18.2%, p=0.21) IHC subtypes. The most common indicators of visceral crisis in the Exp cohort were symptomatic brain metastases (33.3%), malignant hypercalcemia (28.6%), and liver metastases with hepatic tests abnormalities (23.8%). OMD at presentation (35.1% vs 36.8%, p=0.83) and disease-related serious clinical events during 1st month (31.1% vs 37.3%, p=0.42) and between 1-12 months (31.9% vs 34.2%, p=0.77) did not differ between cohorts.

Conclusion: Our study reports a more clinically severe presentation of ABC during the pandemic compared to historical control. This emerged particularly in recurrences and in more aggressive disease subtypes such as HER2+ and TNBC, suggesting a later diagnosis of ABC during the pandemic. These findings require validation in a larger sample, and longer follow-up is needed to assess survival impact.

Table 1. Baseline clinicopathologic characteristics at diagnosis of advanced breast cancer (missing values: 1 for menopausal status, 21 for grade).

	Total (N=150)	Historical cohort (N=76)	Exposure cohort (N=74)	p-value
Age, median (IQR)	60.9 (49.9-70.9)	57.8 (48.1-69.8)	62.7 (51.8-72.9)	0.08
ECOG Performance Status, n (%)				0.72
0-1	125 (83.3)	64 (84.2)	61 (82.4)	
2-4	25 (16.7)	12 (15.8)	13 (17.6)	
Menopausal status				0.58
pre/perimenopausal	38 (25.3%)	20 (26.3%)	18 (24.3%)	
postmenopausal	111 (74.0%)	55 (72.4%)	56 (75.7%)	
Body Mass Index, n (%)				0.43
< 25	41 (27.3%)	21 (27.6%)	20 (27.0%)	
25.0-29.9	75 (50.0%)	41 (53.9%)	34 (45.9%)	
≥ 30	34 (22.7%)	14 (18.4%)	20 (27.0%)	
Charlson Comorbidity Index, n (%)				0.05
≤ 6	121 (80.7%)	66 (86.8%)	55 (74.3%)	
> 7	29 (19.3%)	10 (13.2%)	19 (25.7%)	
De novo vs recurrent, n (%)				0.10
De novo	36 (24.0%)	14 (18.4%)	22 (29.7%)	
Recurrent	114 (76.0%)	62 (81.6%)	52 (70.3%)	
Histology, n (%)				0.81
No special type	115 (76.7%)	57 (75.0%)	58 (78.4%)	
Lobular	21 (14.0%)	12 (15.8%)	9 (12.2%)	
Other	14 (9.3%)	7 (9.2%)	7 (9.5%)	
Grade, n (%)				0.40
I	13 (10.1)	7 (11.7)	6 (8.7)	
II	42 (32.6)	16 (26.7)	26 (37.7)	
III	74 (57.4)	37 (61.7)	37 (53.6)	
IHC subtype, n (%)				0.16
HR+/A-HER2-	100 (66.7%)	55 (72.4%)	45 (60.8%)	
TNBC	31 (20.7%)	11 (14.5%)	20 (27.0%)	
HER2+	19 (12.7%)	10 (13.2%)	9 (12.2%)	
Ki67 index, median % (IQR)	30.0 (15.0-50.0)	25.0 (14.0-30.0)	35.0 (15.0-70.0)	0.03
Metastatic sites, n (%)				0.50
Bone only	32 (21.3%)	19 (25.0%)	13 (17.6%)	
CNS +/- any site	19 (12.7%)	10 (13.2%)	9 (12.2%)	
Visceral non-CNS	99 (66.0%)	47 (61.8%)	52 (70.3%)	

PO2-10-12

The devil is in the details: Workflow analysis of breast cancer treatment decision making and implications for decision support design

Presenting Author(s) and Co-Author(s):

M. Salwei. Vanderbilt University Medical Center, United States

C. Reale. Vanderbilt University Medical Center, United States

While numerous decision aids have been developed to support treatment decision-making in breast cancer¹, widespread implementation remains limited due to challenges integrating these tools in clinical workflows². Given these persistent issues, we need to better understand the complex workflows and needs of decision aid users - patients, their family caregivers, and breast cancer clinicians. Previous studies have explored various aspects of breast cancer team workflows^{3,4}. Despite this work, it is still unclear how these complex workflows support or hinder decision aid use. In this study, we conducted an in-depth analysis of breast cancer team workflow to elicit design requirements for informatics tools to support patient-centered decision-making.

This study was part of a larger project aimed at designing a COMputerized PATient-centered Collaborative Technology (COMPACT) to support personalized decision-making for breast cancer patients. We conducted observations of clinicians and patients at one breast center, using a tablet computer with smart pen to take notes on all aspects of clinic workflow. We uploaded all observation notes into a qualitative data analysis software, Dedoose. Two researchers coded the observations in an inductive, consensus-based process. We met to review our codes and identify key themes emerging in the data.

We observed 95 hours and 127 patient encounters across 20 clinician-centered and 8 patient-centered observations. We identified 10 themes related to the design of decision support, which we grouped into the 4 components of workflow⁶ (see Table 1). We identified numerous patient-specific factors communicated from the patient to the clinical team that influenced treatment decision-making. These “decision factors” covered the broader scope of the patient’s life that was important in the decision-making process (e.g., upcoming family wedding, work). Patients were frequently “knowledge brokers” and were asked to remember and relay information across members of the care team. We identified 28 different tools and technologies used to support treatment decision-making. Patient family caregivers (e.g., aunt, husband) played an important role in treatment decision-making. Based on these findings, we developed design requirements for informatics tools to better support patients (and clinicians).

Our study highlights the complexity and interdependence of breast cancer treatment decision-making. Patients frequently made treatment decisions that influenced subsequent decisions. Decision aids typically focus on one decision or one care specialty and do not support consideration of several treatment options at one time¹. Future research is needed to determine if and how decision support tools could incorporate the broader scope and interdependence between decisions to support patient-centered care. We highlight the need for informatics tools to consider the diverse and unique decision factors (e.g., hobbies) that are crucial to patient-centered decision-making. Decision support could help to elicit and incorporate these factors during treatment decision-making. However, the variable nature of these patient-specific factors presents a challenge to decision support design. Further research is needed to determine how

to optimally incorporate such factors into decision support tools. We found inadequate system support for clinicians' tasks including limited feedback loops to notify clinicians of completed tasks (e.g., mammogram, genetic testing). As a result, patients were often responsible for relaying information to and between different members of the clinical team. Given that patients only remember 50% of what clinicians tell them during visits⁷, a better system is needed to improve the reliability of information transfer. Our design guidelines can be used to improve the design of decision support tools and ultimately improve patient-centered decision-making.

Table 1. Workflow components, themes, and associated challenges to decision support design

Workflow	Theme	Challenges to decision support design
Flow of tasks	1. Numerous types of decisions	<ul style="list-style-type: none"> - <i>It is challenging to...</i> - Identify which of the numerous decisions warrant development of decision support tools - Identify which decisions apply to individual patients at different points in their cancer journey - Increase support for the applicable decisions at the right point in the cancer care workflow
	2. Interdependence of decisions	<ul style="list-style-type: none"> - Develop decision support that adequately captures the inter-related nature of treatment decisions, without overwhelming patients - Identify who should use a decision aid if it incorporates aspects of care across clinical specialties (e.g., surgical and radiation oncologists) - Visually present complex interdependencies in decision-making
	3. Patient participation in decision-making	<ul style="list-style-type: none"> - Adapt decision support tools depending on the type of decision, situation, and a patient's desired involvement in decision-making - Support comparison of treatment options when patients receive second opinions as data from outside institutions is likely incomplete or not available - Systematically collect and incorporate patient and family caregiver questions
	4. Extended diagnostic process	<ul style="list-style-type: none"> - Represent uncertainties including what information is known and unknown and what steps are needed (e.g., MRI) before a final decision can be made - Represent when different diagnostic steps will be completed and how this impacts the treatment timeline
Flow of information	5. Unique decision factors and patient preferences	<ul style="list-style-type: none"> - Incorporate these highly variable factors that are unique to each patient - Conceptualize how unique patient factors relate to the decision at hand - Elicit these in a time constrained clinic visit; most of these factors are not readily available in the EHR
	6. Patient as a knowledge broker	<ul style="list-style-type: none"> - Find relevant information in the EHR from prior encounters (e.g., the patient vomited from prior anesthesia used in surgery) - Track the numerous tasks associated with each patient's care plan - Identify when certain tasks have fallen through the cracks
	7. Complexity of clinical and risk information	<ul style="list-style-type: none"> - Effectively communicate complex information to patients with variable health literacy and numeracy skill levels in a time pressured environment - Identify what information patients need to make each decision - Visually represent risk information in a way that helps patients overcome inherent difficulties with understanding and interpreting probabilities and risks - Represent uncertainty of risk information - Accommodate differences in risk tolerance between patients and clinicians - Represent how combined treatment options (e.g., surgery plus endocrine therapy) impact risk when each treatment option has differing efficacy, risks, and benefits - Manage the timing of information transfer given that the 21st century CURES act means patients get rapid access to their results (e.g., pathology report confirming cancer), but many patients lack the knowledge to appropriately interpret the results without a clinician
Flow of tools and technologies	8. Use of multiple tools and technologies	<ul style="list-style-type: none"> - Integrate decision support with all the different technologies and tools used in cancer care - Transfer information between multiple sources, especially since decision support may rely on information external to the EHR (e.g., genetic results) or from another health system's EHR - Develop decision support for use during clinical encounters given the fact that many physicians did not routinely use the computer while in exam rooms with patients
Flow of people	9. Clinician teamwork	<ul style="list-style-type: none"> - Coordinate decision-making across various roles within the large cancer team - Support the information needs of a variety of clinical roles
	10. Patient support system	<ul style="list-style-type: none"> - Support variable levels of caregiver involvement in decision-making - Determine if and when family caregivers need tailored decision support tools and how the design of these tools might differ from other patient-centered tools

PO2-11-01

Prevalence of Nonadherence to Endocrine Therapy and Cardiovascular Medications Among Breast Cancer Survivors.

Presenting Author(s) and Co-Author(s):

C. Sathe. Columbia University Medical Center, United States

D. DeStephano. Columbia University Irving Medical Center, United States

S. Lee. Columbia University Irving Medical Center, United States

M. Beauchemin. Columbia University Medical Center, United States

N. Liyanage-Don. Columbia University Medical Center, United States

M. Accordino. Columbia University Medical Center, United States

K. Crew. Columbia University Irving Medical Center, United States

I. Kronish. Columbia University Medical Center, United States

D. Hershman. Columbia University, New York, New York, United States

Background: Cardiovascular disease (CVD) and cancer are the two leading causes of death in the U.S, and breast cancer (BC) is the most common cancer among women. Most survivors of early-stage BC are prescribed adjuvant endocrine therapy (ET) to decrease their BC recurrence risk; many of them are also on statins and/or antihypertensives to manage concurrent CVD risk factors. Nonadherence to ET or CVD medications is associated with decreased survival and other poor outcomes, yet little is known about how best to identify nonadherence to multiple classes of medications in BC survivors. Methods: We reviewed pharmacy fill data from our electronic health record (EHR) for a diverse cohort of patients seen in our breast oncology clinic with prescriptions for ET and CVD medications (statin and/or antihypertensive(s)). Patients were excluded if their pharmacy data did not show both an active ET order and an active CVD order or fill. Nonadherence to any medication was defined as proportion of days covered (PDC) < 80% over the previous 180 days. A subset of patients also responded to a patient-reported nonadherence screener administered through our EHR at appointment registration starting in 2/2022. Descriptive statistics were used to determine the prevalence of nonadherence to all medications (defined as PDC < 80% for either ET and/or CVD medications) and for each class of medication separately. We also compared the PDC-based combined nonadherence to the self-reported nonadherence. Results: We identified a total of 1,015 BC survivors on ET and CVD medications last seen in clinic between 2/1/2020 and 6/6/2023 (mean age 69 yo; 23.6% non-Hispanic White, 11.3% non-Hispanic Black, and 38.9% Hispanic). Of these, 567 (55.9%) were prescribed ET and statins, and 745 (73.4%) were prescribed ET and antihypertensives. With nonadherence defined as PDC < 80% for any medication (ET and/or CVD medications), the nonadherence prevalence was 38.4%. The nonadherence prevalence by medication class was slightly lower for ET (20.7%) than for statins (25.9%) and antihypertensives (25.0%). Among patients on ET and statins, 10.1% were nonadherent to both medications and 24.3% were nonadherent to only 1 class of medications; the proportion of patients nonadherent to ET only was almost half that of patients nonadherent to statins only (8.5% vs 15.9%). A similar trend was observed among patients on ET and antihypertensives: 10.3% were nonadherent to both classes of medications and 26.2% were nonadherent to only 1 class of medications, with 11.5% of patients nonadherent to ET only and 14.6% nonadherent to antihypertensives only. Of the 1,015 patients, 390 (38.4%) responded to the nonadherence screener between 2/16/2022 and 6/6/2023, of which 93 (23.8%) reported any level of medication nonadherence. Among these, 57 (61.3%) had PDC ≥ 80% and thus were categorized as adherent under our PDC-

based adherence determination. Of the 297 patients who self-reported adherence to all medications on the screener, 32.3% had PDC < 80% for any medication. When combining nonadherence by PDC and self-report, the overall nonadherence rate for the 390 patients who responded to the screener was considerably higher at 48.5% (vs 33.8% by PDC only and 23.8% by self-report only). Conclusions: EHR-based screening can identify patients with or at risk for medication nonadherence for targeted interventions. Using a combined approach of pharmacy fill data and patient reports, close to 50% of patients were identified as having nonadherence to at least 1 medication. Nonadherence to statins and antihypertensives was more common than nonadherence to ET, which is concerning as early-stage BC survivors are more likely to die from CVD than BC. Interventions to improve adherence to multiple classes of medications are warranted in this population.

PO2-11-02

Incidence, treatment patterns and outcomes of breast cancer during the first year of the COVID pandemic: A population-based study

Presenting Author(s) and Co-Author(s):

J. Leone. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Leone. Grupo Oncológico Cooperativo Del Sur (GOCS), Neuquen, Argentina

M. Hassett. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

R. Freedman. Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Avila. St Elizabeth's Medical Center, United States

C. Vallejo. Grupo Oncológico Cooperativo del Sur (GOCS), Neuquen, Argentina

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

Background: The COVID pandemic created significant challenges in breast cancer (BC) care which were most pronounced during 2020 when screening and treatment access were reduced. The aims of this study were to evaluate and compare the incidence of BC, treatment patterns, and outcomes during the year 2020 versus the immediate pre-pandemic (2018 and 2019) period.

Methods: Using data from the Surveillance, Epidemiology, and End Results (SEER) program, we calculated age-adjusted incidence rates of ductal carcinoma in situ (DCIS) and invasive BC during 2018, 2019 and 2020, with a 95% confidence interval (CI) for each. In the invasive BC cohort, we compared chemotherapy and radiation utilization by year. To account for potential misclassification of cause of death (COD) during the pandemic, we evaluated outcomes by overall survival (OS) in the invasive cohort, defined as time from BC diagnosis until death from any cause. To assess the impact of COVID, OS was truncated at 12 months from diagnosis for each year and we compared OS at 12 months for patients (pts) diagnosed with invasive BC in 2020 versus 2018 and 2019. OS was compared in a multivariable Cox model with diagnosis year 2020 as the reference. The Cox model was adjusted for age at diagnosis, race and ethnicity, sex, tumor grade, histology, stage, tumor subtype, surgery, radiation, chemotherapy, marital status, median household income, and rurality.

Results: There were 37,834 DCIS diagnoses, and 199,594 invasive BC diagnoses between 2018-2020, with the distribution by year shown in the table. In 2020, the age-adjusted incidence of female DCIS decreased to 31.0 cases per 100,000, and the age-adjusted incidence of female invasive BC decreased to 166.6 cases per 100,000. As shown in the table, the incidence of male BC did not change. Among females, the relative reductions in incidence from 2019 to 2020 were: 15% for DCIS, 12% for stage I, 6% for stage II, 3% for stage III, and 2% for stage IV. Comparing 2020 to 2018-2019, we observed small absolute decreases in the proportions of pts who had surgery (2%) or radiation therapy (2.8%), and a small absolute increase in chemotherapy (1.4%) ($p < 0.001$ for each). These treatment changes were present across each individual stage. The table shows the 12-month OS rates for each year of diagnosis. COVID was the COD for 77 pts in 2020, 43 pts in 2019 and 0 pts in 2018. In the Cox

model, there were no significant differences in the risk of death between pts diagnosed 2018 and 2020 (adjusted Hazard Ratio: 0.95; 95% CI, 0.90 – 1.01; p=0.13) or between pts diagnosed 2019 and 2020 (adjusted Hazard Ratio: 0.95; 95% CI, 0.89 – 1.01; p=0.08).

Conclusions: During the first year of the pandemic, the incidence of BC decreased significantly, largely driven by a decrease in DCIS and early-stage diagnoses. Of interest, there was no stage shift observed with respect to the incidence of stage III or de novo stage IV disease, and no change in male BC incidence. We hypothesize that the observed trends are due to a reduction in screening, but this needs further study. It will be critical to evaluate future trends in cancer incidence beyond 2020, as it is possible that the reduction in early-stage diagnoses represent missed diagnoses that will be identified at a later stage in subsequent years. Finally, while there was no difference in 12-month OS by year of diagnosis, the true impact of the COVID pandemic on BC-specific outcomes will require further follow-up.

	2018	2019	2020
DCIS cases (N)	12,623	13,563	11,648
Invasive BC cases (N)	67,308	69,296	62,990
Incidence of DCIS in women (cases per 100,000 and 95% CI)	34.1 (33.5-34.7)	36.4 (35.8-37.0)	31.0 (30.4-31.6)
Incidence of invasive BC in women (cases per 100,000 and 95% CI)	180.8 (179.4-182.2)	184.2 (182.8-185.7)	166.6 (165.2-167.9)
Incidence of invasive BC in men (cases per 100,000 and 95% CI)	1.7 (1.6- 1.9)	1.6 (1.5- 1.8)	1.5 (1.3- 1.6)
Incidence by stage in women (cases per 100,000 and 95% CI)			
Stage I	114.8 (113.6- 115.9)	120.4 (119.3- 121.6)	105.8 (104.7- 106.9)
Stage II	23.1 (22.6- 23.6)	22.5 (22.0- 23.0)	21.2 (20.7- 21.7)
Stage III	11.4 (11.1- 11.8)	11.6 (11.3- 12.0)	11.3 (10.9- 11.6)
Stage IV	10.3 (10.0- 10.7)	10.5 (10.1- 10.8)	10.3 (9.9- 10.6)
Unknown stage	21.2 (20.7- 21.7)	19.3 (18.8- 19.7)	18.1 (17.6- 18.5)
Proportion of stage (%)			
Stage I	64.0	65.9	64.2
Stage II	12.4	11.8	12.3
Stage III	6.1	6.0	6.4
Stage IV	5.8	5.7	6.2
Unknown stage	11.8	10.5	10.9
OS rate at 12 months	95.51%	95.63%	95.43%
Breast cancer-specific survival at 12 months	96.89%	97.00%	97.08%

PO2-11-03

A long-term follow-up of patients who interrupted endocrine therapy to become pregnant following breast cancer surgery

Presenting Author(s) and Co-Author(s):

R. Kasahara. St.Lukes International hospital, Tokyo, Tokyo, Japan

A. Kitano. St.Lukes International hospital, United States

F. Akitani. St. Luke's International Hospital, United States

K. Shiota. St. Luke's International Hospital, United States

K. Kida. Department of Breast Surgical Oncology and Department of Clinical Genetics, St. Luke's international hospital, United States

J. Takei. Department of Breast Surgical Oncology and Department of Clinical Genetics, St. Luke's international hospital, Chu-o-ku, Tokyo, Japan

A. Yoshida. Department of Breast Surgical Oncology and Department of Clinical Genetics, St. Luke's international hospital, United States

Introduction: Regarding discontinuation of adjuvant endocrine therapy to attempt pregnancy, Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer (POSITIVE) clinical trials have revealed that temporary interruption of endocrine therapy to attempt pregnancy did not confer short-term risk of breast cancer events. However, that report involved a short observation period, longer-term follow-up is required. This study was aimed to evaluate the safety of endocrine therapy interruption with long-term follow-up data base. **Methods:** This was a retrospective study using surveying of medical chart data between June 2007 and November 2015 at St. Luke's International Hospital. The subjects were 65 patients with estrogen-receptor positive primary breast cancer (clinical stage I-III) who had been performed fertility preservation prior to starting breast cancer treatment. Adjuvant endocrine therapy completion was defined as 120 months (10 years) and discontinuation was defined as < 120 months. Using the definition, we classified the patients into an endocrine therapy interruption-group and a continuation-group. The primary outcome was the breast cancer free interval (BCFI). We defined breast cancer events as local, regional, or distant recurrence of invasive breast cancer or new contralateral invasive breast cancer during follow-up. **Results:** Median follow-up period was 110 (range, 36–181) months. The number of adjuvant endocrine therapy interruption-group was 30 and continuation-group was 35. Among 65 patients, the mean patient age in the interruption vs. continuation groups were as follows: 38 (range, 26–48) years vs. 36.5 (range, 26–45) years at breast cancer diagnosis and HER2 positive breast cancer was identified in 4 (11.4%) vs 4 (13.3%) patients. Clinical stages were Stage I, 9 (30%) vs. 11 (31.4%) patients; Stage II, 18 (60%) vs. 18 (51.4%) patients; and Stage III, 3 (10%) vs. 6 (17.1%) patients. Chemotherapy was administered in 17 (56.7%) and 23 (65.7%) patients, respectively. The median duration of endocrine therapy before interruption was 25.5 months: 3 (10%) patients received endocrine therapy for 0–18 months, 16 (53.3%) for 18–30 months, and 11 (36.7%) for >30 months. The BCFI was 124 and 119 months in the interruption and continuation groups, respectively ($p = 0.16$). There were 6 (20%) and 9 (25.7%) breast cancer events in the interruption-group and continuation-group, respectively ($p = 0.4$). All the pregnancies were in the endocrine therapy interruption group (17 pregnancies, 16 deliveries), with one pregnancy involving the delivery of twins. Three pregnancies were spontaneous. Endocrine therapy was resumed in 16 (59.3%) patients in the interruption-group (median time to resumption, 20.5 months). One patient developed distant metastasis during endocrine therapy interruption period. **Conclusion:** Among patients who performed fertility preservation

prior to starting breast cancer treatment, our long-term follow-up data, almost 9 years, suggested that the BCFI was not statistically different between endocrine therapy interruption-group and continuation-group. A limitation of this study is that only three cases of Stage III breast cancer were included in the interruption group. Therefore, we consider that careful decisions should be made regarding interruption of endocrine therapy.

PO2-11-04

Assessing quality of Life in breast cancer patients undergoing mHealth mobile monitoring: A descriptive Analysis

Presenting Author(s) and Co-Author(s):

A. Morelle. Oncoclínicas, Porto Alegre, Rio Grande do Sul, Brazil

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

C. Pereira. Respirare Clinic, United States

V. Agibert. LaVÍ Clinical Trials, Rio de Janeiro, Brazil

P. Freitas. Thummi Global, UFRGS, Rio Grande do Sul, Brazil

M. Rocha. Thummi Global, UFCSPA, Rio Grande do Sul, Brazil

P. Schulze. Thummi Global, PUCRS, Rio Grande do Sul, Brazil

Background: Breast cancer (BC) can be associated with a significant symptom burden that can be related both to the disease and to administered therapies. In particular, protocol related toxicity has an extreme impact on patient quality of life (QoL), and can lead to lack of adherence and ultimately, compromise therapy success. There is increasing interest in adopting more effective approaches for active/continuous patient-reported symptom monitoring. Emerging evidence, (Denis et al. 2019), shows that this strategy can reduce toxicity, emergency room visits, and improve QoL. Objectives: We aimed to analyze the QoL of women with BC diagnosis who underwent mobile-based continuous monitoring, searching for possible trends and describing the population. Methods: We conducted a retrospective analysis using data from patients with BC undergoing systemic treatment and monitored by a mobile-based application between January 2022 and June 2023 at an outpatient clinic in Brazil. Thummi is a digital platform for remote monitoring of cancer patients which enables them to record symptoms, toxicities and lifestyle variables. Utilizes the data to generate personalized recommendations and advice. It is available in Brazil at no cost. Doctors indicate the use and can monitor their patients in real time. In addition to an algorithm that informs the user if there is a need to go to the emergency room or not, the medical team can exchange real-time messages with patients. Clinicians have access to patient data through a web tool, allowing them to visualize the information, address symptom alerts, and make informed clinical-therapeutic decisions. The evaluated sample is from patients who come from physicians who indicated the use, without control of their origin, indication of treatment or clinical stage. The data were extracted from the platform's total database. Participants were requested to complete the Quality of Life Questionnaire (EORTC EQ-5D) integrated into the app every month. Inclusion criteria comprised a BC diagnosis, age ≥ 18 , and having responded to the QoL questionnaire with at least a one-month interval between scores. Patients who failed to meet these criteria were excluded from the analysis. A comparison of QoL scores was performed between two periods: T0 (the first recorded response) and T1 (the subsequent response with at least a one-month interval between scores). Descriptive statistical analyses were conducted to search for possible trends, describe the population, and comprehensively examine the differences in QoL scores between T0 and T1. Results: There were 134 active patients in the mobile-based platform with a BC diagnosis, but only 86 (64,17%) met the inclusion criteria for the final analysis. The median age of this group was 54 years old (range 22-78). The most common treatments administered were Cyclophosphamide-Doxorubicin (28 patients, 33%) and Trastuzumab-Deruxtecan (18 patients, 21%). The average QoL score in T0 was 0,70 (SD 0,1379) and 1,0 (SD 0,1560) at T1, representing an increase of 30% after using the app for one

month. Conclusion: This study suggests that mobile-based monitoring has the potential to improve the QoL for women diagnosed with BC. The difference in average QoL scores between the initial and subsequent periods indicates a positive impact of utilizing the platform. Further research is needed to establish a better correlation and to explore the specific interventions that contribute to these improvements. Implementing mobile-based monitoring in clinical practice could enhance patient well-being, treatment adherence, and survival time and can potentially lessen both burden of disease and resource utilization in BC care.

PO2-11-05

Pregnancy Trends Following Breast Cancer Treatment: Insights from a Large Single-Center Experience

Presenting Author(s) and Co-Author(s):

Y. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea., United States

T. Yoo. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

S. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

J. Kim. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea., United States

I. Chung. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

B. Ko. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

J. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea., United States

B. Son. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

H. Kim. Asan medical center, Seoul, Seoul-t'ukpyolsi, Republic of Korea

J. Ahn. University of Ulsan College of Medicine, Seoul, Republic of Korea, United States

S. Kim. Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, United States

Background

The treatment of breast cancer (BC), particularly chemotherapy and long-term endocrine therapy (ETx), can have an impact on fertility which young women with BC have concerns about. This study was therefore conducted with the objective of providing comprehensive real-world data on pregnancy following BC treatment, aiming to shed light on this crucial aspect of survivorship and potentially guide clinical practice and patient counseling.

Methods

A retrospective analysis was conducted using medical records of women aged 18-40 years diagnosed with BC at a single tertiary medical center between December 2010 and September 2020. The pregnancy rate and timing in relation to characteristics and treatment were analyzed, along with the outcomes of discontinuing ETx for the purpose of pregnancy. Statistical analyses including Kaplan-Meier curves and Cox regression were performed.

Results

The study included 995 patients, with a mean age at diagnosis of 31.5 years. Of these, 115 (11.6%) patients became pregnant after BC treatment. Patients with a prior history of pregnancy had a lower likelihood of conception post-treatment (HR=0.39, 95% CI: 0.24-0.67, P< 0.001). Women with hormone receptor positive BC was also associated with lower pregnancy rates than with hormone receptor negative BC (HR=0.52, 95% CI: 0.36-0.77, P=0.001). Age at diagnosis and chemotherapy did not significantly impact pregnancy rates

(P=0.251 and P=0.140, respectively). Among 662 women with hormone receptor positive BC, there were 76 (11.5%) women who discontinued ETx for the purpose of pregnancy and 69.7% (53 out of 76) achieved pregnancies. The median duration of medication before cessation among these women was 26.5 months and the duration of ETx did not significantly affect pregnancy rates (P=0.204). Recurrence after discontinuation of ETx for pregnancy was observed in 17% (13 out of 76) of cases. The median breast cancer-free interval among these cohort was 71 months. Late recurrence, occurring after 5 years of treatment, was observed in 77% (10 out of 13) of cases. Among the patients who experienced recurrence, 62% (8 out of 13) were loco-regional, while 38% (5 out of 13) were distant recurrences and the success rate of achieving pregnancy was 69% (9 out of 13), while 31% (4 out of 13) did not get pregnant.

Conclusion

This study provided real-world data regarding the influence and outcomes of ETx on pregnancy in young BC survivors. The discontinuation of ETx for the purpose of pregnancy appears to result in successful conception. Recurrence rates after therapy discontinuation for pregnancy were observed in a subset of cases, with late and loco-regional recurrences being more common.

Results of uni- and multi-variable cox proportional hazards model evaluating time to pregnancy

Variables	Cases (N)	Events (N)	Rate* (%)	Univariate analysis			Multivariate analysis				
				HR	95% CI		P	HR	95% CI		P
					lower	upper			lower	upper	
Age at diagnosis	≤35	833	104	15.4	Ref			Ref			
	>35	162	11	7.8	0.56	0.30	1.03	0.063	0.69	0.37	1.30
Marriage at diagnosis	No	341	54	17.8	Ref						
	Yes	413	51	13.3	0.76	0.52	1.11	0.160			
Pregnancy history at diagnosis	No	317	50	17.4	Ref					Ref	
	Yes	324	21	6.8	0.37	0.23	0.62	<0.001	0.39	0.24	0.67
TNM stage	0	93	17	20.7	Ref					Ref	
	I - III	902	98	14.3	0.59	0.35	0.99	0.045	0.90	0.49	1.64
HR status	Negative	333	50	18.1	Ref					Ref	
	Positive	662	65	13.5	0.60	0.41	0.87	0.006	0.52	0.36	0.77
Chemotherapy	No	310	44	18.2	Ref					Ref	
	Yes	679	71	13.8	0.69	0.47	1.01	0.054	0.71	0.45	1.12

* The pregnancy rate was calculated using Kaplan-Meier (KM) estimates.

Pregnancy rate according to ETx and its discontinuation

	Total	Pregnancy	Rate
	N=995	N=115	%
Endocrine therapy			
No	337	51	15.1
Yes	655	64	9.8
Unknown	3	0	0.0
Discontinuation of ETx			
Stop for pregnancy	76	53	69.7
Finished planned regimen	48	7	14.6
Stop due to recurrence	46	0	0.0
Other reason (side effect etc.)	20	1	5.0
Unknown	4	0	0.0

Pregnancy rate according to duration of ETx prior to Discontinuation for pregnancy

	Total	Pregnancy	Rate	<i>p</i> *
	N=76	N=53	%	
Duration of ETx, yr				
< 1	7	5	71.4	0.204
1 ~ 2	20	17	85.0	
2 ~ 3	30	20	66.7	
3 ~ 4	12	8	66.7	
4 ~ 5	5	3	60.0	
≥ 5	2	0	0.0	

* The p-value was calculated using Chi-square analysis

PO2-11-06

Anti-Müllerian hormone in Young women with breast CAncer to predict permanent loss of ovarian function after chemotherapy and anti-HER2 therapy (AMYCA): a biomarker analysis of the BETH and KAITLIN trials

Presenting Author(s) and Co-Author(s):

M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy

D. Allegranza. Roche Diagnostics International Ltd, United States

R. Laubender. Roche Diagnostics GmbH, United States

N. Harbeck. University of Munich, Munich, Bayern, Germany

S. Swain. Georgetown University Medical Center, Lombardi Comprehensive Cancer Center and MedStar Health, Washington, DC, USA, United States

C. Geyer. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

D. Slamon. UCLA David Geffen School of Medicine, Los Angeles, California, United States

G. Bobba. Roche Diagnostics International Ltd, United States

C. Lambertini. Oncology Biomarker Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States

S. De Haas. Oncology Biomarker Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States

E. Restuccia. F. Hoffmann-La Roche Ltd, Basel, Switzerland, Basel-Stadt, Switzerland

I. Vaz Luis. Gustave Roussy, Villejuif, France

D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom

I. Krop. Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

R. Anderson. Queens Medical Research Institute, University of Edinburgh, United States

Background: The ability to predict and identify ovarian function loss accurately after anticancer treatment is important for appropriate oncofertility counseling and to aid in therapy decision making for young women with early breast cancer (eBC). Anti-Müllerian hormone (AMH) has been proposed as both a pre- and post-treatment predictor of subsequent permanent loss of ovarian function. The present biomarker analysis conducted within two randomized controlled trials (RCTs) in a large and well-characterized patient population with HER2+ eBC receiving homogeneous treatment aimed to assess AMH use, alone and in combination with other hormonal biomarkers, for predicting loss of ovarian function at 36 months from randomization, i.e. approximately 2 years after end of therapy. **Methods:** BETH (NCT00625898) and KAITLIN (NCT01966471) were RCTs investigating adjuvant chemotherapy (CT) plus anti-HER2 therapy in high-risk HER2+ eBC patients. For the purpose of the present analysis, only samples of patients receiving currently adopted treatments were used, i.e. cohort 1A (6 cycles of docetaxel/carboplatin+trastuzumab (T)) and cohort 2A (3 cycles of docetaxel plus T followed by 3 cycles of anthracycline- and cyclophosphamide-based CT) of BETH trial, and arm 1 (3-4 cycles of anthracycline- and cyclophosphamide-based CT followed by 3-4 cycles of taxane plus T plus pertuzumab (P)) of KAITLIN trial. Women selected for this analysis were ≤45 years with known premenopausal status, available serum samples at baseline (pre-treatment) and/or end

of therapy and 36 months (\pm 6 months) from randomization (i.e. min of 2 samples in all cases). Selected samples were centrally tested measuring AMH, follicle stimulating hormone (FSH) and estradiol (E2) using Roche Elecsys assays. Permanent ovarian loss was defined as FSH >25 IU/L and E2 < 110 pmol/L at 36 months. Results: Of 194 included patients, 62 were from BETH and 132 from KAITLIN. 139 (71.6%) received both taxane and anthracycline- and cyclophosphamide-based CT and 55 (28.4%) taxane only. Pertuzumab was used in addition to trastuzumab in 132 (68.0%) patients. AMH values declined from baseline median 8.44 pmol/L to undetectable levels in many women at end of therapy (median 0.08 pmol/L), with partial recovery at 36 months (median 0.14 pmol/L). Ovarian loss at 3 years was observed in 56 women with AMH available at baseline (29.5%) and in 52 women with AMH available at end of therapy (29.7%). For prediction of ovarian loss, in ROC analysis, AMH measured at baseline showed AUC 0.784 (internally validated using bootstrap: 0.783). While age influenced risk of ovarian loss, addition to AMH only slightly improved AUC to 0.800 (internal validation: 0.795) while addition of baseline FSH and E2 did not improve prediction. AMH measured at the end of therapy showed AUC 0.741 (internal validation: 0.742), which increased slightly to 0.785 (internal validation: 0.781) with addition of age but without improved prediction with the addition of FSH and E2. The combination of AMH at baseline and end of therapy increased prediction slightly to 0.808 (internal validation 0.806) and with addition of age added to 0.820 (internal validation: 0.806). Conclusions: These results support the use of pretreatment measurement of AMH in predicting loss of ovarian function in women with HER2+ eBC aged \leq 45 receiving CT and anti-HER2 therapy. Measurement of AMH at end of treatment was comparably valuable to pretreatment and added slightly to the value of pretreatment sampling. Inclusion of ovarian function assessment by measuring AMH before commencing treatment can inform subsequent risk of ovarian function loss with value for fertility preservation counselling and treatment decisions. Further validation is required in larger cohorts.

PO2-11-07

Early Integration of Exercise into Breast Cancer Care: The MSK Healthy Living Program

Presenting Author(s) and Co-Author(s):

K. Rowed. Memorial Sloan Kettering Cancer Center, United States

S. Shen. Memorial Sloan Kettering Cancer Center, United States

A. Smith. Memorial Sloan Kettering Cancer Center, United States

B. Kelly. Memorial Sloan Kettering Cancer Center, United States

R. Magnoli. Memorial Sloan Kettering Cancer Center, United States

S. Corcoran. Memorial Sloan Kettering Cancer Center, United States

M. Emerzian. Memorial Sloan Kettering Cancer Center, United States

C. Cruz. Memorial Sloan Kettering Cancer Center, United States

E. Salehi. Memorial Sloan Kettering Cancer Center, United States

C. Anselmo. Memorial Sloan Kettering Cancer Center, United States

M. Robson. Memorial Sloan Kettering Cancer Center, United States

N. Iyengar. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: In patients with early-stage breast cancer, quality of life (QoL) worsens within 3-6 months following diagnosis. Physical activity (PA) can mitigate the adverse effects of treatment and improve QoL, and low PA level is associated with cancer recurrence and mortality. However, PA interventions are not included in standard cancer care. Early intervention to increase PA levels may improve QoL during active cancer therapy. The Healthy Living Program (HLP) at Memorial Sloan Kettering Cancer Center (MSK) is a lifestyle and survivorship program that engages early-stage breast cancer patients at the time of diagnosis using lifestyle risk stratification and matched referrals. We investigated whether early exercise intervention through the MSK HLP impacts QoL within the first months after cancer diagnosis. Methods: At the time of diagnosis, patients complete a lifestyle questionnaire (LQ), which is a composite of validated instruments, including the Godin Leisure Time Exercise Questionnaire (GLTEQ). Patients not meeting PA guidelines per the GLTEQ are offered a referral to an exercise physiologist (EP). The EP creates an individualized, home-based exercise program using the FITT Principle (Frequency, Intensity, Time, and Type). Patients meet with the EP every 4 weeks for 16 weeks; if exercise recommendations continue to be unmet, the program is extended. The Functional Assessment of Cancer Therapy-Breast (FACT-B) and 36-Item Short Form Survey Instrument (SF-36) were completed at baseline and the 16-week follow-up. Results: 252 patients enrolled between April 2020 – February 2023, of whom 92 volunteered to complete the QoL assessments. Median age was 53 years [range 23-84]; 12/252 (13.0%) of patients had ductal carcinoma in situ, 60/252 (65.2%) had Stage 1 disease, 17/252 (18.5%) had Stage 2 disease, and 3/252 (3.1%) had Stage 3 disease. 29/252 (31.5%) received chemotherapy, 62/252 (67.4%) received radiation, and 79/252 (85.9%) received hormone therapy. The mean baseline FACT scores were FACT-B: 116, FACT-G: 87, and FACT-B Trial Outcome Index (TOI): 73. At the 16-week follow-up, all QOL scores remained stable from baseline (means FACT-B: 118, FACT-G: 89, and TOI: 75). Improvements were observed among the subscales of the SF-36 from baseline to follow-up. The largest improvements were observed in physical and emotional role function scores, with 22% and 13% improvements from baseline to follow-up, respectively. Conclusions: A clinically implemented exercise intervention embedded in standard of care prevented decreases in QoL and improved physical and emotional functioning during the initial course of adjuvant breast cancer therapy. These findings

support early implementation of lifestyle modification after a breast cancer diagnosis.

PO2-11-08

Divorce and marital dissolution after Breast Cancer diagnosis in young breast cancer survivors in Mexico.

Presenting Author(s) and Co-Author(s):

S. Campos-Gomez. Centro Oncológico Estatal Issemym, Toluca de Lerdo, Mexico, United States

A. Ovando Trujillo. Centro Oncológico Estatal ISSEMyM, Estado de México, Mexico

Background: The current literature suggests that facing breast cancer can have significant effects on the relationship, for the better or for the worse. The needs of younger women with breast cancer are receiving increased attention, as 23.1% of all newly diagnosed invasive cancer occur in women age 50 or younger. Marital relationships, in particular, may be strained for younger cancer patients as they face health, emotional, and financial stressors from their cancer. The few studies that are available to date have examined the effect of breast cancer diagnosis on marital and relationship Purpose: We examined marital outcomes among young locally advanced breast cancer patients in our institution Methods: Eligible participants were women with diagnosis of breast cancer stage I–III, were at least 6 months post diagnosis, and age 50 or younger at the time of diagnosis. Demographic data collected. Participants reported their marital or relationship status at time of breast cancer diagnosis and after at least 6 months post diagnosis, whether they were currently married or a member of an unmarried couple, divorced, widowed or separated Other variables examined regarding a possible separation, the reasons for separation, the influence of the cancer on the relationship, the positive or negative perception of the impact of cancer on the relationship, the highest educational attainment and employment status. Descriptive statistics, percentages, frequencies, mean values and standard deviations were calculated. Results: In total, 75 patients were eligible for inclusion with a total of 250 patient with diagnosis of locally advanced breast cancer. The median age was 44 (range 30–48). Most of the patients, stage I or II tumors (55%). The divorce or separation rate was 36%, higher than reported in the literature (14.5%). Among those who were separated, 77% reported that cancer contributed to the separation or divorce. Also, for those who stayed together, 81% reported an impact of the cancer on the relationship, of which 50% reported a negative impact. Of those who had separated, none were in a new relationship. Conclusions: The emotional burdens of cancer may lead to marital stress for younger cancer survivors.; support systems are needed to assist them in the years following diagnosis. Because the marital relationship has multiple dimensions, it is also important to explore and identify those areas of the couple's life that are affected by the experience

PO2-11-09

European Lobular Breast Cancer Advocates: Bridging the Geographical Gaps in Lobular Breast Cancer Education and Awareness

Presenting Author(s) and Co-Author(s):

S. Freaney. Lobular Ireland, ELBCC, United States

H. Bonval. European Lobular Breast Cancer Advocates, France

E. Geven. European Lobular Breast Cancer Advocates, Netherlands

L. Petitti. Breast Cancer Care & Research Fund, Santa Monica, California, United States

R. Terveer. European Lobular Breast Cancer Advocates, Netherlands

C. Turner. Lobular Breast Cancer UK, United Kingdom

C. Brisken. ISREC - Swiss Institute for Experimental Cancer Research, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, United States

P. Derksen. Division of Molecular Biology, Netherlands Cancer Institute, Amsterdam, The Netherlands, United States

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

T. Koorman. UMC Utrecht, United States

A. LEE. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

S. Oesterreich. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

A. Salomon. Institut Curie, United States

G. Sflomos. Swiss Federal Institute of Technology Lausanne (EPFL), Switzerland

K. Van Baelen. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, Leuven, Vlaams-Brabant, Belgium

T. Lien. European Lobular Breast Cancer Advocates, Norway

D. Vareslija. RCSI University of Medicine and Health Sciences Dublin, United States

S. Linn. Netherlands Cancer Institute, Amsterdam, Netherlands

Introduction In 2019, Invasive Lobular Cancer (ILC) Patient Advocates attended the 3rd meeting of the European Lobular Breast Cancer Consortium (ELBCC), a scientific community focused on lobular research and treatment. European Lobular Breast Cancer Advocates (ELBCA) now have a network of ILC patient advocates across Europe. ILC is classified by the World Health Organisation as the most common Special Type of Breast Cancer. In 2022 there were 576,300 diagnoses of breast cancer in Europe, 15% ~86,500 were ILC. ILC is a histologically distinct breast cancer with diverse presentations including a tendency to metastasize to unique locations. Current endocrine therapies may have different effectiveness for ILC making treatment challenging. Current imaging tools are often unreliable with up to 30% of ILC tumours not identified on mammograms and detection is often delayed. Challenges There are no standardised European diagnostic or treatment protocols for ILC. ELBCA addresses this with collaborative efforts between ILC medical professionals and researchers. It's a major challenge because each European country has a different health care system and economic policy structure. It's also a challenge to streamline the translation of clinically accurate information to European patients in their own language. Not all European countries are members of the EU, there are a minimum of 24 official European languages. Established

European breast cancer patient organizations often don't distinguish between different histological subtypes. Current European policy and administrative processes have hindered the formation of a not-for-profit Advocacy Organization. Without such an organization, fundraising and collaborative efforts with others is difficult. Conclusions ELBCA has made significant progress towards raising awareness and increasing knowledge of ILC across Europe. Our poster will expand on these accomplishments as well as the following goals: Work with European and International ILC research and patient communities to better understand this unique histological subtype. Elevate ILC research priorities and inform European policy to recognize ILC as a distinct disease. Enhance education of ILC among primary HCP's and patients. Establish a recognized European ILC Advocacy Organization and collaborate with established BC organizations. Attend major BC research and clinical conferences. Lobby to achieve increased funding for ILC research and clinical trials.

PO2-11-10

Can chemotherapy-induced peripheral neuropathy be predicted? Implications for future prevention and treatment of this side-effect.

Presenting Author(s) and Co-Author(s):

A. Maity. Department of Hematology/Oncology at Lankenau Medical Center, Main Line Health, United States

N. Metz. Lankenau Institute for Medical Research, United States

K. Fleck. Lankenau Institute for Medical Research, United States

Z. Ali. Department of Hematology/Oncology at Lankenau Medical Center, Main Line Health, United States

A. Shevade. Department of Hematology/Oncology at Lankenau Medical Center, Main Line Health, United States

A. Ghaneie. Department of Hematology/Oncology at Lankenau Medical Center, Main Line Health, United States

M. Wallon. LIMR, United States

Background: The pain and sensory abnormalities associated with chemotherapy-induced peripheral neuropathy (CIPN) may persist for months or even years after chemotherapy. CIPN has a negative impact on routine activities, functions, and behaviors in the domestic, work, and social lives of cancer patients, adversely affecting the quality of their survivorship.

CIPN is a major adverse effect of taxanes and other agents, possibly requiring dose-reduction or early termination of treatment. Taxane-based regimens are first-line treatment in both early-stage and metastatic breast cancer and therefore place numerous women at risk for developing CIPN. Regrettably, taxane-induced neurotoxicity can be arduous to predict, and there are no preventive or curative treatments currently available.

Our work aims to assess a predictive tool for identification of patients at high risk of developing neuropathy and the progression of symptoms towards chronic CIPN.

We hypothesized that oxidative stress might be a triggering event for the development of CIPN and that changes in glutathione recycling can identify patients at high risk for developing prolonged and severe CIPN. This hypothesis is based on reports in the literature proposing that CIPN is triggered by damage to the myelin sheath, which protects nerves from damage, by drug-induced free radicals in and around the nerves. Damage to myelin, a lipid- and protein rich sheath, by lipid peroxidation can result in loss of signal transmission, false signaling, or signal overload. Prolonged exposure to elevated levels of free radicals might result in structural changes to the nerves.

Methods: Cancer patients seeking treatment at the Lankenau Medical Center Cancer center were asked to participate in our Institutional Review Board approved study of adverse effects.

In this on-going study, the cohort ($N_{\text{total}}=352$) includes 104 breast cancer patients that are predominantly Caucasian with 14.9% African American. The median age is 56 (range 26 – 82) and 60.9% were treated with a taxane-based regimen. Nearly half the breast cancer group were diagnosed with Stage I disease. All consented patients donated a tube of blood prior to each treatment and filled out the Rotterdam Symptom Checklist (RSCL). Blood samples were analyzed for glutathione recycling using the ChemoTox assay (MNT™ Test, MYNARI

Biomedical) and lipid peroxidation using a thiobarbituric acid reactive substances (TBARS) test (Cayman Chemical). All samples were analyzed in duplicate, and results analyzed using GraphPad Prism 8.4.3.

Results: Preliminary results from the first 83 breast cancer patients showed African American patients reported a higher rate of NCCN grade 2 and 3 CIPN while Caucasians reported a higher rate of severe, long-lasting CIPN. Our results showed that patients who reported CIPN at later cycles had diminished glutathione recycling capacity already after the first treatment. Drop in recycling capacity had an inverse relationship with lipid peroxidation and grade of CIPN. Both decreased recycling capacity and increase in lipid oxidation were apparent already after the first treatment in patients that reported CIPN after cycle 6-8 or after completion of treatment

Discussion: There are many proposed mechanisms for the development of CIPN. One mechanism that is shared by both most agents is damage induced by free radicals released following chemotherapy. We show that patients with reduced ability to neutralize free radicals have elevated and prolonged lipid peroxidation. Both processes precede the development of CIPN by several treatment cycles. Therefore, this test could identify patients that might benefit from other regimens rather than a taxane-based therapy. The test could also aid in the identification of patients for preventive therapy once such agents become available.

PO2-11-11

'Who's gonna take care of my babies?' The Impact of Children on Treatment Decisions for Women with Metastatic Breast Cancer: A qualitative analysis

Presenting Author(s) and Co-Author(s):

K. Tomczik. University of North Dakota School of Medicine and Health Sciences, Saint Cloud, Minnesota, United States

L. Coombs. University of North Carolina Chapel Hill School of Nursing, Chapel Hill, North Carolina, United States

Background: Many treatment options exist for metastatic breast cancer and decisions may be based on pathology, oncology clinician preference, performance status, financial considerations, patient values, or a combination of these factors. Some studies have characterized the importance that family and a strong support system can have on treatment decisions, but few have explicitly examined the impact that children—and grandchildren—have on treatment decisions in metastatic breast cancer (mBC). This qualitative study examined how being a parent or grandparent influences treatment decisions for women with metastatic breast cancer. Methods: A qualitative sub-analysis was conducted with a purposive diverse sample of thirteen women with metastatic breast cancer in the Eastern United States. Women of color were specifically oversampled relative to the regional population. Semi-structured interviews were conducted to explore treatment decision making, clinician-patient communication, and patient values relevant to their treatment decisions. Interviews were recorded, professionally transcribed, and coded by three independent coders. Any coding discrepancies were resolved through discussion. Thematic analysis identified recurrent themes important to women diagnosed with mBC. Results: Nearly 50% of the participants were women of color and of the 13 participants, 12 had children. When asked about what factors were important to them when making treatment decisions, a list of more than 10 themes emerged. Five participants said that children and grandchildren impacted their treatment decisions and were a crucial part of their cancer care. Other significant themes that emerged were side effects (54% of participants) and quality of life (46% of participants). Women who expressed that children were their top priority were also concerned about “looking sick” in front of their children. For women who said their grandchildren were the most important factor, being able to watch their grandchildren grow up was the primary motivator for their treatment decisions. Among the women who identified that side effects and quality of life were important, children either provided supportive care, helped with activities of daily living, or were too young to provide support. Conclusions: The presence of children and the relationships women with mBC have with their children was primary in making treatment decisions for their cancer. Of the participants in our study, having children—and grandchildren—rivalled other important factors such as quality of life and side effects of treatment, indicating the need to explore the impact that children have on cancer care as it is currently a poorly understood phenomenon. However, it is important not to make assumptions about patient treatment preferences based on whether women with mBC have children, instead, shared decision-making conversations should determine what is most important when deciding on a treatment plan. Future tools should integrate questions about family and children, and how these considerations may impact treatment decisions.

Table 1. Demographics of participants

Baseline characteristics	Participants	
	Average: 55.5	Range: 40-76
Age		
	<i>n</i>	%
Race		
Native American, Latina	1	7.69
Black or African American	4	30.77
White or Caucasian	7	53.85
Mixed Race	1	7.69
Ethnicity		
Hispanic or Latino	2	15.38
Not Hispanic or Latino	11	84.62

Table 2. Key findings of important factors and supporting quotes.

Children are primary factor	Supporting quote
	<i>"I wanted to keep living, and I wanted to try to act or appear to be as normal as I always have been pretty much so my kids—so it would be easier on them. That was very important to me." (Participant 1)</i>
	<i>"What was most important to me was to live, 'cause I had babies. When you get a cancer diagnosis, the first thing you think—the first thing that came to my mind, who's gonna take care of my babies. I was willin' to do whatever I had to do or could do to live." (Participant 4 before grandchildren)</i>
Children are primary factor	Supporting quote
	<i>"I'm gonna be a grandma, my first grandchild...That's even more reason for me to fight on." (Participant 4 after grandchildren)</i>
	<i>"I have a granddaughter I wanna see grow up, and for that to happen, I need to follow what they tell me to do." (Participant 6)</i>
Side effects/quality of life is primary factor	Supporting quote
	<i>"They know that I'm not a quitter, I'm not a giver-upper. I think we both have that understanding that I want to do whatever I can to hang in there and have a good quality of life. As long as I'm the one that's—I think the patient needs to be the one that determines what quality of life. If I want to go through those side effects, that's my choice." (Participant 2)</i>
	<i>"...if they told me that I needed massive surgery or massive chemo, I would've questioned that because I'm not interested in living an unpleasant life for no reason." (Participant 5)</i>

PO2-11-12

The power of storytelling to heal, build community, and understand the experiences of Black breast cancer survivors

Presenting Author(s) and Co-Author(s):

L. McCullough. Emory University, United States

C. Young. CRY Creative, United States

C. Bowden. Emory University, United States

M. Gardner. Emory University, United States

B. Berry. Emory University, United States

A. Smith. Emory University, United States

J. Bryant. N/A, United States

Background: The BRIDGE community focus group was designed to support and empower current and former Black breast cancer patients. The overarching goals of the focus group were to provide a mechanism for participants to amplify their voices through storytelling, foster healing, and establish a supportive community. Additionally, the research team aimed to gather qualitative data on social support, treatment adherence barriers, interactions with medical providers, and experiences with race and racism within and outside of the healthcare system.

Approach: The focus group consisted of six sessions, each with a specific agenda and activities. Participants were encouraged to keep journals throughout the program. Each session began with an icebreaker and journal discussion. Session-specific activities were designed to encourage self-reflection, exploration of personal identities, and discussion of fears. These topics were explored through creative outlets such as role-play, storyboards, and jewelry-making. Each session ended with a unifying affirmation and opportunity for fellowship.

Results: We enrolled 10 Black women previously diagnosed with breast cancer and provided a safe space for them to reflect on their breast cancer journey, associated fears, and the role of race in their healthcare experience. Participants discussed positive and negative experiences with healthcare providers, highlighting the knowledge and access gaps that often exist in marginalized communities. The program also provided insights into the multi-level concept of support and its impact on breast cancer outcomes. Participants discussed the positive aspects of familial and community support but identified several areas where system and structural supports may have improved their outcomes. After completing all six sessions, women reported an improvement in their overall self-actualization and purpose—with several describing their time in the program as 'life-changing'. Notably, the focus group facilitated deep connection and friendship among participants and improved general wellness and satisfaction.

Discussion: Through the sharing of personal narratives and supportive discussions, the focus group created a safe environment where participants felt empowered to express their emotions, address challenges, and dismantle fears related to breast cancer mortality. The BRIDGE research team will summarize the themes that emerged across sessions to share with scientific, clinical, and community stakeholders. In parallel, they will explore opportunities for continued community building and support for participants beyond the focus group sessions. Overall, this storytelling focus group showcased the significance of amplifying the voices of historically marginalized groups, providing support, and fostering community. The insights gained have the potential to inform future interventions and support services for Black breast

cancer survivors, addressing their unique needs and challenges and ultimately improving cancer health equity.

PO2-12-01

Five-year quality of life (QOL) trajectories among young breast cancer (BC) survivors

Presenting Author(s) and Co-Author(s):

T. Sella. Sheba Medical Center, United States

Z. Yue. Data Sciences, Dana-Farber Cancer Institute, United States

K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States

S. Gelber. Dana-Farber Cancer Institute, Boston, MA, USA, United States

R. Tamimi. Weill Cornell Medicine, New York, NY, USA, United States

J. Peppercorn. Massachusetts General Hospital, Boston, MA, USA, United States

L. Schapira. Stanford Cancer Institute, Palo Alto, CA, USA, United States

V. Borges. University of Colorado Cancer Center, Colorado, United States

S. Come. Beth Israel Deaconess Medical Center, Boston, MA, USA, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Rosenberg. Weill Cornell Medicine, New York, New York, United States

Background: Young BC survivors are at risk for impaired QOL in part due to issues that are unique to their life stage. We sought to characterize trajectories of QOL in the 5 years following diagnosis among young BC survivors as well as evaluate patient and clinical characteristics associated with poorer or deteriorating QOL trajectories over time. **Methods:** Women diagnosed with stage I-III BC at age ≤ 40 enrolled in the Young Women's BC Study, a prospective cohort in North America, who completed ≥ 2 study surveys through 5 years of post-diagnosis follow-up. QOL was evaluated with the Cancer Rehabilitation Evaluation System (CARES) physical, psychosocial, and sexual subscale scores. Demographic, treatment, and clinical characteristics were ascertained through surveys and chart review. Longitudinal trajectories for each CARES subscale were defined using group-based trajectory modeling; associations between patient/clinical characteristics and trajectory group membership were estimated for each subscale using multivariable multinomial logistic regression. **Results:** Among 900 women, median age at diagnosis was 36 (range: 17-40) 89% were white, 2% Black, and 4% Hispanic. At baseline, 73% were partnered, 61% parous and 49% perceived themselves as financially comfortable. Most had hormone-receptor positive (74%), HER2-negative (70%) BC, and most received chemotherapy (82%); 36% underwent mastectomy with radiation. Physical and psychosocial scores each clustered into 4 trajectories, with $>75\%$ of participants clustering in groups reflecting excellent or good QOL that was stable over time and few (6% for physical and 4% for psychosocial) clustering into groups that reflected poorer QOL at baseline that did not improve over time. Sexual health trajectories were more variable, clustering into 5 trajectories, with over half of participants clustered into groups reflecting good (35%) or excellent (20%) QOL that remained relatively stable over time, 22% clustered into a trajectory that was poor at baseline but moderately improved over follow-up, 13% in a group that reflected deteriorating from moderate-to-poor QOL and 11% in a group with poor QOL at baseline that did not improve over time. In multivariable regression analyses (Table), factors associated with clustering in a poorer trajectory (vs. clustering in an excellent trajectory), in multiple QOL domains included baseline financial discomfort (associated with poorer QOL across all 3 domains), mastectomy+radiation (vs. lumpectomy, associated with poorer QOL across all 3 domains); chemotherapy receipt (associated with poorer physical and sexual health trajectories); and baseline BMI >25 (vs. 18.5-24.9, associated with poorer physical and poorer/deteriorating

sexual health trajectories). Conclusions: Young BC survivors follow distinct QOL trajectories in survivorship. While most will not experience substantial QOL impairment through the first 5 years following diagnosis, a substantial minority report persistently poor or deteriorating QOL. The association between more extensive local therapy and poorer physical/psychosocial/sexual health trajectories underscores the importance of communicating the potential for negative QOL outcomes when women are making surgical decisions. Additionally, the pervasive impact of financial wellbeing on multiple QOL domains supports the potential value of systematic screening for and addressing of financial distress to prevent or mitigate financial toxicity in survivorship

Factors associated with clustering in poorer/deteriorating (vs. excellent) QOL trajectories

	Poorer Physical Trajectory* OR (95%CI)	Poorer Psychosocial Trajectory* OR (95%CI)	Poorer Sexual Trajectory* OR (95%CI)	Deteriorating Sexual Trajectory* OR (95%CI)
Financially comfortable vs. not	0.11 (0.04-0.27)	0.18 (0.07-0.45)	0.42 (0.24-0.74)	0.76 (0.46-1.28)
Overweight vs. normal weight	3.30 (1.47-7.41)	-	2.76 (1.39-5.48)	1.97 (1.01-3.86)
Obese vs normal weight	3.43 (1.35-8.72)	-	3.42 (1.54-7.58)	1.50 (0.63-3.60)
Chemotherapy vs. not	3.85 (1.07-13.81)	-	3.38 (1.22-9.38)	1.06 (0.55-2.05)
Mastectomy/RT vs lumpectomy	2.64 (1.04-6.73)	4.43 (1.52-12.92)	3.74 (1.79-7.82)	1.41 (0.72-2.78)
Mastectomy/no RT vs lumpectomy	2.12 (0.84-5.36)	2.13 (0.71-6.42)	2.95 (1.38-6.30)	1.72 (0.92-2.82)
*Reference trajectory=excellent QOL				

*Reference trajectory=excellent QOL

PO2-12-02

Frailty among long-term breast cancer survivors

Presenting Author(s) and Co-Author(s):

C. Wang. Vanderbilt University, United States

J. De Vis. Vanderbilt University Medical Center, United States

K. Nguyen. Vanderbilt University, United States

M. Alford. Vanderbilt University, United States

B. Jia. Vanderbilt University, United States

B. Chakravarthy. Vanderbilt University Medical Center, Nashville, Tennessee, United States

X. Shu. Vanderbilt University Medical Center, United States

Background Cancer and its associated treatments may accelerate aging, resulting in increased frailty in survivors. However, the effect of breast cancer (BC) and treatment on frailty among long-term BC survivors has not been well investigated. This study aims to evaluate frailty prevalence and its association with clinical characteristics and treatment among 5-year BC survivors. **Methods** This study included 353 5-year BC survivors and 214 non-cancer control women aged ≥ 40 who were recruited to an ongoing breast health study at Vanderbilt University Medical Center between 2004 and 2017, and completed an online survey between May, 2022 and June 2023. Information collected includes demographics, lifestyle, disease history, and current health/functional status. A 26-item cumulative deficit index (CDI) was calculated as the proportion of deficits presented, including aging-related diseases, physical and mental health, activities of daily living, and social well-being, based on survey responses. CDI was categorized as robust (≤ 0.2), pre-frail ($0.2 < \leq 0.35$), and frail (> 0.35). Cancer characteristics and treatment information was gathered from tumor registry. Multinomial logistic regression models were used to assess the association of CDI levels with case-control status, and BC clinical characteristics and cancer treatment among BC cases, with adjustment for age at survey (years), follow-up duration ($5 \leq 10$ and > 10 years), and baseline Charlson comorbidity index (0, 1, and ≥ 2), and additional adjustment for BC stage and subtype in the analysis of treatment. **Results** The median time interval from BC diagnosis to survey was 12 years (range 5-34 years) for BC survivors. 90% of the participants were White. On average, BC patients were 3.8 years older at survey than controls [mean \pm SD (range) 64.5 \pm 9.2 (40-88) vs 60.7 \pm 10.3 (40-87), $p < 0.001$]. Among BC survivors, 41% had stage I, 39% stage II, and 8% stage III-IV cancer; 62% had a hormone receptor+/HER2- BC, followed by 22% HER2+ and 16% triple-negative BC. The majority of BC survivors underwent surgical resection (97%), and $> 50\%$ received hormone therapy (59%), radiation therapy (53%), and chemotherapy (51%). BC survivors had a higher CDI score than controls (median 0.23 vs 0.19, $p = 0.01$), with 34% and 18% of BC survivors being pre-frail and frail, compared with 25% and 16% in controls. After multivariable adjustment, BC survivors had a non-significantly increased prevalence of pre-frailty with odds ratio (OR) and 95% confidence interval (CI) of 1.49 (0.98-2.25), but a similar prevalence of frailty [OR (95% CI) = 1.08 (0.65-1.79)] compared to controls. BC survivors aged 40-65 had significantly elevated odds of pre-frailty [OR (95% CI) = 2.59 (1.44-4.63)]. Among BC survivors, frailty was significantly associated with stage [stage III-IV vs I: OR (95% CI) = 4.03 (1.27-12.78)] and chemotherapy [OR (95% CI) = 4.39 (1.71-11.30)], particularly among survivors aged ≥ 65 and 10-year survivors, but not BC subtype. Radiation therapy was associated with increased odds of pre-frailty among BC survivors aged 40-65. **Conclusions** This study suggests that long-term BC survivors younger than 65 are at increased odds of pre-frailty than non-cancer women. Frailty is associated with BC stage and chemotherapy among BC survivors, and radiotherapy

among survivors younger than 65. More research is needed to investigate whether specific cancer treatment regimen is associated with frailty and other factors (e.g. lifestyle and genetics) that may modify the risk of frailty.

The associations of frailty with cancer characteristics and treatments among breast cancer survivors

	All participants		Age 40-65		Age ≥65		Follow-up <10 years		Follow-up ≥10 years	
	Pre-frailty	Frailty	Pre-frailty	Frailty	Pre-frailty	Frailty	Pre-frailty	Frailty	Pre-frailty	Frailty
Breast Cancer^a	1.49 (0.98-2.25)	1.08 (0.65-1.79)	2.59 (1.44-4.64)	2.00 (0.97-4.13)	0.79 (0.41-1.52)	0.53 (0.25-1.13)	1.72 (0.73-4.07)	0.86 (0.26-2.65)	1.4 (0.87-2.26)	1.08 (0.61-1.91)
Stage^b										
Stage I	Reference		Reference		Reference		Reference		Reference	
Stage II	1.51 (0.85-2.75)	1.70 (0.83-3.48)	1.6 (0.67-3.81)	1.80 (0.75-5.40)	1.42 (0.57-3.53)	1.33 (0.46-3.87)	1.75 (0.47-6.57)	1.03 (0.39-4.40)	1.54 (0.77-3.10)	1.84 (0.80-4.22)
Stage III-IV	2.61 (0.89-7.65)	4.03 (1.27-12.70)	3.9 (0.95-16.24)	0.96 (0.09-10.20)	1.36 (0.25-8.11)	6.20 (1.29-30.51)	0.91 (0.13-6.31)	0.86 (0.10-7.47)	4.14 (1.05-16.39)	7.08 (1.83-31.27)
Subtype^b										
HR+HER2-	Reference		Reference		Reference		Reference		Reference	
HR-HER2-	0.72 (0.31-1.69)	1.46 (0.61-3.51)	0.66 (0.21-2.08)	2.05 (0.59-7.02)	0.66 (0.16-2.60)	1.29 (0.34-4.80)	0.31 (0.05-3.75)	1.16 (0.14-9.71)	0.86 (0.24-2.19)	1.52 (0.57-4.04)
HER2+	0.83 (0.41-1.68)	0.96 (0.41-2.21)	0.84 (0.32-2.17)	1.33 (0.41-4.34)	0.53 (0.16-1.75)	0.62 (0.17-2.17)	0.36 (0.09-1.51)	0.42 (0.08-2.23)	1.03 (0.44-2.41)	1.21 (0.45-3.25)
Treatment^b										
Surgery only	Reference		Reference		Reference		Reference		Reference	
Chemotherapy	1.23 (0.69-2.55)	4.39 (1.71-11.20)	1.90 (0.67-5.30)	3.73 (0.99-14.02)	1.32 (0.41-4.25)	6.50 (1.44-29.37)	1.70 (0.30-9.25)	0.64 (0.09-5.08)	1.12 (0.46-2.59)	4.14 (1.40-12.22)
Radiation therapy	1.41 (0.85-2.30)	1.34 (0.60-2.19)	2.34 (1.07-5.12)	1.77 (0.71-4.46)	0.95 (0.44-2.05)	0.70 (0.26-1.87)	1.90 (0.52-7.00)	1.42 (0.31-6.45)	1.31 (0.73-2.34)	1.12 (0.53-2.36)
Hormone therapy	0.90 (0.44-1.84)	0.91 (0.37-2.26)	0.63 (0.22-1.86)	0.66 (0.19-2.30)	1.37 (0.47-4.06)	1.42 (0.36-5.63)	0.19 (0.05-1.24)	0.41 (0.04-4.59)	1.32 (0.59-2.95)	1.26 (0.46-3.58)

OR, odds ratio; CI, confidence interval; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

^aOR (95% CI) were estimated using multinomial logistic regression models, with adjustment for age at survey, follow-up time, and baseline comorbidity.

^bOR (95% CI) were estimated using multinomial logistic regression models, with adjustment for age at survey, follow-up time, baseline comorbidity, cancer stage, and cancer subtype.

PO2-12-03

Home-based Resistance Exercise Improves Fatigue and Functional Strength in Female Breast Cancer Survivors Post Chemotherapy

Presenting Author(s) and Co-Author(s):

T. Moncrief. University of Texas Medical Branch at Galveston, United States

C. Moon. University of Texas Health Science Center at San Antonio, United States

A. Gonzalez. University of Texas Health Science Center at San Antonio, United States

A. Stepanenko. University of Texas Health Science Center at San Antonio, United States

T. Cortes. University of Texas Health Science Center at San Antonio, United States

D. Patel. University of Texas Medical Branch at Galveston, Galveston, Texas, United States

Introduction: Chemotherapy is associated with an increase in fatigue and loss of strength in female breast cancer (BCa) survivors. Strength training has been found to reverse these effects, however, the COVID pandemic added a complexity to clinic-based exercise intervention. The purpose of this study is to determine if a home-based resistance exercise program can attenuate these debilitating effects in a cohort of breast cancer survivors that have recently completed chemotherapy. **Methods:** Ten BCa survivors who completed chemotherapy within the previous 6 months were recruited to participate in a 12-week home-based resistance exercise proof of concept study. Exercise was performed 3 times per week, supervised via Zoom. Participants completed 2-3 sets of upper body and lower body exercises to volitional fatigue. Self-reported fatigue was measured using the respective subscale from the EORTC QLQ-C30. Strength was measured using hand grip dynamometry and isometric leg strength. Physical function was measured using the 6-minute walk test. Assessments were completed at baseline and end of study. As a comparison, age matched controls (AMCs) were recruited to complete cross-sectional analysis of each of these variables. A one-way analysis variance was done with Tukey's post hoc test. Significance was set at $p < 0.05$. **Results:** BCa survivors were 46.4 ± 12.5 years old with a BMI of 28.11 ± 5.25 . AMCs were 50.3 ± 13.3 years old with a BMI of 30.8 ± 5.8 . There was no significant difference in patient characteristics. A significant difference in self-reported fatigue was found between groups ($F=18.52$; $p < 0.0001$). Post hoc analysis found significant difference in fatigue between BCa survivors at baseline (48 ± 23) and the age matched controls ($p < 0.0001$). Exercise was able to significantly reduce fatigue in BCa survivors (21 ± 15 ; $p=0.003$) to levels not significantly different to AMCs (3.3 ± 7.5). A significant difference was also observed between groups for right-hand grip strength ($F= 4.923$; $p=0.015$) and left-hand grip strength ($F=8.685$, $p=0.001$). Post hoc analysis found a significant increase in right hand grip strength in the BCa survivor group following the intervention ($p=0.012$). Left hand grip strength was found to be significantly lower at baseline than AMCs ($p=0.048$). Left hand grip strength was significantly increased in BCa survivors at end of study ($p < 0.001$). Finally, a significant difference was observed between groups for isometric leg strength ($F= 3.699$; $p=0.038$). Post hoc analysis found a significant difference in leg strength in the BCa survivor group following intervention (pre: 105.9 ± 50.6 N-M; post: 158.4 ± 13.2 N-M; $p=0.030$) which was 16.5% higher than AMCs (127.4 ± 36.5 N-M). No significant difference was found in 6-minute walk distance. However, there was a 21% increase in the distance walked for BCa survivors after interventions (pre: 441.2 ± 66.5 m; post: 501.4 ± 123 m), identical to distances walked by AMCs (501.4 ± 90.8 m). **Conclusion:** The results of our study suggest that a virtually supervised resistance exercise program can attenuate the negative effects of chemotherapy in BCa survivors to levels similar to their peers that never had breast cancer. Further research

using powered sample sizes is needed to validate these results.

PO2-12-04

Suboptimal adherence to adjuvant endocrine therapy (ET) in Brazilian women with early-stage estrogen receptor-positive (ER+) breast cancer

Presenting Author(s) and Co-Author(s):

- D. Assad-Suzuki. Hospital Sírio-Libanês, Brasília, Brazil, Brazil
- H. Resende. Hospital Jardim Amália, United States
- D. Santos. Hemolabor, Goiânia, Goiás, Brazil, Goiânia, Goiás, Brazil
- F. Moura. Hospital Sírio-Libanês, Brasília DF, Brazil , Instituto Hospital de Base do Distrito Federal, DF, Brazil, Brazil
- S. Oliveira. Liga Norte Riograndense contra o Câncer , RN, Brazil, Brazil
- A. Shimada. Hospital Sirio Libanês, São Paulo , Brazil, Brazil
- A. Galvão. Uniceub, DF, Brazil, Brazil
- B. Souza. DASA Oncologia/Hospital Brasília, Brasília, DF, Brazil, Brazil
- A. Castro. Hospital Sírio-Libanês, Brasília DF, Brazil, Brazil
- M. Andrade. Liga Norte Riograndense contra o Câncer , RN, Brazil, United States
- Y. Beckedorff. Hospital Sirio Libanês, São Paulo, Brazil, Brazil
- M. Magalhães. Hospital Universitário Evangélico Mackenzie, CURITIBA, Parana, Brazil
- C. Souza. Hospital de Câncer de Barretos, Barretos, Brazil
- C. Paiva. Barretos Cancer Hospital, Barretos, Brazil
- D. Pereira. ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, Brazil
- A. Rodrigues. Universidade Federal de Minas Gerais, Brazil; ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, United States
- D. Rosa. Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul, Brazil
- R. Barroso-Sousa. Dasa Oncology, United States

Background: Adjuvant ET reduces breast cancer recurrence and increases overall survival among patients with early-stage ER+ breast cancer, however a suboptimal number of patients in fact takes oral medicine as prescribed. In Brazil, there is a paucity of data about adherence to adjuvant ET. This study aims to evaluate adherence to adjuvant ET in Brazilian women with early breast cancer and to evaluate clinical and sociodemographic characteristics associated with higher or lower adherence. Methods: Women with history of early-stage ER+ invasive carcinoma of the breast on adjuvant ET for at least 6 months were invited to participate of this study. Adherence was assessed with questionnaire Morisky Medication Adherence Scale (MMAS-8) and high adherence was defined by a MMAS-8 score=8. Demographic and medical information, site of treatment (private versus public), degree of education (completed high school vs not) were reviewed from medical records. Quality of life was assessed using EORTC QLQ C30 and BR-23 forms, sexuality was evaluated with the Female Sex Function Index questionnaire. Additionally, patients were interviewed about return to work. Data collection was done with RedCap software. Qualitative variables were compared between groups using the Chi-square or exact Chi-square test and for quantitative variables the non-parametric Mann-Whitney test was used. Multivariable analysis was performed using Poisson regression. $P < 0.05$ was considered significant. Analyzes were performed in SAS 9.4. Results: From June 2021 to May 2023, a total of 461 women with ER+ early-stage breast cancer from 12 Brazilian institutions were included in this analysis. The mean age was 56.0 years (range 22-93), 47.7%

were non-white and 38.7% were premenopausal. A total of 233 women (50.6%) had private insurance and the remaining were treated in public institutions. Median duration of ET use was 2.78 years (range 6 months- 9.61 years). High adherence to adjuvant endocrine therapy was present in 55.7% of patients. Median age of high adherent woman was higher than low adherent ($p=0.005$). Factors significantly associated with high adherence were no use of ovarian suppression ($p=0.0095$), use of anti-Her2 therapy ($p=0.0462$). Furthermore, higher scores for EORTC QLQ-C30 global health status ($p=0.017$) and in specific domains, including role functioning ($p=0.007$), emotional functioning ($p< 0.0001$), cognitive functioning ($p< 0.001$), social functioning ($p = 0,0005$), higher scores for EORTC BR23 body image ($p< 0.001$) and future perspective ($p = 0.0198$) were also associated with high adherence. Higher EORTC QLQ-C30 cognitive function score was the only variable associated with high adherence ($p < 0.0001$) to ET in multivariate model. Conclusion: Using the MMAS-8, only 55.7% of Brazilian women with stage I-III ER+ breast cancer reported high adherence to endocrine therapy. This suboptimal adherence rate leads to important questions such as the impact on the prognosis of this population

Characteristic with adjusted prevalence ratio for the occurrence of High adherence

Characteristic	Adjusted Prevalence Ratio	
	PR (CI 95%)	p-value
EORTC QLQ-C30 cognitive function score	1.0083 (1.0057; 1.0110)	<0.0001

PR: Prevalence ratio; EORTC: European Organisation for Research and Treatment of Cancer

PO2-12-05

Scalp Cooling with the Capelli System to Reduce Doxorubicin-induced Alopecia in Patients with Localized Breast Cancer: A Phase 2 Randomized Controlled Trial

Presenting Author(s) and Co-Author(s):

- C. Paiva. Barretos Cancer Hospital, Barretos, Brazil
- F. Dias. Barretos Cancer Hospital, Barretos, Brazil, United States
- A. Matthes. Hospital NovaBene, Ribeirão Preto, Brazil, United States
- B. Paiva. Barretos Cancer Hospital, Barretos, Brazil, United States
- C. Souza. Hospital de Câncer de Barretos, Barretos, Brazil
- D. Lacerda. Barretos Cancer Hospital, Barretos, Brazil, United States
- A. Antoniazzi. Barretos Cancer Hospital, Barretos, Brazil, United States
- M. Machado. Barretos Cancer Hospital, Barretos, Brazil, United States
- M. Godinho. Barretos Cancer Hospital, Barretos, Brazil, United States
- C. de Lima. Barretos Cancer Hospital, Barretos, Brazil, United States
- C. Cárcano. Barretos Cancer Hospital, Barretos, Brazil, United States
- M. Zorzetto. Hospital das Clínicas Samuel Libânio, Itajubá, MG, United States

Introduction: Chemotherapy-induced alopecia (CIA) is a distressing side effect of breast cancer (BC) treatment. Scalp cooling (SC) devices have shown promise in reducing the severity of CIA. However, the impact of reducing alopecia occurrence on the quality of life of Brazilian patients remains unclear.

Objectives: This study aimed to assess the effectiveness of the Capelli System, a new SC device, in reducing CIA.

Methods: This was a single-center, controlled, randomized phase 2 clinical trial involving women with TNM stage I to III BC undergoing neoadjuvant or adjuvant doxorubicin-based chemotherapy (AC regimen: doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m², i.v., q21 days), with or without a taxane (paclitaxel or docetaxel). Participants were randomized in a 1:3 ratio into the scalp cooling (n = 33) or control (n = 12) groups. All participants were advised to cut their hair short and avoid heat-inducing tools or processes throughout chemotherapy, using cold or lukewarm water and wide-toothed combs for hair washing. The primary efficacy endpoint was grade 2 alopecia (>50% hair loss or hair shaving due to alopecia) after 4 cycles of AC. Secondary endpoints included measures of hair loss distress (BRHL) and body image (BRBI) from the EORTC Quality of Life Questionnaire - Breast Cancer Module (EORTC QLQ-BR23), as well as symptoms of anxiety and depression from the Hospital Anxiety and Depression Scale (HADS). Fitzpatrick phototype and hair type were assessed. Statistical analyses utilized generalized linear models and Fisher's Exact test (p-value < 0.05).

Results: Patients were enrolled from October 11, 2019, to January 17, 2022. Out of the 45 patients included, 8 were excluded: 2 due to intolerance, 1 with alopecia associated with COVID-19, and 5 who withdrew consent (2 with grade 2 headache, 3 without justification). The median age was 44.6 (min-max: 23-63) years, with 18 (40%) and 27 (60%) receiving adjuvant and neoadjuvant chemotherapy, respectively. Grade 2 alopecia or hair shaving occurred in 52% of scalp cooling patients and 100% of controls (p = 0.003), demonstrating a significant 48% reduction in alopecia. There were no significant differences in HADS-A, HADS-D, BRHL,

or BRBI scores between the two groups. Alopecia occurrence did not show significant associations with skin or hair types. No serious adverse events related to the scalp cooling device were reported.

Conclusions: SC with the Capelli System significantly reduced CIA by half. Some patients experienced discomfort or headaches and discontinued device use. Further research is needed to understand why reduced alopecia rates do not correlate with improvements in body image or reduced hair loss distress.

PO2-12-06

Comparative Study on Bone Mineral Density in Premenopausal Patients with Estrogen Receptor-Positive Breast cancer in ASTRRA study: a 5-year follow-up study

Presenting Author(s) and Co-Author(s):

E. Shin. Asan Medical Center, United States

S. Kim. Yonsei University college of medicine, United States

M. Park. Department of Surgery, Chonnam National University Medical School, Gwangju, United States

H. Kim. Korea Cancer Center Hospital, Seoul, Republic of Korea

Y. Jung. Department of Surgery, Ajou University School of Medicine, United States

J. Ryu. Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam, Ulsan-gwangyoksi, Republic of Korea

E. Park. Department of Surgery, Dong-A University College of Medicine, United States

S. Kim. Soonchunhyang University College of Medicine, United States

E. Lee. National Cancer Center, United States

M. Lee. Soonchunhyang University College of Medicine, United States

J. Park. Hallym University Sacred Heart Hospital, United States

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

S. Kang. Yeungnam University Hospital, United States

W. Lim. Department of Surgery, Ewha Womans University School of Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

H. Youn. Surgery, Chonbuk National University Hospital, United States

H. Park. Department of Surgery, Breast Cancer Center, Gil Medical Center, Gachon University College of Medicine, United States

K. Park. Korea University Anam Hospital, Republic of Korea

T. Kim. Department of Surgery, Busan Paik Hospital, College of medicine, Inje University, United States

S. Park. Department of Surgery, Inha University Hospital, Inha University School of Medicine, United States

C. Lim. Soonchunhyang University Bucheon Hospital, United States

G. Kwak. Department of Surgery, Inje University Sanggye Paik Hospital, United States

C. Park. Department of Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, United States

H. Shin. Department of Surgery, Myongji Hospital, United States

Y. Yoo. Konkuk University Medical Center, United States

S. Kang. Department of General Surgery, Keimyung University School of Medicine, United States

B. Kim. Department of Surgery, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, United States

H. Kim. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background With the positive outcomes associated with Ovarian Function Suppression (OFS) treatment as reported in the ASTRRA study, which compare two therapeutic strategies, tamoxifen alone and ovarian function suppression (OFS) in premenopausal patients after chemotherapy, the role of OFS has getting important. However, considering the increased risk of bone density reduction associated with postmenopause in women, the understanding these effects is crucial in devising strategies that not only effectively combat the cancer but also concurrently safeguard the patients' bone health. This study aimed to compare the impacts of two therapeutic strategies, tamoxifen alone and OFS on bone mineral density (BMD) in premenopausal patients after chemotherapy. **Methods** Of the 1483 premenopausal enrolled in ASTRRA study, we focused on a subset of 522 patients who had undergone BMD examinations at diagnosis, 3 years and 5 years after diagnosis. Patients were stratified into three categories: normal, osteopenia, osteoporosis, and we examined the changes in their classifications over the 3-year and 5-year periods from baseline to identify any deterioration in bone density. Also, Patients were examined ovarian function every 6 months for 2 years and have different randomization times. Further categorization was carried out according to the time of randomization, which means starting time of OFS after recovery of ovary function. Lastly, we conducted a subset analysis using data from the Asan Medical Center (AMC), specially focused on the absolute value of one density measured in g/cm³. **Results** The median age of 522 patients was 41.1 and at baseline, a higher incidence of osteopenia was observed in the OFS addition group (p=0.028). Both analysis of change in BMD categories of from baseline to 3-year and baseline to 5-year period showed no significant differences between TAM only and TAM+OFS group (3-year: p=0.567, 5-year: p=0.600). However, there was a significant increased risk of bone density deterioration in the OFS addition group, when randomization occurred at the first visit (HR= 2.970, p=0.008). Within the AMC subset, statistically significant decrease in BMD were observed in the OFS addition group at the spine (p=0.023) and femur (p=0.040) over a baseline to 3-year period. Although a decrease in BMD was also observed over a baseline to 5-year period at both the spine and femur, this change was not statistically significant. **Conclusion** This study revealed a deleterious impact on bone density associated with the addition of OFS, compared to tamoxifen-only treatment. Remarkably, our findings also indicated that early suppression of ovarian function exerts even more detrimental influence on bone health in premenopausal, estrogen receptor-positive breast cancer patients, who have recovered ovarian function.

Change between baseline to 5 years according to randomization time interval

	Time interval(months)	TAM only(ref)(%)	TAM+OFS(%)	Odds ratio(95% CI)	p-value
Overall		62/223(27.80)	77/299(25.75)	0.901(0.609-1.332)	0.600 0.008
Visit1	0	4/31(12.90)	11/36(30.56)	2.970(0.836-10.545)	0.092
Visit2	6	40/116(34.48)	39/158(24.68)	0.623(0.368-1.054)	0.078
Visit3	12	13/42(30.95)	16/70(22.86)	0.661(0.280-1.562)	0.345
Visit4	18	5/21(23.81)	7/23(30.43)	1.400(0.366-5.350)	0.623
Visit5	24	0/13(0.0)	4/12(33.33)	Infinity	

The table shows the risk associated with bone health deterioration according to the duration of randomization, thus specifying the time interval between the recovery and suppression of ovarian function.

PO2-12-07

Risk of anaphylaxis associated with the use of pertuzumab or other biologics with potential for use outside the hospital

Presenting Author(s) and Co-Author(s):

T. Sanglier. F. Hoffmann-La Roche Ltd, Basel, Basel-Stadt, Switzerland

T. Chambers. Roche Products Limited, Welwyn Garden City, UK, United Kingdom

J. Harton. Genentech, Inc., South San Francisco, CA, USA, United States

L. Wahyudi. F. Hoffmann-La Roche Ltd, Basel, Switzerland, Basel-Stadt, Switzerland

M. Genevray. F. Hoffmann-La Roche Ltd, Basel, Switzerland, Switzerland

E. Restuccia. F. Hoffmann-La Roche Ltd, Basel, Switzerland, Basel-Stadt, Switzerland

C. Droz-Perroteau. University of Bordeaux, INSERM CIC-P 1401, Bordeaux PharmacoEpi, Bordeaux, France, France

C. Dang. Breast Medicine Service, Memorial Sloan-Kettering Cancer Center, United States

BACKGROUND

Intravenous (IV) pertuzumab (P) and trastuzumab (H) are approved in the US for the treatment of HER2-positive breast cancer. P and H are also approved as a fixed-dose combination for SC injection (pertuzumab, trastuzumab, and hyaluronidase-zzxf; PH FDC SC). PH FDC SC may offer the possibility of treatment outside a hospital setting by a healthcare professional.

Anaphylactic reactions can be a concern with the use of biologics. PH is also frequently initiated with six to eight cycles of taxanes, which can also be associated with anaphylaxis. We used administrative claims data to evaluate the risk of anaphylaxis associated with the real-world administration of PH or other biologic drugs in the real world.

Our objective was to evaluate the risk of anaphylaxis associated with the administration of P and to contextualize the risk estimate by using other biologics that can be used outside the hospital as a benchmark.

METHODS

Cohorts of incident users were selected using retrospective records from a US healthcare claims database (IQVIA). Patients included were privately insured in the US, aged 16 to 65 years, and initiated a treatment of interest between 2012 and 2021. Possible and severe anaphylactic events (PAEs) were identified using the algorithm developed by the US Food and Drug Administration (FDA) Sentinel Initiative and updated with ICD10 codes (PMID: 34181291). PAEs were attributed to a drug if it occurred on the day of administration or the day after. The prevalence proportion (PP) of PAE was used to approximate the risk of anaphylaxis at each cycle. A sensitivity analysis using the proportion of prior P use amongst the cases of PAE beyond cycle 1 in the H cohort was conducted to approximate how many cases of PAE could have been missed at cycle 1 of P due to a depletion of susceptibles (as P IV and H may be administered sequentially in any order, patients with a PAE from H would not receive scheduled P and thus be excluded from the P cohort).

RESULTS

A total of 1,919,748 patients constituted 27 cohorts. Of them, 184,414 patients initiated monoclonal antibodies (mAbs) in 12 cohorts of which 12,264 and 184 initiated P IV and PH FDC SC, respectively. In the P IV cohort, seven PAE events were observed up to cycle 6 and none after. The PP at cycle 1 of P was 1.63 per 10,000 patients (95% confidence interval [CI] = 0.45, 5.94). The risk was comparable to that of other mAbs where anaphylaxis risk is described

as uncommon/rare (Table). Accounting for a potential depletion of susceptibles increased the PP at cycle 1 of P to 2.45/10,000 (95% CI = 0.83, 7.19). No PAEs were reported in patients treated with PH FDC SC.

CONCLUSIONS

Using one of the largest datasets available, results suggest the risk of PAE with P administration could be within the range of what is observed with other mAbs that can be administered outside of the hospital. All events were observed when patients are expected to receive treatment at the hospital due to taxane administration. No PAE events were identified for PH FDC SC, but there were few patients in this cohort. Efforts are ongoing to identify a larger cohort treated with PH FDC SC.

Risk of anaphylaxis by mAb

Molecule	n	PP per 10,000 patients (95% CI)	Anaphylaxis*
P IV	12,264	1.63 (0.45, 5.94)	Uncommon†
PH FDC SC	184	0.00 (0.00, 204.51)	Uncommon†
Adalimumab	733	13.64 (2.41, 76.87)	Rare‡
Certolizumab	3,457	0.00 (0.00, 11.10)	Missing
Denosumab	68,367	0.15 (0.03, 0.83)	Rare‡
Golimumab	6,763	1.48 (0.26, 8.37)	Rare‡
Infliximab	32,183	2.18 (1.05, 4.49)	Uncommon†
Mepolizumab	2,290	0.00 (0.00, 16.75)	Rare‡
Omalizumab	14,236	3.51 (1.50, 8.22)	Rare‡
Tocilizumab	9,389	3.20 (1.09, 9.39)	Rare‡
H IV	22,885	3.50 (1.77, 6.90)	Rare‡
Ustekinumab	11,543	3.47 (1.35, 8.91)	Rare‡

* According to summary of product characteristics.

† $\geq 1/1,000$ to $< 1/100$.

‡ $\geq 1/10,000$ to $< 1/1,000$.

CI = confidence interval; H = trastuzumab; IV = intravenous; P = pertuzumab;

PH FDC SC = pertuzumab, trastuzumab, and hyaluronidase-zzxf.

PO2-12-08

Increased burden of genetic variants in idiopathic cardiomyopathy genes is associated with cancer therapy-related cardiomyopathy

Presenting Author(s) and Co-Author(s):

N. Norton. Mayo Clinic, United States

T. Nguyen. Mayo Clinic Florida, Jacksonville, Florida, United States

J. Reddy. Mayo Clinic Florida, Jacksonville, Florida, United States

J. Harvey. Mayo Clinic Florida, Florida, United States

M. weidner. Mayo Clinic, United States

A. Arnold. Mayo Clinic Florida, Jacksonville, Florida, United States

L. Evans. Mayo Clinic Florida, Jacksonville, Florida, United States

L. Vallow. Mayo Clinic, Jacksonville, United States

P. Advani. Mayo Clinic, United States

Background: Breast cancer (BC) patients are at significant risk of therapy-related cardiotoxicity, but prediction of which patients will experience cardiotoxicity and the severity of the outcome are lacking. We hypothesized that germline genetic variants are potential risk factors for cancer treatment-related cardiomyopathy (CTRC) and in this study, we focused on rare non-synonymous variants within 57 genes deemed causative of familial and sporadic forms of idiopathic cardiomyopathies.

Methods: We developed a clinical database and biorepository for patients receiving any potentially cardiotoxic cancer therapy at Mayo Clinic Florida. Enrollment is ongoing and includes consent to access external records. Patient data is extracted from records at baseline, completion of treatment and then once per year. The clinical database includes the following datasets: demographics, pathology, chemotherapy, radiation, echocardiography, cardiac MRI, PET/CT scan, blood pressure, BMI, labs, treatment complications. Treatment complications includes pre-existing conditions (smoking, alcohol and drug use history, hypertension, diabetes, coronary artery disease, hyperlipidemia, prior stroke or myocardial infarction, peripheral vascular disease, renal failure); cardiac medications at baseline; cardiac side-effects; time to cardiotoxicity; cardiotoxicity interventions and outcomes.

Exome sequencing was performed by the Mayo Clinic NGS core on the first 86 patients in the registry, average of ~120x read depth following Illumina's standard protocol for the NovaSeq 6000 and S4 flow cell. Genomic variants were extracted for 57 genes known to be causative of dilated, hypertrophic and arrhythmogenic right ventricular cardiomyopathies and channelopathies. Putative risk variants in known cardiomyopathy genes were defined as non-synonymous variants with a frequency of < 0.0004 in the GnomAD database. We compared the number of patients with putative risk variants in those groups with and without CTRC.

Results: 84/86 patients had BC diagnosis. Key characteristics are described in the table below. 60/86 (70%) patients had at least one putative risk variant in one of 31 genes (there were no risk variants identified in 27/57 genes). The average number of putative risk variants per patient within the CTRC group was higher than that observed in patients without CTRC (2.06 vs 1.62). Post-hoc analysis suggested this difference is largely from patients with >2 risk variants in the group who experienced CTRC (N=7/17, 41%) compared to those who did not (N=14/69, 20%),

p=0.023.

Conclusions: Rare missense variants in the causative genes of idiopathic cardiomyopathies are potential risk factors for CTSC and risk may be increased in patients with a higher burden of variants. Analysis of the genetic data from patients that continue to be accrued in this study, including effects of additional clinical risk factors will be undertaken to improve prediction of cardiotoxicity.

Table 1

Drug regimen	# patients total (# radiation)	# patients without CM (# >2 risk variants)	# patients with CM (# >2 risk variants)
Anthracycline, no anti-HER2	30 (22)	24 (5)	6 (1)
Anthracycline + antiHER2 therapy	5 (3)	0 (0)	5 (2)
Taxol + anti-HER2 therapy	48 (29)	42 (8)	6 (4)
Taxotere only	1 (1)	1 (0)	0 (0)
CDK4	1 (1)	1 (1)	0 (0)
Letrozole	1 (0)	1 (0)	0 (0)

Distribution of putative cardiomyopathy genetic variants in 86 cancer patients with and without treatment-related cardiomyopathy, separated by treatment regimen

PO2-12-09

Insomnia, Pain, Anxiety, Distress, Fatigue, and Functional Impairment in Patients with Breast Cancer

Presenting Author(s) and Co-Author(s):

K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States

V. Grzegorzcyk. Department of Health Sciences Research, Mayo Clinic, Rochester, MN, Rochester, Minnesota, United States

D. Pachman. Center for Palliative Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, Rochester, Minnesota, United States

S. Mitchell. Outcomes Research Branch; National Cancer Institute, Bethesda, MD, Bethesda, Maryland, United States

B. Liu. Department of Hospital Internal Medicine, Mayo Clinic Health System, Mankato, MN, Mankato, Minnesota, United States

D. Smith. Department of Oncology, Mayo Clinic, Rochester, MN, United States

C. O'Sullivan. Mayo Clinic, Rochester, MN, USA, ROCHESTER, Minnesota, United States

S. Ehlers. Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, United States

J. Herrin. Yale University School of Medicine, New Haven, CT, New Haven, Connecticut, United States

P. Rahman. Department of Health Sciences Research, Mayo Clinic, Rochester, MN, United States

A. Cheville. Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery and Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN, United States

Background: SPPADE symptoms (Sleep disturbance, Pain, Physical function impairment, Anxiety, Depression/distress, and Energy deficits/fatigue) may result from cancer and its treatment. The aim of this analysis was to characterize SPPADE symptoms in patients with breast cancer.

Methods. SPPADE data were drawn from the Enhanced, EHR-facilitated Cancer Symptom Control (E2C2) study, a stepped-wedge pragmatic cluster-randomized trial designed to evaluate a symptom management intervention in routine practice (NCT03892967). Symptom severity was measured on a 0-10 scale via a survey administered by patient portal, in-clinic tablet, or interactive voice response system (by phone) prior to, during, or soon after an outpatient oncology encounter. Scores of 4-6 were categorized as "moderate" and ≥ 7 as "severe." In this analysis, only the data from each patient's initial survey were included.

Results. A total of 9,651 patients with breast cancer completed an initial E2C2 survey between March 2019 and January 2023. The proportion of patients with moderate or severe SPPADE symptoms were as follows: 22% moderate and 10% severe for insomnia; 18% moderate and 7% severe for pain; 17% moderate and 7% severe for anxiety; 15% moderate and 5% severe for emotional distress; 25% moderate and 12% severe for fatigue; and 22% moderate and 8% severe for impaired physical function. Table 1 presents score means and standard deviations by demographic subgroup.

Conclusions. SPPADE symptoms are common in patients with breast cancer. These observations warrant routine implementation of symptom surveillance and management in breast oncology.

Funding acknowledgement: The Improving the Management of symPToms during And following Cancer Treatment (IMPACT) Consortium is a Cancer Moonshot Research Initiative under the authorization of the 2016 United States 21st Century Cures Act. This research was supported by the National Cancer Institute of the NIH, UM1CA233033 (Mayo Clinic, Rochester, MN).

Insomnia, Pain, Anxiety, Distress, Fatigue, and Functional Impairment in Patients with Breast Cancer

Characteristic	N	Insomnia mean score (SD)	Pain mean score (SD)	Anxiety mean score (SD)	Emotional distress mean score (SD)	Fatigue mean score (SD)	Physical dysfunction mean score (SD)
Age at enrollment							
< 40	488	2.8 (2.5)	2.7 (2.3)	3.1 (2.5)	2.5 (2.3)	3.3 (2.5)	2.1 (2.2)
40-64	3,905	2.9 (2.5)	2.3 (2.4)	2.5 (2.4)	2.1 (2.3)	3.2 (2.6)	2.4 (2.4)
≥ 65	3,791	2.4 (2.5)	2.2 (2.4)	1.9 (2.2)	1.7 (2.2)	3.0 (2.5)	2.6 (2.5)
Gender							
Female	9,518	2.6 (2.5)	2.2 (2.4)	2.2 (2.3)	1.9 (2.2)	3.0 (2.5)	2.4 (2.4)
Male	133	2.0 (2.3)	1.9 (2.3)	1.6 (2.3)	1.6 (2.2)	3.2 (2.7)	2.9 (2.5)
Ethnicity							
Hispanic	181	3.1 (2.8)	2.7 (2.6)	2.7 (2.7)	2.3 (2.6)	3.4 (2.6)	2.6 (2.4)
Non-Hispanic	9,344	2.6 (2.5)	2.2 (2.3)	2.2 (2.3)	1.9 (2.2)	3.0 (2.5)	2.4 (2.4)
Unknown/not reported	126	3.0 (2.9)	2.5 (2.3)	2.7 (2.7)	2.3 (2.6)	3.0 (2.6)	2.6 (2.6)
Race							
White	9,120	2.6 (2.5)	2.2 (2.3)	2.2 (2.3)	1.9 (2.2)	3.0 (2.5)	2.4 (2.4)
Black/African American	149	3.8 (3.2)	3.4 (3.1)	3.0 (3.1)	2.7 (3.0)	3.7 (2.9)	3.2 (2.9)
American Indian/Alaskan Native	28	2.6 (2.5)	2.9 (2.4)	2.5 (2.4)	2.2 (2.2)	3.8 (2.5)	2.6 (2.3)
Asian/Pacific Islander	200	2.9 (2.7)	2.4 (2.5)	2.6 (2.5)	2.3 (2.4)	3.2 (2.5)	2.4 (2.4)
Other/Unknown	154	3.3 (3.0)	2.8 (2.6)	2.9 (3.0)	2.6 (2.9)	3.5 (2.8)	2.6 (2.6)
Marital status							
Married/Life Partnership	6,653	2.6 (2.4)	2.0 (2.2)	2.1 (2.3)	1.8 (2.2)	2.9 (2.4)	2.2 (2.4)
Divorced/Separated	938	3.0 (2.6)	2.6 (2.7)	2.7 (2.6)	2.3 (2.4)	3.6 (2.7)	2.9 (2.6)
Widowed	1,124	2.4 (2.5)	2.2 (2.5)	1.9 (2.3)	1.9 (2.3)	3.1 (2.6)	2.8 (2.5)
Single	917	3.0 (2.7)	2.6 (2.6)	2.5 (2.6)	2.2 (2.4)	3.5 (2.7)	2.6 (2.5)
Unknown	19	2.4 (2.8)	1.8 (2.0)	2.5 (2.9)	2.1 (2.3)	2.7 (2.6)	2.0 (2.0)
Employment							
Retired	4,273	2.4 (2.5)	2.2 (2.4)	1.9 (2.2)	1.7 (2.2)	3.0 (2.6)	2.6 (2.5)
Employed	4,187	2.6 (2.4)	2.0 (2.1)	2.3 (2.3)	1.9 (2.1)	2.9 (2.4)	2.0 (2.2)
Not employed/not working for pay	857	3.2 (2.8)	2.7 (2.6)	2.9 (2.7)	2.5 (2.6)	3.7 (2.7)	2.8 (2.6)
Disabled	303	3.6 (2.9)	4.2 (2.9)	3.6 (2.8)	3.2 (2.7)	4.8 (2.7)	4.27 (2.6)
Education							
Less than high school	149	3.0 (2.9)	2.9 (2.8)	2.5 (2.8)	2.1 (2.8)	3.5 (2.9)	2.9 (2.6)
High school graduate	1,762	2.5 (2.6)	2.2 (2.4)	2.0 (2.4)	1.8 (2.3)	3.0 (2.5)	2.5 (2.5)
Some college/Associate	2,550	2.7 (2.5)	2.3 (2.4)	2.2 (2.3)	1.9 (2.2)	3.1 (2.5)	2.5 (2.5)
Bachelor's degree	1,948	2.7 (2.4)	2.1 (2.2)	2.2 (2.3)	1.9 (2.1)	2.9 (2.4)	2.2 (2.3)
Master's/Doctoral degree	1,441	2.4 (2.3)	1.8 (2.0)	2.0 (2.1)	1.7 (1.9)	2.7 (2.3)	2.1 (2.2)
Unknown	1,801	2.6 (2.6)	2.3 (2.5)	2.6 (2.5)	2.3 (2.5)	3.4 (2.7)	2.6 (2.6)

PO2-12-10

Age-specific outcomes in breast cancer patients treated with aromatase inhibitors - A national inpatient sample database analysis

Presenting Author(s) and Co-Author(s):

R. Patel. Community hospital of San Bernardino, CA, United States

A. Chitkara. University of California, Riverside, United States

Z. Patel. University of California, Riverside, United States

M. Patel. Trumbull regional medical center, Ohio, United States

D. Patel. Rush University, Illinois, United States

H. Kavani. Geisinger Community Medical Center, PA, United States

F. Anamika. Hackensack Meridian Ocean University Medical Center, United States

F. Patel. University of California, Riverside, United States

Background:

This study aims to investigate the age-specific outcomes of breast cancer patients undergoing aromatase inhibitors therapy. Currently, no research exists on the age-specific differences in outcomes for this patient population. This study seeks to fill this knowledge gap and provide valuable insights into the various outcomes of these patients.

Methods:

This retrospective study analyzed hospitalization data from the National Inpatient Sample (NIS) between January 2016 and December 2019 using STATA/BE 17.0 for statistical analysis. It focused on breast cancer patients treated with aromatase inhibitors, evaluating outcomes like mortality, length of stay, charges, and clinical outcomes. We used univariate regression and logistic analysis, with ICD-10 codes utilized for data classification.

Results:

A total of 5,994 weighted hospitalizations were identified, consisting of breast cancer patients being treated with aromatase inhibitors. For patients aged below 65 (n=1,919), the inpatient mortality rate was 1.8% (n=35), while for patients aged 65 and above (n=4,075), it was slightly higher at 2.3% (n=94). However, there was no statistically significant difference in inpatient mortality between the two age groups (adjusted odds ratio [aOR] = 1.21 [0.82-1.78], p=0.339).

The average length of stay (LOS) was similar for both age groups, with patients below 65 having a mean LOS of 4.75 days and those aged 65 and above having a mean LOS of 4.71 days. Total charges (\$) in the younger population (< 65) were incurred at a mean of \$60,782.73 (56,764.18-64,801.27), compared to lesser charges in the elderly at a mean of \$54,734.38 (52,339.83-57,128.94).

The occurrence of pathological fractures was higher in patients below 65, with a rate of 1.6% (n=31), compared to 0.8% (n=33) in patients aged 65 and above (aOR = 0.47 [0.28-0.78], p=0.004). Regarding venous thromboembolism (VTE), the occurrence was 5.5% (n=105) in patients below 65 and 4.8% (n=195) in patients aged 65 and above. There was no significant difference between the two age groups (aOR = 0.86 [0.68-1.10], p=0.237).

The occurrence of acute cerebrovascular accidents (CVA) was 0.6% (n=11) in patients below 65 and 1.6% (n=65) in patients aged 65 and above, with an aOR of 2.58 (1.38-4.80), indicating

a significantly higher likelihood of CVA in the older age group (p=0.003).

Patients aged 65 and above had a higher occurrence of myocardial infarction (MI) compared to patients below 65, with rates of 2.1% (n=85) and 0.1% (n=2), respectively. The aOR for MI was 2.35 (1.39-3.98), indicating a significantly higher likelihood of MI in the older age group (p=0.001). There was no statistically significant difference in the occurrence of hypertensive crisis (HTN crisis) between the two age groups (aOR=1.47 [0.93-2.34], p=0.09).

Conclusion:

Among breast cancer patients receiving aromatase inhibitors, there was no significant difference in in-patient mortality between those aged below 65 and those aged 65 and above. Both age groups had similar lengths of stay and charges incurred. There was no statistically significant difference in VTE and HTN crisis odds. However, patients below 65 had a higher occurrence of pathological fractures, while patients aged 65 and above had a higher likelihood of acute cerebrovascular accidents and myocardial infarction. Further guidelines must be established to improve inpatient morbidity and mortality in this patient population.

Breast cancer patients on aromatase inhibitors therapy

Breast cancer patients on aromatase inhibitors therapy

	% Age <65 (n= 1919)	% Age >=65 (n= 4075)	aOR
Mortality	1.8	2.3	1.21 (0.82 -1.78) (p=0.339)
LOS (Days)	4.75 (4.52 - 4.98)	4.71 (4.57 - 4.85)	-
Pathological fractures	1.6	0.8	0.47(0.28-0.78) (p=0.004)
VTE	5.5	4.8	0.86(0.68-1.10) (p=0.237)
Acute CVA	0.6	1.6	2.58(1.38-4.80) (p=0.003)
HTN crisis	1.4	2.0	1.47(0.93-2.34) (p=0.09)
MI	0.1	2.1	2.35(1.39-3.98) (p=0.001)

PO2-12-11

Ocular Toxicity of Tamoxifen in Patients with Breast Cancer

Presenting Author(s) and Co-Author(s):

H. alhouz. Damascus University, United States

A. azmeh. Damascus University, United States

M. Saifo. Damascus University, United States

Background: The latest recommendations in breast cancer treatment protocols with tamoxifen indicate that it should be used from five to 10 years. It depends mainly on the cumulative dose of the drug in the body. Despite its multiplicity, the various studies conducted on this subject did not reach conclusive results. **Objectives:** This research aims to study retinopathy associated with hormonal treatment of breast cancer using tamoxifen. **Methods:** A cross-sectional study was conducted at Al-Mouwasat University Hospital on a sample of 130 eyes according to (G-Power) with a statistical power of 95%. The participants were briefed on the research and consented on the ethical considerations. Then, the patients who entered the study were interrogated, clinically examined, and were asked about their medical history, the time of breast cancer diagnosis along with the details about the treatment protocols they underwent or currently undergoing. The refractive errors were measured with an automatic refractive device, then they were examined on the slit lamp to investigate the refractory media, then the corrected and uncorrected visual acuity were taken. Finally, after ensuring that the inclusion criteria were met and excluding those who fulfil one or more of the exclusion criteria, optical coherence tomography was performed using SD-OCT technique to measure and review the retinal thickness map in circles of 1-3-6 mm, respectively, to notice possible changes on it. **Results:** We found that the use of tamoxifen irrespective to cumulative dose leads to increase in the macula thickness values in the upper and lower sectors within the 3 mm circle, and to significant decrease in the macula thickness values in the upper and lower sectors within the 6 mm circle, in addition to decrease in nasal sector thickness within the circles of 3 and 6 mm. **Conclusion:** We conclude that the difference between people treated with tamoxifen and those not treated with it is not limited to the occurrence of crystals deposition in the macular area or the presence of a cavity in the central macula (with or without typical cystic macular edema), but rather to existence of macula thickness differences unrelated to the cumulative dose of the drug, whether by increase or decrease in thickness of the upper, lower and nasal segments.

PO2-12-12

REaCT 5G: A randomized study comparing bone pain after 5 days of filgrastim or one day of pegfilgrastim for primary febrile neutropenia prophylaxis during neo-/adjuvant chemotherapy for early breast cancer

Presenting Author(s) and Co-Author(s):

T. Ng. The Ottawa Hospital Cancer Centre, Ottawa, Ontario, Canada
Y. Zhang. Ottawa Hospital Research Institute, Ottawa Methods Centre, Ontario, Canada
C. Stober. Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
J. Shamess. Champlain Regional Cancer Care Patient and Family Advisory Council, United States
N. Mills. St. Joseph Family Medical Clinic, United States
S. Nicholls. Ottawa Hospital Research Institute, Ottawa Methods Centre, United States
M. Ibrahim. Northern Ontario School of Medicine University, United States
D. Davoudpour. Thunder Bay Regional Health Sciences Centre, United States
C. Armiento. Thunder Bay Regional Health Sciences Centre, United States
M. Savard. The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada, United States
M. Rushton. University of Ottawa & Ottawa Hospital Research Institute, United States
A. Awan. University of Ottawa, Ottawa Hospital Research Institute, United States
S. Sehdev. University of Ottawa, Ottawa Hospital Research Institute, United States
J. Hilton. The Ottawa Hospital Cancer Centre, United States
X. Song. University of Ottawa, Ottawa Hospital Research Institute, United States
R. Goel. University of Ottawa, Ottawa Hospital Research Institute, United States
F. Macdonald. The Ottawa Hospital Cancer Centre, United States
K. Daigle. The Ottawa Hospital Cancer Centre, United States
L. Vandermeer. Ottawa Hospital Research Institute, Ontario, Canada
M. Taljaard. University of Ottawa, Ottawa Hospital Research Institute, Ottawa Methods Centre, United States
M. Clemons. Ottawa Hospital, Ottawa, Ontario, Canada

Background: Granulocyte colony stimulating factor (G-CSF) such as filgrastim (FIL) or pegfilgrastim (PEG) significantly reduces the risk of febrile neutropenia (FN) and treatment-related hospitalization in patients with early breast cancer receiving chemotherapy. However, patients receiving G-CSF can experience clinically significant bone pain. Previous studies examining post-G-CSF bone pain were mostly based on physician pain assessment and compared mixed doses (30/60/100 µg/kg) of PEG vs. FIL (5µg/kg/day or 300 µg/day) given for 7 to 14 days. Based on a randomized non-inferiority study, 5 days of FIL is considered non-inferior to 10 days of FIL to prevent FN and hospitalizations and is frequently used in patients receiving chemotherapy for breast cancer. Patient-reported bone pain after 5 days of FIL vs. single dose of PEG has never been compared in a prospective randomized study and has important implications for patient and physician treatment preferences.

Methods: In this multicenter, open-label trial, patients receiving neo- / adjuvant chemotherapy for early-stage breast cancer requiring primary FN prophylaxis with G-CSF were randomized

1:1 to either 5 days of FIL (300 µg or 480µg if ≥ 90 kg) or 1 day of PEG (6 mg) with each cycle of chemotherapy. The primary endpoint was bone pain using area under the curve (AUC) of the daily pain score from days 1-5 (AUC score 0 to 40) during cycle 1. We used linear regression adjusting for stratification factors [cancer center (2 centers) and chemotherapy regimen (taxane (TAX) or anthracycline (ANTH)-based during cycle 1] and prespecified baseline covariates: age, pain, and use of pain medications pre-chemotherapy. Supportive analysis of bone pain across cycles 1 to 4 was conducted using repeated linear regression. Key secondary endpoints included incidence of FN, hospitalizations, chemotherapy delay, dose-reduction or discontinuation, and chemotherapy-related deaths.

Results: From June 2021 to March 2023, 233 patients were enrolled, with 217 patients (108 FIL / 109 PEG) in the intention-to-treat analysis; 16 (7.4%) patients were excluded because of incomplete follow-up. Participants were mean age 55.6 years; almost exclusively female (99.1%), on chemotherapy regimen TAX 57% vs. ANTH 43%, had mean baseline pain score 1.12, and prevalence of pain medication use pre-chemotherapy was acetaminophen 14.7%, non-steroidal anti-inflammatory drugs (NSAIDs) 6.0% and opioids 3.2%. Characteristics were balanced between arms (Table 1). After repeated measures linear regression adjusted for age, chemotherapy regimen, baseline pain, and use of pain medications pre-chemotherapy, mean AUC for bone pain at cycle 1 was 10.94 for FIL and 10.12 for PEG (mean difference 0.82; 95% CI: -1.59, 3.23; $p = 0.516$). There was no significant difference between arms across treatment cycles (interaction $p = 0.785$; mean time-averaged difference 0.28; 95% CI: -1.75, 2.32). Across cycles 1 to 4, mean peak pain over 5 days post-GCSF was 3.27 vs. 3.41 ($p=0.700$); frequency of bone pain during first 8 days (pain score > 0) was 52.5% vs. 51.3%; $p=0.358$, and mean frequency of severe pain (pain score ≥ 5) was 17.5% vs. 15.2%; $p=0.014$ for FIL vs. PEG, respectively. The incidence of FN [4.6% vs. 0%, absolute difference 4.6% (95% CI: -0.3%, 9.5%; $p=0.069$)] and hospitalization [FN and non-FN related: 10.2% vs. 1.8%, absolute difference of 8.4% (95% CI: 1.2%, 15.5%; $p=0.021$)] was higher in the FIL group. There were no significant differences in chemotherapy delay (13% vs. 11%; $p=0.815$), dose reduction (14.8% vs. 14.7%; $p=0.999$), early discontinuation (8.3% vs. 5.5%; $p=0.580$), or chemotherapy-related death (0.9% vs. 0%; $p=0.996$) in the FIL vs. PEG groups, respectively.

Conclusion: There was no difference in patient-reported bone pain after 5 days of FIL or PEG, even after controlling for important clinical factors. Importantly, the study observed higher rates of FN and hospitalizations in patients receiving FIL for 5 days only.

Table 1

	5-Day-FIL	PEG
N	108	109
Age [median (IQR)]	56.5 (18.3)	57.0 (19.0)
Sex (MF)	female: 106 male: 2	female: 109
Chemotherapy (%)		
- Anthracycline-based	46 (43)	47 (43)
- Taxane-based	62 (57)	62 (57)
Trastuzumab %	25.9	36.7
Baseline pain score		
- Mean (SD)	1.07 (1.77)	1.17 (1.82)
Pain medications at baseline (%)		
- Opioid	4 (3.7)	3 (2.8)
- Acetaminophen	15 (13.9)	17 (15.6)
- NSAIDs	5 (4.6)	8 (7.3)
- Other	0 (0)	1 (0.1)

Baseline Characteristics

PO2-13-01

Weight change in early breast cancer-based baseline body mass index and treatment

Presenting Author(s) and Co-Author(s):

M. Schoen. Department of Medicine, Saint Louis University School of Medicine, United States

D. Gopukumar. Department of Health & Clinical Outcomes Research, Saint Louis University School of Medicine, United States

A. Akula. Department of Health & Clinical Outcomes Research, Saint Louis University School of Medicine, United States

K. Farrell. Department of Surgery, Saint Louis University School of Medicine, United States

A. Schad. Department of Medicine, Saint Louis University School of Medicine, United States

L. Hinyard. Department of Health & Clinical Outcomes Research, Saint Louis University School of Medicine, United States

Background: Early-stage breast cancer is a common condition with significant effects on health, both as a result of treatment and underlying conditions. Breast cancer has been associated with obesity, weight gain, and diabetes. Little is known about changes in weight after breast cancer diagnoses based on baseline weight. Additionally, weight change may differ due to treatments, such as chemotherapy or hormone therapy.

Methods: A retrospective study was conducted using deidentified electronic medical records data from a national health informatics provider and insurer database to identify the cohort. The cohort inclusion criteria included women with a diagnosis of breast cancer, a breast biopsy procedure, and a breast cancer surgery within a 1-year period of time from 2010-2018. Body-mass index (BMI) within 1 month of initial biopsy was collected, and weight at 6 months and 1 year after initial biopsy was used to calculate the percentage change in weight. Treatment with chemotherapy within 1 year of diagnosis and hormone therapy within 6 months was also collected. Patients were divided into standard BMI categories as well as BMI >25 vs. ≤25. ANOVA was used to compare outcomes of weight change based on BMI, chemotherapy, and hormone therapy. Linear regression was used to analyze the effects of age, BMI, chemotherapy, and hormone therapy with weight change at 1 year.

Results: In 4,541 patients diagnosed with breast cancer, 3,896 patients had weight available at 6 months and 3,406 had weight available at 1 year. Mean age at diagnosis was 61.5 years (standard deviation (SD) 12.4) with mean BMI of 29.9 at baseline (SD 7.3) and weight of 79.5 kg (SD 20.2). Chemotherapy was administered in 1206 patients (26.6%) and hormone therapy in 1,644 (36.2%) with 210 (4.6%) receiving both therapies. Overall, patients lost a mean of 0.6 kg (0.5% change, SD 5.1) at 6 months and 0.6 kg at 1 year (0.4% change, SD 5.7). At one year, patients with BMI < 25 gained 0.74% of body weight vs. lost 1.1% of weight in BMI >25 ($p < 0.001$). Patients treated with chemotherapy lost 1.4% body weight vs. lost 0.23% in patients without chemotherapy ($p < 0.001$) and patients treated with hormone therapy lost 0.12% of body weight vs. lost 1.3% without hormone therapy. A linear regression model including age, BMI, chemotherapy, and hormone therapy to explain weight change at one year was statistically significantly better than a baseline model at explaining the weight change at one year [$F(4,2474)=61.05$]. Increasing age ($b=-0.125$; $t=-10.546$; $p < .001$; 95% CI for beta :0.14 -0.10), BMI ($b=-0.178$; $t=-9.428$; $p < .001$; 95%CI :0.22 -0.14), and chemotherapy ($b=-1.643$; $t=-4.645$; $p < .001$; 95% CI: 2.4 -0.95) were all significant predictors associated with weight loss at one year while hormone therapy was also a significant predictor but was associated with weight

gain (b=0.846; t=2.428; p=.015; 95% CI: 0.16-1.5).

Conclusions: Women with early breast cancer experienced significant changes in weight in the year after diagnosis. Women with lower BMI gained weight while those with BMI >25 lost weight. Increasing age, BMI, and treatment with chemotherapy was associated with weight loss while use of hormone therapy was associated with weight gain. Further study of weight changes after breast cancer diagnosis are appropriate to understand outcomes and mitigate effects of treatments.

Table 1: Percentage weight change across BMI groups by chemotherapy use

	<18 n=28	18-25 n=922	25-30 n=987	30-35 n=725	>35 n=744
No chemotherapy	2.4%	0.60%	0.26%	-0.70%	-1.6%
Chemotherapy	2.9%	0.88%	-1.2%	-1.5%	-4.1%
Total	2.5%	0.68%	-0.15%	-0.97%	-2.5%

PO2-13-02

Detection of SPEN mutations in advanced breast cancer by circulating tumor cell-free DNA

Presenting Author(s) and Co-Author(s):

C. Dai. Massachusetts General Hospital, United States

H. Barnes. Massachusetts General Hospital, United States

A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States

A. Putur. Massachusetts General Hospital, United States

J. Keenan. Massachusetts General Hospital Cancer Center, United States

B. Moy. Massachusetts General Hospital, United States

S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States

R. Corcoran. Massachusetts General Hospital, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background: Alterations in the SPEN gene are rare in primary breast cancer (~3%, ref: TCGA). SPEN is a hormone-inducible transcriptional repressor with known functions in orchestrating X-inactivation in females. Additionally, SPEN has been implicated as a potential estrogen receptor co-repressor and molecular partner of NCOR2 as well as epigenetic modifiers such as KMT2D and HDACs via C-terminal interactions. SPEN loss-of-function is associated with tamoxifen resistance in preclinical models. However, the landscape of SPEN alterations in advanced breast cancer remains poorly described. The primary objective of this study was to evaluate the frequency and different types of SPEN alterations in metastatic breast cancer (MBC).

Methods: A query was performed on all patients at an academic institution with available genomic testing from Guardant360, a next-generation sequencing cell-free DNA (cfDNA) assay, evaluating 500 genes in total. Patients with MBC were identified, and specific alterations in SPEN as well as co-alterations were extracted. Silent and germline mutations were excluded from analysis. Retrospective review was conducted to determine clinicopathologic characteristics such as age, hormone and HER2 receptor status, menopausal status, and therapy at time of the detected mutation.

Results: Among 366 patients with MBC and available cfDNA, 8.5% (n=31) had an alteration detected in the SPEN gene. Median age of patients with SPEN mutations was 66 years (range 33-92). A majority of patients (90%) had HR+ disease (n=28/31), with HR-/HER2+ disease and TNBC additionally representing 3% (n=1/31) and 6% (n=2/31) of cases, respectively. SNVs were most frequent, comprising 89% (n=42/47) of all alterations. Indels were additionally identified in 11% (n=5/47), and no CNVs or fusions were noted. Nonsense and frameshift mutations represented 8/47 (17%) and 2/47 (4%) of all alterations respectively. No recurrent mutational hotspots were detected. The most common co-alterations in descending order were PIK3CA, TP53, ERBB2, ARID1A, MDM4, PPM1D, NF1, DNMT3A, ATM, and ESR1. Association between SPEN mutations and clinical outcomes will be presented at the meeting.

Conclusions: SPEN mutations were detected mostly in patients with HR+/HER2- MBC and at a higher frequency than reported in primary disease via TCGA. SNVs were common, though it

remains unclear whether these comprise driver versus passenger mutations. While no mutational hotspots were identified, several novel loss-of-function truncating mutations were identified, which warrant further validation of functional and clinical significance.

SPEN alterations in metastatic breast cancer

Alteration	Type	Receptor status
Q743E	Missense	HR+/HER2
S2481L	Missense	HR+/HER2
D134H	Missense	HR+/HER2
D2577H	Missense	HR+/HER2
E1001K	Missense	HR+/HER2
E1036K	Missense	HR+/HER2
E1190K	Missense	HR+/HER2
E1190Q	Missense	HR+/HER2
E1412Q	Missense	HR+/HER2
E1655K	Missense	HR+/HER2-
E2029K	Missense	HR+/HER2-
E2176K	Missense	HR+/HER2-
E2260*	Truncating	HR+/HER2-
E2595K	Missense	HR+/HER2-
E330*	Truncating	HR+/HER2-
E44A	Missense	HR+/HER2-
H1209_K1213del	Deletion	HR+/HER2+
I1560T	Missense	HR+/HER2+
I2453M	Missense	HR+/HER2-
K2066N	Missense	HR+/HER2-
K2404N	Missense	HR+/HER2-
K2774fs	Frameshift	HR+/HER2+
L1407fs	Frameshift	HR+/HER2-
L38F	Missense	HR+/HER2-
M1495I	Missense	HR+/HER2-
P2289S	Missense	HR+/HER2-
Q1939*	Truncating	HR+/HER2-
Q256*	Truncating	HR+/HER2-
Q2849H	Missense	HR+/HER2-
Q3450*	Truncating	HR+/HER2-
R128C	Missense	HR+/HER2-
R2081Q	Missense	HR+/HER2-
R589Q	Missense	HR+/HER2-
S1918C	Missense	HR+/HER2-
S241L	Missense	HR+/HER2-
S248Y	Missense	HR+/HER2-
S2493I	Missense	HR+/HER2-
S2675L	Missense	HR+/HER2+
S488_A492del	Deletion	HR+/HER2-
S529*	Truncating	HR+/HER2-
S760*	Truncating	HR+/HER2-
T3449G	Missense	HR+/HER2-
T3568M	Missense	TNBC
V1840I	Missense	HR+/HER2+
V2062_V2063dup	Duplication	TNBC
V3527L	Missense	HR+/HER2-
W1467*	Truncating	HR+/HER2-

Alterations detected by cell-free DNA sequencing in patients with metastatic breast cancer and annotated by type of alteration and receptor subtype.

PO2-13-03

Spatial HER2 heterogeneity on HER2-PET in HER2-low and negative disease: potential biomarker for antibody-drug conjugate effect

Presenting Author(s) and Co-Author(s):

C. Schroder. Netherlands Cancer Institute, Amsterdam, Netherlands
J. van Geel. University Medical Center Groningen, Groningen, the Netherlands, Netherlands
B. Eisses. University Medical Center Groningen, United States
A. Brouwers. University Medical Center Groningen, United States
S. Elias. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, United States
F. Bensch. University Medical Center Groningen, United States
E. Kuip. Radboud Medical Center, Nijmegen, United States
A. Jager. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, Rotterdam, Netherlands
A. Glaudemans. University Medical Center Groningen, United States
B. van der Vegt. University Medical Center Groningen, United States
W. Menke-van der Houven van Oordt. Amsterdam University Medical Centers-location VUMc, Amsterdam, The Netherlands, United States
E. de Vries. University Medical Center Groningen, United States

Spatial HER2 heterogeneity on HER2 PET in HER2-low and negative disease: potential biomarker for ADC effect

C.P. Schröder^{1, 2}, J.J.L. van Geel², B. Eisses², A. H. Brouwers³, S.G. Elias⁴, F. Bensch⁵, E.J.M. Kuip⁶, A. Jager⁷, A.W.J.M. Glaudemans³, B. van der Vegt⁸, C.W. Menke-van der Houven van Oordt⁹, E.G.E. de Vries² on behalf of the IMPACT-MBC consortium

1. Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands
2. Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
3. Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
4. Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
5. Department of Pulmonology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
6. Department of Medical Oncology, Radboud Medical Center, Nijmegen, The Netherlands
7. Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
8. Department of Pathology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
9. Department of Medical Oncology, Amsterdam University Medical Centers-location VUMc, Amsterdam, The Netherlands

Background: Anti-HER2 antibody drug conjugates (ADCs) can assert an effect in part of patients with HER2-low breast cancer. In light of patient burden and financial sustainability, biomarkers to select responding patients are urgently needed, but so far, none have been

identified. In the IMPACT trial (NCT01957332), patients with newly diagnosed and non-rapidly progressive metastatic breast cancer (MBC) of all subtypes (including HER2-negative, -low, and -positive disease) were included. We assessed the performance of Zirconium-89 (⁸⁹Zr)-trastuzumab positron emission tomography (HER2-PET) in HER2-low and negative MBC.

Methods: All patients received extensive workup, including a metastasis biopsy and HER2-PET at baseline. HER2 status was determined by immunohistochemistry (IHC) and in situ hybridization. ⁸⁹Zr-trastuzumab uptake was quantified as maximum and mean standardized uptake values (SUVmax, SUVmean) in metastases and healthy background tissue. Quantitative ⁸⁹Zr-trastuzumab uptake of all metastases and corresponding biopsied metastasis, was related to HER2 IHC status.

Results: In 200 patients, ⁸⁹Zr-trastuzumab uptake was quantified in 5,163 metastases. With increasing HER2 IHC status, uptake was higher (geometric mean SUVmax 7.0, 7.6, 7.3, and 17.4 with HER2 IHC 0, 1, 2, or 3+, in respectively 71, 71, 20, and 24 biopsied metastases (P < 0.001 between IHC 0 and 3+). SUVmax in lesions was heterogeneous within and between patients for all HER2 IHC groups. All HER2 IHC groups, also HER2-negative and -low, had uptake exceeding that of the healthy background (geometric mean tumor-to-background ratio SUVmax >1 in all groups, increasing with higher HER2 IHC). Of patients with a HER2 IHC 0 biopsy, 27.8% had at least one metastasis elsewhere in the body, with uptake exceeding the overall 90th SUVmax percentile of 14.6; in HER2 low IHC1+ and 2+, this was 31.9% and 30%.

Conclusions: In this largest series with HER2-PET in patients with MBC, we show that ±30% of patients with HER2-low or -negative IHC in the biopsy, in fact, have metastases with high HER2 uptake elsewhere in the body. This spatial heterogeneity provides novel insights into HER2-negative and -low disease compared to standard HER2 IHC of a single biopsy. As HER2-PET uptake is related to ADC response in HER2 positive MBC1, HER2-PET is a potential biomarker for anti-HER2 ADC effect in HER2-low and -negative MBC as well.

Reference: 1. Gebhart G, et al. Ann Oncol 2016;27(4): 619-624.
Supported by the Dutch Cancer Society grant 2012-5565

PO2-13-04

Single cell characterization of senescent CD8+ T cell promotes immunotherapy resistance in early-stage triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

T. Fu. Fudan University, United States

Y. Chen. Fudan University Shanghai Cancer Center, United States

X. Jin. Fudan University Shanghai Cancer Center, United States

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background: Immune checkpoint blockade (ICB) has been explored in triple-negative breast cancer (TNBC) and has been proven to improve patient survival in advanced TNBCs (IMpassion130) or increase the pathological complete response rate in early TNBCs (KEYNOTE522). However, ICB could only benefit a subset of patients, highlighting the urgent need to optimize patient selection. Unlike in advanced TNBCs, a predictive biomarker for ICB in early TNBCs is still lacking. The main reason might be that previous studies neglected the heterogeneity of tumor ecosystems between early and advanced TNBCs. There is an urgent need to understand the unique ecosystem of early-stage TNBC and develop biomarkers for precision immunotherapy. Objective: This study aims to characterize the micro-loop associated with the immune efficacy of early TNBC, so as to explain the mechanisms behind the differences in early and late efficacy markers, identify efficacy markers in early TNBC immunotherapy, and search for clinical targeting strategies to sensitize TNBC for neoadjuvant therapy. Methods: We conducted an in-depth analysis of 32 single-cell transcriptomes, comprising 26 early-stage TNBC enrolled in prospective clinical trials (NCT04418154 and NCT04613674), receiving neoadjuvant chemotherapy alone (n=8) or combined with anti-PD1 (n=18), and 6 advanced TNBC. We analyzed the microenvironmental differences between early and advanced tumors, and between different treatment response groups in early stages, and identified a subpopulation of cells specific to early stages and associated with immunotherapeutic efficacy. We used mIHC, flow-through, and validated the presence of this cell in clinical samples. We also explored its predictive performance on four independent cohorts of TNBCs with ICB treatment (GSE194040, NCT04129996, GSE169246, GSE124821). Furthermore, to understand the impact of ISG+ T cells on immunotherapy efficacy and explore targeting strategies, we employed a multi-faceted approach to assess their tumor-killing ability, response to Anti-PD1 treatment, and sensitization effect of drugs targeting ISG+ T cells. ISG+ T cells were sorted using flow cytometry for further experiment. In vitro, we established a co-culture model of primary TNBC patients-derived organoid (PDO) and tumor infiltrated CD8+T cells and evaluated the tumor cell viability as well as T cell cytotoxicity. In vivo, we established TS/A tumor cell bearing BalB/c mouse and E0771 tumor cell-bearing C57BL mouse and measured tumor size and tumor microenvironment by flow cytometry. Results: We obtained 236,017 high-quality cells and identified cell subsets across 32 samples with different stages, treatments and responses. We then uncovered an enriched subset of interferon-induced (ISG+) CD8+ T cells specific to early TNBC, serving as a predictive factor for ICB resistance. Mechanistically, the upregulation of the IFN pathway in early-stage TNBC triggers a transition in ISG+ CD8+ T cells, resulting in cellular senescence, diminished cytotoxicity, and impaired response to ICB. Encouragingly, we made a noteworthy discovery that Nicotinamide

mononucleotide, an anti-aging drug, effectively restores the functionality of ISG+ CD8+ T cells, amplifying immunotherapy sensitivity. Conclusions: This study provided a comprehensive single-cell transcriptome atlas of early-stage TNBC and depicted stage-related ISG+CD8+ T cell for predicting ICB response in early TNBC. We emphasize the critical role of T cell dysfunction prompted by cellular senescence in driving ICB resistance during the early stages of TNBC and propose an approach for sensitizing immunotherapy with aging drugs.

PO2-13-05

Deciphering pregnancy-associated breast cancer: distinctive molecular profile and clinical implications from GEICAM/2017-07 EMBARCAM study

Presenting Author(s) and Co-Author(s):

J. de la Haba-Rodríguez. Instituto Maimónides de Investigación Biomedica, Hospital Reina Sofía, Universidad de Córdoba. GEICAM Spanish Breast Cancer Group., Spain

R. Peña. Instituto Maimónides de Investigación Biomédica (IMIBIC). Hospital Universitario Reina Sofía, Universidad de Córdoba., United States

M. Pollán. Centro Nacional de Epidemiología. Instituto de Salud Carlos III. CIBERONC.CIBERESP. GEICAM Spanish Breast Cancer Group, Spain

Y. Jerez Gilarranz. Hospital General Universitario Gregorio Marañón, Madrid, Spain

J. Ponce. Hospital General Universitario Dr. Balmis, ISABIAL, Alicante, Comunidad Valenciana, Spain

A. Fernández Aramburu. Hospital General Universitario de Albacete, Albacete, Spain, Spain

B. Cantos. Hospital Puerta de Hierro, Majadahonda, Madrid, Spain, United States

A. Santaballa Bertrán. Hospital Universitario y Politécnico La Fe, Valencia, Spain. Instituto de Investigación Sanitaria La Fe, Valencia, Spain. GEICAM Spanish Breast Cancer Group, Valencia, Spain

E. Galve. Hospital Universitario de Basurto, United States

M. Pérez. Hospital Universitario A Coruña (HUAC), A Coruña, Spain. GEICAM Spanish Breast Cancer Group, Spain

S. de la Cruz. SOLTI Cancer Research Group; Complejo Hospitalario de Navarra, Pamplona, United States

M. López-Ceballos. Hospital San Pedro de Alcántara, Cáceres, Spain, United States

Y. Fernández. Hospital Central de Asturias, Spain, United States

F. moreno. Hospital Clínico San Carlos, Madrid, Spain, United States

S. González. Hospital Universitario Mutua de Terrasa, Barcelona, Spain, United States

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

I. Blancas. Medical Oncology Dept, University Hospital San Cecilio, Granada, Spain

J. Alonso-Romero. Hospital Clínico Universitario Virgen de la Arrixaca. GEICAM Spanish Breast Cancer Group., United States

□. Jiménez-Arranz. Instituto Maimónides de Investigación Biomédica (IMIBIC). Hospital Universitario Reina Sofía, Universidad de Córdoba., United States

R. Rincón. GEICAM Spanish Breast Cancer Group, United States

S. Guil. Instituto Maimónides de Investigación Biomédica (IMIBIC). Hospital Universitario Reina Sofía, Universidad de Córdoba., United States

A. Díaz-Chacón. Instituto Maimónides de Investigación Biomédica (IMIBIC). Hospital Universitario Reina Sofía, Universidad de Córdoba., United States

R. Caballero. GEICAM Spanish Breast Cancer Group., Spain

B. Bermejo. Hospital Clínico Universitario de Valencia, Valencia, Spain, United States

A. Guerrero. Fundación Instituto Valenciano de Oncología (FIVO). GEICAM Spanish Breast Cancer Group., Valencia, Comunidad Valenciana, Spain

Background: Pregnancy-Associated Breast Cancer (PABC) is defined as BC diagnosed during pregnancy, breastfeeding, or within the first year postpartum. This challenging entity has a distinct biology and worst prognosis and presents an increased risk for metastasis and death compared to non-PABC patients. Identification of molecular pathways that define this malignancy is crucial to explain its biological characteristics and potential association with pregnancy as well as serve to identify new biomarkers with preventive and clinical implications. This study assesses the gene expression profile of a PABC cohort from the Registry Study of Pregnancy and Breast Cancer (GEICAM/2017-07 EMBARCAM study, NCT04603820) to identify distinct molecular signatures and altered pathways for this entity. Methods: This was a multicenter, observational and ambispective age-matched cohort of PABC patients (n=46) and non-PABC patients (n=49). We analyzed the expression of 776 genes involved in 23 key breast cancer pathways, using the nCounter[®] Breast Cancer 360[™] Panel (NanoString Technologies) on BC tumor samples, including molecular subtypes by PAM50 gene signature. Associations between individual differential genes and epidemiological and clinical features of these patients were explored. Normalized differential expression values were log₂-transformed for statistical analysis in nSolver Software (NanoString Technologies). P-values were adjusted within each gene/signature and on the grouping variable level difference t-test using the Benjamini and Yekutieli False Discovery Rate (FDR) adjustment. Results: PABC patients' clinical subtypes were distributed as 43,5% HR-positive/HER2-negative, 17,4% HER2-positive and 39,1% triple negative BC. These patients reported higher family history of BC/ovarian cancer compared to non-PABC (52.17% vs 26.53%; p=0.0124). Differential gene expression showed distinct molecular profiles in PABC and non-PABC patients: significantly genes enrichment involved in cell proliferation and p53 signature for PABC patients and higher expression of apoptosis, TGF- β , and PTEN signatures for non-PABC (adj p< 0.05). Furthermore, CDK4 expression signature (adj p=0.124) and DNA damage repair signatures Homologous Recombination Deficiency (HRD) (adj p=0.083) and BRCAness (adj p=0.220) were also upregulated in PABC tumors. The most significantly upregulated genes in PABC patients (CCNA2, DEPDC1, FAM83D, CDC20, CDKN3, TRIP13, TTK, MAD2L1, KIF2C, and UBE2C) (adj p< 0.05) were involved in cell cycle regulation and DNA damage repair. PABC basal-like tumors were found to be significantly more prevalent than non-PABC, as per the PAM50 classification (45.7% vs 20.4%; p=0.020). Interestingly, basal-like PABC showed higher expression of ESR1 than basal-like non-PABC (logFC=1.486; p=0.022). In contrast, luminal A PABC tumors exhibited lower ESR1 expression vs non-PABC (logFC=-1.5; p=0.021). Additionally, HER2-enriched PABC tumors displayed lower B7-H3/CD276 expression compared to HER2-enriched non-PABC (adj p=0.031). Conclusions: Our study shows that PABC is potentially a clinical and molecular different entity with predominance of the basal-like subtype. Moreover, our results suggest the activation of oncogenic pathways related to cell proliferation, DNA damage repair and p53 mutations which may lead to a clinically more aggressive phenotype for PABC patients. Likewise, the enrichment of BRCAness and HRD signatures found in PABC patients in our study may suggest an increased genetic instability due to a breakdown in the DNA damage repair. These findings may be clinically relevant and translate to new treatment options in PABC patients, who may benefit from therapies targeting DNA repair or cell-cycle checkpoints, such as PARP inhibitors.

PO2-13-06

Analysis of Antibody Response to SV-BR-1-GM Therapeutic Vaccine in Breast Cancer Patients Using Human Protein Microarrays: Potential Correlations with Therapy Response

Presenting Author(s) and Co-Author(s):

M. Lopez-Lago. BriaCell Therapeutics corp., United States

M. Chang. BriaCell Therapeutics, Pennsylvania, United States

G. Del Priore. BriaCell Therapeutics, Philadelphia, Pennsylvania, United States

V. Bhardwaj. BriaCell Therapeutics corp., United States

P. Cournoo. BriaCell Therapeutics corp., United States

P. Ramos. CDI laboratories INC, United States

T. Hulett. CDI laboratories INC, United States

C. Wiseman. Briacell Therapeutics, Jerusalem, Israel

W. Williams. BriaCell Therapeutics, Havertown, Pennsylvania, United States

Background: Therapeutic cancer vaccines aim to stimulate the immune system by utilizing tumor antigens to trigger an antitumor response. In our clinical trials, we have focused on evaluating the efficacy of the breast cancer cell line secreting GM-CSF, SV-BR-1-GM as a therapeutic vaccine, and we have observed encouraging clinical outcomes. The SV-BR-1-GM regimen has been used alone (“monotherapy”, ClinicalTrials.gov NCT03066947 – study completed) and in combination with checkpoint inhibitors (“combination”, ClinicalTrials.gov NCT03328026 – study ongoing). To further improve the therapeutic efficacy of this vaccine we have initiated a study to characterize patient’s immune response to this treatment. It has been demonstrated that cancer vaccines can generate both humoral and cellular immune responses. However, predicting immune responses to cancer vaccines, especially when whole cells are employed as immunogens, presents significant challenges. We present here a preliminary analysis of the antibody response to SV-BR-1-GM in breast cancer patients using antigen arrays. Methods: Large-scale protein arrays are versatile and sensitive platforms for antibody specificity evaluation. The HuProt™ Human Proteome Microarray (CDI Laboratories, Inc., Baltimore, Maryland, United States) provides the largest number of unique, full-length, individually purified human proteins on a single microscope slide. This allows thousands of interactions to be profiled in a high-throughput manner. We utilized here an unbiased human protein microarray platform encompassing >21,000 proteins and isoforms from ~19,000 unique genes to identify IgG and IgM responses against self-antigens elicited by treatment. Serum samples from SV-BR-1-GM-treated patients were analyzed, comparing pre- and post-treatment. The human serum samples were probed at 1:1000 dilution. After sample processing and data collection the raw signal intensities on all arrays were quantile normalized using CDI software. Heatmaps were generated using MetaboAnalyst 5.0, which utilizes the R pheatmap package (version 0.7.7). For paired analysis, fold changes (FCs) were calculated by determining the ratio between paired pre- and post-treatment samples, resulting in one FC per pair. The means of these FCs (pair means) were then computed. ANOVA tests were performed using the RStatix R package, which automatically determines the appropriate Type I, II, or III errors for the analysis. Results: By using this approach, we were able to evaluate a broader range of antigens compared to previous investigations. Using a variety of statistical approaches, potential correlations with patient survival on SV-BR-1-GM were evaluated. Antibody responses to galectin antigens demonstrated the most consistent relationships with survival. Further

confirmation with additional patients and prospective analysis are needed to fully understand relationships with clinical benefit and survival.

PO2-13-07

SMARCA2 compensation of SMARCA4 loss mediates adaptive resistance to neoadjuvant systemic therapy in triple-negative breast cancer: paired transcriptomic analysis of pre- and post-treatment samples from NeoSTOP and NeoPACT

Presenting Author(s) and Co-Author(s):

S. Stecklein. University of Kansas Medical Center; Kansas Institute for Precision Medicine, Kansas City, Kansas, United States

R. Yoder. The University of Kansas Cancer Center, United States

J. Staley. The University of Kansas Cancer Center, United States

Z. Schmitt. University of Kansas Medical Center, United States

A. O'Dea. University of Kansas Medical Center, United States

L. Nye. University of Kansas Medical Center, United States

D. Satelli. University of Kansas Medical Center, United States

G. Crane. University of Kansas Medical Center, United States

R. Madan. University of Kansas Cancer Center, United States

M. O'Neil. University of Kansas Cancer Center, United States

A. Godwin. University of Kansas Medical Center; Kansas Institute for Precision Medicine; The University of Kansas Cancer Center, United States

H. Pathak. University of Kansas Cancer Center, United States

Q. Khan. University of Kansas Medical Center, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

P. Sharma. University of Kansas Medical Center Westwood, Westwood, Kansas City, Kansas, United States

Objectives/Rationale: Triple-negative breast cancer (TNBC) patients with residual disease (RD) after neoadjuvant systemic therapy (NAST) are at high risk for disease recurrence and death. While multiple prognostic biomarkers associated with response to NAST have been identified, adaptive resistance mechanisms to NAST remain poorly understood. Identifying and characterizing adaptive resistance mechanisms can illuminate novel therapeutic approaches and improve outcomes for TNBC patients with RD.

Methods: Total RNA was isolated from pre-treatment and paired surgical specimens (for patients with RD) from TNBC patients treated with chemotherapy on the NeoSTOP (NCT02413320) or chemoimmunotherapy on the NeoPACT (NCT03639948) neoadjuvant trials and was subjected to RNA exome sequencing. Comparative marker selection analysis was performed by computing the two-sided paired samples t-test for each gene followed by pre-ranked gene set enrichment analysis (GSEA) amongst 23,797 annotated gene sets. Gene sets with false-discovery rate (FDR) corrected P values < 0.001 were determined to be significant.

Results: Pre-treatment sequencing data were available for N=200 patients and the overall pathologic complete response (pCR) rate was 56.5%. Paired pre- and post-treatment sequencing data were available for N=58 patients with RD (N=27 from NeoSTOP and N=31 from NeoPACT). 165/23,797 gene sets were significantly enriched in post-treatment compared to pre-treatment samples. SHEN_SMARCA2_TARGETS_UP (M29) was among the top five

significantly enriched gene set and was selected for further analysis based on the known role of the SWI/SNF complex in cell survival and the availability of clinically viable SMARCA2 degraders. Pre-treatment SMARCA4 expression was associated with pCR, with lower median expression noted in patients with RD compared to patients who achieved pCR ($P=0.04$). Pre-treatment SMARCA2 expression was not associated with pCR ($P=0.48$). On paired sample analysis there was pronounced downregulation of SMARCA4 in post-treatment compared to pre-treatment samples in all patients (mean $Z=-1.46$, $P<0.0001$), in patients treated with chemotherapy (mean $Z=-1.65$, $P<0.0001$), and in patients treated with chemoimmunotherapy (mean $Z=-1.28$, $P<0.0001$). Although there was no difference in SMARCA2 expression between paired pre- and post-treatment samples (mean $Z=0.03$, $P=0.83$), there was enrichment of SMARCA2 target expression on GSEA analysis (NES=2.63, FDR $q<0.00001$) indicating that SMARCA2 activity is compensating for therapy-induced SMARCA4 loss.

Conclusions: We identified 165 gene sets that were significantly enriched in paired post-treatment compared to pre-treatment TNBC samples. Altered activity of the SMARCA2 subunit of the SWI/SNF chromatin remodeling complex was identified as one of the top hits. SMARCA2 and SMARCA4 are mutually exclusive subunits of SWI/SNF, and inactivation of both SMARCA2 and SMARCA4 is synthetic lethal. We observed an association of lower pre-treatment SMARCA4 expression with resistance to NAST and pronounced therapy-induced downregulation of SMARCA4 and induction of SMARCA2 target genes in post-treatment compared to pre-treatment samples, suggesting that SMARCA2 compensates for adaptive SMARCA4 loss. SMARCA2 degraders are in early-phase clinical trials and are known to induce synthetic lethality in SMARCA4-deficient cells. Our results identify adaptive loss of SMARCA4 and synthetic lethal targeting of compensatory SMARCA2 as an attractive therapeutic target in TNBC patients with RD after neoadjuvant chemotherapy or chemoimmunotherapy.

PO2-13-08

Cell-free orphan noncoding RNAs and AI enable early detection of invasive breast cancer and ductal carcinoma in-situ

Presenting Author(s) and Co-Author(s):

N. Tbeileh. Exai Bio Inc, United States

T. Cavazos. Exai Bio, United States

M. Karimzadeh. Exai Bio Inc, United States

J. Wang. Exai Bio, United States

A. Huang. Exai Bio, United States

D. Lam. Exai Bio, United States

S. Kilinc. Exai Bio, California, United States

J. Wang. Exai Bio, United States

X. Zhao. Exai Bio, United States

A. Pohl. Exai Bio, United States

H. Li. Exai Bio, United States

L. Fish. Exai Bio, United States

K. Chau. Exai Bio, United States

M. Francis. Exai Bio, United States

L. Schwartzberg. William N. Pennington Cancer Institute - Renown Health, United States

P. Arensdorf. Exai Bio, United States

H. Goodarzi. University of California, San Francisco, United States

F. Hormozdiari. University of California, Davis, United States

B. Alipanahi. Exai Bio, United States

Background Earlier detection of breast cancer through mammography screening has reduced disease-specific mortality; however, confounding issues such as technical challenges, breast density, and tumor size can result in false negatives and ultimately later stage diagnosis. Next generation liquid biopsy has the potential to complement mammography and enable earlier detection for more women. We have previously demonstrated high sensitivity and specificity for early detection of invasive breast cancer (IBC) by utilizing a novel category of cancer-associated small RNAs, termed orphan noncoding RNAs (oncRNAs), through a liquid biopsy platform. Here, we further improve the ability to detect breast cancer in a larger, multi-source cohort through an AI-driven approach and demonstrate potential for detection of ductal carcinoma in-situ (DCIS). **Methods** We utilized The Cancer Genome Atlas (TCGA) small RNA-seq database to discover a library of 20,538 oncRNAs, through a female-specific analysis, that were significantly enriched among 1,103 breast tumors compared to 349 normal tissue samples spanning multiple tissue sites. The diagnostic performance of these oncRNAs were assessed in an independent cohort of archived serum samples from 663 female individuals, sourced from Indivumed (Hamburg, Germany), Proteogenex (Inglewood, CA), and MT Group (Los Angeles, CA), including 279 breast cancer patients of various stages (221 IBC and 58 DCIS; mean age: 57.0 ± 13.8 years; ever-smoker: 25.8%) and 304 age-matched controls (mean age: 58.5 ± 13.9 years; ever-smoker: 23.4%) without breast cancer. All samples were collected between 2010–2022 at time of diagnosis for breast cancer patients. We sequenced the small RNA content of

these samples at an average depth of 25.28 ± 9.37 million 50-bp single-end reads. We detected 18,025 (87.8%) unique breast cancer-specific oncRNA species within at least one sample from the study cohort. We then trained a generative AI model using 5-fold cross-validation to predict cancer status for all samples. Results Our oncRNA-based model achieved an overall AUC of 0.95 (95% CI, 0.93–0.97) for prediction of IBC versus cancer-free controls with a sensitivity of 0.87 (0.82–0.91) at 90% specificity. We observed high sensitivities, also at 90% specificity, across all tumor stages and tumor sizes (Table 1). Sensitivities for the earliest stage and smallest tumor size were 0.87 (0.78–0.93) and 0.81 (0.61–0.93) for Stage I (n=83) and T1a–b (>1mm to ≤10mm; n=26), respectively. Additionally, in a small single-source cohort, we also saw high model accuracy and sensitivity for DCIS, which we aim to confirm in additional cohorts. While our overall cancer cohort primarily consisted of individuals with luminal breast cancer, our model had high sensitivities across all breast cancer subtypes at 0.90 (0.84–0.94), 0.73 (0.59–0.85), and 0.86 (0.42–1.0) for luminal (n=181), HER2 positive (n=49), and triple negative (n=7), respectively. Conclusions We further demonstrate the potential utility of oncRNAs as a blood-based biomarker using an AI algorithm for sensitive and accurate early detection of breast cancer in a large cohort. Additionally, we have shown that this oncRNA-based assay performs well in detecting small, early-stage invasive breast tumors, with potential to detect precursors of breast cancer.

Table 1: Model sensitivity in breast cancer by tumor stage and size

	Group	N	Sensitivity (95% CI)
Tumor Stage	Stage I	83	0.87 (0.78–0.93)
	Stage II	78	0.86 (0.76–0.93)
	Stage III	42	0.86 (0.71–0.95)
	Stage IV	18	1.00 (0.81–1.00)
TNM T Category	T1a–b	26	0.81 (0.61–0.93)
	T1c	72	0.90 (0.81–0.96)
	T2	88	0.89 (0.80–0.94)
	T3	20	0.90 (0.68–0.99)
	T4	12	0.75 (0.43–0.95)

For each tumor stage and size, as defined by the AJCC 7th Edition breast cancer staging system, sensitivity and 95% Pearson-Clopper confidence intervals (CI) are reported at 90% specificity for the number of samples (N).

PO2-13-09

Delayed alopecia among breast cancer survivors

Presenting Author(s) and Co-Author(s):

S. Premji. Department of Oncology, Mayo Clinic, Rochester, Minnesota, United States

K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States

N. Larson. Mayo Clinic, United States

C. Loprinzi. Department of Oncology, Mayo Clinic, United States

B. Dulmage. Department of Dermatology, Ohio State University, United States

m. lustberg. Yale Cancer Center, New Haven, Connecticut, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

J. Olson. Mayo Clinic, United States

E. Cathcart-Rake. Mayo Clinic, United States

Background: Retrospective studies suggest that breast cancer survivors report treatment-associated hair loss or thinning years after their initial diagnosis. This study investigates patient perceptions of alopecia persisting 6 years after the diagnosis of breast cancer. Methods: Breast cancer survivors who had signed informed consent for participation in a prospective longitudinal cohort study, the Mayo Clinic Breast Disease Registry (MCBDR), after diagnosis of breast cancer approximately six years prior, were mailed a survey. This survey asked about degree of bother from hair thinning and hair loss on a scale from 0 "not at all" to 4 "extremely" and about use of hair thickening/regrowth products. PROMIS-10 project scales assessed global mental health (5: worst mental health, 20: best mental health). Data were analyzed using descriptive statistics. Results: 969/1476 participants responded (response rate 65.7%); 819 participants were available for analysis. Participant median age was 65.7 years (range 34 -100 years). 604 (73%) had been diagnosed with stage I-II breast cancer, 248 (30%) had received chemotherapy (+/- endocrine therapy), 365 (45%) had received only endocrine therapy, and 206 (25%) had received neither. Nearly half (381, 47%) reported hair loss and over half (468, 57%) reported hair thinning. 155 (19%) used hair regrowth products. Amongst the 526 who were 55 years and older, 270 (51%) reported hair loss and 323 (61%) hair thinning; 111 (38%) of the 291 women under 55 years reported hair loss and 145 (50%) hair thinning. Twenty-eight percent of chemotherapy recipients, 18% of patients who did not receive chemotherapy but received endocrine therapy, and 14% of patients who had received neither reported continued difficulty with moderate to extreme hair loss. Moderate to extreme bother from hair thinning was reported by 34% of chemotherapy recipients, 22% of endocrine therapy-only recipients, and 18% of those who had received neither. See the table for associations between mental health scores and hair loss/thinning. Use of hair growth products was reported by 29% of chemotherapy recipients, 14% of endocrine therapy-only recipients, and 15% of those who had received neither oncologic therapy. Conclusions: Hair loss and thinning are frequently reported as persistently bothersome symptoms from breast cancer survivors. Future investigations into the incidence, predictors, and treatment of chemotherapy and endocrine therapy-associated alopecia are needed.

Global mental health scores on PROMIS scale for hair loss and hair thinning

	<i>Hair Loss</i>		<i>Hair Thinning</i>	
Mental Health Score	None to Slight (%)	Moderate to Extreme (%)	None to Slight (%)	Moderate to Extreme (%)
5 to 8	6 (37%)	10 (63%)	5 (31%)	11 (69%)
9 to 12	88 (68%)	41 (32%)	80 (63%)	47 (37%)
13 to 16	314 (81%)	74 (19%)	293 (75%)	96 (25%)
17 to 20	232 (86%)	38 (14%)	226 (84%)	42 (16%)

PO2-13-10

Predicting outcomes in locally advanced breast cancer through profiling post-neoadjuvant tissue-based minimal residual disease.

Presenting Author(s) and Co-Author(s):

J. Ransohoff. Stanford University School of Medicine, Palo Alto, California, United States

M. Carleton. Stanford University School of Medicine, United States

A. Birk. Stanford University School of Medicine, United States

G. Bean. Stanford University School of Medicine, United States

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

A. Alizadeh. Stanford University School of Medicine, United States

J. Ford. Stanford Cancer Institute, Stanford University School of Medicine, Stanford CA, Stanford, California, United States

G. Duran. Stanford University School of Medicine, United States

M. Khodadoust. Stanford University School of Medicine, United States

D. Kurtz. Stanford University School of Medicine, United States

Background:

Neoadjuvant chemotherapy (NAC) for locally advanced breast cancer can down-stage disease prior to surgery, monitor chemo-sensitivity, and provide key prognostic information via pathologic response that guides adjuvant treatment. Greater residual disease as assessed by the residual cancer burden (RCB) index is associated with inferior outcomes but imperfectly predicts recurrence, particularly in triple negative breast cancer (TNBC) where there is heterogeneity of outcomes across RCB scores. As an alternative to RCB and PCR, blood-based minimal residual disease (MRD) from circulating tumor DNA (ctDNA) has been explored. However, poor sensitivity limits ctDNA, which is typically negative post-NAC when treatment decisions are made in patients who later recur.

Methods:

To address this lack of sensitivity, we developed tissue-based MRD (t-MRD) to assess molecular disease burden in post-NAC breast and lymph node resection tissue. We performed whole exome sequencing on diagnostic tumor and matched germline tissues from five pilot patients with early-stage TNBC with a range of responses to NAC. For each patient, we designed a personalized assay to track tumor-specific SNVs, combined with limited panel of genes recurrently mutated in breast cancer, to enable MRD detection. We then applied this assay to DNA from individual pathology blocks from the tumor resection via ultra-deep targeted hybrid capture. We assessed each sample for the presence of MRD using a Monte Carlo statistical framework to integrate all tumor mutations as previously described (Newman et al, Nature Biotechnology 2016). We aggregated results across all pathology blocks from each case to define each patient's t-MRD profile and assessed the performance of t-MRD versus gold standard pathologic assessment.

Results:

We tracked a mean of 136 MRD reporters per case across 119 post-NAC blocks derived from five patients. Twenty-five samples had pathologic residual disease and 28 had detectable t-MRD. There was strong concordance between t-MRD mean allele frequency (AF) and tumor cellularity as assessed by pathology, defined as percent cellularity within the region containing

viable tumor (Spearman $r = 0.9052$, $p < 0.0001$), and excellent classification of true positive pathology samples by genomic sequencing (AUC = 0.9675, $p < 0.0001$). Samples ($n = 6$) where t-MRD but not pathologic residual disease was detected had a lower mean AF than those where there was also histologic residual disease ($p=0.0001$). Among the five studied cases, we confirmed a molecular complete response with no t-MRD detected in the RCB-0 case (0/44 t-MRD positive blocks). In the two RCB-III cases, we observed more diffuse t-MRD than that assessed by pathology ($n = 4$ additional blocks with t-MRD but not pathologic disease detected), and in the RCB-II case, we detected minimal t-MRD in only a single block where pathology did not detect residual disease.

Significance:

By applying blood-based MRD assessment tools to tumor tissue, we developed t-MRD to profile molecular residual disease at the landmark post-NAC timepoint when disease burden is low and adjuvant treatment decisions are made. We demonstrated high concordance with gold standard pathologic assessment, with increased sensitivity and minimal false positive signal. Further studies assessing the additional prognostic value of t-MRD beyond stage-based prognostication and post-NAC RCB scores are ongoing.

PO2-13-11

High circulating tumor DNA (ctDNA) concentration was associated with shorter progression free survival in patients with metastatic breast cancer

Presenting Author(s) and Co-Author(s):

H. Yi. Seoul National University Hospital, United States

T. Kim. Seoul National University Hospital, United States

M. Song. Biomedical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea, United States

H. Kim. IMBdx Inc., Seoul, Republic of Korea, United States

T. Kim. Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; Cancer Research Institute, Seoul National University, Seoul, Republic of Korea; IMBdx Inc., Seoul, Republic of Korea, United States

J. Kim. Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, United States

D. Lee. Seoul National University Hospital, United States

K. Lee. Seoul National University Hospital, United States

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

Background: Metastatic breast cancer can be classified into different subtypes depending on hormone receptor (HR) and HER2 status. The subtype can change during tumor progression, and repeated biopsy is needed to deliver the most appropriate treatment every time a new lesion is found. It is not always possible to get a new biopsy from metastatic sites, and therefore liquid biopsy using circulating tumor DNA (ctDNA) is suggested as an alternative method to replace conventional biopsy. Methods: We performed a prospective serial collection of 65 ctDNA samples from 17 patients with metastatic breast cancer (mBC) at Seoul National University Hospital from October 2020 to March 2022. We used IMBdx AlphaLiquid[®]100 method to detect the genetic changes and analyzed the correlation with clinical outcomes. Results: Median age was 45 (range 32 – 62). Fifteen patients (88.2%) were relapsed mBC and most of the patients (14/17: 82.4%) were HR-positive and HER2-negative. Most of the patients had their ctDNA examined at baseline and at the time of maximal response and/or at progression. Fifteen patients (88.2%) received systemic therapy including hormone therapy, anti-HER2 therapy, and cytotoxic chemotherapy. Eight patients (47.1%) were on the first-line treatment for mBC, and 7 patients (41.2%) were on the second or later lines for mBC at the time of baseline sampling. The concentration of ctDNA and the sum of mutated allelic frequency was calculated for each sample. The ctDNA concentration ranged from 0.71 to 1386.00 ng/mL, and the median value was 5.37 ng/mL. We dichotomized these samples into two groups, with ctDNA concentration either higher or lower than the median value. Then we analyzed progression free survival (PFS) of each group. Patients with higher ctDNA concentration showed shorter PFS (7 mo. vs. not reached, $p < 0.001$). The sum of mutated allelic frequency ranged from 0.00% to 223.46% and the median value was 6.36%. Patients with higher mutated allelic frequency showed shorter PFS (6 mo. vs. 22 mo., $p < 0.001$). In addition, the PFS was significantly worse in patients who had mutated PIK3CA (5 mo vs. 22 mo, $p < 0.001$). The patients with mutated TP53 also showed shorter PFS (6 mo vs. 17 mo, $p < 0.001$) in univariate analysis. High estrogen receptor positivity in immunohistochemistry was correlated with lower mutated allelic frequency in ctDNA ($p=0.003$) but had no impact on the

concentration of ctDNA ($p=0.165$). The concentration of ctDNA differed by metastatic sites. Patients with metastases to bones ($p=0.007$), liver ($p < 0.001$), soft tissue or lymph nodes ($p=0.002$) were more likely to have higher concentrations of ctDNA, while patients with brain metastases had significantly lower ctDNA concentration ($p=0.006$). When the sum of mutated allelic frequency of ctDNA and metastatic sites was analyzed, bone ($p=0.001$), liver ($p < 0.001$), and soft tissue or lymph node ($p < 0.001$) metastases had a positive correlation, while brain had negative correlation ($p=0.017$). Lung or pleural metastases had no significant correlation with ctDNA, neither concentration ($p=0.271$) nor mutated allelic frequency ($p=0.965$). Conclusion: Patients with mBC with higher concentrations of ctDNA or higher mutated allelic frequency of ctDNA at baseline showed significantly shorter PFS. PIK3CAmt and TP53mt detected by liquid biopsy could be used as a poor prognostic biomarkers for mBC patients.

PO2-13-12

Serum Thioredoxin 1 Enhances Breast Cancer Detection in Mammography and Breast Ultrasound, Including Dense Breasts.

Presenting Author(s) and Co-Author(s):

Y. kim. E&S Healthcare co.,Ltd., United States

H. Ko. Chungnam national university hospital, United States

Y. Lee. E&S Healthcare Co.,Ltd, United States

K. Shin. E&S Healthcare Co.,Ltd, United States

J. Song. E&S Healthcare Co.,Ltd, United States

J. Kim. Chungnam national university hospital, United States

K. Suh. E&S Healthcare Co.,Ltd, United States

J. Lee. Chungnam national university hospital, United States

Background: Breast cancer (BC), when detected in its early stages, generally carries a more favorable prognosis than other types of cancer. Currently, the screening and early detection of breast cancer rely predominantly on image-oriented diagnostic methods. However, these methods inherently fall short in capturing the dynamic nature of cancer cells. Mammography has known limitations in clinical sensitivity, particularly in cases with high breast density. While breast ultrasound can mitigate some of these limitations, there remain unmet needs in this field. Previously, we reported the promising clinical performance (Sensitivity: 96.43%, Specificity: 97.32%) of serum thioredoxin 1 (Trx1) as a potential novel means for detecting breast cancer. In this study, we aim to evaluate the extent to which serum Trx1 can enhance the accuracy of breast cancer diagnosis, including in dense breasts, within the imaging-based diagnostic system powered by mammography and ultrasonography.

Methods: We have generated monoclonal antibodies against Trx1 and developed an ELISA kit (DxMe[®] BC Kit, E&S Healthcare, Korea) that quantifies Trx1 in serum. A total of 308 biopsy-confirmed breast cancer patients, who had undergone mammography prior to their final diagnosis, were recruited. The clinical information of these 308 patients was retrospectively examined and collected. The data from 254 individuals, who also had results from breast ultrasound, and 261 individuals, who had records of breast density, were analyzed collectively. Freshly collected blood was prepared as previously indicated, and then tested with the kit to determine the level of Trx1. All serum samples were measured twice, and statistical analyses were conducted using ROC analysis, one-way ANOVA, and unpaired t-tests.

Results: Clinical sensitivity for BC detection was analyzed using the Trx1 levels of the 254 subjects who underwent both mammography and breast ultrasound. The respective sensitivities of mammography, breast ultrasound, and the DxMe[®] BC Kit were 72.83%, 92.91%, and 96.46%. With combined analysis of mammography, breast ultrasound, and Trx1, the sensitivity increased to 98.43% for mammography + breast ultrasound, and 98.82% for mammography + Trx1. When breast ultrasound + Trx1 was considered, the sensitivity rose to 99.61%. Likewise, the sensitivity of mammography + breast ultrasound + Trx1 was also measured at 99.61%. Among the 261 breast cancer patients with available information about breast density, 186 patients (71.3%) had dense breasts. The clinical sensitivity of mammography and Trx1 was specifically analyzed for these dense breast cases. Mammography demonstrated a sensitivity of 64.3%, while the DxMe[®] BC kit exhibited a

sensitivity of 97.2%. When mammography and Trx1 were analyzed in parallel, sensitivity increased to 99.7%.

Conclusion: This study demonstrated that the DxMe[®] BC kit, which quantifies serum Trx1 levels, can enhance the accuracy of conventional image-based diagnostics for breast cancer screening and early detection by more than 25%. This improvement in sensitivity was observed when mammography and breast ultrasound were each used in conjunction with Trx1, with no significant difference noted between these two combinations. Notably, in the case of dense breasts, the Trx1 test improved sensitivity by more than 30% compared to mammography. Given that sensitivity increases when mammography and Trx1 tests are used together, it showed that incorporating the Trx1 test alongside traditional mammography could significantly enhance diagnostic performance in dense breasts up to 35%. This approach has the potential to streamline the breast cancer diagnostic process, reduce time and cost, and improve the reliability of current breast cancer screening and early detection methods, regardless of breast density.

PO2-14-02

Clinical significance of urinary microRNA expression in primary breast cancer

Presenting Author(s) and Co-Author(s):

Y. Inoue. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States
N. Uehiro. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States
N. Yamashita. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, Koto-ku, Tokyo, Japan
H. Yamaguchi. CRAIF Inc, United States
S. Maezono. CRAIF Inc., United States
M. Palfalvi. CRAIF Inc., United States
Y. Ando. CRAIF Inc., United States
Y. Nishiyama. CRAIF Inc., United States
M. Mizunuma. CRAIF Inc., United States
Y. Ichikawa. CRAIF Inc., United States
Y. Matsunaga. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States
A. Iesato. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States
Y. Ozaki. The Cancer Institute Hospital Of JFCR, Koto-ku, Japan
T. Maeda. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States
Y. Takahashi. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States
F. Hara. Breast Medical Oncology, Cancer Institute Hospital of JFCR, United States
T. Kobayashi. The Cancer Institute Hospital Of JFCR, Tokyo, Tokyo, Japan
T. Osako. Division of Pathology, Cancer Institute of JFCR, United States
T. Sakai. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States
T. Ueno. Breast Surgical Oncology, Breast Oncology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan, Tokyo, Tokyo, Japan
S. Ohno. Breast Oncology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Backgrounds: MicroRNAs (miRNAs) are small functional nucleic acids that regulate homeostasis by maintaining a balance of regulatory functions within cells. In humans, more than 2,000 miRNAs have been discovered, and each type of cancer has its own unique pattern of miRNA expression. Like circulating tumor DNA, miRNAs circulate in the blood in the form of exosomes, and some of them are excreted in the urine. Therefore, miRNAs in blood and urine are considered potential biomarkers in cancer. We examined miRNAs in urine, which can be collected without invasive procedures. Aims: This study aimed to investigate the clinical significance of urinary microRNA in primary breast cancer. Patients: Two hundred patients with stage 0-III primary breast cancer treated in our hospital (breast cancer group) and 105 healthy volunteers (control group) were included in the study. Methods: Small RNA seq was performed using a next-generation sequencer, and urinary miRNA profiles were obtained and analyzed. Student's t-tests were conducted between breast cancer group and the control group, and miRNAs with p-values p -values < 0.05 and $\text{Log}_2\text{FC} > 0.5$ were differentially expressed-miRNAs(DEMs). In the present study, miEAA API version 2.0 and miRDIP were used to predict the target genes of the functional DEMs. The functional enrichment of the target genes of the

DEMs was assessed using KEGG signalling pathway analyses. A machine learning model for binary classification of breast cancer and control group was created and its performance was evaluated using cross-validation method. Results: The median age was 50.3 years old in the breast cancer group and 46.1 years old in the control group. Of the breast cancer group, 13.5% were at clinical stage 0. Approximately 80% of the patients had HR+HER2- tumors. Twenty-eight miRNAs were identified to differentiate between the breast cancer group and the control group. Of the 28 miRNAs, fifteen miRNAs were up-regulated and thirteen miRNAs were down-regulated in the breast cancer group and compared to the control group. Pathway analysis revealed that miRNAs upregulated in the breast cancer group were associated with the PI3K-Akt signaling pathway and the MAPK signaling pathway. No association was observed between expression patterns of the identified miRNAs and clinicopathological factors other than nodal status and lymphatic invasion, including tumor size and hormone receptor/HER2 expressions. MicroRNA-486-5p, miRNA-486-3p and miRNA-126-3p expressions were decreased in patients with lymph node metastasis or lymphatic invasion. A machine learning model using urinary miRNAs identified breast cancer with an accuracy of AUC=0.83. The model maintained accuracy to diagnose breast cancer at any stage including ductal carcinoma in situ (DCIS), suggesting its usefulness in screening for early-stage cancers, including DCIS. Discussion: Previous reports have shown that miRNA-486-5p and miRNA-486-3p in breast cancer tissues are downregulated in patients with lymph node metastasis, and miRNA-126-3p is downregulated in patients with positive sentinel lymph nodes, which were consistent with the present study urine. This is the same trend as in the present study, which was conducted in using urine miRNAs. Conclusion: We identified miRNAs in urine to differentiate primary breast cancer from healthy controls. The miRNA-486 may correlate with lymph node metastasis and lymphatic invasion.

PO2-14-03

Novel Metrics of HER2 Heterogeneity in HER2-Positive and HER2-Low Breast Cancer via High Dimensional Multiplexed Immunofluorescence Spatial Profiling

Presenting Author(s) and Co-Author(s):

D. Tallman. Ohio State University Comprehensive Cancer Center, United States

A. Juncker-Jensen. NeoGenomics, United States

H. Nunns. NeoGenomics, United States

K. Gallagher. NeoGenomics, United States

H. LeFebvre. The Ohio State University, United States

K. Yamamoto. NeoGenomics, United States

K. Collier. The Ohio State University, United States

M. Vater. The Ohio State University, United States

A. Strahan. The Ohio State University, United States

M. Cherian. The Ohio State University Comprehensive Cancer Center, Dublin, Ohio, United States

A. Pariser. The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

P. Sudheendra. The Ohio State University Comprehensive Cancer Center, United States

B. Ramaswamy. The Ohio State University Comprehensive Cancer Center, United States

M. Gatti-Mays. The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

A. Kyshtoobayeva. NeoGenomics, United States

Z. Li. The Ohio State University, United States

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

K. Johnson. The Ohio State University Comprehensive Cancer Center, United States

Background: Categorizing breast cancer HER2/ERBB2 expression as “positive” or “negative” is no longer sufficient, with evidence that treatment response and outcomes are associated with HER2 “low” status and HER2 intratumoral heterogeneity. We hypothesized that interrogating HER2 heterogeneity (HER2het) across multiple spatial resolutions would more accurately capture HER2 diversity and be associated with clinical outcomes.

Methods: We interrogated tumor cell and microenvironmental features by profiling 1,113,204 single cells in tissue sections from 171 HER2+/HER2low cancers via custom 25-marker high dimensional multiplexed immunofluorescence (HDmIF) using NeoGenomics MultiOmyx, with adjacent section HER2 immunohistochemistry (IHC). We developed novel metrics to concurrently: 1) interrogate HER2 heterogeneity at four spatial resolutions; 2) use machine learning to translate HER2 IF to IHC, termed ‘HAIQu’ (HER2 Automated Immunofluorescence Quantification), scoring HER2 IF expression according to ASCO/CAP guidelines; 3) delineate HER2 signaling phenotypes at the tumor cell level based on six HER2-related proteins; 4) evaluate immunophenotype of 23 immune cell types. We evaluated the association of these novel HER2het metrics with patient clinicopathologic features, recurrence-free survival (RFS), overall survival (OS), and diverse antibody markers representing tumor cell intrinsic processes

and tumor-immune microenvironment (TME).

Results: 1166 regions of interest were analyzed from 208 unique tumors profiled. Median follow-up from diagnosis was 143 months and 98.9% (n=183/185) received HER2-directed therapy in the (neo)adjuvant or metastatic setting. Our HAIQu scoring system effectively translated adjacent section HER2 IF to IHC with 97.9% concordance between HAIQu and clinical IHC scoring. Single-cell phenotypic analyses of 392,984 HER2+/PanCK+ tumor cells' concurrent expression of six HER2-positive breast cancer related proteins (HER2, HER3, EGFR, pAKT, ER, KI67) using an unsupervised neural network-based self-organizing map approach resulted in 7 HER2 signaling cell phenotypes. Most patient samples are dominated by a single cell cluster but, intriguingly, Cluster 1 cells (EGFR-low) predominate in tumors with high HER2 cell membrane heterogeneity (ANOVA p=0.003). Evaluation of immunophenotype in hormone receptor-negative, HER2+ tumors, demonstrated significant association with immune cluster and recurrence-free survival (RFS; log-rank p=0.024) with zero RFS events among immune-high versus median survival of only 53.5mo among immune low-PDL1 low tumors. A multivariable Cox proportional hazards model including single cell HER2-heterogeneity (only significant metric on univariate), receptor subtype, and immunophenotype cluster demonstrated significant association with RFS (overall model log-rank p=0.005) and each significantly contributed to the model (all p< 0.05).

Conclusions: We present novel metrics of HER2 heterogeneity via HDmIF, which offer detailed characterization of the diversity of HER2 expression in a large, clinically-annotated cohort with long-term follow-up. Identification of a strong association between immunophenotype and RFS supports further investigation of the highly immune activated subsets of ER-/HER2+ breast cancer. Strong correspondence of HER2 IF and IHC and our HAIQu methodology offers a pathway to translation of HER2het metrics to clinical practice.

Table 1. Association of HER2 Heterogeneity Metrics with Recurrence-Free Survival

Feature	Recurrence-Free Survival		
	Hazard Ratio	95% Confidence Intervals	P-value
Individual HER2 Heterogeneity Cox Models			
Single Cell Heterogeneity			
Univariate	0.97	0.94 – 0.997	0.028
Multivariate	0.95	0.92 – 0.99	0.02
Multivariate w/ stage	0.95	0.92 – 0.999	0.04
Neighborhood Heterogeneity			
Univariate	0.62	0.12 – 3.4	0.58
Multivariate	0.65	0.09 – 4.6	0.67
Multivariate w/ stage	0.48	0.04 – 5.3	0.55
Core Heterogeneity			
Univariate	1	0.9 – 1.1	1
Multivariate	0.98	0.87 – 1.1	0.82
Multivariate w/ stage	0.99	0.87 – 1.1	0.90
Patient Heterogeneity			
Univariate	1	1 – 1	0.72
Multivariate	1	1 – 1	0.88
Multivariate w/ stage	1	1 – 1	0.51
Combined Cox Model			
Single Cell Heterogeneity	0.97	0.94 – 0.998	0.04
Receptor Subtype			
Hormone receptor negative	Ref	--	--
Hormone receptor positive	0.35	0.15 – 0.79	0.01
Immune Cluster			
Immune-High + -Intermediate	Ref	--	--
Immune-Low / tPDL1 high	1.88	0.64 – 5.51	0.22
Immune-Low / tPDL1 low	3.40	1.15 – 10.1	0.03

PO2-14-04

Circulating tumor DNA after neoadjuvant chemotherapy is a better prognostic test than Residual Cancer Burden in patients with triple negative breast cancer and residual tumor

Presenting Author(s) and Co-Author(s):

M. Basik. Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada, United States

T. Roseshter. Lady Davis Institute, Quebec, Canada

A. Klemantovich. Lady Davis Institute, United States

L. Cavallone. Lady Davis Institute, United States

A. Aguilar-Mahecha. Lady Davis Institute, United States

J. Lafleur. Lady Davis Institute, United States

C. Lan. Lady Davis Institute, United States

O. Elebute. MIMS Inc., United States

S. Jenna. MIMS, United States

J. Boileau. Jewish General Hospital Segal Cancer Centre, McGill University, Montréal, Quebec, Canada

M. Pelmus. Jewish General Hospital, United States

Background The presence of residual tumor at surgery (non-pathological complete response or non-pCR) occurs in about half of TNBCs treated with neoadjuvant chemotherapy (NAC) signals chemoresistance. Although the addition of further adjuvant chemotherapy (Capecitabine/Xeloda) significantly improves RFS in these patients, the majority of patients nevertheless have a good prognosis, and thus may not require adjuvant Capecitabine. One of the best prognostic biomarkers in these patients is Residual Cancer Burden (RCB), which relies on the pathological examination of the residual tumor bed and lymph nodes obtained at surgery. Circulating tumor DNA (ctDNA) is a plasma-based biomarker, which has been shown to accurately detect minimal residual disease in breast cancer. We have previously shown that detection of ctDNA after NAC but before surgery in patients with non-pCR signals very poor prognosis, while non-detectable ctDNA is associated with an excellent prognosis. We now compare ctDNA to RCB score in TNBC patients with non-pCR. **Methods** In the multicenter TRICIA study, 44 TNBC patients with non-pCR after NAC in 5 hospital centers had consented to serial plasma collection prior to and after surgery. RCB score was calculated from pathology records. Whole exome sequencing (WES) was performed on DNA extracted from primary tumor biopsies or residual tumors at surgery to identify tumor-specific mutations (5 variants/patient). Digital droplet PCR (ddPCR) assays were developed for these mutations and tests were run in an academic hospital setting. Patients with at least one detectable mutation were considered ctDNA positive for a given time point. The detection of ctDNA was correlated with relapse-free survival (RFS). **Results:** The median follow up was 40 months. 19 of the 44 patients relapsed within 2 years after surgery. Detection of ctDNA at the end of NAC but before surgery (T1) was correlated with very poor RFS (H.R. = 0.15, $p < 0.0001$ (95% CI = 0.067-0.35)). 14/15 patients (93%) without detectable ctDNA did not recur, while 76% of patients with detectable ctDNA relapsed. The RCB score distribution was as follows: 7 RCB1, 21 RCB2 and 16 RCB3. According to RCB score, 1/7 RCB1, 11/21 RCB2 and 11/16 RCB3 patients relapsed. All but one of the relapsed patients had detectable ctDNA in at least one timepoint. All 11 RCB3 patients that relapsed had detectable ctDNA while none of the 5 RCB3 patients without relapse had detectable ctDNA. The one RCB1 patient with detectable ctDNA also relapsed. In cox

regression analysis, the lack of ctDNA detection was significantly associated with excellent RFS in RCB2 (HR=0.16, p=0.003, (95% CI=0.05-.53)) and RCB3 groups (HR=0.10, p=0.0005, 95% CI= 0.03-.36). Conclusion ctDNA testing using ddPCR in an academic hospital-based setting at the post-NAC time point identifies an excellent prognostic group in TNBC patients with non-pCR and can discriminate very good from very poor prognosis in both RCB2 and RCB3 score subgroups. The detection of ctDNA may be superior to RCB scores in assessing prognosis in patients with non-pCR.

PO2-14-05

COMPARISON OF HER2 mRNA PCR LEVELS AND IMMUNOHISTOCHEMISTRY (IHC) IN HORMONE RECEPTOR POSITIVE (HR+) / HER2 NEGATIVE (HER2-) EARLY BREAST CANCER.

Presenting Author(s) and Co-Author(s):

J. Tejerina-Peces. Hospital Clínico San Carlos, United States

M. Amann-Arévalo. Hospital Clínico San Carlos, United States

P. Ballestín. Hospital Clínico San Carlos, United States

B. González-Diez. Hospital Clínico San Carlos, United States

M. Paz-Cabezas. Hospital Clínico San Carlos, United States

A. Pascual. Hospital Clínico San Carlos, United States

A. de Luna. Hospital Clínico San Carlos, Madrid, Spain, United States

V. García-Barberán. Hospital Clínico San Carlos, United States

A. López de Sá. Hospital Clínico San Carlos, United States

J. García-Sáenz. Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), United States

F. moreno. Hospital Clínico San Carlos, Madrid, Spain, United States

BACKGROUND IHC assays were developed to identify HER2-positive breast cancers deemed to be treated with trastuzumab-based therapies. However, these assays lack sensitivity to reliably identify tumors with low levels of HER2 protein on the cell surface. HR+/HER2-low may benefit from Trastuzumab Deruxtecan (TDXd) and therefore accurate quantification of HER2 expression levels becomes a critical issue. As a result, additional technologies are needed to achieve a quantitative and reproducible detection of HER2 in the low range expression compared with the standard IHC testing. **METHODS** We conducted a retrospective study of all incident stage I-II HR +/-HER2- breast cancer patient whose genomic risk was assessed with the Oncotype 21 gene assay from 2009 to 2022 in Hospital Clínico San Carlos (Spain).

Local HER2 expression (IHC w/wo cerbB2 FISH) was performed in all patients according to ASCO/CAP guidelines available during the different periods. HER2 mRNA expression levels by RT-PCR were obtained from OncotypeDx patient reports.

The primary objective was to determine the distribution of HER2 mRNA levels across the different HER2 expression groups. Other objectives were to compare the clinicopathological characteristics, management and OncotypeDX Recurrence Score (RS) in the different HER2 expression groups.

Qualitative variables are presented with their frequency distribution. Quantitative variables are summarized in their mean and standard deviation (SD). Welch's F-test ANOVA was used to measure association between the two HER2 measuring methods. **RESULTS** 500 early breast cancer patients with HER2 IHC 0, 1+ and 2+ (FISH negative) and HER2 mRNA expression by RT-PCR tumors were included. Among them, 169 (34%) were IHC 0, 211(42%) were IHC 1+ and 120 (24%) were IHC 2+ (FISH negative).

The distribution of clinicopathological characteristics was similar between different IHC HER2 expression groups, and the distribution of chemotherapy treatment was also similar among

them (Table 1). All patients had undergone surgery, and most of them had received hormone therapy (487, 97%) and radiotherapy when indicated (375, 77%).

The mean OncotypeDx® recurrence score across HER2 IHC 0, 1, 2 showed not significant difference between groups (16,85, 17,36 and 17,89 respectively).

The mean OncotypeDx® HER2 gene score expression across the different levels of HER2 (0, 1+, 2+) determined by IHC were 9.07, 9.25 and 9.51, respectively. One-way ANOVA and Games-Howell post-hoc test revealed that differences between all the groups were significant. The ranges of HER2 gene score data for the 3 IHC groups were widely overlapped, with IQR of [8,5-9,5], [8,83-9,7] and [9,07-10] respectively. CONCLUSIONS Our data show statistically significant differences between HER2 mRNA expression levels and IHC groups. This suggests that RT-qPCR could complement the data obtained by IHC. However, the wide range and dispersion of mRNA expression within groups limits its clinical utility.

Clinicopathological characteristics and management between different IHC HER2 expression groups.

Clinicopathological characteristics and management between different IHC HER2 expression groups		HER2 0+	HER2 1+	HER2 2+ (FISH+)	OVERALL
Age	Age (median)	55	57	58	57
Menopausal status	Premenopausal	67 (41%)	64 (32%)	32 (27%)	163 (34%)
	Perimenopausal	10 (6%)	12 (6%)	7 (6%)	29 (6%)
	Postmenopausal	87 (53%)	124 (62%)	78 (67%)	289 (60%)
Type of tumour	NOS	133 (79%)	175 (83%)	96 (80%)	404 (81%)
	Lobullar	23 (14%)	25 (12%)	17 (14%)	65 (13%)
	Other	13 (8%)	11 (5%)	7 (6%)	31 (6%)
Grade	1	34 (21%)	50 (24%)	16 (13%)	100 (20%)
	2	116 (70%)	146 (70%)	94 (78%)	356 (72%)
	3	15 (9%)	13 (6%)	10 (8%)	38 (8%)
Tumor Size (T)	1	113 (67%)	153 (73%)	81 (68%)	347 (69%)
	2	54 (32%)	56 (27%)	39 (32%)	149 (30%)
	3	2 (1%)	2 (1%)	0 (0%)	4 (1%)
Node involvement (N)	0	133 (79%)	159 (75%)	96 (80%)	388 (78%)
	1	35 (21%)	52 (25%)	23 (19%)	110 (22%)
Chemotherapy	Non chemotherapy	130 (76%)	158 (75%)	95 (79%)	383 (77%)
	Anthracycline-based	6 (3%)	9 (4%)	4 (3%)	19 (4%)
	Non anthracycline based	33 (19%)	44 (21%)	21 (16%)	98 (19%)

PO2-14-06

CIRCULATING TUMOR DNA DYNAMICS IN THE FIRST TREATMENT LINE OF THE SONIA TRIAL

Presenting Author(s) and Co-Author(s):

E. Jongbloed. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

S. Stella. Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy, United States

L. van Bergen. Department of Medical Oncology, Erasmus MC Cancer institute, Rotterdam, the Netherlands, United States

C. Beaufort. Department of Medical Oncology, Erasmus MC Cancer institute, Rotterdam, the Netherlands, United States

J. Helmijr. Department of Medical Oncology, Erasmus MC Cancer institute, Rotterdam, the Netherlands, United States

V. de Weerd. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

F. Erdkamp. Department of Medical Oncology, Zuyderland Medical Centre, Geleen, The Netherlands, United States

J. Heijns. Amphia, Breda, Noord-Brabant, Netherlands

Y. Kamm. Department of Medical Oncology, Maasziekenhuis Pantein, Boxmeer, The Netherlands, United States

A. van Riel. Department of Medical Oncology, Elisabeth Twee Steden Hospital, Tilburg, The Netherlands, United States

Q. van Rossum-Schornagel. Franciscus Gasthuis & Vlietland, Schiedam, The Netherlands, United States

M. Jansen. Department of Medical Oncology, Erasmus MC Cancer institute, Rotterdam, the Netherlands, United States

I. Konings. Amsterdam UMC, United States

G. Sonke. Netherlands Cancer Institute, Amsterdam, Netherlands

J. Martens. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, Rotterdam, Zuid-Holland, Netherlands

A. Jager. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, Rotterdam, Netherlands

S. Wilting. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

Background and objective: CDK4/6 inhibitors (CDK4/6i) improve the outcome of patients with ER+/HER2- advanced breast cancer when added to endocrine therapy in the first line or second line of treatment. The recently reported SONIA trial shows no difference in progression free survival after two lines of treatment (PFS2), overall survival (OS) or quality of life benefit of CDK4/6i in first-line compared to second-line, while adverse events are substantially higher when CDK4/6i is added in the first-line. However, a subgroup of patients shows early progression on endocrine mono-treatment and not all patients respond equally well to CDK4/6i. This highlights the need for early response markers during the first weeks of treatment to reduce unnecessary toxicity while providing the most optimal care. In this SONIA side study, we aim to investigate whether we could identify patients who will progress rapidly during first line of therapy by using circulating tumor DNA (ctDNA) dynamics.

Methods: Blood samples were obtained from patients included in the SONIA trial in both the first line CDK4/6i + aromatase inhibitor (AI) combination arm (arm A) and the first line AI monotherapy arm (arm B) at three time points: before start, after two weeks and after three months of first line treatment. Cell free DNA (cfDNA) was isolated from all samples and subsequently baseline cfDNA was sequenced with the Oncomine™ Breast cfDNA Assay v2 (Thermofisher), a focused NGS panel of 10 genes. Dedicated dPCR assays were used to track an identified driver mutation over time.

Results: Blood samples of 332 patients (206 in arm A and 126 in arm B) before start of first line treatment and after two weeks of treatment were obtained. At baseline, in 142 of the 332 (42.7%) patients at least one somatic mutation was detected. In 30 patients two or more mutations were identified, in which case the mutation with the highest variant allele frequency (VAF) was followed over time. The most frequently mutated genes were PIK3CA (102 patients (30.7% of the total included cohort)), TP53 (32 patients (9.6%)), SF3B1 (8 patients (2.4%) and ESR1 (6 patients (1.8%)). The median observed VAF at baseline was 4.1% (IQR: 1.5%-13.1%). Of the 142 patients with detectable ctDNA at baseline, 141 patients and 100 patients, respectively, had blood samples taken after 2 weeks and after 3 months of treatment. After two weeks, the VAF of the tracked mutation was increased in 15.2% (14/92) of the patients in arm A and in 18.4% (9/49) of the patients in arm B. At the same time 40.2% (37/92) of the patients in arm A and 34.7% (17/49) of the patients in arm B had cleared ctDNA. No difference was observed between the arms for both an increase in VAF (P=0.63, Chi-square test) and ctDNA clearance (P=0.52, Chi-square test). After 3 months an increased VAF of the tracked mutation compared to baseline was observed in 6.3% (4/64) of the patients in arm A and 8.3% (3/36) of the patients in arm B. At this timepoint 59.4% (38/64) of the patients in arm A and 61.1% (22/36) of the patients in arm B had cleared ctDNA. No difference was observed between the arms for both ctDNA clearance (P=0.86, Chi-square test) and increase in VAF (P=0.70, Chi-square test) after three months.

Conclusions: ctDNA was detected at baseline in almost half of the patients in the SONIA study. Compared to baseline, a decreasing number of patients had an elevation of the VAF of the tracked mutation and an increasing number of patients showed ctDNA clearance from 2 weeks to 3 months after start of treatment. There was no difference between the two arms observed regarding ctDNA dynamics. Interestingly, irrespective of treatment arm, about 1/3rd of patients remained ctDNA-positive even after 3 months of treatment. Associations of these ctDNA data with the clinical outcome data are currently being evaluated and will be presented at the meeting.

PO2-14-07

Association between expression of androgen receptor in tumor tissue and risk of breast cancer recurrence among premenopausal Danish women

Presenting Author(s) and Co-Author(s):

R. Nash. Emory University, United States

A. Kjærsgaard. Aarhus University Hospital, Denmark

K. Christensen. Aarhus University Hospital, United States

T. Ahern. Department of Surgery, The Robert Larner, M.D. College of Medicine, University of Vermont, Burlington, Vermont, United States

L. Collin. Huntsman Cancer Institute, University of Utah, United States

S. Hamilton-Dutoit. Department of Clinical Medicine and Department of Pathology, Aarhus University Hospital, Aarhus N, Denmark, United States

L. McCullough. Emory University, United States

J. Schildkraut. Emory University, Georgia, United States

H. Sørensen. Aarhus University and Aarhus University Hospital, United States

K. Ward. Emory University, Georgia, United States

K. Woolpert. Department of Clinical Epidemiology, Aarhus University Hospital, United States

T. Lash. Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA, United States

D. Cronin-Fenton. Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Background: Breast cancer prognosis is influenced by tumor biomarker expression. For example, tumors that express the estrogen receptor (ER+) have a lower hazard of recurrence in the first five years following treatment than tumors that do not express the estrogen receptor. Identifying additional biomarkers that are prognostic of breast cancer recurrence may aid in risk stratification and the development of targeted therapies. The androgen receptor (AR) is one such candidate biomarker. While some previous studies have found lower breast cancer mortality associated with AR expression, others have shown no association. However, these studies were conducted in populations exclusively or primarily comprised of postmenopausal women. Since menopause is associated with an increased concentration of androgens relative to estrogens, the role of AR may differ in premenopausal women. Methods: Using the Predictors of Breast Cancer Recurrence cohort (N=5,959)—a prospective cohort study of premenopausal women diagnosed with stage I–III primary breast cancer between 2002 and 2011 and registered in the Danish Breast Cancer Cooperative Group (DBCG) clinical database—we measured the association between tumor AR expression and breast cancer recurrence. The majority of the cohort (77%) had ER+ tumors and were intended to be treated with tamoxifen. Primary paraffin-embedded tumors were collected from treating hospitals, and 2–3 cores were included in a tissue microarray for immunohistochemistry. AR staining of each core was automatically scored using a trained software application and quantified as the percent of tumor nuclei with positive staining. Patients were considered to have AR positive (AR+) tumors if the maximum score across replicate cores was >1% positive. Otherwise patients were classified as having AR negative (AR–) tumors. Patients were followed from breast cancer diagnosis until the first of recurrence, death, emigration, another malignancy, or 10 years. The DBCG defines breast cancer recurrence as any breast cancer diagnosed after the initial course of treatment, including contralateral breast cancers. The association between

AR expression and breast cancer recurrence was computed as an unadjusted risk ratio and corresponding 95% confidence interval. Results: Among the 4,658 cohort members with available tumor tissue, 72% had AR+ tumors; 720 recurrences occurred over the 10-year follow-up. Patients with AR+ tumors were less likely to experience a recurrence than patients with AR- tumors [14% vs. 18% respectively; unadjusted risk ratio=0.80, 95% CI: (0.70, 0.92)]. Conclusion: AR expression in primary tumor tissue was associated with a lower risk of breast cancer recurrence in a large population-based cohort of premenopausal women. Additional analyses adjusting for clinical factors, examining the association by breast cancer subtype, and accounting for time to recurrence are forthcoming.

PO2-14-08

Development and characterization of breast cancer organoids representing epithelial heterogeneity and drug response

Presenting Author(s) and Co-Author(s):

D. Brown. University of Pittsburgh, Pittsburgh, Pennsylvania, United States

K. Ding. UPMC, United States

F. Chen. University of Pittsburgh, United States

J. Chen. Institute for Precision Medicine, University of Pittsburgh, United States

S. Oesterreich. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

P. Lucas. UPMC Hillman Cancer Center / NSABP Foundation, Pittsburgh, Pennsylvania, United States

P. McAuliffe. UPMC Magee-Womens Hospital, United States

J. Atkinson. Institute for Precision Medicine, University of Pittsburgh, United States

A. LEE. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

Organoids serve as an important preclinical model in multiple cancers including breast cancer, demonstrating preservation of biological features and feasibility of drug screening, with reasonable cost and high scalability. It has been reported that patient-derived organoids (PDOs) can be robustly derived from both primary and metastatic breast tumors, with high resemblance to source tissues in histological, genomic, and transcriptomic features, as well as consistency in drug response compared to xeno-transplantations or patients (Sachs et al, 2018).

Since 2018, the Institute for Precision Medicine (IPM) has developed a panel of breast cancer organoids. The current inventory now consists of 128 PDOs from 94 primary tumors, 12 metastases, 12 rapid-autopsy tumors, and 10 normal breast tissues with a 60% success rate of culture; as well as 33 organoids from animal models including 11 patient-derived xenograft organoids (PDXOs), 15 rat (RDO) and 7 mouse (MDO) tumor organoids with 85% success rate. For PDOs, the protocol includes in-lab processing of fresh, deidentified tissue within 60 minutes of surgical operation, thanks to close collaboration with surgeons, consented patients, and an institutional biospecimen core.

BC organoids have been comprehensively characterized in terms of morphology, histology, genomics, transcriptomics, and functional experiments. Key biological features are preserved. PDOs (n=56) exhibit a mutational spectrum consistent with human breast cancers. ER expression is detectable in a subset of cultures with robust estradiol response indicated by GREB1 expression; and PDOs from invasive lobular carcinoma (ILC) mostly showed more discohesive structures than PDOs from no special type (NST), with clear E-cadherin loss under immunofluorescence. We have also successfully constructed transcriptionally and genetic modified BC PDOs with shRNA and CRISPR, which showed replicable performance in proliferation assay, drug response, and signaling by western blot. Of note, longitudinal tracking of PDOs with single cell RNA-sequencing (scRNA-seq) revealed well-preserved heterogeneity compared to primary tumor, while transcriptomic clonality was mildly decreased in later passages from pilot data. Future work will include expansion of current collection from various sources, longitudinal characterization with scRNA-seq and DNA sequencing, as well as more

functional studies. We aim to construct a robust resource of well-characterized and reliably-usable model bank for preclinical breast cancer research.

PO2-14-09

Baseline genomic alterations and the activity of lasofoxifene (LAS) plus abemaciclib (Abema) in patients with ER+/HER2- metastatic breast cancer (mBC): the ELAINE 2 study

Presenting Author(s) and Co-Author(s):

S. Damodaran. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Cristofanilli. Weill Cornell Medicine, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

C. O'Sullivan. Mayo Clinic, Rochester, MN, USA, ROCHESTER, Minnesota, United States

G. Riordan. Reg Pro1, LLC, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

S. Wander. Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

D. Carroll. Sermonix Pharmaceuticals, United States

P. Plourde. Sermonix Pharmaceuticals, United States

D. Portman. Sermonix Pharmaceuticals, United States

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

Introduction: Estrogen receptor-positive (ER+)/HER2-negative (HER2-) breast cancers commonly acquire constitutively active mutations in the ER α -encoding gene (ESR1), resulting in endocrine therapy (ET) resistance. In the phase 2, ELAINE 2 study (NCT04432454), LAS (a breast ER antagonist) combined with Abema provided a median progression-free survival (PFS) of ~13 months (mos) and clinical benefit rate (CBR) of 66% in patients with endocrine-resistant, ER+/HER2- mBC and ESR1 mutations (mESR1; Damodaran. J Clin Oncol 2023;41:suppl16;1057). Our objective was to describe baseline genomic alterations co-occurring with mESR1 and treatment responses to LAS plus Abema in patients with these concurrent genomic alterations.

Methods: Women (age \geq 18 yrs) with ER+/HER2- mBC that progressed after prior ET and CDK4/6 inhibitor (CDK4/6i) with an mESR1 detected in blood using the Sysmex-Inostics SafeSeq circulating tumor DNA (ctDNA) test were enrolled in ELAINE 2. Oral LAS 5 mg/day and Abema (provided by Eli Lilly and Co) 150 mg BID were taken until disease progression, death, unacceptable toxicity, or withdrawal. The Guardant360 CDx test was used to identify and describe baseline genomic alterations in ctDNA (including mESR1). Median PFS and CBR were assessed in patients with mESR1 and co-existing baseline genomic alterations. For patients who withdrew before disease progression, their last observation time was used as the progression time for PFS estimation. Data were summarized descriptively with no formal hypothesis testing.

Results: Of the 29 patients (median age 60 yrs) enrolled, mutations in ESR1 were identified in 26 by Guardant360; all these 26 patients had received prior CDK4/6i, 21 (81%) prior fulvestrant, and 12 (46%) prior chemotherapy for mBC. Alterations in 39 genes were

concurrently identified with mESR1, including TP53 mutations (n=11), PIK3CA mutations (n=8), CCND1 amplifications (n=6), and FGFR1 amplifications (n=5); co-amplification of CCND1 and FGFR1 was identified in 3 patients. LAS plus Abema treatment was associated with a CBR of 73% and a median PFS of 12.9 mos in the 26 patients with mESR1 (Table). CBRs were 63% in the co-occurring PIK3CA mutation subgroup and 64% in the TP53 mutation subgroup; median PFS times were 7.8 and 8.3 mos, respectively. All patients in the CCND1 and FGFR1 amplification subgroups achieved clinical benefit (CBR 100%) and the median PFS was 16.6 mos for both subgroups. In patients with mESR1 and co-alterations in ≥ 2 other genes of interest (PIK3CA, FGFR1, CCND1, TP53, ERBB2, CCNE1, or RB1), CBR was 83% and median PFS was 16.6 mos.

Conclusion: Using Guardant360 ctDNA profiling from patients in ELAINE 2, we demonstrate that other baseline genomic alterations are frequently detected concurrently with mESR1 in the endocrine resistant setting, but without apparent compromise on the efficacy of LAS plus Abema. These results should be interpreted with caution considering the small numbers of patients and the exploratory nature of the analysis. The ELAINE 2 study suggests the potential of LAS plus Abema for treating ESR1-mutated, ER+/HER2- mBC in the post-CDK4/6i setting. This will be further evaluated in the larger, registrational, phase 3, ELAINE 3 study (NCT05696626) that compares LAS plus Abema with fulvestrant plus Abema.

Table. Treatment response by genomic alterations concurrent with ESR1 mutations (n=26).

Genomic alteration	Baseline n (%)	CBR, %	mPFS ^a , mos
ESR1 mutation	26 (100)	73	12.9
+ TP53 mutation	11 (42)	64	8.3
+ PIK3CA mutation	8 (31)	63	7.8
+ CCND1 amplification	6 (23)	100	16.6
+ FGFR1 amplification	5 (19)	100	16.6
+ co-alterations in ≥ 2 of any other genes of interest ^b	12 (46)	83	16.6

aFor patients who withdrew before disease progression, the last observation time was used as the progression time for PFS estimation.

bOther genes of interest include PIK3CA, FGFR1, CCND1, TP53, ERBB2, CCNE1, or RB1. CBR, clinical benefit rate; mPFS, median progression-free survival.

PO2-14-10

A selective MCL-1 inhibitor AZD5991 showed tumor regression in a triple-negative inflammatory breast cancer xenograft model

Presenting Author(s) and Co-Author(s):

M. Mughees. The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, Houston, Texas, United States

M. Tacam. MD Anderson Cancer Center, United States

A. tan. M D Anderson Cancer center, United States

M. White. AstraZeneca, United States

B. Debeb. MD Anderson Cancer Center, United States

E. Villodre. MD Anderson Cancer Center, United States

X. Hu. MD Anderson cancer center, houston, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

W. Woodward. UT MD Anderson Cancer Center, Houston, Texas, United States

R. Layman. The University of Texas MD Anderson Cancer Center, United States

G. Bartholomeusz. MD Anderson Cancer Center, United States

C. Bartholomeusz. MD Anderson Cancer Center, United States

Background Triple-negative breast cancer (TNBC) accounts for 15-20% of all breast cancer diagnoses but up to 30% of breast cancer-related deaths. Similarly, Inflammatory breast cancer (IBC) accounts for 2-4% of breast cancer diagnosis but causes 8%–10% of all breast cancer-related deaths. The myeloid cell leukemia-1 (MCL-1) is a member of the BCL-2 family of proteins, which is highly amplified in numerous human cancers and associated with cell immortalization, transformation, and chemoresistance. In fact, MCL-1 is amplified in 55% of TNBC after preoperative chemotherapy. Amongst the MCL-1 inhibitors that have been developed, AZD5991 showed high selectivity and affinity for MCL-1. In myeloma and acute myeloid leukemia cells AZD5991 induces apoptosis and showed anti-tumor effects in in vivo models. In the present study, we evaluated the biological role of the MCL-1 inhibitor AZD5991 in IBC and TNBC in vitro and in vivo models. **Materials and methods** The expression of the MCL-1 gene was analyzed in the World Consortium IBC patient dataset. Next, we screened a panel of TNBC and IBC cell lines for MCL-1 expression by western blot analysis. The effect of AZD5991 on TNBC and IBC cells was analyzed via cell titer-blue proliferation, clonogenic assays and soft agar assay. To further validate these findings, we used siRNA to knockdown MCL-1 and performed cell proliferation, clonogenic and migration assays. To identify signaling pathways involved in MCL-1 Inhibitor's effects we performed a proteome profiler human apoptosis array in TNBC cells in the presence of AZD5991. The anti-tumor effect of the MCL-1 inhibitor was evaluated using a SUM-149 (TN-IBC) orthotopic xenograft mouse model. The mice were treated with AZD5991 at doses of 15 and 30mg/kg once weekly via tail vein injection for a duration of 4 weeks. **Results** The mean expression level of MCL-1 was higher in patients with TNBC than in those with non-TNBC. Further, compared to the patients with ER positive, HER-2 negative tumors those with TNBC showed an increased in the mean expression of MCL-1 gene (p value= 0.05). We screened a panel of TNBC and IBC cell lines in which most of the cell lines showed high levels of MCL-1. The cell proliferation assay showed IC₅₀ ranging from 0.27 – 19.6 µM. The SUM149, SUM190, FCIBC02, MDA-IBC3 and MDA-MB-468 cells

showed high sensitivity and showed significant decrease in the proliferation rate while BCX010, KPL4, MDA-MB-231, 4T1.2 and E0771 cells as well as the normal breast cells MCF10A exhibited resistance with no significant decrease in proliferation. The clonogenic and soft agar assays with these sensitive and resistant cell lines showed similar results. Further, these findings were validated via genetic knockdown of MCL-1 which resulted in a significant decrease in cell proliferation, colony formation and migration capability of the TNBC cells. To identify signaling pathways involved in MCL-1 Inhibitor's phenotypic changes, we performed a proteome profiler human apoptosis array which showed a decreased in BCLx expression, and an increase in expression of BAX and phospho-Rad17 proteins in the AZD5991 treated TN-IBC cells. Finally, in a SUM-149 (TN-IBC) orthotopic xenograft mouse model, mice injected with 30mg/kg showed a significant tumor regression compared to the vehicle-treated mice (vehicle vs 30 mg/kg, p value=0.0006). Conclusions and Future directions Our data demonstrates that AZD5991 inhibits tumorigenesis in an inflammatory breast cancer xenograft model. We are currently validating several significant targets to understand the biological mechanisms related to our candidate drug. Our long-term goal is to develop MCL-1 targeted therapy in combination with standard-of-care treatment for inflammatory and triple-negative breast cancers.

PO2-14-11

Proteogenomic approaches for the identification of NF1/neurofibromin-depleted estrogen receptor positive breast cancers for targeted treatment

Presenting Author(s) and Co-Author(s):

B. Kim. AstraZeneca, United States

Z. Zheng. Baylor College of Medicine, United States

J. Lei. Baylor College of Medicine, United States

M. Holt. Baylor College of Medicine, United States

A. Chen. Baylor College of Medicine, United States

J. Peng. Baylor College of Medicine, United States

D. Fandino. Baylor College of Medicine, United States

P. Singh. Baylor College of Medicine, United States

H. Kennedy. Baylor College of Medicine, United States

Y. Dou. Baylor College of Medicine, United States

M. Chica-Parrado. University of Texas Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, United States

E. Bikorimana. UT Southwestern Medical Center, United States

D. Ye. UT Southwestern Medical Center, United States

Y. Wang. UT Southwestern Medical Center, United States

A. Hanker. UT Southwestern Medical Center, Dallas, Texas, United States

N. Mohamed. Baylor Scott and White Health, United States

S. Hilsenbeck. Baylor College of Medicine, United States

B. Lim. Baylor College of Medicine, Houston, Texas, United States

J. Asirvatham. Baylor Scott & White Health, United States

A. Sreekumar. Baylor College of Medicine, United States

B. Zhang. Baylor College of Medicine, United States

G. Miles. Baylor College of Medicine, United States

M. Anurag. Baylor College of Medicine, United States

M. Ellis. AstraZeneca, United States

E. Chang. Lester Sue Smith Breast Center, Baylor College of Medicine, Houston, Texas, United States

NF1 is a key tumor suppressor that represses both RAS and estrogen receptor- α (ER) signaling in breast cancer. Blocking both pathways by fulvestrant (F), a selective ER degrader (SERD), together with binimetinib (B), a MEK inhibitor, promotes tumor regression in NF1-depleted ER⁺ models. We aimed to establish approaches to determine how NF1 protein levels impact B+F treatment response to improve our ability to identify B+F sensitive tumors. We examined a panel of ER⁺ PDX models by DNA and mRNA sequencing and found that more than half of these models carried an NF1 shallow deletion and generally have low mRNA levels. Consistent with RAS and ER activation, RET and MEK levels in NF1-depleted tumors were elevated when

profiled by mass spectrometry (MS) after kinase inhibitor bead pull-down. MS showed that NF1 can also directly and selectively bind to palbociclib-conjugated beads, aiding quantification. An immunohistochemistry (IHC) assay was also established to measure NF1, but the MS-based approach was more quantitative. Combined IHC and MS analysis defined a threshold of NF1 protein loss in ER⁺ breast PDX, below which tumors regressed upon treatment with B+F. These results suggest that we now have a MS-verified NF1 IHC assay that can be used for patient selection as a complement to somatic genomic analysis.

PO2-14-12

Accurate quantification of slide-level HER2 scores in breast cancer using a machine-learning model, AIM-HER2 Breast Cancer

Presenting Author(s) and Co-Author(s):

Z. Shanis. PathAI, Boston, Massachusetts, United States
R. Cabeen. PathAI, Boston, Massachusetts, United States
S. Chakraborty. PathAI, Boston, Massachusetts, United States
J. Shamshoian. PathAI, United States
M. Thibault. PathAI, Boston, Massachusetts, United States
H. Padigela. PathAI, Boston, Massachusetts, United States
D. Juyal. PathAI, Boston, Massachusetts, United States
S. Javed. PathAI, Boston, Massachusetts, United States
W. Qian. PathAI, Boston, Massachusetts, United States
J. Kim. PathAI, United States
B. Rucker. PathAI, United States
J. Brosnan-Cashman. PathAI, Boston, Massachusetts, United States
H. Pokkalla. PathAI, Boston, Massachusetts, United States
J. Mehta. PathAI, Boston, Massachusetts, United States
A. Taylor-Weiner. PathAI, Boston, Massachusetts, United States
B. Glass. PathAI, Boston, Massachusetts, United States
S. Balasubramanian. PathAI, Boston, Massachusetts, United States

Background: HER2 expression level is a key factor in determining the optimal treatment course for breast cancer patients. Roughly 15% of breast cancers are HER2(+), and determination of HER2 status is routinely assessed by immunohistochemistry (IHC). Accurate assessment of the HER2 IHC score (0, 1+, 2+, 3+) by pathologists is therefore critical, especially in light of novel therapeutic approaches demonstrating efficacy in the HER2-low setting (IHC scores 1+, and 2+/FISH-)^{1,2}. To assist pathologists with the consistent provision of reproducible and accurate scores across the entire HER2 scoring range, we developed a machine-learning model (“AIM-HER2”) to generate accurate, slide-level HER2 scores aligned with ASCO-CAP guidelines in clinical breast cancer HER2 IHC specimens. Methods: AIM-HER2 was developed using whole-slide images (WSI; N=4261) from clinical and commercial sources. WSI were split into training (N=2694, 63%) and optimization (N=1567, 37%) sets. An additive multiple instance learning (aMIL) model³ was trained to predict HER2 scores directly from WSI and create interpretable heatmaps that depict HER2 predictions in tissue images. Image artifacts and in situ carcinomas were identified using previously trained artifact and tissue segmentation models and were excluded, leaving only regions of invasive carcinoma to be analyzed. AIM-HER2 performance was assessed on additional slides obtained from five academic or commercial sources (N=804 total, 770 evaluable) on which HER2 IHC was performed. Board-certified pathologists (N=52) with relevant experience provided manual HER2 scores based on ASCO-CAP guidelines. Nested pairwise non-inferiority analysis⁴ was used to compare model performance to that of pathologists (N=3 pathologists per slide). In the nested pairwise framework, agreement among pathologists was compared to agreement between AIM-HER2 and pathologists via linear

kappa, so that summary metrics account for inter-pathologist variability. Results: High concordance was observed between AIM-HER2-predicted and pathologist-labeled slide-level HER2 scores, both overall and for each scoring level. Similar results were observed when assessing AIM-HER2 performance on multiple slide scanners and after IHC with multiple HER2 IHC antibody clones. Results are summarized in Table 1. Conclusions: We developed AIM-HER2, a novel aMIL-based approach for predicting slide-level HER2 IHC scores. AIM-HER2 has similar levels of agreement with pathologists as pathologists have with each other for determining HER2 score. This result is upheld when slides imaged using multiple scanning platforms and stained using multiple HER2 antibody clones. The performance of AIM-HER2 on multiple scanners and after multiple assays supports broad applicability of this algorithm in clinical laboratories, including for the identification of HER2-low cases. Work is ongoing to perform similar analyses in an independent, real-world dataset. References: ¹Fernandez, AI, et al. JAMA Oncol. 2022 8(4):1-4. ²Modi, S et al. N Engl J Med. 2022 387:9-20. ³Javed, SA, et al. Adv Neural Inf Process Syst. 2022 35: 20689-702. ⁴Gerardin, Y, et al. 2023 arXiv:2306.04709

Table 1. Agreement between AIM-HER2 and pathologists compared to agreement among pathologists.

	Agreement between AIM-HER2 and pathologists	Agreement among pathologists
Overall (N=770)	0.63 (0.60, 0.67)	0.63 (0.59, 0.66)
Per HER2 Score		
0 (N=199)	0.68 (0.64, 0.72)	0.68 (0.64, 0.73)
1+ (N=230)	0.44 (0.39, 0.49)	0.45 (0.41, 0.50)
2+ (N=120)	0.49 (0.43, 0.55)	0.42 (0.36, 0.48)
3+ (N=221)	0.88 (0.85, 0.91)	0.88 (0.84, 0.91)
Scanner Type		
Aperio AT2 (N=392)	0.69 (0.65, 0.73)	0.67 (0.63, 0.71)
Aperio GT450 (N=206)	0.56 (0.50, 0.63)	0.55 (0.48, 0.61)
Hamamatsu s360 (N=91)	0.47 (0.37, 0.58)	0.48 (0.35, 0.59)
Aperio ScanScope v1 (N=81)	0.64 (0.55, 0.74)	0.59 (0.50, 0.68)
HER2 Antibody Clone		
Dako Herceptest (N=128)	0.61 (0.50, 0.70)	0.59 (0.49, 0.69)
Ventana 4B5 (N=642)	0.60 (0.57, 0.64)	0.59 (0.56, 0.63)

Linearly weighted kappa values and 95% confidence intervals are shown.

PO2-15-01

EZH2 protein expression in early hormone receptor positive HER2 negative breast cancer with high recurrence score

Presenting Author(s) and Co-Author(s):

S. Lin. Montefiore Einstein Cancer Center, United States

Y. Lo. Albert Einstein College of Medicine, United States

D. Makower. Montefiore Medical Center, United States

J. Lu. Montefiore Einstein Cancer Center, United States

S. Fineberg. Albert Einstein College of Medicine, United States

Background: The 21 gene recurrence score assay (RS) is both prognostic and predictive of chemotherapy benefit in hormone receptor positive (HR+) HER2 negative (HER2-) breast cancer (BC). While patients (pts) with RS>26 benefit from chemoendocrine therapy, they remain with poorer outcomes than pts with lower RS. Overexpression of the enhancer of zeste homolog 2 oncoprotein (EZH2) is linked to poor prognosis in multiple cancers, and is associated with resistance to endocrine therapy in HR+/HER2- BC. We evaluated association between EZH2 expression and distant metastases in a single institution cohort of pts with HR+/HER2- BC and RS>26. Methods: Pts with ER+/HER2- BC and RS>26 who underwent surgery at our institution between 2011 and 2017 were identified from pathology database. All pts with available tumor specimens were included in analysis. Immunohistochemistry was performed to evaluate EZH2 protein expression within invasive tumor cells and quantified as follows: nuclear staining intensity was scored as 3 (strong), 2 (moderate), 1 (weak), and 0 (no stain). Percentage of positive nuclei at each intensity was multiplied, and all values were added to arrive at a final EZH2 score multiplied by 100, ranging from 0 (no nuclei staining) to 300 (strong nuclear staining in 100% of cells). The investigator scoring EZH2 staining was blinded as to pts clinical outcomes. EZH2 score was both evaluated as a continuous variable and dichotomized at a score of 140. Associations between EZH2 score and age at diagnosis, progesterone receptor (PR) status, tumor size, grade, node involvement, RS, and metastatic recurrence were determined by Kruskal-Wallis or Wilcoxon rank-sum tests for categorical variables and Spearman correlation coefficients for continuous variables. Results: 45 pts were included. Median (IQR) age was 60 (55, 69). 32 (71.1%) pts received chemotherapy. 37 (82.2%) pts received endocrine therapy. Tumor size was ≤2 cm in 26 pts (57.8%), and >2 cm but ≤5 cm in 19 pts (42.2%). 7 pts (15.6%) had involved axillary nodes. Median RS was 31 (28, 37). Median EZH2 score was 120 (90, 170). With median follow-up of 7.6 (5.7, 9.2) years, 4 pts (8.9%) developed distant metastatic disease. EZH2 score was significantly associated with development of metastatic disease, both when EZH2 was expressed as a continuous variable ($p=0.040$) and when dichotomized at 140 ($p=0.015$). EZH2 score was positively associated with RS ($r = 0.37$; $p=0.013$) and negatively associated with age at diagnosis ($r = -0.44$; $p=0.002$), but was not associated with clinicopathologic features such as tumor size, grade, node involvement, and PR status. Younger age was also associated with development of metastatic disease ($p=0.023$), whereas tumor size, grade, node involvement, PR status, RS, and receipt of chemotherapy were not. Conclusion: In this single institution cohort of pts with early HR+/HER2- BC and high RS, EZH2 protein expression and younger age were associated with development of distant metastases. This preliminary data suggests that determination of EZH2 expression levels may assist in risk stratification of pts with high RS. This should be investigated in a larger data set.

PO2-15-02

Personalized circulating tumor DNA (ctDNA) monitoring can early identify disease progression and predict prognosis in patients with breast cancer undergoing neoadjuvant therapy

Presenting Author(s) and Co-Author(s):

Y. Liu. Department of Breast Center, Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, P.R. China ; Hebei Provincial Key Laboratory of Tumor Microenvironment and Drug Resistance, Shijiazhuang, 050011 P.R. China, United States

C. Shi. Department of Breast Center, Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, P.R. China ; Hebei Provincial Key Laboratory of Tumor Microenvironment and Drug Resistance, Shijiazhuang, 050011 P.R. China, United States

X. Zhang. Department of Breast Center, Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, P.R. China ; Hebei Provincial Key Laboratory of Tumor Microenvironment and Drug Resistance, Shijiazhuang, 050011 P.R. China, United States

X. Ren. Department of Breast Center, Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, P.R. China ; Hebei Provincial Key Laboratory of Tumor Microenvironment and Drug Resistance, Shijiazhuang, 050011 P.R. China, United States

S. Wu. Department of Breast Center, Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, P.R. China ; Hebei Provincial Key Laboratory of Tumor Microenvironment and Drug Resistance, Shijiazhuang, 050011 P.R. China, United States

Y. Wang. Shanghai Origimed Co., Ltd., Shanghai, 201112 P.R. China, United States

Y. Che. Shanghai Origimed Co., Ltd., Shanghai, 201112 P.R. China, United States

Z. Xu. Shanghai Origimed Co., Ltd., Shanghai, 201112 P.R. China, United States

F. Pang. Shanghai Origimed Co., Ltd., Shanghai, 201112 P.R. China, United States

Background:

Circulating tumor DNA (ctDNA) analysis offers a non-invasive method to assess tumor burden during treatment. Although some data have been reported on the use of ctDNA in neoadjuvant therapy (NAT) for breast cancer (BC), there is a lack of data on neoadjuvant efficacy and prognosis in China specifically using tumor-informed personalized ctDNA monitoring panel.

Methods:

We performed personalized ctDNA analyses at different time of NAT (before, during, and after) in 19 patients with Stage IIA-IIIB BC. WES was conducted on tumor tissues, and single nucleotide variants (SNVs) (20-40) were selected for each patient to ensure accurate and sensitive detection of individual ctDNA (Shanghai Origimed Co., Ltd.) .

Results:

A total of 19 BC patients, 6 HER2-negative and 13 HER2-positive, were enrolled at the Breast Center, Fourth Hospital of Hebei Medical University (China) from June 2022 to May 2023. The median age of the patients was 53 (min-max: 28-64) years old. Through WES, it was discovered that 78.5% (3377/4303) of the mutated genes were unique to each patient. Additionally, 96.1% (637/663) of the selected tumor-informed SNVs were VUS variants. These findings suggest that tumor-informed ctDNA monitoring is more effective than panel-based ctDNA monitoring in BC. Among the patients, 84% (16/19) completed baseline blood collection, 63% (12/19) completed blood collection after NAT and 42% (8/12) patients completed blood

collection after the surgery. The baseline positivity rate was 100%, and the baseline ctDNA variant allele frequency was significantly associated with T stage and N stage (both $p < 0.01$). This suggests that designing a panel based on puncture samples is feasible for ctDNA analysis. The detection of ctDNA before surgery after NAT correlated with the postoperative ctDNA status. Patients with persistently negative ctDNA during NAT were associated with pathologic complete response (pCR), although the difference was not statistically significant due to the small sample size ($n=7$). In 84% of patients, dynamic changes in ctDNA aligned with imaging findings, indicating a correlation between ctDNA and disease progression.

A 56-year-old patient with HER2-negative stage IIIC BC had persistent ctDNA positivity during NAT. Imaging evaluation showed disease progression, with ctDNA allele frequency increasing 18 days before detection on imaging. After surgical tumor removal, the pathology assessment revealed a change in HER2 status from negative to positive. The patient received adjuvant chemotherapy combined with HER2-targeted therapy, resulting in a transition from positive to negative ctDNA status. The disease has remained stable for nearly 9 months. A 29-year-old patient with HER2-positive stage IIIA BC underwent NAT for 8 cycles. Due to drug intolerance, the treatment was interrupted multiple times during the first 4 cycles, and ctDNA remained positive. After modifying the treatment regimen in the 5th cycle, ctDNA became negative until the patient underwent surgery. The postoperative pathology evaluation revealed a pCR.

Conclusions:

Personalized ctDNA monitoring is more effective than panel-based ctDNA (a predefined set of cancer-associated genes) monitoring in BC. The status of ctDNA before and after surgery following NAT may be correlated, suggesting that patients with positive ctDNA before surgery may benefit from intensive therapy. More importantly, dynamic changes in ctDNA closely align with radiological findings, enabling early detection of disease progression and guiding treatment modifications.

PO2-15-03

Platelet-to-lymphocyte ratio in patients with metastatic breast cancer treated with eribulin.

Presenting Author(s) and Co-Author(s):

H. Shimada. Saitama Medical University International Medical Center, United States

K. Matsuura. Department of Breast Oncology, Saitama Medical University International Medical Center, United States

S. Kohyama. Saitama Medical University International Medical Center, Saitama, United States

A. Asano. Saitama Medical University International Medical Center, United States

M. Ohara. Saitama Medical University International Medical Center, United States

H. Ishiguro. Saitama Medical University International Medical Center, Saitama, Japan

A. Osaki. Saitama Medical University International Medical Center, United States

T. Saeki. Breast Oncology Service, Saitama Medical University International Medical Center, Saitama, Japan

Eribulin is widely used to treat metastatic breast cancer (BC). Higher neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte ratios (PLR) are associated with higher mortality in several cancer types. However, the association between BC prognosis and peripheral immune status remains controversial. We quantified the relative effects of NLR and PLR on survival in patients with recurrent/stage IV BC and evaluated their clinical prognostic value.

This retrospective study included 156 patients with recurrent/stage IV BC who received eribulin monotherapy at Saitama Medical University International Medical Center. We examined clinicopathological features (peripheral blood findings and biochemical liver and kidney function test results) and conducted univariate and multivariate analyses of the overall survival (OS).

The 156 eribulin-treated patients had a median follow-up duration of 18.3 months. Before eribulin treatment, patients with absolute lymphocyte counts (ALC) $>1500/\mu\text{L}$, NLRs < 3.0 , and PLRs < 150 had significantly longer OS than those with lower ALCs, and higher NLR and PLRs (median OS, 25.5 vs. 15.5 months; $p < 0.01$; 20.3 vs. 13.6 months, $P < 0.01$; and 29.2 vs. 14.8 months; $P < 0.001$, respectively). Patients with anemia (hemoglobin $< 10 \text{ g/dL}$) or liver dysfunction (albumin-bilirubin grade 2/3) had significantly shorter OS than those without ($P < 0.001$, respectively). Multivariate analysis revealed low albumin-bilirubin grade ($P < 0.001$), high hemoglobin ($P < 0.01$), and low PLR ($P < 0.05$) as independent factors of longer OS after eribulin administration.

Low PLR, anemia, and liver dysfunction might be factors associated with prolonged OS in patients with recurrent/stage IV BC on eribulin therapy, which could be clinically useful, as their evaluation requires neither new equipment nor invasive testing.

PO2-15-04

Fas/FasL expression on circulating tumor and immune cells in the peripheral blood of patients with metastatic breast cancer (BC): correlation with clinical outcome

Presenting Author(s) and Co-Author(s):

M. Papadaki. Laboratory of Translational Oncology, School of Medicine, University of Crete, Heraklion, Greece, United States

M. Vassilakopoulou. Laboratory of Translational Oncology, Medical School, University of Crete (UoC), Heraklion, Greece; Department of Medical Oncology, University General Hospital of Heraklion, Greece, United States

E. Papadaki. Laboratory of Translational Oncology, Medical School, University of Crete (UoC), Heraklion, Greece, United States

D. Aggouraki. Laboratory of Translational Oncology, Medical School, University of Crete (UoC), Heraklion, Greece, United States

C. Zioudas. Department of Medical Oncology, University General Hospital of Heraklion, Greece, United States

A. Mala. Department of Medical Oncology, University General Hospital of Heraklion, Greece, United States

S. Agelaki. Laboratory of Translational Oncology, School of Medicine, University of Crete, Heraklion, Greece; Department of Medical Oncology, University General Hospital of Heraklion, Greece, United States

D. Mavroudis. Laboratory of Translational Oncology, School of Medicine, University of Crete, Heraklion, Greece; Department of Medical Oncology, University General Hospital of Heraklion, Greece, United States

Background: The activation of Fas (CD95/APO-1) death receptor by Fas ligand (FasL/CD95L) can trigger a signal transduction pathway leading to apoptosis, which is a common pathway used by immune cells for tumor elimination. Cancer cells also exploit FasL expression to induce immune cell apoptosis, known as "Fas counterattack", and thus to increase their invasion and migration capacity. We herein assessed the expression of Fas and FasL on circulating tumor cells (CTCs) and immune cells in the peripheral blood (PB) of patients with metastatic BC. **Methods:** PB was obtained from 98 patients with metastatic BC at baseline before first-line treatment. Peripheral blood mononuclear cells (PBMCs) were isolated and immunofluorescently stained with antibodies against cytokeratins (CK; clones: AE1/AE3 & C11) and CD45 for CTC detection, along with antibodies for Fas, FasL and dapi. Fas/FasL expression was individually assessed on CTCs and PBMCs using the Ariol microscopy system (2×10^6 PBMCs were analyzed per patient). **Results:** CTCs were detected in 26/98 (26.5%) patients (total CTC count: $n=70$). Fas+ CTCs and FasL+ CTCs were identified in 88.5% and 92.3% of CTC-positive patients, respectively, representing the 57.1% and 82.9% of total CTCs. Regarding co-expression at single cell level, Fas+/FasL+ CTCs were detected in 84.6% of patients, whereas Fas+/FasL- CTCs, Fas-/FasL+ CTCs and Fas-/FasL- CTCs were identified in 7.7%, 19.2% and 11.5% of patients, respectively. Regarding PBMCs, the Fas+/FasL+ phenotype was identified in 70.3%, of patients, whereas Fas-/FasL+ PBMCs and Fas-/FasL- PBMCs were detected in 24.2% and 5.5% of patients, respectively; interestingly the Fas+/FasL- expression pattern was not observed in any patient. A reduced progression-free survival (PFS) was demonstrated among CTC-positive as compared to CTC-negative patients (median PFS: 9.5 versus 13.4 months; $p=0.004$), and specifically those harboring Fas+/FasL+ CTCs (median PFS: 9.5 vs 13.4 months; $p=0.009$). Increased overall survival (OS) was demonstrated among patients

harboring Fas+/FasL+ PBMCs, as compared to those with Fas-/FasL+ PBMCs and Fas-/FasL- PBMCs (median OS: 35.7 vs 25.9 vs 14.4 months; $p=0.008$). Conclusion: Herein we provide for the first time evidence on Fas/FasL expression on CTCs and PBMCs with significant prognostic relevance for patients with metastatic BC. The findings highlight the Fas/FasL signaling pathway as a putative mechanism of immune evasion and metastatic progression of BC. Their role as prognostic biomarkers in BC patients merits further investigation.

PO2-15-05

Mesenchymal-like immune-activated: the 4th robust triple-negative breast cancer molecular subtype

Presenting Author(s) and Co-Author(s):

M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France

P. Jézéquel. Institut de Cancérologie de l'Ouest, United States

F. Ben Azzouz. Institut de Cancérologie de l'Ouest (ICO), United States

W. Gouraud. Institut de Cancérologie de l'Ouest, Saint Herblain, Pays de la Loire, France

a. Basseville. ICO, United States

B. Michel. LAREMA, United States

H. Lasla. ICO, United States

J. FRENEL. ICO, United States

Triple-negative breast cancer (TNBC) accounts for 15-20% of primary BC. This heterogeneous disease is the most aggressive BC subtype. TNBC is characterized by young age at onset, high-grade tumors, high risk of early recurrence and poor prognosis. Until recently, TNBC patients were considered as one group and all patients were treated with conventional chemotherapy. With the emergence of new therapies targeting distinct biological pathways, personalized medicine is now accessible by defining finer TNBC subtypes, e.g. molecular subtypes, and identifying their specific targetable pathways. Several studies based on transcriptomics have identified three to six TNBC molecular subtypes. Today, there is a clear consensus on three TNBC robust subtypes: luminal androgen receptor (LAR), basal-like immune-activated (BLIA) and basal-like immune-suppressed (BLIS). The debate about the robustness of other subtypes is still open, notably mesenchymal-like (M) and mesenchymal stem-like (MSL or MES).

The goal of this study was to establish a robust molecular classification of TNBC that allow to determine the best treatment options. To optimize this process, we harvested as much transcriptomic data as possible. Available clinicopathological data linked to these data were also imported. To our knowledge, this is the largest study aimed at subtyping TNBC; it exploits a total of 1942 TNBC patient data collected from 19 datasets: 1243 samples from microarray technology (14 datasets) and 699 from RNAseq technology (five datasets including a new one from our institution [GSE225002]).

We performed independent unsupervised analyses on these two large cohorts with consensus k-means clustering including selection of optimal number of clusters and optimal number of variables. Both consensus clustering analyses separated TNBC microarray and RNAseq TNBC cohorts into four optimal clusters. These clusters were then characterized using clinicopathological features, gene ontology enrichment analyses (GOEA), gene set enrichment analysis (GSEA), 70 gene expression signatures (GES) and expression of 47 immune checkpoint genes.

We concluded that TNBC are composed of four robust subtypes: LAR, mesenchymal-like immune-activated (MLIA), BLIA and BLIS. Importantly, we propose that MLIA acronym should replace M or MSL, because it highlights the two main biological characteristics of this subtype, i.e. mesenchymal-like features and a high IR comparable to that of BLIA. Furthermore, we showed that each subtype shares common biological characteristics with another one: LAR and

MLIA (androgen receptor pathway activation); MLIA and BLIA (immune activation, notably high levels of immune checkpoints); BLIA and BLIS (basal-like features); BLIS and LAR (immune suppression).

As regards microarray cohort, LAR included 19.23% (n = 239) of TNBC, MLIA 17.38% (n = 216), BLIA 32.50% (n = 404) and BLIS 30.89% (n = 384). Concerning RNAseq cohort, LAR included 19.60% (n = 137) of TNBC, MLIA 17.31% (n = 121), BLIA 28.47% (n = 199) and BLIS 34.62% (n = 242). Distributions of patients among the four clusters in the two cohorts were similar (p = 0.3583). Distributions were also similar between studies for microarray cohort (p = 0.2479) and RNAseq cohort (p = 0.1775). Pooled data (n = 1942 patients) gave the following distribution: 19.36% for LAR; 17.35% for MLIA; 31.06% for BLIA; 32.23% for BLIS, confirming that TNBC are largely but not exclusively basal-like (63.29%).

In brief, according to the TNBC subtype molecular characterisation, anti-androgen therapy could be prescribed for LAR, immune checkpoint inhibitors for MLIA and BLIA, alone or in combination, and TAM-focused and antineurogenic therapies for BLIS.

As an extension of this work, TNBC transcriptomic data associated with their clinicopathological features and TNBC subtype annotations were included in bc-GenExMiner v5.0 web tool (<http://bcgenex.ico.unicancer.fr>).

PO2-15-06

ctDNA-based DNADX in hormone receptor-positive and HER2-negative (HR+/HER2-) advanced breast cancer following endocrine therapy and CDK4/6 inhibition: a correlative analysis from the randomized phase 2 PARSIFAL trial

Presenting Author(s) and Co-Author(s):

F. Brasó-Maristany. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), United States

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

J. Pérez-García. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Catalonia, Spain

R. Vega-León. Vall d'Hebrón Institute of Oncology, Spain

L. Paré. Reveal Genomics, United States

G. Villacampa. REVEAL GENOMICS S.L., Spain

J. Matito. Vall d'Hebrón Institute of Oncology, Spain

F. Pardo. Institut d'Investigacions Biomediques August Pi I Sunyer, Spain

M. Gomez-Rey. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

M. Mancino. MEDSIR, United States

E. Martínez-García. MEDSIR, Spain

C. Mora Gallardo. MEDSIR, Spain

L. Mina. MEDSIR, Spain

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

M. Bellet- Ezquerra. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

M. Gil-Gil. Institut Català d'Oncologia, Insitut d'Investigació Biomèdica Bellvitge. GEICAM Spanish Breast Cancer Group, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

C. Perou. Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA., United States

J. Parker. University of North Carolina, United States

P. Villagrasa. REVEAL GENOMICS, United States

A. Vivancos. Cancer Genomics Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain., Barcelona, Spain

A. Prat. Hospital Clinic Barcelona, Spain

A. Llombart-Cussac. Arnau de Vilanova Hospital, Valencia, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US, Comunidad Valenciana, Spain

ctDNA-based DNADX in hormone receptor-positive and HER2-negative (HR+/HER2-) advanced breast cancer following endocrine therapy and CDK4/6 inhibition: a correlative analysis from the randomized phase 2 PARSIFAL trial

Background: DNADX, a novel machine learning-based approach, utilizes DNA from tumor tissue or plasma ctDNA to identify clinically relevant phenotypic tumor features and classify breast cancer into 4 subtypes (Nat Comm 2023). Here, we evaluated DNADX's ability to predict prognosis and treatment benefit in HR+/HER2- advanced breast cancer following endocrine therapy and a CDK4/6 inhibitor.

Methods: DNADX was evaluated centrally in available baseline plasma ctDNA samples from PARSIFAL trial (NCT02491983) which randomized 486 patients (pts) with HR+/HER2- advanced breast cancer to receive (1:1 ratio) first line palbociclib with either fulvestrant or letrozole. Shallow whole genome sequencing was performed on ctDNA, and the 4 DNA-based subtypes (Clusters-1, -2, -3, and -4) were identified if the ctDNA tumor fraction (TF) $\geq 3\%$. The main objective was to evaluate the association of DNADX subtypes with progression-free survival (PFS) and overall survival (OS). Secondary objective was to identify the subgroup of pts who benefit more from each endocrine treatment. Uni- and multi-variable Cox regression models were used after adjusting for TF, menopausal status, ECOG status, de novo metastasis (vs. recurrence), visceral disease and number of metastatic sites.

Results: DNADX was evaluated in plasma ctDNA samples from 122 pts (25.1%). Clinical variables and median PFS (27.6 months) were similar as the overall PARSIFAL population. DNADX identified 56.6% pts with TF of $< 3\%$, 14.8% with Cluster-1, 19.7% with Cluster-2, 5.7% with Cluster-3 and 3.3% with Cluster-4. In terms of PFS, pts classified with TF $< 3\%$ had a lower risk of progression compared to Cluster-1, Cluster-2, Cluster-3, Cluster-4 subtypes (pairwise PFS hazard ratios [HRs] of 1.88, 2.02, 3.15, and 5.62, respectively, with a global log-rank test of $p=0.010$). Similar results were obtained after adjusting for other clinical-pathologic variables. A numerical benefit of fulvestrant in comparison with letrozole was observed in pts classified in Cluster-1 and Cluster-4 (HR=0.42, 95% CI 0.14-1.24) in contrast to the other groups (HR=1.21, 95% CI 0.68-2.18), and the interaction test was statistically significant after adjusting for clinical-pathologic variables (anova p -value=0.037). In terms of OS, pts classified with TF $< 3\%$ had a lower risk of death compared to Cluster-1, Cluster-2, Cluster-3, and Cluster-4 subtypes (pairwise OS HRs of 1.90, 4.23, 11.13, and 6.80, respectively, with a global log-rank test of $p=0.003$). In the multivariable analysis, results were consistent after adjusting for clinical-pathologic variables and TF.

Conclusions: Liquid biopsy-based DNADX subtypes predict outcomes in pts with HR+/HER2- advanced breast cancer on endocrine therapy and CDK4/6 inhibitors, potentially identifying the most optimal endocrine treatment for each pt.

PO2-15-07

HER2DX genomic assay in triple-negative breast cancer (TNBC) patients treated with 12-weeks of neoadjuvant chemotherapy: a correlative analysis from WSG-ADAPT-TN phase II trial

Presenting Author(s) and Co-Author(s):

O. Gluz. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; University Clinics Cologne, Moenchengladbach, Nordrhein-Westfalen, Germany

F. Brasó-Maristany. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), United States

U. Nitz. West German Study Group and Breast Center Niederrhein, United States

L. Paré. Reveal Genomics, United States

M. Christgen. Medizinische Hochschule Hannover, Hannover, Niedersachsen, Germany

G. Villacampa. VHIO, London, England, United Kingdom

B. Conte. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain, United States

S. Kuemmel. West German Study Group, Moenchengladbach, Germany; Breast Unit, Kliniken Essen-Mitte, Essen, Germany; Charité - Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany

R. Kates. West German Study Group, Moenchengladbach, Germany

C. Kolberg-Liedtke. University Hospital Essen, Germany

E. Grischke. Universitäts-Frauenklinik Tübingen, Eberhard Karls University, Tübingen, Germany

H. Forstbauer. West German Study Group, United States

M. Braun. Rotkreuzklinikum München, Germany

M. Warm. West German Study Group, United States

J. Hackmann. West German Study Group, United States

C. Uleer. West German Study Group, United States

B. Aktas. Universitätsklinikum Leipzig, United States

C. Schumacher. St. Elisabeth Hospital, Cologne, Germany

A. Vivancos. Cancer Genomics Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain., Barcelona, Spain

R. Wuerstlein. Breast Center, Dept. OB&GYN and CCC Munich, LMU University Hospital, Munich, Germany

J. Parker. University of North Carolina, United States

M. Graeser. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; Department of Gynecology, University Medical Center Hamburg, Moenchengladbach, Nordrhein-Westfalen, Germany

C. Perou. Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA., United States

C. zu Eulenburg. West German Study Group, Moenchengladbach, Germany; Department of Medical Biometry and Epidemiology, University Medical Center Hamburg, Hamburg, Germany

P. Villagrasa. REVEAL GENOMICS, United States

H. Kreipe. Medical School Hannover, Institute of Pathology, Hannover, Germany; Institute of Neuropathology, United States

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

N. Harbeck. University of Munich, Munich, Bayern, Germany

HER2DX genomic assay in triple-negative breast cancer (TNBC) patients treated with 12-weeks of neoadjuvant chemotherapy: a correlative analysis from WSG-ADAPT-TN phase II trial
Background: Biomarkers for de-escalation and escalation of systemic therapy in early-stage TNBC are needed. HER2DX is a standardized prognostic (risk-score) and predictive (pathological complete response [pCR]-score) assay based on clinical and gene expression-based data. Here we aimed to test the value of HER2DX assay in early TNBC. Methods: Standardized HER2DX was evaluated centrally using RNA from baseline FFPE tumor biopsies from the WSG-ADAPT-TN study (NCT01815242), a multicenter phase II trial that randomized 336 patients with stage I–III early TNBC to 12-weeks of nab-paclitaxel 125 mg/m² plus gemcitabine 1000 mg/m² d1,8 every 3 weeks (arm A) versus nab-paclitaxel 125 mg/m² plus carboplatin AUC2 day 1,8 every 3 weeks (arm B). The primary aim was to test the ability of HER2DX pCR and risk-score models to predict pCR (ypT0/isN0) and survival endpoints, respectively, such as invasive disease-free survival (iDFS), distant disease-free survival (DDFS) and overall survival (OS). Secondary objectives were to assess the association of the i) HER2DX immune signature score and ii) percentage (%) of stromal tumor infiltrating lymphocytes (sTILs) with efficacy endpoints. Uni- and multi-variable logistic regression and Cox models tested the association of each variable with each endpoint. Results: HER2DX was evaluated in 126 (37.5%) baseline pre-treatment tumors. Mean age was 52.1 (range 26-76). cT1 represented 40.5% of cases and 72.2% were cN0. Overall, pCR rate was 34.1% (95%CI 26.1 – 43.2) and median follow-up was 5.0 years. Median sTILs at baseline was 31.6% (range 0-90) and moderately correlated with the IGG signature (coefficient=0.57). The % of HER2DX high-, medium- and low-pCR groups was 41.3%, 47.6% and 11.1%, respectively. HER2DX pCR score (as a continuous variable) was significantly associated with pCR in univariate (odds ratio [OR per 10-unit increase]=1.31, 1.06-1.64, p=0.016) and after adjusting by treatment arm (OR=1.31, 1.06-1.65, p=0.015). Overall, the pCR rates in HER2DX pCR-high, -medium and -low groups were 46.2%, 26.7% and 21.4%, respectively (high vs medium/low OR=2.48, 1.17-5.34, p=0.018). In arm B (n=51), the pCR rates in HER2DX pCR-high, -medium and -low groups were 47.8%, 25.0% and 0.0% respectively (high vs medium/low OR=3.36, 1.02-12.0, p=0.051). In terms of the risk-score, the % of HER2DX low-risk and high-risk groups was 60.3% and 39.7%, respectively. HER2DX risk score as a continuous variable was significantly associated with iDFS, DDFS and OS (p< 0.001 in all univariate analysis), and after adjusting by variables such as arm and pCR status (all p< 0.05). sTILs were not associated with any survival endpoint (all p >0.35). The HER2DX immune signature was significantly associated with iDFS (p=0.012), DDFS (p=0.022) and OS (p=0.012). Conclusion: The HER2DX genomic test in TNBC provides valuable insights into the response and survival following neoadjuvant taxane-based chemotherapy in the absence of immunotherapy. The development of a tailored genomic assay for TNBC is currently in progress.

PO2-15-08

Exploring Essential Immune Genes Linked to Pathological Complete Response and Survival in Early-Stage Triple-Negative Breast Cancer (TNBC) after Chemotherapy Treatment

Presenting Author(s) and Co-Author(s):

F. Brasó-Maristany. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), United States

L. Paré. Revel Genomics, United States

B. Conte. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain, United States

L. Angelats. Hospital Clínic Barcelona/IDIBAPS, United States

A. Vivancos. Cancer Genomics Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain., Barcelona, Spain

J. Parker. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA, United States

C. Perou. Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA., United States

P. Villagrasa. REVEAL GENOMICS, United States

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

Exploring Essential Immune Genes Linked to Pathological Complete Response and Survival in Early-Stage Triple-Negative Breast Cancer (TNBC) after Chemotherapy Treatment
Background: De-escalation and escalation of systemic therapy in early-stage TNBC will require the implementation of biomarkers to guide therapy. To date, high expression of a variety of immune genes has been associated with higher pathological complete response (pCR) rates following neoadjuvant chemotherapy or with improved survival, or both, in early-stage TNBC. However, it is currently unknown which are the key genes influencing survival (i.e., the Core Immune Genes [CIG]) and if combinations of these genes can improve their association with both clinical endpoints. Methods: The expression of up to 185 genes was evaluated on pre-treatment tumor biopsies from 3 independent publicly available datasets of early-stage TNBC: CALGB40603 (n=388) (NCT00861705), BrighTNess (n=482) (NCT02032277), and SCAN-B (n=498). Patients in CALGB40603 and BrighTNess were treated with neoadjuvant chemotherapy-based therapy and had response data. Patients in CALGB40603 and SCAN-B had survival outcome data (event-free survival [EFS] or relapse-free interval [RFI]). Each individual gene was associated with each clinical endpoint within each dataset using Cox model and logistic regression analyses, adjusting for treatment arm. Genes found in common across datasets were selected as CIG, except for PDCD1, which was not available in BrighTNess. Using the CIGs, we evaluated whether combinations of 2 genes enhance their association with each clinical endpoint using different methods: adding, subtracting, multiplying, and ratio. Likelihood ratio testing was used to evaluate the added contribution of each gene in 2 combined cohorts evaluating pCR (i.e., CALGB40603 and BrighTNess) and survival (i.e., CALGB40603 and SCAN-B). Results: 10 CIGs related to B-cells and T-cells (i.e., IRF4, LAX1, POU2AF1, CD274, CD79A, TNFRSF17, PIM2, PDCD1, CXCR6, and SLAMF1) were associated with higher pCR rates and improved survival outcome across datasets. Of note, 5 (50%) genes are known components of the 14-gene immunoglobulin/B-cell (IGG) signature. The correlation coefficient among the 10 CIG genes was 0.63 (moderate). In general, the sum

of 2 CIGs provided more prognostic information than a single gene ($p < 0.001$). Specifically, the sum of 2 CIGs provides more prognostic information than a single gene in 30 of 45 (66.6%) cases. Two-gene subtraction, multiplication or ratio decreased the amount of prognostic information ($p < 0.001$). The top 10 2-gene CIGs associated with prognosis ($p < 0.001$) were CD274_TNFRSF17, IRF4_CD274, PDCD1_TNFRSF17, CD79A_CD274, CD274_POU2AF1, CXCR6_TNFRSF17, LAX1_TNFRSF17, SLAMF1_TNFRSF17, CD274_LAX1 and CD79A_CXCR6. In general, the sum of 2 CIGs provided more information about pCR than a single gene ($p < 0.001$). Specifically, the sum of 2 CIGs provided numerically more information about pCR than 1 gene in 17 of 36 (47.2%) cases. Two-gene subtraction, multiplication or ratio decreased the amount of information about pCR ($p < 0.001$). The top 10 2-gene CIGs associated with pCR were CD274_PIM2, CD274_POU2AF1, CXCR6_PIM2, CD274_CXCR6, IRF4_CD274, CXCR6_POU2AF1, CD274_LAX1, IRF4_CXCR6, CXCR6_LAX1, and POU2AF1_SLAMF1. Conclusion: The expression of CIGs associated with B-cell and T-cell adaptive immune response is closely linked to pCR and survival outcomes following (neo)adjuvant chemotherapy. When combining the expression of 2 specific CIGs through addition, we found that this method provides more informative insights into pCR and survival outcomes compared to other combination methods. This approach enhances the predictive power of CIGs, enabling a better understanding of treatment response and patient prognosis, ultimately contributing to improved clinical decision-making and patient outcomes.

PO2-15-09

Immune related cell fraction in peripheral blood and outcomes of advanced breast cancer patients treated with Eribulin

Presenting Author(s) and Co-Author(s):

M. Nagahashi. Hyogo Medical University, United States

A. Bun. Hyogo Medical University, United States

M. Kuroiwa. Hyogo Medical University, United States

M. Komatsu. Hyogo Medical University, United States

S. Urano. Hyogo Medical University, United States

Y. Fujimoto. Hyogo Medical University, United States

A. Oshiro. Hyogo Medical University, United States

A. Mitsuyoshi. Hyogo Medical University, United States

H. Kanaoka. Hyogo Medical University, United States

A. Hattori. Hyogo Medical University, United States

R. Fukui. Hyogo Medical University, United States

T. Higuchi. Hyogo Medical University, United States

A. Nishimukai. Hyogo Medical University, United States

K. Murase. Hyogo Medical University, United States

Y. Takatsuka. Hyogo Medical University, United States

Y. Miyoshi. Dept of Surgery, Division of Breast and Endocrine Surgery, Hyogo Medical University, Nishinomiya-hama, Hyogo, Japan

Background: Eribulin prolongs overall survival (OS) of patients with advanced breast cancer, and an ad-hoc analysis of the EMBRACE trial showed that baseline absolute lymphocyte count (ALC) was a predictor of OS prolongation. It has been suggested that eribulin improves the immune response to the tumor by improving the hypoxic environment through remodeling of local tumor vessels and reducing hypoxic stress, leading to OS prolongation. However, the details of the immune response mediated by eribulin remain to be fully elucidated. CD8⁺ cells attack cancer cells as cytotoxic T cells, while regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) suppress activated T cells that attack cancer cells. In this study, we focused on CD8⁺ cytotoxic T cells, Tregs, MDSCs, and CD4⁻CD25⁻FoxP3⁺ cells in peripheral blood, analyzed the changes of those immune cells before and after eribulin treatment, and examined the effects on the outcomes of breast cancer patients. Methods: Nineteen patients with advanced or recurrent breast cancer treated with eribulin from April 2021 to May 2023 at our hospital were included. Peripheral blood was collected before drug administration as the first treatment (pre-treatment) and before drug administration in the second course (post-treatment), and the cell fractions, including CD4⁺ cells, CD8⁺ cells, CD4⁺CD25⁺FoxP3⁺ Tregs, CD11b⁺CD14⁺CD33⁺ MDSCs, and CD4⁻CD25⁻FoxP3⁺ cells, were analyzed by flow cytometry. The cutoff value for ALC was set at 1000 and NLR at 3.0, and each cell fraction was set to its respective median. Kaplan-Meier plots and logrank tests for progression-free survival (PFS) or OS were applied. Results: CD4⁺ cells were significantly lower post-treatment compared to pre-treatment (p=0.0140). Further, Tregs were significantly lower post-treatment compared to pre-treatment (p=0.0258). There were no significant changes in the levels of CD8⁺ cells, MDSCs,

and CD4⁻CD25⁻FoxP3⁺ cells between pre- and post-treatment. We examined the association between each cell fraction and ALC or NLR, and found that CD4⁻CD25⁻FoxP3⁺ cells were significantly higher in cases with high NLR (p=0.0110). Analysis of the association between each cell fraction and prognosis at pre-treatment revealed that the high CD8⁺ cell group had significantly better PFS and OS than the low CD8⁺ cell group (p=0.0129 and p=0.0077, respectively). Interestingly, the high CD4⁻CD25⁻FoxP3⁺ cell group had significantly worse PFS than the low CD4⁻CD25⁻FoxP3⁺ cell group (p=0.0026). Conclusion: In the current study, Tregs in the peripheral blood of breast cancer patients significantly decreased after eribulin treatment, suggesting that eribulin may improve the immune microenvironment by suppressing immunosuppressive cells in cancer, including Tregs. In addition, the CD4⁻CD25⁻FoxP3⁺ cell fraction may serve as a biomarker for eribulin therapy, and further studies are needed to elucidate the details, including analysis of the constituent cells within the fraction.

PO2-15-10

Identifying new immune-related biomarkers in TNBC with a look at PD-L1 cell-autonomous role.

Presenting Author(s) and Co-Author(s):

C. Costa. clinical researcher, United States

C. von Arx. Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, United States

A. Calabrese. Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, United States

F. Pentimalli. Department of Medicine and Surgery, LUM University "Giuseppe DeGennaro", United States

M. Luciano. Department of Biotechnological and Applied Clinical Sciences, University of Aquila, United States

A. Giordano. Sbarro Institute for Cancer Research and Molecular Medicine, Temple University, Philadelphia, PA, United States, United States

M. De Laurentiis. Istituto Nazionale dei Tumori IRCCS 'Fondazione Pascale, Napoli, Italy

Background The programmed death ligand 1 (PD-L1) has recently emerged as a target immunotherapy in Triple-negative breast cancer (TNBC). However, the tumor-intrinsic role of PD-L1 and its pathway still needs to be fully clarified. Recently, a close association between CD73, PD-L1, cancer cell stemness and epithelial-to-mesenchymal transition phenotypes is emerging. In addition, we have previously demonstrated that miR-320a and miR-145 target PD-L1, whereas miR-30 family is known to target CD73. In this study, we aimed at investigating the role of these miRNAs as prognostic and predictive dynamic biomarkers for immunotherapy in TNBC. Additionally, we investigated whether PD-L1 exerts cellular autonomous functions in TNBC beyond its role in the immune checkpoint. **Results** CD73 and PD-L1 expression was assessed in a panel of breast cancer lines and the non-malignant breast cells MCF-10. We showed a significantly higher CD73 and PD-L1 expression in MDA-MB-231 (TNBC, Basal B) than in MCF-10. Conversely, in MCF-7 cells (HR +, Luminal A), CD73 and PD-L1 expression is lower than in MCF-10. Furthermore, we showed that low PDL1 expression is correlated with high levels of miR-320a and miR-145, and CD73 expression is inversely related to miR-30 expression. These putative biomarkers were also validated in two patients with different PD-L1 status. From the analysis of the data obtained by real-time qRT-PCR, we found high plasma level of CD73 and low plasma level of miR-320a, miR-145 and miR-30 in the patient with PD-L1 positive BC. On contrary, in the patient with PD-L1-negative BC, we found low plasma level of CD73 and high plasma level of miR-320a, miR-145 and miR-30. Furthermore, to explore whether PD-L1 could also have an intrinsic role in tumor development and invasiveness, we used stably MDA-MB-231 PD-L1-silenced cells. We found that cell growth, colony formation, migration rate and the ability to form spheres are consistently reduced upon shRNA-mediated PDL1 silencing. In particular, we observed a reduction in the number, diameter and volume of the 3D spheres compared to the control cells. To further demonstrate the role of PD-L1, we treated the PDL1-high expression cells MDA-MB-231, PD-L1 silenced MDA-MB-231 clones, and PD-L1 low expression cells MCF-7 with Durvalumab, an anti-PD-L1. Interestingly, we observed that in PD-L1 silenced clones and MCF-7 cells, the sphere-forming ability was increased in presence of Durvalumab treatment. On the contrary, in MDA-MB-231, Durvalumab inhibited the sphere-forming ability. **Conclusion** Our data confirm that PD-L1 and CD73 are targets of miR-320a/miR-145 and miR-30 respectively. These could be potential predictive dynamic biomarkers for chemotherapy, ICIs and anti-CD73 therapeutic approach. Future validations of these biomarkers in an extensive series of TNBC patients are needed to support

their use in clinical practice. Here, we further characterized the cellular autonomic role of PD-L1 in breast cancer and showed a differential role of basal PD-L1 expression in PD-L1 checkpoint inhibitors treatment efficacy. This suggests a potential role in monitoring PD-L1 expression indirect biomarkers (i.e. miR-320a, miR-145 and CD73) during ICIs treatment. References 1. Costa C, Indovina P, Mattioli E, Forte IM, Iannuzzi CA, Luzzi L, Bellan C, De Summa S, Bucci E, Di Marzo D, De Feo M, Mutti L, Pentimalli F, Giordano A. P53-regulated miR-320a targets PDL1 and is downregulated in malignant mesothelioma. *Cell Death Dis.* 2020 Sep 14;11(9):748. doi: 10.1038/s41419-020-02940-w. PMID: 32929059.

PO2-15-11

Kinetic Analysis of [5-¹¹C] glutamine PET tracer data in breast cancer: Preclinical studies in mouse models

Presenting Author(s) and Co-Author(s):

C. Hensley. University of Pennsylvania, United States

P. Padakanti. University of Pennsylvania, United States

H. Choi. University of Pennsylvania, United States

C. Dulal. University of Pennsylvania, United States

H. Lee. University of Pennsylvania, United States

A. Pantel. University of Pennsylvania, United States

R. Zhou. University of Pennsylvania, United States

D. Mankoff. University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Glutamine is an important metabolic substrate in many aggressive tumors, with comparable importance to glucose metabolism. Utilizing human breast cancer mouse xenograft models, we studied the kinetics of the PET imaging agent, [5-¹¹C] glutamine, a biochemical authentic substrate for glutamine metabolism, to further characterize the metabolism of glutamine and downstream labeled metabolites. Studies were performed with and without inhibition of the enzyme, glutaminase (GLS), the first step in glutamine catabolism that generates glutamate, and key target for therapy directed to glutamine-metabolizing cancers.

Methods: The study used xenograft mouse models for two breast cancer cell lines, HCC1806, a highly glutaminolytic triple-negative cell line, and MCF-7, a hormone receptor positive line with only low levels of glutaminolysis. Mice were injected with 5-[¹¹C]L-glutamine, and the contributions of individual metabolites to the total [¹¹C] signal in blood and tumor tissue were estimated at 10, 20, and 30 minutes after injection by assaying the fractional contributions of [5-¹¹C] glutamine and labeled metabolites, specifically [5-¹¹C] glutamate, [¹¹C] CO₂ and all other metabolites with [¹¹C], in both blood and tumor tissue. This generated estimated time activity curves for [5-¹¹C] glutamine and downstream metabolites in both HCC1806 and MCF-7 mouse models with and without CB-839 treatment, an inhibitor of GLS. We also investigated a compartment model that describes these data, including model simulations that fit the model to match the measured curves.

Results: We found that, out to 30 minutes post-injection, the vast majority of tumor radioactivity was in the form of either 5-¹¹C] glutamine or [5-¹¹C] glutamate, with smaller amounts of radioactivity in the form of more downstream metabolites, including [¹¹C]CO₂. Systemic administration of the glutaminase inhibitor alters the arterial input curve by reducing the systemic rate of conversion of [5-¹¹C] glutamine to [5-¹¹C] glutamate. However, in GLS active tumors, [5-¹¹C] glutamate retained in the large cellular glutamate pool represents a greater fraction of total radioactivity than in the blood and leads to a total tumor time-activity curve that is only marginally different than the total tumor time-activity curve after GLS inhibition. Data from blood and tissue analysis were used to test a hypothetical kinetic model for [5-¹¹C] glutamine, which provided estimates of glutamate and glutamate tumor tissue concentrations and tumor GLS activity that agree with direct measurements in the animal models.

Conclusion: The study of [5-¹¹C] glutamine in breast cancer models leads to kinetic insight that are in line with biochemical studies and direct measurement taken for tumor tissue obtained from the animal models. Retention of metabolized [5-¹¹C] glutamine as [5-¹¹C] glutamate in a large tissue pool in tumors with high GLS activity makes non-invasive inference of GLS activity challenging without additional ex vivo analysis, supporting the use of non-metabolized glutamine analogs such as such as [18F](2S,4R)4-fluoroglutamine ([18F]4F-Gln) to infer in vivo glutamine metabolism.

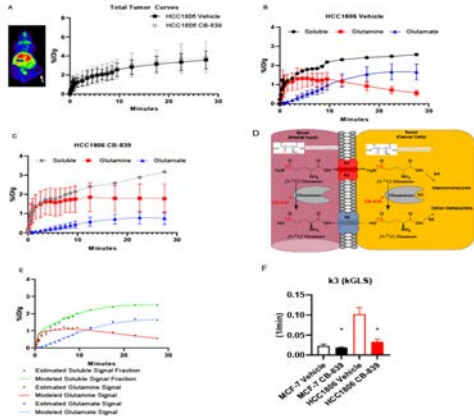


Figure: A) Image-derived, total tumor curves, comparing vehicle (n=9) to CB-839 (n=7) treated mice. Tumor soluble signal curves partitioned into individual metabolites. (B) HCC1806 Vehicle (n=9), or (C) CB-839 (n=7). (D) Schematic representation of 4-compartment model used to estimate kinetic parameters. (E) Example of curve fitting model to estimate tumor signal curves, utilizing HCC1806 vehicle treated tumor. Dotted lines denote estimated signal curves, and solid lines denote model curve visually optimized to fit the estimated curve. Fits of glutamine and glutamate soluble metabolites to estimate curves from total soluble estimated curves. (F) Modified k3 (kGLS), the glutaminase parameter, per condition (N=5 mice for each condition). P values calculated from a 1-tailed, 2 sample equal variance t-test. * - p < 0.05, NS - p > 0.05.

PO2-15-12

Novel Transcriptomic Classification System Unveils HER2-Low Breast Tumors

Presenting Author(s) and Co-Author(s):

P. Turova. BostonGene, Corp., United States

V. Kushnarev. BostonGene, Corp, United States

O. Baranov. BostonGene, Corp., United States

A. Butusova. BostonGene, United States

S. Menshikova. BostonGene Corp., United States

S. Yong. BostonGene, Corp., United States

A. Love. BostonGene Corp., United States

K. Chernyshov. BostonGene, Corp., United States

N. Kotlov. BostonGene Corp., United States

Breast cancers (BCs) are segregable into subtypes based on their intrinsic molecular features. When evaluating HER2 status, clinicians often rely on IHC, which is plagued by reproducibility issues. The widely used PAM50 transcriptomic system also does not include the HER2-low subtype. Addressing these limitations is particularly important given the recent approval of targeted therapy for HER2-low BCs. Here, we developed a unique transcriptomic classification system that can identify HER2-low BCs. Accurate identification of HER2-low BCs can help physicians navigate treatment selection and, in turn, allow patients to benefit from the new targeted therapy. We analyzed 6,361 BC samples with clinical and pathological annotation, including FISH and IHC data, from three public datasets (TCGA BRCA and SCAN-B [total n = 4,457]; METABRIC [n = 1,904]) for gene expression, differential expression, gene enrichment, copy number alterations, and mutations. An algorithm was applied to categorize samples from TCGA and SCAN-B into subtypes by customizing a gene set, employing UMAP dimensionality reduction, and utilizing clustering with the HDBSCAN algorithm. Each resulting cluster that was associated with a specific gene set was named and excluded from the next analysis. After four iterations, five subtypes were sequentially identified: Basal, HER2-high, HER2-low, Luminal B (LumB), and Luminal A (LumA). The Light GBM-based hierarchical classifier model was trained on the TCGA and SCAN-B cohorts and validated on the METABRIC dataset. Samples with high ERBB2 expression and copy number amplification were classified as HER2-high, and samples with similar PAM50 expression profiles but lacking ERBB2 expression were considered HER2-low. Luminal samples were grouped into two subtypes: LumA, characterized by low proliferation rates, and LumB, characterized by high proliferation rates. HER2-high, Basal, LumA, and LumB subtypes exhibited expected mutational and gene expression profiles. We observed ERBB2 copy number amplification and high gene expression in HER2-high samples from the TCGA and METABRIC cohorts, as confirmed by FISH and IHC in 97% and 93% of samples, respectively. Conversely, we did not see high ERBB2 expression or copy number amplification in the HER2-low samples, which was concordant with an absence of HER2 3+ expression by IHC. HER2-low samples had high mutational frequencies in PTEN, KMT2C, and ERBB2 (12%, 14%, and 8% respectively, adj. p < 0.005, chi-square test). HER2-low samples also showed increased EGFR (logFC = 2.8, adj. p < 0.001) and CLDN8 (logFC = 3.4, adj. p < 0.001) expression levels. The novel classifier identified 55% of the HER2-low samples as the luminal androgen receptor (LAR) Burstein subtype, as a result of higher AR expression than in HER2-high samples (logFC = 2.9, p = 0.04). Classification of SCAN-B luminal samples into the LumA and LumB subtypes also better predicted Ki-67 positivity ($\geq 20\%$

of Ki-67+ malignant cells by IHC, F1-score = 0.77) than the previously reported PAM50 classification (F1-score = 0.62). Our refined classifier effectively defined five breast cancer subtypes, including the HER2-low subtype, based on their molecular profiles. By determining HER2 status with transcriptomic data, our classifier may help minimize IHC-related reproducibility issues and, in turn, facilitate more precise treatment decision-making. Given its concordance with copy number amplification, IHC, and FISH data, our classification system can distinguish between HER2-high and HER2-low BCs. Since HER2-low BCs may represent a unique group that requires different treatment approaches, further optimization of our classifier may assist in identifying effective therapies for patients with HER2-low BCs.

PO2-16-01

Molecular correlates of drug response to guide therapy in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

N. Merrill. University of Michigan, United States

N. Vandecan. University of Michigan, United States

A. Apfel. University of Michigan, United States

H. Serhan. University of Michigan, United States

P. Ulintz. University of Michigan, United States

L. Bao. University of Michigan, United States

X. Cheng. University of Michigan, United States

A. Morikawa. University of Michigan School of Medicine, Ann Arbor, Michigan, United States

S. Merajver. University of Michigan, United States

M. Soellner. University of Michigan, United States

TNBC accounts for 10-20% of total breast cancer cases in the US and is more aggressive, higher grade, and has a poorer prognosis than other forms of breast cancer. TNBC is more likely to metastasize within 3-5 years than other forms of breast cancer and has a median survival of 17.6-21.3 months after metastasis. Advances in immunotherapy are promising, but recent trial results of immunotherapy-chemo combination have resulted in a 3-year overall survival rate under 36% in a PD-L1 based selected cohort. Thus, there is an unmet need for innovations that lead to new treatment options and improve outcomes for patients with TNBC in a personalized manner beyond only one or a few markers.

In our recently published study (PMID: 31655920), we tested the dose response for a panel of 78 investigational drugs and plotted this readout against molecular characterization to identify statistically significant DNA, RNA, and protein predictors of drug efficacy in TNBC. We have expanded on this published study by identifying correlates from 3D cell culture. According to the literature, 3D culture systems are more representative of in vivo activity. We have increased our sample number (now 27 cell lines and 8 ex vivo PDXs) and expanded our drug library to 387 compounds, selected for their diverse mechanisms and promise in other cancers. Following screening, we prioritized 35 compounds based on their elevated activity and variance of response. From these 35 prioritized compounds, we identified molecular correlates of drug response for 27 compounds (77% of prioritized compounds yielding molecular correlates compared to 50% in our previously published study).

Focusing on a known active drug in TNBC that is approved for patients with metastatic TNBC, we identified multi-omic (protein expression/activity and RNA expression) molecular correlates of response to a chemotherapeutic- SN-38, the payload of Sacituzumab and the active metabolite of irinotecan. We utilized a sub-panel of RNA correlates to characterize treatment-naive PDXs and predict response to SN-38. We then tested SN-38 response ex vivo for 5 PDXs to show that we could accurately identify sensitive/resistant models to SN-38 therapy. From significant protein correlates, we identified that the autophagy and AKT pathways were elevated in models with poor response to SN-38. Co-targeting the autophagy or AKT pathway with SN-38 was an effective strategy to identify rational, synergistic therapeutic combinations at therapeutically relevant levels (effective dose (ED) 50 and ED75). We evaluated irinotecan in vivo using a cell line with sensitivity in our 3D assay, demonstrating strong activity in vivo to

validate that our screening assay accurately predicts in vivo response.

We have further applied this methodology to targeted inhibitors with potential activity in TNBC. We have identified an ATR inhibitor, berzosertib, that targets the DNA damage response (DDR) pathway and correlates with protein expression and activity of Aurora kinases (AKs). Furthermore, combining the pan-AK inhibitor danusertib with berzosertib results in synergistic killing of TNBC cells. As a future direction, we are evaluating this combination in vivo utilizing an ethnically diverse patient-derived xenograft library grown in mice to evaluate this novel combination in a mock clinical trial and to identify molecular correlates of response and resistance that could be used to guide future human trials.

PO2-16-02

RBsig gene-expression signature in patients with endocrine resistant metastatic breast cancer treated with palbociclib and fulvestrant in the PYTHIA trial

Presenting Author(s) and Co-Author(s):

- M. Benelli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy
- S. Tyekucheva. International Breast Cancer Study Group Statistical Center, Department of Data Science, Dana-Farber Cancer Institute and Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States
- T. Crestani. Breast International Group, Belgium
- M. Ignatiadis. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Brussels Hoofdstedelijk Gewest, Belgium
- P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium
- M. Colleoni. Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Lombardia, Italy
- S. Henry. Department of Medical Oncology, Hematology, Radiotherapy and Nuclear Medicine, Université catholique de Louvain, CHU UCL Namur (Site Ste Elisabeth), Namur, Belgium
- K. Papadimitriou. Multidisciplinary Oncologic Centre Antwerp (MOCA), Antwerp University Hospital, Antwerp, Belgium
- A. Bernardo. ICS Maugeri, United States
- E. Seles. Ospedale Degli Infermi, Ponderano, Italy
- F. Duhoux. Cliniques universitaire Saint-Luc-institut Roi Albert II, United States
- I. Macpherson. University of Glasgow - Institute of Cancer Sciences, United Kingdom
- A. Thomson. Royal Cornwall NHS Trust, United States
- D. Davies. Department of Oncology, South West Wales Oncology Center, Swansea, United Kingdom
- I. Migliaccio. Translational Research Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States
- G. Zoppoli. Department of Internal Medicine and Medical Specialties DiMI, University of Genoa, Italy
- R. Kammler. ETOP IBCSG Partners, Bern, Bern, Switzerland
- H. De Swert. Breast International Group (BIG)-aisbl, Brussels, Belgium, Brussels, Belgium
- B. Ruepp. ETOP IBCSG Partners Foundation, Coordinating Center, Bern, Switzerland
- P. Aftimos. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium
- J. Seoane. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain
- D. Romagnoli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy
- D. Venet. Institut Jules Bordet, Belgium
- T. Goulioti. Breast International Group (BIG)-aisbl, Brussels, Belgium
- D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom
- S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
- M. Piccart. Institut Jules Bordet, Anderlecht, Brussels Hoofdstedelijk Gewest, Belgium

M. Regan. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

L. Malorni. Translational Research Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

Background: We have previously identified RBsig, a gene-expression signature of resistance to CDK4/6 inhibitors composed of E2F1/E2F2 dependent genes, which is associated with genetic loss of RB1. Although RBsig has been previously tested in vitro and in clinical trials with CDK4/6 inhibitors, further clinical validation is needed. Additionally, data on the correlation of RBsig with other prognostic/predictive biomarkers for CDK4/6 inhibitors such as serum Thymidine Kinase activity (sTKa), is lacking. Here, we aimed to investigate RBsig in patients (pts) treated with palbociclib (P) + fulvestrant (F) within the PYTHIA trial (IBCSG 53- 14/BIG 14-04; NCT02536742), a downstream trial of the AURORA molecular program (BIG 14-01; NCT02102165). **Methods:** PYTHIA is a biomarker discovery phase II trial which enrolled 122 pts with endocrine-resistant ER+ and HER2 - metastatic breast cancer (MBC) who received P+F at standard schedule and dose. We analyzed a subset of 38 pts enrolled in PYTHIA and successfully included in AURORA who had available RNAseq from tumor tissue samples (24 primary, 24 metastatic, 10 both). Ki67 by IHC was also available. The PYTHIA biomarker assessment included sTKa at baseline and during treatment (D15 and D28) measured using DiviTum^o TKa (Biovica International). Evaluation of the prognostic role of RBsig was a pre-specified primary objective of PYTHIA. RBsig is composed of 87 genes and was calculated as previously described. Wilcoxon rank sum test was used to compare continuous RBsig values between groups defined by sTKa. Median progression free survival (mPFS) was estimated using Kaplan-Meier method for groups defined by dichotomizing RBsig at zero. **Results:** Median RBsig was higher in metastatic than in primary samples; in paired samples, RBsig increased in metastatic for 7/10 pts vs primary. When evaluated as continuous variables, RBsig correlated with tissue Ki67 both in primary (Spearman R 0.8) and in metastatic (R 0.68) samples. Additionally, RBsig was higher in Basal and Luminal B intrinsic subtypes in metastatic samples. RBsig was significantly higher in pts with high baseline sTKa (median cut-off) (Wilcoxon test, $p=0.04$ and $p=0.03$ in primary and metastatic samples respectively), with a similar direction, albeit not statistically significant, observed in the group of pts with no sTKa clearance at D15 (below limit of detection cut-off). When evaluated in the combined cohort, where RBsig values were taken from metastatic samples when available and from primary samples otherwise, higher RBsig values were associated with poorer PFS as compared to lower RBsig values [mPFS 5.5 months (95% CI 3.7, 14) vs 13 months (95% CI 8.6, 28); Log-rank p -value=0.004]. **Conclusions:** Higher RBsig was associated with higher tumor proliferation (measured by both tissue ki67 and sTKa), luminal B status, and shorter PFS on treatment with P+F. This analysis reinforces prior data on RBsig prognostic significance in pts treated with CDK4/6 inhibitors. Further investigation on the added value of RBsig as a novel biomarker for patients' stratification, including in the early setting, is warranted.

PO2-16-03

ESR1 genomic alterations (GAs) and coexistent putative resistance alterations in comprehensive genomic profiling (CGP) of metastatic breast cancer (MBC)

Presenting Author(s) and Co-Author(s):

H. McArthur. UT Southwestern, Dallas, Texas, United States

H. Tukachinsky. Foundation Medicine Inc., United States

A. Schrock. Foundation Medicine Inc., United States

R. Madison. Foundation Medicine Inc., United States

O. Holmes. Foundation Medicine Inc., United States

S. Sivakumar. Foundation Medicine Inc., United States

E. Sokol. Foundation Medicine Inc, United States

R. Graf. Foundation Medicine Inc., United States

J. Quintanilha. Foundation Medicine Inc., United States

K. Dougherty. Foundation Medicine Inc., United States

L. Pasquina. Foundation Medicine Inc., United States

G. Oxnard. Foundation Medicine Inc., United States

M. Levy. Foundation Medicine, Inc., Cambridge, Massachusetts, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

Title: ESR1 genomic alterations (GAs) and coexistent putative resistance alterations in comprehensive genomic profiling (CGP) of metastatic breast cancer (MBC) Background: ESR1 mutations (ESR1mut) are an established biomarker of endocrine therapy (ET) resistance in patients (pts) with hormone receptor positive (HR+) MBC. Moreover, ESR1mut acquired in response to standard-of-care ET now confer access to novel ET recently approved by health authorities. However, the nuanced genomic landscape beyond the simple presence or absence of ESR1mut may be critically important. We report on detailed ESR1 GAs detected by tissue and liquid biopsies (TBx, LBx) and examine the prevalence of co-occurring GAs in other genes reported to confer intrinsic or acquired resistance to ET. Methods: CGP results from MBC biopsies were retrospectively analyzed (TBx 33,653 pts; LBx 7,134 pts) using FoundationOne® CDx and FoundationOne® Liquid CDx, hybrid-capture based sequencing platforms profiling 324 cancer-related genes. Foundation Medicine's ctDNA tumor fraction (TF) is a composite algorithm prioritizing aneuploidy at higher levels to avoid germline signal and prioritizing variant allele frequency (VAF) of canonical alterations at lower levels to maximize dynamic range. Results: ESR1mut were detected in 3,755 (11.2%) TBx and 1,513 (21.2%) LBx. Among samples with ESR1mut, multiple ESR1mut were more common in LBx (19% 2, 12% 3+) than in TBx (6% 2, 0.5% 3+), with up to 10 different ESR1mut seen in one LBx. The most common mutations were D538G (39% and 52% of TBx and LBx with ESR1mut), Y537S (27%, 38%), Y537N (10%, 15%), and E380Q (10%, 14%). Activating ESR1 insertion-deletion mutations (indels) were detected in 81 TBx and 62 LBx (2% and 4%), representing 23 distinct variants at the protein level, including V422del (107), indels affecting codons 532-538 (29), G344_L345insC (7), and Y328_S329del (6). 28 fusions of the ESR1 DNA binding domain to 13 unique gene partners were detected; 10/28 (36%) were ESR1-CCDC170 fusions. ESR1 amplifications (ESR1amp) were detected in 704 (2.1%) TBx; 62 (8.8%) also harbored ESR1mut. ESR1amp were detected among 34 (0.5%) LBx; 8 (24%) also had ESR1mut. In TBx with ESR1mut and LBx collected from the same pt within 8 months (43 pairs), LBx sensitivity of

detection of ESR1mut was 96% (26/27, 95% confidence interval CI [95%CI]: 79%-99%) when TF was $\geq 1\%$, but only 6% (1/16, 95%CI: 0.3%-32%) when LBx had TF $< 1\%$. In 988/1,513 (65%) of LBx with ESR1mut, ≥ 1 mutations or fusions in genes associated with alternative ET resistance pathways were detected, including PIK3CA (46% of ESR1mut LBx), RB1 (12%), PTEN (10%), NF1 (7%), ARID1A (7%), AKT1 (5%), FGFR2 (4%), and KRAS (4%) and ERBB2 (3%). Prevalence of co-occurring GA associated with ET resistance was higher in LBx than in TBx (RB1, NF1, FGFR2, PTEN, EGFR, KRAS, PIK3CA, FDR < 0.001). Moreover, prevalence was higher in 240 LBx where ESR1 was a minor allele (VAF/TF $< 10\%$) compared to 1,273 LBx where ESR1 was a major allele (FGFR2, PIK3CA, FGFR3, BRAF, ERBB2, RB1, FDR < 0.05). In pts with ESR1mut LBx and a historical TBx collected < 5 years earlier (182 pairs), GAs in RB1, FGFR2, KRAS, EGFR, and BRAF were detected primarily on the LBx but not the preceding TBx. Conclusions: CGP detects a wide spectrum of mutations in ESR1, including missense and indel mutations and fusions. When LBx TF is $< 1\%$, sensitivity for ESR1mut is reduced and repeat testing should be considered. ESR1mut can coexist with complementary or competing resistance mechanisms, particularly when ESR1 is a minor allele, which could impact benefit from novel ET approved for patients with ESR1 mutations. Currently, CGP of LBx informs therapeutic recommendations for pts with HR+ MBC based on the binary presence or absence of ESR1mut; however, the clinical implications of the ESR1 mutation spectrum described herein and the potential impact of co-expression of other key pathway signals warrant further investigation.

PO2-16-04

Proteogenomic characterization of non-luminal A versus luminal A breast cancer tumor cells enriched by laser microdissection

Presenting Author(s) and Co-Author(s):

P. Raj Kumar. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

X. Lin. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

T. Liu. Pacific Northwest National Laboratory, Richland, WA, United States

L. Sturtz. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

M. Gritsenko. Pacific Northwest National Laboratory, Richland, WA, United States

V. Petyuk. Pacific Northwest National Laboratory, Richland, WA, United States

T. Sagendorf. Pacific Northwest National Laboratory, Richland, WA, United States

B. Deyarmin. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

J. Liu. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

A. Praveen-Kumar. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

G. Wang. Murtha Cancer Center Research Program, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, United States

J. McDermott. Pacific Northwest National Laboratory, Richland, WA, United States

A. Shukla. Pacific Northwest National Laboratory, Richland, WA, United States

R. Moore. Pacific Northwest National Laboratory, Richland, WA, United States

M. Monroe. Pacific Northwest National Laboratory, Richland, WA, United States

B. Webb-Robertson. Pacific Northwest National Laboratory, Richland, WA, United States

J. Hooke. Henry Jackson Foundation, Rockville, Maryland, United States

L. Fantacone-Campbell. Murtha Cancer Center Research Program, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, United States

B. Mostoller. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

L. Kvecher. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

J. Kane. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

J. Melley. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

S. Somiari. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

P. Soon-Shiong. NantWorks, Culver City, CA, United States

R. Smith. Pacific Northwest National Laboratory, Richland, WA, United States

R. Mural. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

K. Rodland. Pacific Northwest National Laboratory, Richland, WA, United States

C. Shriver. Uniformed Services University, Bethesda, Maryland, United States

A. Kovatich. HJF, Bethesda, Maryland, United States

H. Hu. Chan Soon-Shiong Institute of Molecular Medicine at Windber, United States

Introduction: Breast cancer (BC) is classified into four widely-accepted intrinsic subtypes based on PAM (Prediction Analysis of Microarray) 50 gene expression profiles: Luminal A (LumA), Luminal B (LumB), Her2-enriched (Her2) and basal-like (Basal). Recent multi-omic studies of human BC have identified many potential therapeutic biomarkers for these subtypes and have also revealed the extensive molecular heterogeneity of the disease. Patients with LumA tumors generally have better outcomes because these tumors are typically slower-growing and responsive to hormone therapy. However, there is still considerable variation in the clinical outcomes of patients with non-LumA tumors. Here, we strive to understand the proteogenomic characteristics of intrinsically-defined non-LumA tumors in reference to LumA tumors.

Methods: A total of 117 retrospectively-collected, untreated primary breast tumor specimens, with a focus on non-LumA subtypes, were selected from the Clinical Breast Care Project and consented using a HIPAA-compliant, IRB-approved protocol. The study cohort had a median patient follow-up of 9.3 years, enabling clinical outcome-related analyses.

Immunohistochemistry (IHC) subtyping was used to enrich the cohort with non-LumA subtypes. Breast tumors were embedded in OCT (Optimal Cutting Temperature) compound and processed by laser microdissection (LMD) to enrich for tumor cells. DNA, RNA, and protein were simultaneously extracted from each tumor using the illustra triplePrep kit. Paired-end RNA sequencing and whole genome sequencing (WGS) were performed for 117 and 99 tumors, respectively, using the Illumina HiSeq platform. Quantitative global proteomics and phosphoproteomic analyses were performed on 112 and 50 tumors, respectively, using isobaric TMT 6-plex labeling with the “universal reference” strategy.

Results: We observed significantly lower stromal, immune and microenvironment scores in non-basal-like tumors, especially the LumA subtype from LMD-processed samples, compared to that of the same tumors but bulk-processed in TCGA-breast cancer study. There was also significantly lower stromal gene expression in LMD LumA compared to TCGA LumA. Unlike a recent report on proteomics clustering of bulk-processed tumors, we did not observe a stromal-enriched cluster, probably because the use of LMD minimized stromal components. Many common patterns of somatic mutations were observed among non-LumA tumors, such as dominant TP53 mutations and 5q deletion, suggesting a potentially common cell-of-origin for non-LumA tumors, such as an ER negative cancer stem cell or progenitor cell for these tumor subtypes. Cell proliferation-associated genes were amplified and proliferation pathways strongly enriched in non-LumA tumors. In addition to this, we identified two distinct phosphoproteomic profiles for relapsed and relapse-free basal-like BC. Moreover, we also identified 17 differentially expressed phosphopeptides that could identify cases of relapsed and relapse-free basal-like BC with a significant difference in progression-free interval of surviving cases.

Conclusion: This study provides an integrated proteogenomic characterization of non-LumA vs LumA tumor specimens enriched for cancer cells. We identified many common features of non-LumA tumors and also identified phosphopeptides that could serve as potential biomarkers for

less aggressive basal-like BC and possibly guide treatment selections.

Disclaimer: The contents of this publication are the sole responsibility of the author(s) and do not necessarily reflect the views, opinions or policies of USUHS, HJF, the DoD or the Departments of the Army, Navy or Air Force or the DOE or PNNL. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

PO2-16-05

ESR1 mutations (ESR1mut) in HR(+)HER2(-)patients with metastatic breast cancer (MBC): prevalence along treatment course and predictive value for endocrine therapy (ET) resistance in real-world practice

Presenting Author(s) and Co-Author(s):

M. Bhave. Emory University School of Medicine, Atlanta, Georgia, United States

J. Quintanilha. Foundation Medicine Inc., United States

R. Graf. Foundation Medicine Inc., United States

T. Scott. Foundation Medicine, United States

H. Tukachinsky. Foundation Medicine Inc., United States

G. Li. Foundation Medicine, United States

A. Schrock. Foundation Medicine Inc., United States

G. Oxnard. Foundation Medicine Inc., United States

M. Levy. Foundation Medicine, Inc., Cambridge, Massachusetts, United States

K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

Background: ET combined with CDK4/6 inhibitors (CDKi) is the standard of care for HR(+)HER2(-) patients with MBC. ESR1mut is an acquired resistance mechanism to ET, especially aromatase inhibitors (AI). The prevalence and behavior of ESR1mut in patients receiving the selective estrogen receptor degrader (SERD) fulvestrant remains in question. This study aimed to characterize the prevalence of ESR1mut at start of successive lines of therapy and to evaluate clinical outcomes of ET by ESR1 status in 1st line therapy in real-world practice. Methods: This study included patients with HR(+)HER2(-) MBC who underwent genomic testing using Foundation Medicine tissue or liquid comprehensive genomic profiling (CGP) assays, with specimens collected within 60 days of therapy initiation. Patient clinical data was obtained by the nationwide (US-based) de-identified Flatiron Health and Foundation Medicine real-world clinicogenomic breast database (FH-FMI CGDB), originated from ~280 US cancer clinics (~800 sites of care) between 01/2011 and 04/2023. ESR1mut prevalence was calculated in tissue and liquid samples collected in the 1st, 2nd, and 3rd lines of therapy. Real-world progression free-survival (rwPFS), time to treatment discontinuation (rwTTD), and overall survival (rwOS) were compared between patients who received AI + CDKi and between patients receiving fulvestrant + CDKi 1st line therapy [ESR1mut vs. ESR1 wild-type (wt) by tissue CGP] by Cox models. Multivariable analyses adjusted for adjuvant therapy, age, ECOG, menopausal status, histology, stage at diagnosis, metastatic site, and specific ESR1mut (Y537S, D538G, E380W, or others) were performed. Results: The prevalence of ESR1mut in tissue samples collected in 1st, 2nd, and 3rd lines of therapy was 7.9% (n=159/2004), 26.4% (n=66/250), and 34.0% (n=68/200), respectively. The prevalence of ESR1mut in liquid samples collected in the 1st, 2nd, and 3rd lines of therapy was 11.6% (n=30/259), 34.4% (n=63/183), and 35.9% (n=42/117), respectively. Among patients receiving AI + CDKi 1st line therapy (n=485), those with ESR1mut vs. ESR1wt had less favorable rwPFS [median 6.1 vs. 20.8 months, hazard ratio (HR) 2.36, 95% CI 1.35-4.14, p=0.003]. rwTTD and rwOS assessments were consistent with the magnitude of effect of rwPFS. Among patients receiving fulvestrant + CDKi 1st line therapy (n=302), those with ESR1mut vs. ESR1wt had less favorable rwPFS (median 10.5 vs. 14.5 months, HR 1.5, 95% CI 1.05-2.15, p=0.025), but no difference was observed for rwTTD and

rwOS ($p > 0.05$). Notably, the multivariable analyses found the independent association of ESR1mut and less favorable rwPFS (HR 2.18, 95% CI 1.15-4.1, $p=0.018$), rwTTD (HR 3.34, 95% CI, 1.84-6.1, $p < 0.001$), and rwOS (HR 2.46, 95% CI 1.04-5.9, $p=0.041$) in patients receiving AI + CDKi. The multivariable analyses confirmed no association between ESR1mut and outcomes in patients receiving fulvestrant + CDKi ($p > 0.05$). No substantial differential associations were observed between specific ESR1mut and clinical outcomes in the multivariable analyses. Conclusion: In our dataset, ESR1mut is prevalent in about 8-11% of baseline tissue and liquid samples of patients with HR(+)HER2(-) MBC. Baseline ESR1mut is associated with less favorable outcomes in patients receiving AI + CDKi 1st line therapy, but not in patients receiving fulvestrant + CDKi. Specific ESR1mut do not seem to be associated with different outcomes to ET. ESR1mut prevalence increased during treatment course. Further investigation is warranted to determine optimal endocrine partner with CDKi based upon ESR1 status, particularly with development of oral SERDs.

PO2-16-06

Treatment Patterns of Neoadjuvant Therapy in Chinese Patients with HR-Positive/HER2-Positive Early or Locally Advanced Breast Cancer: A Real-World Study Using NCID Data in 2019-2022

Presenting Author(s) and Co-Author(s):

Z. Liu. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

J. Zhu. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

C. Wang. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

Z. Lu. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

X. Chen. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

L. Li. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

X. Sun. Affiliated Cancer Hospital of Zhengzhou University, United States

C. Zhang. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

J. Qiao. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

M. Yan. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

Background: With the approval of pertuzumab (P) in China in 2019, P plus trastuzumab (T) and chemotherapy has become a standard of care in the neoadjuvant setting for patients with HER2-positive (HER2+) early or locally advanced breast cancer (BC). As a unique subtype, HR-positive (HR+)/HER2+ BC is less responsive to neoadjuvant chemotherapy plus HER2 targeted therapy with lower pathologic complete response (pCR) rates compared with the HR-/HER2+ subgroup. In China, the treatment pattern of HR+/HER2+ BC patients is unclear. In this real-world study, we summarized the current treatment patterns of Chinese patients diagnosed with HR+/HER2+ BC at an early or locally advanced stage based on national-level data to drive clinical decision support.

Methods: A representative sample of 51 hospitals (31 cancer centers and 20 general hospitals) covering 29 provinces from NCID (National Cancer Information Database) were generated. Anonymous individual patient data from electronic medical records (EMR) were retrieved to extract information on therapy modalities. Early or locally advanced HR+/HER2+ BC patients who were initially diagnosed between January 1, 2019 and May 31, 2022 were included. Data were analyzed both by year and in the aggregate to ensure accuracy and stability.

Results: The types of hospitals and study period reflected the current treatment landscape of HR+/HER2+ early or locally advanced BC in Chinese clinical practice. From 2019 to 2022, the results were consistent by year. In the aggregate, a total of 290,626 patients were initially diagnosed with BC during the study period. 84% (243,528/290,626) were at an early or locally advanced stage, of which 50% (121,548/243,528) had a pathologic diagnosis, 24% (29,390/121,548) were identified as HER2+, 69% (20,370/29,390) were both HR+ and HER2+, and 87% (17,630/20,370) underwent surgery. After excluding those without post-operative pathologic reports or with other primary cancers, 15,368 patients were analyzed regarding treatment patterns. 30% (4,598/15,368) received neoadjuvant therapy but 69% (10,677/15,368) had no neoadjuvant therapy. Among 4,598 patients, 31% (1,434/4,598) received T as single anti-HER2 targeted therapy, 36% (1,649/4,598) received dual HER2 blockade (1,522 T plus P,

127 T plus a TKI [tyrosine kinase inhibitor]), and the rest (1,515) received treatment that not contain a targeted agent. For patients treated with T plus P, 1,465 received concurrent chemotherapy (410 anthracyclines-based, 828 platinum-based); for patients treated with T plus TKI, 123 received concurrent chemotherapy (15 anthracyclines-based, 79 platinum-based). The most frequently prescribed chemotherapies were platinum-based regimens (57% for T plus P plus chemotherapy and 64% for T plus TKI plus chemotherapy).

Conclusions: Based on the largest nationwide database, strong representativeness and stability of our data sources, our findings are of great significance to clinical decision-making. The proportion of patients who underwent neoadjuvant therapy of HR+HER2+ BC is much lower than in many other countries, with T plus P in combination with chemotherapy appearing to be the most commonly used targeted regimen. We also found some distinctions between neoadjuvant patterns of early-stage BC in the real world of China and guidelines, which would be further explored in subsequent research.

Disclosures: None of the authors has any financial relationships to disclose.

Funding: This study was funded by Shanghai Roche Pharmaceuticals Ltd.

Acknowledgments: This project was supported by the National Anti-Tumor Drug Surveillance System of the National Cancer Center. Also thank Beijing Yiyong Technology Ltd. for statistical assistance. Support for third-party writing assistance for this abstract, provided by Content Ed Net (Shanghai) Co., Ltd., was funded by Shanghai Roche Pharmaceuticals Ltd., Shanghai, China

PO2-16-07

Real-world eligibility for adjuvant CDK4/6 inhibitors among patients without genomic risk for chemotherapy: a GBECAM multicenter retrospective study.

Presenting Author(s) and Co-Author(s):

L. Oliveira. Grupo Oncoclínicas, São Paulo, Brazil, Brazil
T. Megid. Centro de Oncologia - Hospital Sírio-Libanês, São Paulo, Brazil, Brazil
D. Rosa. Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul, Brazil
D. Assad-Suzuki. Hospital Sírio-Libanês, Brasília, Brazil, Brazil
D. Argolo. Clion, Grupo Oncoclínicas, Salvador, Brazil, Salvador, Bahia, Brazil
S. Sanches. AC Camargo Cancer Center, São Paulo, Brazil, Brazil
L. Testa. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil
J. Bines. Instituto Nacional de Câncer (INCA), Brazil
R. Kaliks. Hospital Israelita Albert Einstein, United States
D. Gagliato. Hospital Beneficência Portuguesa, São Paulo, Brazil, Brazil
R. Barroso-Sousa. Dasa Oncology, United States
T. Correa. Hospital Sirio-Libanês, United States
A. Shimada. Hospital Sirio Libanês, São Paulo , Brazil, Brazil
D. Batista. 2. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil., Brazil
D. Musse. Oncologia Dor, United States
M. Cesca. AC Camargo Cancer Center, São Paulo, Brazil, Brazil
D. Gaudêncio. Clínica CLION, Grupo Oncoclínicas, Salvador, Brazil, Brazil
L. Moura. Clínica CLION, Grupo Oncoclínicas, Salvador, Brazil, United States
J. Araujo. Hospital Beneficência Portuguesa, São Paulo, Brazil, Sao Paulo, Sao Paulo, Brazil
R. Colombo Bonadio. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil
A. Katz. Centro de Oncologia - Hospital Sírio-Libanês, São Paulo, Brazil, Brazil
M. Mano. Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil, Brazil

Background: Oncotype DX (ODX) is a genomic signature (GS) for the prediction of risk of recurrence and benefit of chemotherapy (CT) in both node negative (N0) and positive (N1), hormone receptor positive (HR+), HER2 negative (HER2-) early breast cancer (eBC). ODX was not an inclusion criterion in the MonarchE but was one in the Natalee study, in which trials most patients received neo-adjuvant chemotherapy. We aim to evaluate the proportion of patients potentially eligible for adjuvant CDK4/6 inhibitors (CDK4/6i) without CT indication by genomic risk using real-world data from a large dataset of patients from various Brazilian institutions. Methods: Clinicopathologic and ODX information were reviewed for patients with T1-T3, N0-N1, HR+/HER2- eBC who had an ODX performed between 2005 and 2020. Projections of CT indication by genomic criteria were based on TAILORx and RxPONDER data. Projections of adjuvant CDK4/6i indication were based on the MonarchE and Natalee criteria. Results: Of 636 patients, 27.5% / 51.8% / 20.8% were T1mic-a-b/T1c/T2-3, respectively. 19.5% were grade 1 (G1), 66.9% G2 tumors and 12.9% G3. 74 (11.6%) were N1. The ODX indicated low (< 11), intermediate (11-25) and high (>25) risk in 117 (18.4%), 408 (64.1%) and 111 (17.5%) patients, respectively. 408 patients (64.2%) had low clinical risk and 228 patients (35.8%) had

high clinical risk disease. In the overall cohort, 439 (69%) did not have genomic indication for CT, 25 (3.9%) and 133 (21%) were eligible for adjuvant abemaciclib and ribociclib, respectively. Among patients eligible for adjuvant CDK4/6i, greater than 50% did not meet genomic criteria for recommendation of CT (Table 1). Conclusions: In times of rapid incorporation of both GES (as valuable treatment de-escalation tools) and adjuvant CDK4/6i, our results suggest that a meaningful proportion of patients could be eligible for adjuvant abemaciclib and/or ribociclib independently of CT indication. However, little is currently known about the role of these agents in patients not treated with chemotherapy because they were largely unrepresented in these studies.

Proportion of patients eligible for adjuvant CDK4/6i in the overall and non-CT eligible population.

Table 1: Proportion of patients eligible for adjuvant CDK4/6i in the overall and non-CT eligible population.

Population	Overall (n=636)	Not eligible for CT (n=439)
Indication for abemaciclib	25 (3.9%)	14 (2.2%)
Indication for ribociclib	133 (21%)	77 (12.1%)

CT: chemotherapy

CT: chemotherapy

PO2-16-08

Adjuvant Treatment Selection for County-Level Patients with HR+/HER2- Early Breast Cancer in a Real-Life Setting in China

Presenting Author(s) and Co-Author(s):

Y. Ji. The First Affiliated Hospital of Xinxiang Medical University, United States
H. Qu. Inner Mongolia Forestry General Hospital, United States
F. Zhou. The People's Hospital of Liuyang, Hunan, China (People's Republic)
J. Wang. Honghe Prefecture Third People's Hospital, Yunnan, China (People's Republic)
Q. Wu. Guiping People's Hospital, Guangxi, China (People's Republic)
G. Dai. Pingyu County People's Hospital, Henan, China (People's Republic)
M. Liu. Lixin County People's Hospital, Anhui, China (People's Republic)
W. He. Dingzhou City People's Hospital, Hebei, China (People's Republic)
W. Liang. Huixian City People's Hospital, United States
Q. Meng. Gongyi City People's Hospital, United States
Y. Ren. Taihe County People's Hospital, United States
G. Luo. Xiantao First People's Hospital Affiliated To Yangtze University, Hubei, China (People's Republic)
H. Wang. Tengzhou Central People's Hospital, United States
H. Liu. Dingyuan General Hospital, Anhui, China (People's Republic)
Z. Qin. People's Hospital of Lixian, Hunan, China (People's Republic)
Y. Tian. The People's Hospital of Yuechi County, United States
H. Tang. Central Hospital of Zhuanghe City, United States
H. Liu. Central Hospital of Ningcheng, United States
J. Luo. Fengcheng People's Hospital, Jiangxi, China (People's Republic)
Z. Yu. Central Hospital of Qinghe, United States
G. Hu. Dongyang People's Hospital, United States
J. Gao. Zhuozhou City Hospital, United States
X. Tan. Anyue County People's Hospital, United States
Y. Liu. People's Hospital of Macheng City, Hubei, China (People's Republic)
Y. Zhang. Changshu NO.2 People's Hospital, Jiangsu, China (People's Republic)
M. Wang. Hebei Yanda Hospital, United States
M. Zhang. The First Affiliated Hospital of Xinxiang Medical University, United States
P. Lu. The First Affiliated Hospital of Xinxiang Medical University, China (People's Republic)

Background: CHASE001 (NCT05544123), a prospective, non-interventional multicenter study exploring real-world treatment and referral behavior of Chinese county patients (pts) with HER2+ or HR+/HER2- breast cancer is ongoing since September 2022. A prespecified interim analysis (IA) on 750 HER2+ and HR+/HER2- early breast cancer (eBC) was reported at the ESMO Congress 2023. In the 2nd IA from CHASE001, adjuvant treatment selection for patients with HR+/HER2- eBC will be evaluated. Methods: The study was designed to enroll 2500 pts, including four cohorts (HER2+ eBC, HR+/HER2-eBC, HER2+ advanced BC, and HR+/HER2-

aBC). In this IA, HR+/HER2- eBC pts after surgery were included. Descriptive statistics reported patient demographics, clinical and disease characteristics and treatment patterns. To investigate the factors associated with chemotherapy-free regimen, non-anthracycline chemotherapy regimen and ovarian function suppression (OFS), univariate and multivariate logistic regression analyses were conducted. Results: At data cutoff (May 17, 2023), 697 HR+/HER2- eBC pts (median age 52 years, 45.77% pT2, 50.93% pN0, 56.10% G2) were included from 26 institutions in China county areas, 338 (48.49%) were premenopausal. 584 (83.79%) received adjuvant chemotherapy, with a few (47/584, 8.05%) initially developing their treatment plan at a higher level hospital (national or provincial tertiary hospital). AC-T (309/584, 52.91%) was the most commonly used regimen. 181 (30.99%) pts received non-anthracycline chemotherapy regimen (mainly TC), and pts with N0, age \geq 65 years and ki67 < 20% had the strongest association to this regimen (multivariate OR=0.082, 95%CI [0.037,0.179], OR=0.463, 95%CI [0.250,0.859], and OR=0.642, 95%CI [0.418,0.985], respectively). Interestingly, on univariate analysis pts initially diagnosed in a higher level hospital were significantly associated with non-anthracycline regimen (P=0.0109), however on multivariate analysis it was no longer significant. 483 pts received endocrine therapy, including 234 (48.45%) premenopausal pts. The most commonly used endocrine regimen for premenopausal pts was OFS/OFS+ (122/234, 52.14%), of which half (61, 50%) were prescribed OFS+TAM/TOR; followed by TAM/TOR monotherapy (69/234, 29.49%). The proportions of patients classified as low, intermediate, and high clinical risk for recurrence (investigator assessed) were 33.62%, 42.67% and 23.71%. The OFS rate were 39.74% in low, 61.62% in intermediate and 70.91% in high risk pts, respectively. Multivariable analyses found that high clinical risk, age < 45 years and ki67 < 20% were strongly associated with the use of OFS (OR=0.210, 95%CI [0.066,0.674], OR=0.327, 95%CI [0.165,0.649], and OR=0.405, 95%CI [0.194,0.845], respectively). For postmenopausal pts, AI monotherapy (84.74%) was the most commonly used endocrine regimen. Conclusions: To our knowledge, this is the first real-world study evaluating the treatment patterns and referral behavior of BC pts in China counties. The 2nd IA results presented showed the current systemic adjuvant treatment preferences and influence factors from a large sample of HR+/HER2- eBC pts in China counties, which were generally consistent with China BC treatment guidelines.

Table 1. Utilization of adjuvant systemic therapy regimens in 697 HR+/HER2- eBC pts, China counties

Regimen	n(%)
Chemotherapy	584
AC-T	309 (52.91%)
TC	170 (29.11%)
AC	90 (15.41%)
TAC	10 (1.71%)
Other	6 (1.03%)
Endocrine therapy	483
Premenopausal	234
TAM	60 (25.64%)
OFS+TAM	58 (24.79%)
OFS+AI	51 (21.79%)
AI	38 (16.24%)
TOR	9 (3.85%)
OFS+AI+CDK4/6i	6 (2.56%)
OFS	4 (1.71%)
OFS+TOR	3 (1.28%)
Other	5 (2.14%)
Postmenopausal	249
AI	211 (84.74%)
TAM	16 (6.43%)
OFS+AI	10 (4.02%)
OFS+TAM	6 (2.41%)
TOR	5 (2.01%)
Other	1 (0.40%)

AC-T: (dd)doxorubicin/epirubicin, cyclophosphamide, followed by (dd)paclitaxel/docetaxel; TC: paclitaxel/docetaxel, cyclophosphamide; AC: doxorubicin/epirubicin, cyclophosphamide; TAC: docetaxel, doxorubicin/epirubicin, cyclophosphamide; TAM: tamoxifen; OFS: ovarian function suppression; AI: aromatase inhibitors; TOR: toremifene; CDK4/6i: cyclin-dependent kinase 4/6 inhibitors; "Other" category includes various therapies used in <1% of patients each

PO2-16-09

Dose-dense versus 3-weekly AC during Neoadjuvant Chemoimmunotherapy for Early-Stage Triple-Negative Breast Cancer (TNBC): a Real-World Safety and Efficacy Data Analysis

Presenting Author(s) and Co-Author(s):

R. Colombo Bonadio. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

F. Madasi. Instituto D'Or de Pesquisa e Ensino (IDOR), Rio de Janeiro, Brazil, Brazil

J. Bines. Instituto Nacional de Câncer (INCA), Brazil

R. Ferreira. Hospital Moinhos de Vento, Porto Alegre, Brazil, Brazil

D. Rosa. Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul, Brazil

C. Santos. Instituto D'Or de Pesquisa e Ensino (IDOR), Recife, Brazil, Brazil

Z. Souza. Hospital Sírio-Libanês, Brasília, Brazil, Brazil

D. Assad-Suzuki. Hospital Sírio-Libanês, Brasília, Brazil, Brazil

J. Araujo. Hospital Beneficência Portuguesa, São Paulo, Brazil, Sao Paulo, Sao Paulo, Brazil

D. Gagliato. Hospital Beneficência Portuguesa, São Paulo, Brazil, Brazil

C. dos Anjos. Hospital Sírio-Libanês, São Paulo, Brazil, Brazil

B. Zucchetti. DASA, United States

a. Ferrari. DASA, United States

M. Lopes. DASA Oncology - Clínica AMO, Salvador, Brazil, Brazil

R. Cangussu. Instituto D'Or de Pesquisa e Ensino (IDOR), Salvador, Brazil, Brazil

M. Monteiro. Instituto do Câncer do Ceara, Fortaleza, Brazil, United States

P. Hoff. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

L. Testa. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil

R. Barroso-Sousa. Dasa Oncology, United States

Background: The Keynote-522 (KN-522) study established the use of pembrolizumab in combination with neoadjuvant carboplatin-paclitaxel, followed by 3-weekly (3w) anthracycline-cyclophosphamide (AC), as the standard of treatment for stage II-III TNBC. However, dose-dense chemotherapy (CT) improves survival rates compared to the standard schedule in early-stage breast cancer and several groups have been modifying the KN-522 regimen with dose-dense AC (ddAC). The objective of this study was to compare the safety and effectiveness of ddAC versus the q3w schedule. **Methods:** We conducted a multicentric real-world analysis of patients (pts) with early-stage TNBC who received neoadjuvant CT plus pembrolizumab at nine cancer centers. Safety endpoints included grade ≥ 3 adverse events (AEs), drug discontinuation, hospitalization due to AEs, and the use of antibiotics during neoadjuvant therapy. Pathologic complete response (pCR) was used as the effectiveness endpoint, and we performed univariate and multivariable logistic regression to evaluate factors associated with pCR. **Results:** To date, we included 168 pts in this study of which 137 pts have finished the neoadjuvant therapy phase and constituted our safety cohort. Among them, 86 pts (62.8%) received ddAC and 51 pts (37.2%) were treated with the 3w schedule. The two groups exhibited no significant differences in baseline characteristics; the median age was 42 years (range 29 - 75), 70.8% had stage II and 25.5% had stage III TNBC, 46.7% had positive lymph nodes, and 74.4% had a Ki67-index $\geq 50\%$. Overall, 30.2% and 27.4% presented grade ≥ 3

AEs with ddAC and 3w AC, respectively, with no significant difference between the two groups (p=0.177). Grade ≥ 3 immune-related AEs (irAEs), occurred in 8.1% with ddAC and 3.9% with 3w AC (0.335). The most common grade ≥ 3 irAEs were pneumonitis (n=4) and hepatitis (n=2). The ddAC group had a higher rate of any drug discontinuation due to toxicities (24.4% vs. 11.8%, p=0.043) and a greater use of antibiotics (27.9% vs. 11.8%, p=0.009) compared to the 3w group. There was a trend toward more rates of hospitalization due to AEs in the ddAC group, although this was not statistically significant (17.4% vs 11.8%, p=0.131). At the time of data analysis cutoff, a total of 119 pts underwent surgery and have pathology report available and were included in the efficacy cohort. In the univariate analysis, the pCR rates were 65.8% with ddAC and 55.8% with 3w AC (OR 1.52, 95% CI 0.70-3.27, p=0.282). The rates of RCB (residual cancer burden) 0-1 were 81.2% and 67.6%, respectively (OR 2.06, 95% CI 0.82 – 5.16, p=0.120). Factors influencing rates of pCR were Ki67 index $\geq 50\%$ and tumor staging, which remained significant in the multivariable analysis (Table). In the 3w AC group, no difference in pCR was observed between pts who used or not granulocyte colony stimulating-factors (61.1% vs 52%, p=0.553). Conclusion: No difference in grade ≥ 3 AEs was observed between ddAC and 3w AC in pts with early-stage TNBC receiving neoadjuvant CT plus pembrolizumab. Nevertheless, the dose-dense regimen was linked to higher rates of drug discontinuation and antibiotic use. Although the pCR rates numerically favored ddAC, the difference was not statistically significant. Thus, the medical community should consider carefully risks and benefits of using ddAC within the KN522 regimen. Larger studies and longer follow-up are warranted to assess the long-term outcomes of the CT schedules.

Multivariable regression of factors associated with pCR

Multivariable regression of factors associated with pCR	OR	95% CI	p-value
Stage (III vs II)	0.28	0.11 – 0.69	0.006
Ki67-index ($\geq 50\%$ vs $< 50\%$)	4.42	1.53 – 12.7	0.006
CT schedule (ddAC vs 3w AC)	1.13	0.47 – 2.72	0.770

PO2-16-10

Characterising HER2-low status in metastatic breast cancer: a real-world retrospective study of patients at a metropolitan cancer centre in Australia.

Presenting Author(s) and Co-Author(s):

M. Li. Peter MacCallum Cancer Centre, Fitzroy, Victoria, Australia

B. Yeo. Olivia Newton John Cancer and Wellness Centre, United States

Background:

Traditionally, breast cancer subtyping has described patients as HER2-negative or HER2-positive, with the latter being those in whom HER2-directed therapies are utilised. A proportion of HER2-negative cancers can be classified as “HER2-low” as they express IHC 1+ or 2+ and are non-amplified on in-situ hybridisation (ISH). Until recently, our widely available HER2-targeted therapies have proven to be ineffective in this subtype. The DESTINY-BREAST04 trial (Modi et al, NEJM 2022) showed progression-free and overall survival efficacy of HER2-directed therapy using the antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) in HER2-low disease, suggesting a need to identify this population for selected therapy. This study evaluated a real-world population of metastatic breast cancer (MBC) patients treated according to traditional breast cancer subtypes to determine the frequency of HER2-low histology, with a focus on selection of first-line therapy.

Methods:

This retrospective audit identified patients being treated for MBC at a single tertiary hospital (Austin Health in Melbourne, Australia) over a 3.5 year period. Patients were identified from an electronic database, with a date of last follow-up as August 2022. Medical records were interrogated for clinicopathological information including review of pathology reports for breast cancer subtypes. Traditional breast cancer subtypes were defined as (i) ER positive and HER2-negative (HER2 0 or 1+, or 2+ and non-amplified); (ii) HER2-positive (HER2 3+ and/or amplified) and (iii) TNBC (negative for ER and PgR, and HER2 0 or 1+, or 2+ and non-amplified). Selection and duration of first-line treatment for MBC was also recorded.

Results:

Between March 2018 and August 2022, 202 MBC patients were identified. Based on traditional subtypes, 126 (62%) were ER positive and HER2-negative, 46 (23%) were HER2-positive, 26 (13%) were TNBC and 4 (2%) were unknown. In the total population, 87 (43%) were classified as having HER2-low disease based on retrospective pathology reports. HER2-low represented 61% of ER positive, HER2-non amplified patients and 45% of TNBC patients.

Metastatic specimen data was known for 172 cases and of these, 95 patients (55%) were re-biopsied on metastatic progression. This occurred more commonly with HER2-positive (81%) and ER positive HER2-negative (78%) primaries.

The most common change in subtype was loss of ER, which occurred in 7 patients (3%). Changes in HER2 status occurred in 29 (14%) of patients, most commonly as either an increase from 1+ to 2+ or decrease from 1+ to 0. HER2-low status remained consistent for 67% of patients who underwent biopsy on recurrence.

For patients with ER positive HER2-negative MBC, first-line combination therapy with a CDK4/6 inhibitor + AI was preferred (51%), followed by single agent endocrine therapy (30%) and chemotherapy (17%). The majority (84%) of HER2-positive patients received first-line dual

HER2 therapy (trastuzumab and pertuzumab) with taxane chemotherapy. Half of TNBC patients received upfront chemotherapy, with physician preference being capecitabine (45%).

There was no significant difference in PFS between the HER2-low vs. HER2-0 cohorts, for either ER positive or TNBC subtypes. No patients in this series were treated based on HER2-low definition due to no funded access to such therapies at the time.

Conclusion:

HER2-low has emerged as an identifier for patients who may respond to HER2-directed therapies using ADCs such as T-DXd. However, its clinical significance as a discrete clinical subtype remains uncertain. In this retrospective audit, HER2-low patients were identified in both ER positive and TNBC subtypes. Dynamic changes in HER2 staining occurred infrequently. Further evaluation is needed to address whether HER2-low expression provides any prognostic value and whether prospective reporting of HER2-low status may alter how these new HER2-directed therapies are used in future.

PO2-16-11

Real-World Data of Neuroendocrine Neoplasms of Breast

Presenting Author(s) and Co-Author(s):

S. Unlu. Cleveland Clinic Fairview Hospital, United States

O. Ogbue. Cleveland Clinic Fairview Hospital, United States

g. Lewis. Cleveland Clinic Pathology & Laboratory Medicine Institute (Robert J. Tomsich), United States

A. Haddad. Cleveland Clinic Moll Cancer Center, United States

H. Daw. Cleveland Clinic Moll Cancer Center, United States

B. Maiti. Cleveland Clinic Moll Cancer Center, United States

Background: Primary neuroendocrine neoplasms (NEN) of breast are rare and heterogeneous. WHO has classified NENs of non-endocrine organs into three distinct categories in 2022, however real-world data on outcomes of patients with NENs of non-endocrine organs under this new classification system are still sparse. Real world experience regarding demography, clinical presentation, treatment response, and prognosis can help identify potential areas of improvement in the management of breast NEN. Methods: Here, we present our findings from patients with NEN of breast in the Cleveland Clinic Foundation between 2000 and 2023. Pathology reports were reviewed to confirm NEN of breast origin. Neuroendocrine differentiation was determined by tumor histology and immunohistochemistry (IHC). For metastatic tumors at presentation, primary organ was determined by IHC and clinical presentation. Overall survival (OS) was from date of diagnosis of NEN. Recurrence is redemonstration of tumor following curative intent therapy, and progression is increase in tumor burden. T-test and log-rank test were used in statistical analyses. Results: Total of 97 patients were identified. Of these, 79 presented with localized disease, 18 were metastatic at presentation. 88 (91%) were invasive ductal carcinoma (IDC), and 64 (81%) were local disease at presentation and rest were metastatic. Gender spread was 92:5 (F:M). Patients with ER + disease was 84/96, PR + disease was 71, and 4/93 patients had overexpression of HER2. Median age was 70 at diagnosis. 11 patients underwent neoadjuvant chemotherapy, 15 patients underwent adjuvant chemotherapy (AC), and 58/84 patients underwent hormonal adjuvant therapy. For localized disease, median recurrence free survival (RFS) was 165 months (144-NA), and recurrence rate was 8/79 (10%). Recurrence rate for local IDC was 10% (6/64). Patients with metastatic disease at presentation had a median progression free survival (PFS) of 30 months, and progression rate was 7/18 (39%). For patients with metastatic disease, median lines of palliative therapy used was 2, with median duration of first line treatment being 3.5 months, and 10 months for second line. Most common surgical procedure was mastectomy, with 37% of patients undergoing management. Median duration from diagnostic biopsy to definitive surgery was 1 month. Median follow up was 28 months. Most common hormonal adjuvant option was anastrozole (58%), most common AC regimen was docetaxel and cyclophosphamide (39%), and most common first line palliative agent was letrozole (42%). Patients who underwent AC did not reach median OS, and patients who did not receive AC had a median OS of 148 months (p=0.8). Patients with grade 3 tumors had a median OS of 58.6 months, and grade 1 and 2 had a median OS of 148.1 months (p=0.5). Discussion: Current treatment strategies for NEN of breast mirror those of non-NEN of breast with similar histology and stage based on extrapolation of data. Recurrence rate was similar between IDC and SPC. In our cohort, survival was not significantly dependent on grade and use of AC. This might be due to the number of patients included in our study, as there was a

non-significant trend towards lower OS in patients with high-grade neoplasms, and further limitations from retrospective design of study. Further research towards benefit of AC in NEN of breast and prognostic value of grading is necessary to explore management options in comparison to non-NEN of the breast.

Number of Patients	97
Gender (F:M)	92:5
Median Age at Diagnosis (Range)	70 (34-97)
Pathological Subtype (IDC:SPC)	88:9
Estrogen Receptor Expression	90% (84/93)
Estrogen Receptor Expression	76% (71/93)
HER2 Overexpression	4% (4/93)
Pathological Grade (1)	11 (13%)
Pathological Grade (2)	52 (60%)
Pathological Grade (3)	23 (27%)
Neoadjuvant Chemotherapy	11/97
Adjuvant Chemotherapy	15/97
Adjuvant Endocrine Therapy	61/97
Median RFS after Curative Treatment	165 (144-NA)
Median PFS after Palliative Treatment	30 (23-NA)
Median OS (95% CI)	125 (90.7-NA)

PO2-16-12

Real world evidence of neoadjuvant chemotherapy for breast cancer treatment in a Brazilian multicenter cohort: correlation of pathological complete response and overall survival

Presenting Author(s) and Co-Author(s):

M. ANTONINI. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, Sao Paulo, Sao Paulo, Brazil

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

F. BAUK RICHTER. Hospital Pérola Byington, São Paulo, Sao Paulo, Brazil

G. PANNAIN. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

A. Amorim. Perola Byington Hospital, United States

M. Diogenes. HOSPITAL PEROLA BYINGTON, SÃO PAULO, Sao Paulo, Brazil

O. FERRARO. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

L. Gebrim. Womens' Health Hospital, São Paulo Brazil, Sao Paulo, Brazil

R. COELHO LOPES. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

J. REAL. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

Introduction: Breast cancer is the most common malignancy among women in Brazil and worldwide. Neoadjuvant chemotherapy (NAC) has been increasingly used for the treatment of breast cancer conditions ranging from locally advanced tumors to early-stage triple-negative and HER-2 positive tumors. Nowadays only 5% of breast cancer patients are enrolled in clinical trials. Real-world data is important to evaluate how clinical trial treatments behave in the real world with all the heterogeneous patient characteristics of those treated differently from the homogeneity of clinical trials. **Objectives:** To evaluate the rates of pathological complete response (pCR) in patients undergoing neoadjuvant chemotherapy (NAC) for the treatment of breast cancer (BC) To examine the differences in pathological complete response (pCR) rates between HER-2 positive breast cancer patients with and without trastuzumab treatment, and between triple-negative breast cancer (TNBC) patients with and without platinum-based treatment. Additionally, we aim to assess the impact of pCR on overall survival (OS) and disease-free survival (DFS) using real-world data (RWD). **Methods:** This was a retrospective, multicentric cohort study, that included female patients over 18 years of age, with a diagnosis of non-metastatic breast cancer undergoing NAC. As an exploratory real-world data study, no confirmatory hypothesis was established, so no corrections for multiple comparisons were necessary. Overall survival (OS) and disease-free survival (DFS) were estimated by the Kaplan-Meier method calculated at five years. Additionally, we conducted a multivariate analysis to identify significant associations with pathologic complete response (pCR) and overall survival (OS). We employed a forest plot to visually represent these associations **Results:** From 2011 to 2020, 1,891 patients were included in the study, and 421 (22,3%) achieved pCR (ypT0 ypN0) and considering the presence of residual in situ carcinoma (DCIS) the pCR was seen in 467 patients (23,5) without significant difference ($p=0,567$). The pCR rate varied between the subtypes: luminal A 17,0%, luminal B 21,3%, luminal HER2 23,0%, TNBC 22,5% and HER2 28,5% ($p = 0,057$). The type of neoadjuvant chemotherapy (NAC) regimen was correlated with pathological complete response (pCR). Among HER2-positive patients, those who received Trastuzumab had a significantly higher rate of pCR compared to those who did not receive it ($p < 0.0001$). Similarly, in patients with TNBC, those who underwent treatment with platinum-based regimens also showed higher rates of pCR ($p < 0.0001$). There were 694

deaths, and the 5-year OS rate was 62.9%. OS was also grouped according to pCR status, and pCR OS rate was 88,3% and non-pCR 58.1% significant difference observed ($p < 0.0001$). Five-year DFS of pCR was 92.2% and non-pCR 64.3% ($p < 0.0001$). Conclusion: this real-world data study evaluated the rates of pathological complete response (pCR) in breast cancer patients undergoing neoadjuvant chemotherapy (NAC). The results revealed varying pCR rates among different breast cancer subtypes, with HER2-positive and triple-negative subtypes showing higher rates. The use of Trastuzumab in HER2-positive patients and platinum-based regimens in triple-negative patients correlated with significantly higher pCR rates. Furthermore, achieving pCR was associated with improved overall survival (OS) and disease-free survival (DFS). These findings emphasize the importance of considering individual tumor characteristics and tailoring treatment strategies for breast cancer patients to optimize outcomes.

Clinicopathological characteristics of patients

Characteristics	pCR (n=421)		non-pCR (n=1470)		p-value
	N	%	N	%	
Mean Age years [standard deviation]	49,93	[10,80]	50,50	[10,76]	0,722
Status menopausal					
Pre-menopausal	230	54,6%	843	57,3%	0,321
Menopausal	192	45,6%	626	42,6%	0,270
Family history					
Yes	95	22,5%	354	24,1%	0,884
No	326	77,5%	1.116	75,9%	0,519
Histological type					
IDC	402	95,5%	1.393	94,8%	0,550
IDC with ILC	14	3,3%	52	3,5%	0,834
Others	5	1,2%	25	1,7%	0,458
Histological grade					
G1	106	25,2%	359	24,4%	0,751
G2	199	47,3%	729	49,6%	0,400
G3	116	27,6%	382	26,0%	0,520
Ki-67					
<14	59	14,0%	249	16,9%	0,152
>14	362	86,0%	1.221	83,1%	0,152
Subtypes					
Luminal A	39	9,3%	190	12,9%	0,042
Luminal B	133	31,5%	489	33,3%	0,519
Luminal HER-2	53	12,6%	177	12,0%	0,762
TNBC	132	31,4%	454	30,9%	0,854
HER-2 +	64	15,2%	160	10,9%	0,016
Tumor size (T)					
T1	13	3,1%	42	2,9%	0,804
T2	133	31,6%	404	27,5%	0,099
T3	162	38,5%	577	39,3%	0,775
T4	113	26,8%	447	30,4%	0,158
Lymphnode involvement (N)					
N0	112	26,6%	319	21,7%	0,034
N1	166	39,4%	652	44,3%	0,072
N2-3	143	34,0%	499	33,9%	0,994
Clinical staging (TNM) AJCC					
I	11	2,6%	33	2,2%	0,659
IIA	29	6,9%	120	8,2%	0,392
IIIB	100	23,8%	327	22,2%	0,514
IIIA	215	51,1%	575	39,1%	<0,001
IIIB	62	14,7%	381	25,9%	<0,001
IIIC	4	1,0%	34	2,3%	0,079

AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; TNBC triple negative breast cancer.

NAC schemas and correlation with pCR.

All Subtypes	pCR (n=421)		non-pCR (n=1470)		p-value
	N	%	N	%	
AC-T	215	51,0%	1087	73,9%	<0,001
AC-TPlatinum	101	24,4%	197	13,4%	<0,001
AC-TH	105	24,6%	186	12,7%	<0,001

HER-2	pCR (n=117)		non-pCR (n=337)		p-value
	N	%	N	%	
AC-T	12	10,3%	151	44,8%	<0,0001
AC-TH	105	89,7%	186	55,2%	

TNBC	pCR (n=132)		non-pCR (n=454)		p-value
	N	%	N	%	
AC-T	31	23,5%	260	57,3%	<0,0001
AC-TPlatinum	101	76,5%	197	42,7%	

AC-T, doxorubicin + cyclophosphamide – taxane; AC-TPlatinum, doxorubicin + cyclophosphamide – taxane+carboplatin; AC-TH, doxorubicin + cyclophosphamide – taxane+herceptin.

PO2-17-01

Impact of the introduction of CDK4/6 inhibitors on treatment duration in patients with HR+, HER2– advanced breast cancer: Final analysis of TreatER+ight, a Canadian prospective, real-world, observational study

Presenting Author(s) and Co-Author(s):

C. Doyle. Hemato-oncology, CHU de Québec, Quebec City, QC, Canada, United States

A. Lohmann. London Health Sciences Centre, United States

N. Iqbal. Medical Oncology, Saskatchewan Cancer Agency, Saskatoon, SK, Canada, United States

J. Henning. Medical Oncology, Tom Baker Cancer Center, Calgary, Alberta, Canada, United States

S. Kulkarni. Windsor Regional Hospital, United States

N. Califaretti. Medical Oncology, Grand River Regional Cancer Center, Kitchener, ON, Canada, United States

J. Hilton. Medical Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, ON, Canada, United States

C. Ferrario. Jewish General Hospital, Montreal, QC, Canada, United States

N. Bouganim. Medical Oncology, McGill University Health Centre, Montreal, QC, Canada, United States

M. Mates. Cancer Centre of Southeastern Ontario, Canada

S. Guillemette. Novartis Pharmaceuticals Canada, Montreal, QC, Canada, United States

R. Leite. Novartis Pharmaceuticals Canada, Montreal, QC, Canada, United States

S. Chia. British Columbia Cancer Agency, Vancouver, British Columbia, Canada

Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) are the established first-line targeted therapy (TT) for patients with hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2–) advanced breast cancer (ABC). TreatER+ight, the first prospective, real-world study evaluating the treatment patterns, safety and effectiveness of ET alone or ET + TT in Canadian patients with HR+, HER2– ABC (2016 to 2020) recorded ET as the standard of care (SOC) in the first interim analysis report. However, treatment with CDK4/6i combined with ET have rapidly evolved as the SOC in the metastatic setting.

Methods: This prospective, multicenter, observational study (NCT02753686) enrolled patients with HR+, HER2– ABC with or without prior exposure to ET and up to one line of prior CT in the advanced setting. The patients were enrolled by the line of their therapy (first-line, second-line or third-line) and grouped into 2 cohorts (ET and ET + TT). Duration of therapy, and overall survival (OS) are estimated using Kaplan–Meier method. Here, we report the final outcome with CDK4/6i treatment evolution with sequencing strategy and duration in routine clinical practice.

Results: At data cutoff (December 1, 2022), a total of 439 enrolled patients (ET, n=104; ET + TT, n=335) from 25 centers in Canada, constituted the full analysis set. The median age (range) was 71.5 (37.0–96.0) years in ET cohort and 65.0 (23.0–87.0) years in ET + TT cohort. About 84.6% and 66.4% were postmenopausal patients in the ET and ET + TT cohorts, respectively. Patients with ECOG PS scores 0 to 1 composed of 82.0% and 93.5% in the ET

and ET + TT cohorts, respectively. In the overall population, ET alone and ET + CDK4/6i were the most common treatment received by patients in first-line (43.5% and 43.3%) and second-line (36.3% and 24.6%) treatment settings. In third-line treatment setting, CT was the most common treatment received by patients (38.4%).

Conclusions: Data from final analysis of TreatER+ight have further confirmed the evolution to primary use of CDK4/6i-based combination therapy in the first-line setting for Canadian patients with HR+, HER2– ABC. Additional details on duration of therapy by CDK4/6i agents, overall survival data and age subgroup analysis will be presented at SABCS 2023

Table 1_Baseline characteristics, treatment patterns, and duration of treatment

TreatER+ight Final Analysis Abstract SABCS 2023

Table: Baseline characteristics, treatment patterns, and duration of treatment

	ET (n=104)	ET + TT (n=335)	
Median age, years (range) at baseline/study entry	71.5 (37.0–96.0)	65.0 (23.0–87.0)	
ECOG PS at baseline/study entry*			
0-1	64 (82.0%)	216 (83.5%)	
Menopausal status at initial diagnosis*			
Post-menopausal	88 (84.6%)	219 (66.4%)	
Pre/perimenopausal	16 (15.4%)	111 (33.6%)	
Overall therapy during the study	N=439		
CDK4/6i + ET	237 (54.0%)		
ET	104 (23.7%)		
Other	98 (22.3%)		
CDK4/6i therapy during the study by line of treatment	n=237†		
First-line	159 (67.1%)		
Second-line	56 (23.6%)		
Third-line	19 (8.0%)		
Treatment patterns by line of therapy	First-line (n=439)	Second-line (n=342)	Third-line (n=245)
CDK4/6i + ET	190 (43.3%)	84 (24.6%)	31 (12.7%)
ET	191 (43.5%)	124 (36.3%)	95 (26.5%)
mTORi + ET	17 (3.9%)	67 (19.6%)	44 (18.0%)
CT	26 (5.9%)	46 (13.5%)	94 (38.4%)
Others	13 (3.0%)	21 (6.1%)	11 (4.5%)
Duration of treatment by line of therapy for patients on CDK4/6i treatment (in months)	Median duration		95% CI
First-line (n=307)	19.32		15.21–21.91
Second-line (n=218)	9.23		7.89–11.07
Third-line (n=148)	5.22		4.44–6.60

*All percentages are calculated based on total number of non-missing entries of each variable/stratum. †These patients were enrolled onto the ET arm of CDK4/6i. CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance scale; ET, endocrine therapy; mTORi, mammalian target of rapamycin inhibitor; TT, targeted therapy.

PO2-17-02

Can body mass index be a complete pathological response predictor in breast cancer patients submitted to neoadjuvant chemotherapy? A real-world data trial.

Presenting Author(s) and Co-Author(s):

F. BAUK RICHTER. Hospital Pérola Byington, São Paulo, Sao Paulo, Brazil

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

M. Antonini. Hospital do Servidor Publico Estadual, Sao Paulo, Brazil, Sao Paulo, Brazil

J. REAL. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

L. Gebrim. Hospital perola Byington, United States

R. COELHO LOPES. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

Background: Breast cancer is a prevalent disease, and its incidence has increased annually worldwide. The prognosis depends on several factors, such as patient characteristics, tumor characteristics and treatment efficacy. In this scenario, neoadjuvant chemotherapy (NAC), previously used only to make surgical approach possible in advanced cases, has been increasingly used in more aggressive initial tumors such as HER 2 positive and triple negative and, in these tumors, the presence of pathological complete response is directly correlated with survival and the disease-free interval. Obesity is very common in Brazil and in the world, and its incidence grows annually. There is a direct relationship between the risk of breast cancer and obesity, especially in postmenopausal women. Justification: Many authors suggest that obese patients are less likely to achieve this pathological complete response (pCR). Real-world data is important to evaluate how patients behave in the real world, only 5% of the patients are enrolled in clinical trials. Most of the clinical trials have strict inclusion and exclusion criteria that ends up selecting a patient that almost doesn't exist in the real world. Objective: To correlate complete pathological response with Body Mass Index (BMI) and, secondarily, to evaluate the relationship between overall and disease-free survival with BMI. Methods: This was a retrospective observational study that has evaluated patients with invasive breast cancer in two Brazilian hospitals. Clinical and pathological characteristics were extracted from the database, being eligible the patients diagnosed with invasive breast cancer, stages I to III, and who underwent neoadjuvant chemotherapy (NAC). Patients were categorized using the World Health Organization (WHO) definition: BMI 18.5 to < 25 kg/m²: normal weight; BMI 25 to < 30 kg/m²: overweight; BMI ≥30kg/m²: obesity. pCR was defined as the absence of breast and axillary invasive tumor. The t test or chi-square test were used to individually analyze the association of each variable between the groups with and without pCR. Univariate and multivariate analyzes to calculate odds ratios (OR) and 95% confidence intervals (CI) of the independent variables BMI, age, clinical stage, histological type, and subtype of cancer, correlated with pCR. where p value < 0.05 was considered statistically significant. Results: 1,779 records were included in the analyses, with a mean age of 50 years at diagnosis and a mean BMI of 28.08 kg/m². Most patients had stage III cancer (68.1%) at diagnosis and the invasive carcinoma nonspecial type was predominant (95.2%). Immunohistochemistry allowed us to divide the groups into Luminal A like (12.4%), Luminal B like (31.1%), HER2+ like (25.3%) and triple negative like (31.2%). After NAC, 1461 had residual disease and 390 (22.3%) had a pCR. Regarding stages, 2% of the patients were in stage I, 30% in stage II and 68% in stage III. No correlation was found between BMI categories and pCR (p=0.7607). In the multivariate analysis, the results were also not significant for the correlation between the BMI categories after adjusting for age, clinical stage, tumor histology and subtype of breast cancer. We observed, however, that the most aggressive types of cancer were predictors of pathologic

complete response. The estimated average overall survival (OS) was 102 months for those of normal weight, 99 months for the overweight ones and 101 months for the obese ones. As for recurrence-free survival, the data were immature. Conclusion: This study with Brazilian real-world data found no correlation between BMI and pCR after NAC and BMI and OS in patients with breast cancer. As an additional finding, most patients were obese or overweight at diagnosis (69%) and public policies should be encouraged to act in this scenario. Trials considering stratification of patients between different regions of the country or specific subtype of cancer can elucidate this finding.

PO2-17-03

Patient reported outcomes (PROs) and survival with toremifene versus aromatase inhibitors (AI) in patients with moderate/high-risk premenopausal hormone receptor (HR)-positive breast cancer: A real-world study

Presenting Author(s) and Co-Author(s):

Y. Yang. Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, United States

F. Gan. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, United States

W. Yang. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China, United States

Y. Xia. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China, United States

Q. Liu. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

C. Gong. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Background:

The selective estrogen receptor modulator (SERM) toremifene, a synthetic analogue of tamoxifen, has shown similar efficacy to tamoxifen in patients with HR-positive breast cancer and is widely used in China for the treatment of premenopausal women with breast cancer. Multiple studies have confirmed the benefit of ovarian function suppression (OFS) combined with AI and SERMs in premenopausal women with HR-positive breast cancer. However, to date, there are no data comparing the efficacy and safety of toremifene plus OFS versus AI plus OFS. In this real-world study, we compared PROs and survival with toremifene or AI combined with OFS in patients with moderate/high-risk premenopausal HR-positive breast cancer.

Methods:

We enrolled premenopausal female patients with HR-positive, moderate/high-risk breast cancer who received OFS combined with toremifene or AI between January 1, 2010 and December 31, 2017 at the Breast Cancer Center of Sun Yat-sen Memorial Hospital. The primary endpoint was PROs, which were collected from January 1 to March 31, 2023, including the SF-36 and five-level EuroQol five-dimensional (EQ-5D-5L) questionnaires. Disease-free-survival (DFS) and safety were secondary endpoints. Associations between treatment group and SF-36 scores were evaluated using a Student's t test and between treatment group and EQ-5D-5L scores using nonparametric tests. DFS was assessed using the Kaplan–Meier method and Cox regression.

Results:

A total of 392 patients were enrolled; 171 (43.6%) received toremifene and 221 (56.4%) received AI. Mean \pm standard deviation scores for the role physical and general health dimensions of SF-36 were higher in the toremifene group versus the AI group (7.44 ± 1.21 vs 7.15 ± 1.48 , $P=0.034$ and 22.90 ± 3.95 vs 21.78 ± 4.33 , $P=0.009$, respectively). Scores on the anxiety/depression (AD) dimension of EQ-5D-5L were significantly different between the toremifene and AI treatment groups (mean rank: 184.14 vs 206.07, $P=0.038$); 'no problems' was selected by 49.7% and 37.1% of patients in the toremifene and AI groups, respectively.

There were no significant differences in the other dimensions of SF-36 and EQ-5D-5L between the toremifene and AI groups ($P>0.05$). Similar estimated 5- and 8-year DFS rates were reported for the toremifene and AI groups; 96.5% (95% CI: 93.7-99.2) and 91.9% (95% CI: 88.2-95.5), and 87.4% (95% CI: 81.1-93.8) and 87.8% (95% CI: 81.1-94.4), respectively, and the hazard ratio for DFS was 0.75 (95% CI: 0.38-1.46), $P=0.39$. DFS was also comparable in the two treatment groups when stratified by HER2 status, age (≤ 40 y vs >40 y) and estrogen receptor expression level ($\leq 20\%$ vs $>20\%$). Adverse event rates were generally similar in the two treatment groups, except for a higher rate of endometrial thickening (17.5% vs 1.8%, $p< 0.001$) and a lower rate of morning stiffness (7.6% vs 14.5%, $p< 0.001$) in the toremifene versus the AI group.

Conclusion:

Patients who received toremifene plus OFS had better role physical and general health dimensions on SF-36 and AD dimensions of EQ-5D-5L than those receiving AI plus OFS. There were no significant differences in 5- or 8-year DFS between the toremifene and AI groups. Both treatments were generally well tolerated.

PO2-17-05

Pharmacy fills but not baseline distress or other clinical factors can identify those at high risk for early adjuvant endocrine therapy discontinuation

Presenting Author(s) and Co-Author(s):

J. Neuner. Medical College of Wisconsin, Wisconsin, United States

R. Sparapani. Medical College of Wisconsin, United States

J. Tiegs. Medical College of Wisconsin, United States

V. Makris. Medical College of Wisconsin, United States

M. Stolley. Medical College of Wisconsin, United States

S. Kamaraju. Medical College of Wisconsin, Milwaukee, Wisconsin, United States

B. Crotty. Medical College of Wisconsin, United States

K. Flynn. Medical College of Wisconsin, United States

Background

Completion of the recommended 5-10 year course of adjuvant endocrine therapy (AET) course is low, and few risk factors for discontinuation have been identified. We examined factors associated with early AET discontinuation in a large cohort with patient-reported outcomes (PROs) and other measures routinely used in clinical care at four sites within an academic health system's multidisciplinary cancer center.

Methods

We examined postmenopausal women with stage I-III hormone-receptor positive breast cancer identified using the registry at an academic multidisciplinary cancer center 2014-19 who received a prescription for AET, and followed them for up to 5 years. Breast cancer extent of disease and treatments, Elixhauser comorbidity index, medication number and sociodemographic characteristics (age, race/ethnicity, insurance, area deprivation index of zip code of residence) were abstracted from the electronic health record (EHR). PRO measures included the Distress Thermometer (DT, scored 0-10) and its associated problem list (39 yes/no questions), and the Patient Health Questionnaire-9 (depression), all administered routinely as part of clinical care between diagnosis date and start of AET. If >1 PRO performed during that time, the measure closest to AET start was used. DT was dichotomized using the clinically accepted score of 4 as the threshold for severe distress, as was Patient Health Questionnaire-9 (PHQ-9) depression (>5). AET prescription information included both prescription date from the EHR, and prescription fills assessed using an all-payer pharmacy data source. AET was defined as discontinued (d/c) when no prescription had been filled at any pharmacy for at least 90 days. We used nonparametric hypotheses test for two-samples (d/c vs. no d/c) as well as Kaplan-Meier product-limit time-to-event analyses with censoring for recurrence, death, or change of provider, and advanced machine learning to examine the association of these variables with discontinuation prior to five years. 54 curated covariates were examined in all, corresponding to a Bonferroni statistical significance p-value threshold of 0.001 to control type I error. Sensitivity analyses were performed to 1) use alternative date of DT (closest to diagnosis date) and 2) to examine d/c defined as 180 days.

Results

Among the cohort of 985 women (74% stage I, 25% Elixhauser comorbidity score >2), 36.9% had a DT >4, and 6.7% a PHQ-9 >5. The cohort had a median followup time of 954 days, and during followup 291 women (29.5%) discontinued before completion of the 5-year course or

censoring for death, change to a provider outside the system or study end date in 2021. Over 40% of women who stopped filling prescriptions never had their prescriptions discontinued by their physician in the EHR. None of the examined variables including those for Distress and PL, PHQ-9 and measures of extent of disease, cancer treatments, medication number and sociodemographic characteristics were associated with early discontinuation. Results were similar in analyses using the DT date closest to diagnosis or a 180-day prescription fill gap. We also used advanced machine learning with respect to time to event discontinuation had similar results.

Conclusions.

Clinically available EHR data including two PRO measures were not reliable predictors of early discontinuation. However, many women who had discontinued still had orders for AET in the EHR, suggesting that their physicians were unaware that they had stopped filling prescriptions. Future work should examine whether routine monitoring of prescription fills might be enlisted to identify these women and assist with education, supportive care or other assistance to restart.

PO2-17-06

Real world treatment patterns and clinical outcomes by germline BRCA (gBRCA) mutation status in patients with HER2-negative early breast cancer in the US community oncology setting: a retrospective observational chart-review study

Presenting Author(s) and Co-Author(s):

J. Andersen. Compass Oncology, United States

J. Earla. Merck & Co., Inc., Rahway, New Jersey, United States

N. Fulcher. Ontada, United States

J. Ndukum. Ontada, United States

N. Robert. Ontada, United States

M. Robson. Memorial Sloan Kettering Cancer Center, New York, United States

W. Li. AstraZeneca, Gaithersburg, Maryland, United States

J. Mejia. Merck & Co., Inc., Rahway, New Jersey, United States

Background: Women with early-stage breast cancer (eBC) who have inherited BRCA1 or BRCA2 mutations (gBRCAm) are typically diagnosed at a younger age and often require more intensive treatment. In the randomized, double-blind OlympiA trial of HER2-negative (HER2-) gBRCAm patients, olaparib, a targeted poly (ADP-ribose) polymerase inhibitor (PARPi), significantly improved invasive disease free survival (IDFS), distant disease free survival (DDFS) and overall survival (OS) and was subsequently approved for adjuvant treatment of gBRCAm HER2- high-risk eBC patients. This study examined the real-world patient characteristics, treatment patterns and clinical outcomes by gBRCA status among patients with HER2- eBC in a US community oncology setting prior to olaparib US approval for treatment of eBC. Methods: This retrospective observational study used chart review data from The US Oncology Network's iKnowMed database to examine adult patients diagnosed with HER2- eBC (stage I-III) initiating systemic neoadjuvant or adjuvant therapy with chemotherapy and/or endocrine therapy between January 1, 2012 and December 31, 2018. Patients with valid gBRCAm test results (all gBRCAm and randomly selected BRCAwt patients) were included and followed through December 31, 2021. Patients were excluded if they had HER2+ tumors and progressed to stage IV within 6 months after initiation of neoadjuvant therapy or were diagnosed with another primary cancer. Descriptive analyses assessed patient characteristics. Kaplan Meier methods and multivariate Cox proportional hazard models (CPHM) were used to evaluate IDFS, DDFS and OS by gBRCA status and by HR+/HER2- or TNBC eBC subsets. Results: Among 298 BC patients meeting initial criteria, 42% had gBRCAm (n=124, 43% hormone receptor positive [HR+], 56% triple-negative BC [TNBC], 1% unknown), and 58% had gBRCAwt (n=174, 74% HR+, 22% TNBC). Median (interquartile) age at surgery was numerically lower in gBRCAm (45 [36,55] years) than gBRCAwt (48 [41,55] years) patients. A numerically higher proportion of gBRCAm patients received neoadjuvant therapy compared with gBRCAwt (Neoadj: gBRCAm 37.1% vs gBRCAwt 12.6%) but the reverse was true for adjuvant (Adj: gBRCAm 42.7% vs gBRCAwt 65.5%) and neoadjuvant + adjuvant use was numerically similar (Neoadj+Adj: gBRCAm 20.1% vs gBRCAwt 21.8%). The majority of TNBC patients received neoadjuvant therapy while the majority of HR+ patients received adjuvant therapy (Neoadj: TNBC 51.4% vs HR+ 6.6%, Adj: TNBC 29.0% vs HR+ 71.4%, Neoadj+Adj: TNBC 19.6% vs HR+ 22.0%). Median IDFS, DDFS, and OS in both study cohorts were not reached. Median follow-up from surgery was < 5 years (overall 59.0 months; gBRCAm 50.6 months; gBRCAwt 61.3 months). At 60 months, in gBRCAm and gBRCAwt respectively, estimated IDFS were 85.5% and 90.9%, estimated DDFS 88.1% and 92.2%, and estimated

survival 91.9% and 95.2%. At 60 months, in HR+/HER2- and TNBC respectively, estimated IDFS were 92.4% and 81.2%, estimated DDFS 93.9% and 85.7%, and estimated survival 96.3% and 90.9%. CPHM results showed that risks of invasive disease (HR 1.74; 95% CI 0.83-3.64; p=0.15), distant disease (HR 1.24; 95% CI 0.50-3.07; p=0.65) and death (HR 1.79; 95% CI 0.52-6.13; p=0.353) were similar between gBRCAm and gBRCAwt patients. Between HR+/HER2- and TNBC patients, risks of invasive disease (HR=0.63; 95% CI 0.21-1.89; p=0.41), distant disease (HR=0.42; 95% CI 0.11-1.67; p=0.22) and death (HR 0.48; 95% CI 0.09-2.70; p=0.41) were similar. Conclusions: This real-world chart review study of data through 2021 (before PARPi approval for eBC) with limited follow up of 5 years found that gBRCAm patients had a numerically shorter survival (IDFS, DDFS and OS) than gBRCAwt, but this difference was not statistically significantly different. Given that the follow-up period was too short to draw conclusions, further studies examining clinical outcomes over a longer follow-up period after approval of PARPi may be of interest.

PO2-17-07

Risk analysis of the differences in eligibility criteria between monarchE and POTENT clinical trials

Presenting Author(s) and Co-Author(s):

M. Yu. Chiba University, Japan

M. TAKADA. Chiba University, United States

H. Yamada. Japan/ Chiba University/ Breast surgery, United States

H. Fujimoto. Chiba University, United States

J. Sakakibara. Chiba University, United States

H. Yamamoto. Chiba University, United States

T. Nagashima. Chiba University, United States

M. Otsuka. Chiba University, United States

Background

Luminal subtype recurrence risk classifications for breast cancer have been updated and put into practice with the development of treatment. Despite this, it is noteworthy that from 2008 to 2016, early breast cancer (EBC) of luminal subtype has been reported to have little improvement in survival probability. For early-stage luminal breast cancer, several clinical trials, such as monarchE, NATALEE (which is not available in Japan) or POTENT, were being conducted. In order to avoid overtreating individuals who might not benefit from adjuvant therapy, those at high risk of recurrence ought to be accurately picked up. In monarchE and POTENT trials, abemaciclib and S-1 have shown to be effective in adjuvant therapies for luminal breast cancer although it is unrevealed if the eligible patients for each criterion are at higher risk of recurrence than ineligible patients. Besides, some of the eligibility for POTENT overlaps with those for monarchE, the patients who met POTENT but did not meet monarchE criteria at how much risk of recurrence still remains unknown. Here, we investigated recurrence risk according to the criteria of each trial in Japanese patients in real world.

Methods

We reviewed the records of 1209 patients who received surgery for stage I–III breast cancer from January 2016 to May 2022 and selected 637 analytic cohort patients and retrospectively analyzed the recurrence-free survival (RFS) of the patients using the Kaplan–Meier method. High-recurrence-risk was defined according to monarchE trial and POTENT trial. Patients' RFS was the primary endpoint.

Results

The 5-year RFS for all luminal breast cancer patients was 94.87% at Chiba University Hospital. Among monarchE eligible patients, the 5-year RFS was 82.49% and cohort 1 and cohort 2 eligible patients was 78.62% and 92.18% respectively, which were statistically lower than monarchE non-eligible patients (98.58%) ($p < 0.0001$, $p = 0.0216$, respectively). Even though the 5-year RFS rate for POTENT eligible patients (91.16%) was lower than POTENT non-eligible patients (99.13%) ($p < 0.0001$), while excluding those who met the monarchE criteria, the prognosis of POTENT eligible patients (5-year RFS rate 97.76%) had no significant differences from the patients with POTENT non-eligible breast cancer ($p = 0.0660$). Our results suggested that the eligible patients of both monarchE and POTENT were associated with poor prognoses so the criteria set are considered to be appropriate. However, although POTENT criteria suggested a reasonable capacity for recurrence prediction, there

was no dramatic difference in recurrence between POTENT non-eligible patients and the patients who are POTENT eligible but are not monarchE eligible. This might offer justification for reconsidering the use of S-1 in monarchE non-eligible patients. With the use of clinicopathological factors, it may assist in identifying individuals with high recurrence risk who would benefit from lengthier adjuvant chemotherapy regimens.

Conclusion

MonarchE criteria accurately identifies patients at high risk of relapse but the relapse in the patients who only qualified for POTENT is statistically almost the same as that in POTENT non-eligible patients.

PO2-17-08

A RETROSPECTIVE ANALYZES OF 4,885 PATIENTS OF HORMONAL RECEPTOR POSITIVE, HER2 NEGATIVE BREAST CANCER TREATED IN A REFERENCE CENTER, A REAL-WORLD DATA.

Presenting Author(s) and Co-Author(s):

A. Mattar. Womens' Health Hospital, São Paulo Brazil., São Paulo, Sao Paulo, Brazil

M. Antonini. Hospital Servidor Publico estadual, United States

M. Diogenes. HOSPITAL PEROLA BYINGTON, SÃO PAULO, Sao Paulo, Brazil

A. Amorim. Perola Byington Hospital, United States

F. Pimentel Cavalcante. Hospital Geral Fortaleza (HGF), United States

L. Gebrim. Perola Byington Hospital, United States

Background: Hormonal receptor positive Her2 negative also described as luminal breast cancer (LBC) is the most frequent tumor corresponding to about 60-65% of cases. There is great heterogeneity in these tumors and a great difference between treatments due to lack of access, mainly in developing countries. Clinical trials are important to understand the benefit of the treatments but only 5% of the breast cancer patients are enrolled in these trials and is because of that that Real World Data (RWD) is It's becoming more and more frequent. Objectives: To evaluate LBC and describe treatments and overall survival (OS) of patients treated in public hospital in São Paulo Brazil. Methods: This was a retrospective, single cohort study, that included female patients over 18 years of age, with a diagnosis of LBC. Clinical and pathological data was collected (date of diagnose, first treatment, type of treatment, stage, type of surgery, DFS and OS). This study was approved by our local ethics committee. Results: We've enrolled 5,510 patients in Perola Byington 'database from 2010 to 2021. After excluding patients without minimal complete records, a total of 4,885 patients were analyzed. Most patients were diagnosed in stage I (26,9%) and II (38,2%). There was 23,4% in stage III, 3,1% in stage IV and 5,7% in stage 0. In 2,6% the of the patient's information was not complete. Mean age at diagnosis was 57.6 years. We identified 4,761 (86.4% of 5510) patients who underwent 4,848 surgical procedures. Of the total, 47.2% were mastectomies, 50.9% partial mastectomies and 1.9% were skin sparing mastectomy. Immediate reconstruction was done in 470 patients (69.8% underwent reconstruction with an expander, 22.3% with flap rotation and 7.9% reconstruction with implants). The mean and median time between diagnosis and the beginning of treatment was analyzed, in the sample it was observed that patients who were diagnosed in stages I, II and IV had the same mean of 2.6 months, but stage IV had the lowest median 1 ,9 months. 474 patients were treated in the first line setting during the follow up, 43 % received hormone therapy (HT) and 57% received chemotherapy (CT) as first line. The duration of the treatment in first line was 17,7 months for HT and 7,7 months for CT ($p < 0,01$). OS for patients diagnosed in stages I and II did not reach the median in the available period, for patients in stages III and IV, a median of 80.4 months and 41.2 months of overall survival was identified, respectively. Conclusions: These are the first results of this large cohort of luminal patients treated in the public reference center. Most patients are diagnosed in stage I or II and more than half undergo conservative surgery. Immediate reconstruction is not routinely performed. In the public setting CDK4/6 inhibitors are not available and that led to more chemotherapy use in first line (57%) and worse survival when compared to clinical trials. Discussions on the incorporation of drugs consolidated in the literature are important to improve the treatment of advanced cancer.

PO2-17-09

Overall survival differences between HER2 Low and other breast cancer subtypes in a reference center in Brazil.

Presenting Author(s) and Co-Author(s):

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

A. Amorim. Perola Byington Hospital, United States

M. Diogenes. HOSPITAL PEROLA BYINGTON, SÃO PAULO, Sao Paulo, Brazil

M. Antonini. Hospital Servidor Publico estadual, United States

F. Pimentel Cavalcante. Hospital Geral Fortaleza (HGF), United States

L. Gebrim. Perola Byington Hospital, United States

Background: Breast cancer (BC) is a heterogeneous disease, and its subtypes have different prognosis and diverse responses to endocrine therapy and chemotherapy. In clinical practice, immunohistochemical markers are often used to classify BC into subtypes according to the presence of hormone receptors, human epidermal growth factor receptor 2 (HER2) and evaluation of proliferation measured by Ki67. Recently, there has been a suggestion for a possible alternative terminology for situations involving IHC 1+ or 2+ with negative ISH, this proposed term is referred to as HER2-low and represents about 50 to 55% of all primary BC. There are relevant gaps regarding the outcomes of HER2-low BC. Considering the new emerging therapies for HER2-low, a better description of the epidemiology, response to treatment and results of this population is extremely relevant. Objective: The purpose of this study was to use real-world data in order to investigate the Brazilian patients with BC treated in a Reference Center and evaluate the survival outcomes in different subtypes identified by molecular immunohistochemistry including HER2-Low and evaluate the survival in subtypes by stage. Methods: This retrospective cohort study included women, age > 18 years with breast cancer treated between 2010 and 2019 at Perola Byington Hospital in the city of São Paulo, Brazil. After the diagnose, the included patients were submitted to an immunohistochemical analysis to identify the subtype of the BC. Institutional Review Board of Pérola Byington Hospital approved the use of patients' data before the beginning of the study, under the reference number CAAE 7238317.6.0000.0069). An informed consent was dismissed, and this study was carried out according to the Declaration of Helsinki, including protection of patients' confidentiality. The primary outcome measure was overall survival (OS), which was defined as the length of time (in months) from the date of diagnosis to the date of death (from any cause). The secondary outcome measure was disease-free survival (DFS), which was defined as the length of time after the end of the primary cancer treatment in which the patient survives without any signs or symptoms of cancer. Continuous variables were summarized using their mean. Qualitative variables were summarized for the general population and by HCl subgroups using counts, percentages, and absolute numbers. The Kaplan-Meier method was used to estimate survival rates and mean survival times in the general population and by groups. All statistical tests were bilateral and $p < 0.05$ was considered significant. Statistical analyses were performed using the Python programming language version 3.8. Results: Between January 2010 and December 2019, 1,826 women were diagnosed with breast cancer and classified as a HER2-low subtype, among the 9,278 participants included in the study (19,68%). Regarding the OS analysis, patients with the "Luminal A" subtype had better survival (106 months) results when compared with the other subtypes and women with triple negative disease had the worse prognosis with OS of 96 months. The median survival in HER2-low with hormonal receptor positive was 101 months and statistically significant when compared with 90 months in HER2-

low hormonal receptor negative ($p < 0,01$). When looking for stage IV HER2-low and HER2+ have better overall survival rates compared to other subtypes. Conclusion: This real-world data study shows difference in the prevalence of the HER2-low subtype. In addition, there is a difference in OS between tumor subtypes and when evaluating the HER2-low subtype with or without the presence of receptors, this difference is marked.

PO2-17-10

Metaplastic breast cancer: description of 16 cases treated at a reference center and review of the literature.

Presenting Author(s) and Co-Author(s):

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

M. Antonini. Hospital Servidor Publico estadual, United States

M. Diogenes. HOSPITAL PEROLA BYINGTON, SÃO PAULO, Sao Paulo, Brazil

A. Amorim. Perola Byington Hospital, United States

F. Pimentel Cavalcante. Hospital Geral Fortaleza (HGF), United States

L. Gebrim. Perola Byington Hospital, United States

Background: Metaplastic breast carcinomas (MBC) are very rare and represent less than 1% of all invasive breast carcinomas. It is a heterogeneous neoplasm characterized by a mixture of adenocarcinoma with other histological elements such as squamous cells, spindle cells or other mesenchymal differentiation. Most MBC are hormone receptor and Her2 negative and tend to have a worse prognosis when compared to triple negative carcinomas. Clinically, they manifest as a rapidly growing palpable mass, without necessarily involving lymph nodes. According to the nomenclature of the WHO Classification of Tumors of the Breast (2012), tumors were classified into 4 variants: spindle cell, squamous cell, mesenchymal and mixed. Since publications on MBC are scarce in the literature, we studied the cases that were attended at Hospital Pérola Byington in the period 2010-2021. Methods: A retrospective study was carried out by reviewing the medical records of patients treated at the Reference Center for Women's Health - Pérola Byington Hospital, São Paulo, Brazil. Patients with breast cancer, with anatomopathological result confirming the diagnosis of metaplastic carcinoma were reviewed. Clinical data and histopathological characteristics were evaluated, as well as the type of treatment performed and the evolution. Results: A total of 16 female patients diagnosed with MBC were included. The median age was 56 years (ranging from 34 to 88). The mean initial size observed was 7 cm (ranging from 2 to 20 cm) and 94% of patients presented with a palpable mass. The initial clinical staging were I (12%), II (32%), III (50%) and IV (6%). The most common histological subtype was spindle cell (50%), of which 2 were squamous (12%), 3 mesenchymal (20%), 1 mixed spindle/squamous (6%) and 2 were not classified. Regarding immunohistochemistry, 14 patients (88%) had hormone negative and Her2 negative (triple negative). Of the 16 cases, 8 underwent mastectomy and 6 partial mastectomy and 2 patients did not undergo surgical treatment because they died despite treatment with neoadjuvant chemotherapy. All operated patients underwent sentinel lymph node biopsy or axillary dissection and 85% of them did not have axillary lymph node involvement. Radiotherapy was indicated in 13 patients. Chemotherapy was performed in 10 patients, 6 of which were neoadjuvant (since the tumors were not resectable) and 4 received adjuvant chemotherapy. Of the 6 patients that underwent neoadjuvant chemotherapy, 2 had disease progression, 3 partial response and 1 complete pathological response. During follow-up, 4 (25%) evolved with locoregional recurrence and 5 (31%) with metastatic disease. Of these women, 44% (7) are still alive. We also found that 6 of the 16 cases (37%) did not receive a diagnosis of MBC in the initial biopsy, requiring revision, a new biopsy or study of the surgical specimen for confirmation. Conclusion: As verified in the literature, MBC is a very rare histological type and corresponded to 0.2% of all cases of breast cancer in the period described above. Most patients have an advanced tumor at the time of diagnosis and little axillary involvement. The most common histological classification is the spindle cell variant and almost all tumors are

triple negative. The CMM has an aggressive behavior and little response to chemotherapy treatments. Therefore, radical surgical treatments are preferred. Due to the rarity of this entity there is little data published in the international literature.

PO2-17-11

Management guidelines for epithelial atypia diagnosed in breast screening, based on an analysis of a large prospective cohort study (Sloane Project)

Presenting Author(s) and Co-Author(s):

- K. Freeman. University of Warwick, United States
- D. Jenkinson. University of Warwick, United States
- K. Clements. NHS England, United States
- M. Wallis. Cambridge University Hospitals NHS Trust, United States
- S. Pinder. King's College London, United States
- E. Provenzano. Cambridge University Hospitals NHS Trust, UK and Cambridge Biomedical Research Centre (NIHR), United Kingdom
- H. Stobart. Independent Cancer Patients' Voice, United States
- N. Stallard. University of Warwick, United States
- O. Kearins. NHS England, United States
- N. Sharma. Leeds Teaching Hospitals NHS Trust, United States
- A. Shaaban. Queen Elizabeth Hospital, Birmingham, United States
- C. Kirwan. The University of Manchester, United States
- B. Hilton. NHS England, United States
- A. Thompson. Baylor College of Medicine, Houston, Texas, United States
- S. Taylor-Phillips. University of Warwick, United States

Background: Epithelial atypia in the breast is most frequently detected through breast screening. Internationally, guidelines differ between advising diagnostic surgical excision of screen-detected atypia versus vacuum-assisted excision (VAE), often with annual follow up surveillance mammography. Prospective data with detailed follow-up and outcomes for subsequent cancer events is lacking. We evaluated a large prospective cohort of screen-detected atypia (Sloane Project) and an expert consensus meeting to develop management recommendations. Methods: We undertook an observational analysis of women with screen-detected epithelial atypia (Atypical Ductal Hyperplasia (ADH), Flat Epithelial Atypia (FEA), Lobular In Situ Neoplasia (LISN), or mixed atypia) reported to the National Health Service (NHS) Breast Screening Programme (BSP) between 01/04/03 and 20/06/18. We estimated cumulative incidence of invasive cancers per 1000 women within 1 and 2 subsequent screening rounds using cumulative incidence functions and repeated these by women's age, type of atypia and year of diagnosis. Flexible parametric modelling produced hazard ratios (HR). The results were presented at a consensus meeting with clinical experts, patient representation, national decision-makers and commissioners from the NHS in England. A consensus on management recommendations was reached. Results: Among 3238 women (19088 person-years of follow up) with screen-detected atypia, diagnoses increased from 2010 (n=119) to 2015 (n=502). This coincided with the introduction of digital mammography into English screening centres from 2010 and changes in biopsy technique. A total of 141 invasive breast cancers were detected up to December 2018. Cumulative incidence of invasive breast cancer per 1000 women with atypia (ADH, FEA, LISN or mixed) was 14.2 (95% CI 10.3, 19.1) and 45.0 (36.3, 55.1) at 3- and 6-years post atypia based on 40 and 94 cancers, respectively. Women diagnosed with atypia during 2013-2018 had an invasive cancer detected less frequently within 3 years than women with an atypia diagnosis between 2003-2007 or 2008-2012 (6.0 invasive

cancers (3.1, 10.9) per 1000 women in 2013-2018 Vs 24.3 (13.7, 40.1) and 24.6 (14.9, 38.3) in 2003-2007 and 2008-2012), suggesting that atypia diagnosis may increasingly contribute to 'overdiagnosis'. Cancers detected were similar to the general screening population regarding grade, size and nodal involvement. Ipsilateral and contralateral cancers were detected in equal numbers, supporting the concept that atypia represents a risk factor rather than precursor of invasive cancer in the short term. Results by age and type of atypia did not suggest a need for risk-stratified management. Considering subsequent invasive cancer, VAE appeared to be as safe as diagnostic surgical excision of atypia (HR 0.75 (0.45, 1.25)). The expert consensus considered that increased screening of women with screen-detected atypia over and above routine 3-yearly screening was not beneficial, given the overall low numbers of cancers at three years. This applied to all types of atypia and all women who received digital mammography and diagnosis of atypia on core or vacuum-assisted biopsy followed by VAE within a quality assured NHS BSP. Conclusions: Breast atypia represents a risk factor for invasive cancer and does not necessitate surgical excision. Changes to mammography (digital vs plain film) and biopsy techniques (gauge of needle and use of vacuum-assistance) may lead to detection of atypia which is then 'over-managed'. Current recommendations for annual mammography for 5 years after a diagnosis of epithelial atypia may be overly cautious. We suggest that women with screen detected atypia should be followed up with routine screening appointments.

PO2-17-12

Phase I Trial of alpha-lactalbumin vaccine in high risk operable triple negative breast cancer (TNBC) and patients at high genetic risk for TNBC

Presenting Author(s) and Co-Author(s):

J. Johnson. Cleveland Clinic, Cleveland, Ohio, United States

E. Rhoades. Cleveland Clinic Foundation, United States

H. Levensood. Cleveland Clinic, United States

H. Moore. Cleveland Clinic, United States

M. Kruse. Cleveland Clinic, Cleveland, Ohio, United States

E. Roesch. Cleveland Clinic, Ohio, United States

J. Abraham. NSABP Foundation and Cleveland Clinic, Cleveland, OH, USA, Ohio, United States

B. Elliott. Cleveland Clinic, United States

R. Swartz. Cleveland Clinic, United States

H. Pederson. Cleveland Clinic, Cleveland, Ohio, United States

E. Haury. Cleveland Clinic, United States

A. Ali. Cleveland Clinic, United States

T. Onger. Cleveland Clinic, United States

A. Sciallis. Cleveland Clinic, United States

Z. Al-Hilli. Cleveland Clinic, Ohio, United States

W. Wei. Cleveland Clinic, United States

T. Stappenbeck. Cleveland Clinic, United States

G. Budd. Cleveland Clinic, Cleveland, Ohio, United States

Background:

Triple-negative breast cancer (TNBC) has a poor prognosis and may be associated with germline mutations. α -Lactalbumin (aLA) is expressed in lactating breasts but not at other times or in other tissues. Expression of aLA is found in 70% of TNBC (PMID: 27322324) so could be an immunologic target for TNBC based on the "retired protein hypothesis" (PMID: 31926646).

In pre-clinical studies, vaccination with aLA provided protection from development of autochthonous tumors in transgenic murine models of breast cancer and inhibited growth of established 4T1 transplantable breast tumors in BALB/c mice (PMID: 20512124). Methods: To determine the safety and immunogenicity of aLA, patients with early stage TNBC are being entered in a Phase I trial of aLA with GMP-grade zymosan adjuvant in Montanide ISA 51 VG vehicle. Subjects receive 3 vaccinations given once every 2 weeks. Events of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 are considered dose-limiting toxicities (DLTs). Results:

CTCAE toxicity by dose level is summarized below. All DLTs were injection site reactions, with ulceration and need for incisional drainage representing the grade 3 events. Seven (7) of 10 patients assayed to date have met protocol specified definitions of an immune response based on ELISpot assays to determine frequencies of T cells producing IFN γ and IL-17 in response to recombinant aLA. Assays for an additional 6 patients will be available in September 2023.

Conclusion:

Dose level ≤ 2 appears to be the maximum tolerated dose. Based on immune response,

additional intermediate dose levels may be studied. An additional cohort of patients receiving concurrent anti-PD1 treatment is being accrued. Accrual of patients with BRCA1/2 or PALB2 mutations planning to undergo prophylactic mastectomy is beginning in order to define the toxicity and immunologic effects in this group and to determine whether inflammatory changes from occult lactational foci will be produced. Funding Source: Department of Defense (W81XWH-17-1-0592 and W81XWH-17-1-0593)

Dose Level	aLA Dose (mcg)	Zymosan Dose (mcg)	n Patients	n Grade 0	n Grade 1	n Grade 2	n Grade 3
1	10	10	6		6		
2	100	10	6		5		1
3	500	10	3		2		1
Original 2	100	100	1				1

Worst Toxicity by Dose Level

PO2-18-01

Assessment of Initial Dosing and Dose Management of Sacituzumab Govitecan-hziy (SG) and How Dosing Practices Impact Duration of Therapy (DOT)

Presenting Author(s) and Co-Author(s):

V. Gorantla. University of Pittsburgh Medical Center, United States

E. Alwon. Integra Connect, United States

M. Gart. Integra Connect, United States

J. Li. Integra Connect, United States

S. Blanc. Integra Connect, United States

D. Brenneman. Integra Connect, United States

P. Varughese. Integra Connect, United States

J. Scott. Integra Connect, United States

H. Katzen. Integra Connect, United States

Background: As the Phase 3 ASCENT trial's safety analysis found that a 10m/kg dose of SG resulted in better efficacy than treatment with a lower dose, this examination sought to use real-world data to evaluate how patients (pts) were dosed compared to the recommended starting dose for SG as well as how the starting dose impacted pt DOT.¹ In addition, this assessment sought to understand the rate of dose reductions for pts treated with SG and how the use of dose reductions impacted DOT.

Methods: This assessment utilized the Integra Connect PrecisionQ real-world de-identified database of over 2 million cancer pts across 500 sites of care to evaluate starting dose and rate of dose reduction, as well as whether starting dose and use of dose reductions impacted DOT for pts treated with SG. In analyzing the DOT, pts were required to have had a follow-up of 12 months or greater. The SG pt data utilized reflects treatments through May 31, 2023. Comparisons of proportions were conducted using a two sample two-tailed z-test and compared median DOT using a Wilcoxon Rank Sum test. Descriptive analyses were used to summarize pt demographic statistics.

Results: 433 pts treated with SG were identified with an average age at treatment start of 59.6 (median of 61); 17% identified as Black or African American and 62% identified as White or Caucasian. Of the 433 pts treated with SG, 83% received the recommended starting dose of 10mg/kg, 13% initiated treatment at 7.5mg/kg and the remaining 5% received 5mg/kg or less. Among the 433 pts, 37% had a dose reduction. The rate of dose reductions for those who started at 10 mg/kg was 35% compared to 43% for pts who started at 7.5mg or less ($p > 0.05$). The rate of dose reductions for those who started on 7.5mg/kg were 39% (N = 57) compared to 55% (N = 18) for those who started on 5mg/kg or less ($p > 0.05$). The median DOT among the pts regardless of starting dose was 116 days (N = 336). The median DOT for pts who started on 10mg/kg was 136 days (N = 254) compared to 77 (N = 61) for pts who started on 7.5 mg/kg or less ($p = .012$). The median DOT for pts who started on 7.5mg/kg was 91 days (N = 166) compared to 58 (N = 17) for those who started on 5mg/kg or less. The median DOT for pts who had a dose reduction was 172 days (N = 125) compared to 89 days (N = 190) for those who did not have a dose reduction ($p < 0.001$).

Conclusion: The assessment found that SG-treated pts who received the recommended

starting dose had a longer DOT than those who received a lower starting dose. In addition, dose reductions on SG contributed to a longer time on therapy for pts. These findings suggest using the recommended starting dose for SG and then dose managing via reductions to help keep pts on therapy and delay disease progression. Further evaluation of the impact of starting dose would be needed to understand pt differences in prior lines of therapy and hormonal status to understand how those factors impact DOT.

[1] Rugo, H.S., Tolaney, S.M., Loirat, D. et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. *npj Breast Cancer* 8, 98 (2022). <https://doi.org/10.1038/s41523-022-00467-1>

PO2-18-02

Utilization of Granulocyte Colony-Stimulating Factor (GCSF) in the Management of Patients (pts) on Sacituzumab Govitecan-hziy (SG) and Impact on Duration of Therapy (DOT)

Presenting Author(s) and Co-Author(s):

V. Gorantla. University of Pittsburgh Medical Center, United States

E. Alwon. Integra Connect, United States

M. Gart. Integra Connect, United States

J. Li. Integra Connect, United States

S. Blanc. Integra Connect, United States

D. Brenneman. Integra Connect, United States

E. Genser. University of Pittsburgh Medical Center, United States

P. Varughese. Integra Connect, United States

J. Scott. Integra Connect, United States

H. Katzen. Integra Connect, United States

Background: An examination was conducted to understand the prevalence of neutropenia in pts managed with SG in the real-world setting, as the ASCENT trial demonstrated a 63% rate of neutropenia in those pts treated with SG¹. In addition, an assessment was performed to see whether pts who developed neutropenia on SG received a GCSF and how GCSF use impacted pt DOT on SG.

Methods: This assessment utilized the Integra Connect PrecisionQ real-world de-identified database of over 2 million cancer pts across 500 sites of care to evaluate the prevalence of neutropenia (< 1500 neutrophils) among those who were treated with SG, GCSF utilization among those with neutropenia, and the difference in DOT between neutropenic pts who received a GCSF and those who did not. In analyzing the DOT, pts were required to have had a follow-up of 12 months or greater. The SG pts data utilized reflects treatments through May 31, 2023. Comparisons of median DOT were conducted using a Wilcoxon Rank Sum test. Descriptive analyses were used to summarize pt demographic statistics.

Results: 447 pts treated with SG were identified with an average age at treatment start of 58.5 (median of 60); 15% identified as Black or African American and 69% identified as White or Caucasian. Of the 447 pts treated with SG, 98% (N = 438) developed neutropenia while on therapy. Among those 438 pts who developed neutropenia, 61% received a GCSF and 39% did not. Of the 330 pts with at least 12 months of follow-up, the median DOT was 119.5 days. Among the 204 pts who received a GCSF, the median DOT was 147 days, compared to a median DOT of 97 days for the 126 pts who did not receive a GCSF (p < 0.001).

Conclusion: The DOT for pts treated with SG who received a GCSF was longer than those who did not receive a GCSF while treated with SG. This assessment revealed that approximately 40% of SG treated pts who developed neutropenia did not receive a GCSF. Thus, increasing utilization of GCSFs presents an opportunity to improve management of pts who develop neutropenia while on SG to extend the time on therapy and potentially delay disease progression. These findings warrant further research on the use of prophylactic GCSFs for managing pts who receive SG and suggest further clinical guidance may be needed to provide

best practices for managing pts on SG.

[1] Rugo, H.S., Tolaney, S.M., Loirat, D. et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. *npj Breast Cancer* 8, 98 (2022). <https://doi.org/10.1038/s41523-022-00467-1>

PO2-18-03

Comparison of Provider Adoption of Antibody-Drug Conjugates Among Breast Cancer Patients (pts) and Impact on Duration of Therapy (DOT)

Presenting Author(s) and Co-Author(s):

R. Choksi. University of Pittsburgh Medical Center, United States

V. Gorantla. University of Pittsburgh Medical Center, United States

M. Gart. Integra Connect, United States

S. Blanc. Integra Connect, United States

E. Alwon. Integra Connect, United States

D. Brenneman. Integra Connect, United States

P. Varughese. Integra Connect, United States

J. Scott. Integra Connect, United States

H. Katzen. Integra Connect, United States

Background: An assessment was performed to understand the degree of post-approval provider adoption of two antibody-drug conjugates, fam-trastuzumab deruxtecan-nxki (FTD) and sacituzumab govitecan-hziy (SG), to treat breast cancer in the community oncology setting. In addition, an evaluation was performed to assess pt DOT based on the volume of pts on those therapies treated by each provider. In breast cancer, FTD was initially approved in the U.S. on December 20, 2019, and SG was initially approved in the U.S. on April 22, 2020.

Methods: This assessment used the Integra Connect PrecisionQ real-world de-identified database of over 2 million cancer pts across 500 sites of care to assess SG and FTD treatment use by provider and DOT for those treated with SG and FTD. It included only breast cancer pts treated with SG or FTD who started after the initial approval dates of the respective therapies. In analyzing the DOT, pts were required to have had a follow-up of 12 months or greater, and only monotherapy treated pts were included to rule out any additional confounders. The FTD pts included were treated between December 2019 to May of 2023, whereas the SG pts included were treated between April 2020 to May 2023. Comparisons of proportions were conducted using a two sample two-tailed z-test and compared median DOT using a Wilcoxon Rank Sum Test. Descriptive analyses were used to summarize pt demographic statistics.

Results: 827 pts treated with SG were identified across 376 providers, with an average age at SG treatment start of 60.2 (median of 61); 14% of pts identified as Black or African American and 59% identified as White or Caucasian. Among 827 pts treated with SG across 376 providers, 23% of pts were treated by providers who treated 6 or more pts with SG, which accounted for 6% of all providers. 23% of pts were found to be treated by a provider who used only SG once, which accounted for 56% of all providers. The median DOT among providers who treated 6 or more pts with SG was 168 days (N = 83) compared to 110 days (N = 303) among providers who treated 5 or less pts ($p < 0.01$). The median DOT for all SG pts was 119 days (N = 386). Of the 1438 pts treated with FTD, the average age at FTD treatment start was 62.1 (median of 63), with 8% of pts identified as Black or African American and 54% identified as White or Caucasian. Among 1438 pts treated with FTD across 485 providers, 38% of pts were treated by providers who treated 6 or more pts with FTD, which accounted for 12% of all providers. 14% of pts were found to be treated by a provider who only used FTD once, which accounted for 40% of all providers. The median DOT among providers who treated 6 or more

pts with FTD was 281 days (N = 158) compared to 263 days (N = 234) among providers who treated 5 or less pts ($p > 0.05$). The median DOT for all FTD pts was 269 days (N = 392). The difference in the number of pts treated by a provider who used SG once (23% of 827 pts) vs. the number of pts treated by a provider who used FTD once (14% of 1438 pts) was found to be statistically significant ($p < .01$). The difference in pts treated by a provider who used SG in 6 or more pts (23% of 827 pts) vs. compared to providers who used FTD in 6 or more pts (38% of 1438 pts) was found to be statistically significant ($p < .01$).

Conclusion: A large percentage of providers have only used the respective antibody-drug conjugates once (for SG it was 56% of all providers; for FTD 40%), which suggests an opportunity for greater awareness and guidance around effective therapy use and management of antibody-drug conjugates. Providers who used SG more often (6 or more pts) showed a longer DOT for their SG treated pts compared to those providers who used SG in 5 or less pts. This suggests that the slower adoption of SG and lack of experience across the community oncology provider base may be impacting overall pt DOT on SG.

PO2-18-04

STX-478 is a potentially best-in-class mutant-selective PI3K α inhibitor that demonstrates robust efficacy in ER+ breast cancer models as monotherapy and in combination with standard of care agents

Presenting Author(s) and Co-Author(s):

T. Tieu. Scorpion Therapeutics, United States
L. Buckbinder. Scorpion Therapeutics, Boston, Massachusetts, United States
D. St. Jean. Scorpion Therapeutics, Boston, Massachusetts, United States
S. Manimala. Scorpion Therapeutics, Boston, Massachusetts, United States
G. Dowdell. Scorpion Therapeutics, United States
M. Huff. Scorpion Therapeutics, United States
j. Alltucker. Scorpion Therapeutics, United States
E. Jackson. Scorpion Therapeutics, United States
A. Guzman-Perez. Scorpion Therapeutics, Boston, Massachusetts, United States
D. Stuart. Scorpion Therapeutics, Boston, Massachusetts, United States

Activating mutations in PI3K α are among the most prevalent genetic aberrations in breast cancer. Constitutive signaling of PI3K α is an established oncogenic driver in these cancers, as these mutations are predictors of response to alpelisib, an approved PI3K α inhibitor, which inhibits both wild type and mutant PI3K α . While inhibiting PI3K α has proven to be efficacious, the concomitant inhibition of wild type enzyme in normal tissue results in metabolic dysfunction and ultimately dose-limiting toxicities. Selectively targeting the mutant PI3K α enzyme is expected to inhibit tumor growth while sparing normal tissues, thus increasing the therapeutic index compared to non-mutant selective PI3K α inhibitors. Therefore, we have developed STX-478, an allosteric, CNS penetrant, mutant-selective PI3K α inhibitor.

In a high-throughput viability screen, STX-478 selectively inhibited growth of cell lines with kinase domain and helical domain mutations in PI3K α . In a panel of PI3K α mutant CDX and PDX models, STX-478 provided efficacy that was similar or superior to higher than clinically achievable doses of alpelisib. Robust suppression of pharmacodynamic (PD) markers, pAKT, was observed in tumors, but not in skeletal muscle. Importantly, the efficacy achieved with STX-478 occurred at doses that did not cause metabolic dysfunction, in contrast to alpelisib which caused insulin release and suppressed glucose uptake in skeletal muscle in a 13C glucose tolerance test. Collectively, these data indicate that STX-478 has an expanded therapeutic window to selectively target mutant PI3K α in vivo.

In efficacy studies using human tumor xenograft models, STX-478 caused tumor regressions as a single agent. In multiple advanced ER+ breast cancer PDX models including models that are insensitive to the approved CDK4/6 inhibitor palbociclib, STX-478 combined with standards of care was highly efficacious and well tolerated. In a representative PDX model, STX-478 combined with the ER degrader fulvestrant and palbociclib was well tolerated for > 90 days of dosing in mice and resulted in durable tumor regressions that were superior to STX-478 alone. In conclusion, these data demonstrate STX-478 is a highly efficacious, well tolerated, mutant-specific PI3K α inhibitor that can be combined safely with standards of care in breast cancer and provide the therapeutic benefits of PI3K α inhibition without the side effects associated with inhibiting WT PI3K α . These properties combined with the potential for CNS penetration and

excellent pharmacokinetic profile in higher species make STX-478 a potentially best-in-class mutant-selective PI3K α inhibitor. STX-478 is currently being evaluated in a Phase I clinical trial (NCT05768139).

PO2-18-05

Blocking soluble TNF to improve potency of trastuzumab deruxtecan by increasing internalization and antitumor innate immune response in a resistant HER2-positive breast cancer model

Presenting Author(s) and Co-Author(s):

S. Bruni. Instituto de Biología y Medicina Experimental, United States

F. Mauro. Instituto de Biología y Medicina Experimental, United States

S. Naveiro. Instituto de Biología y Medicina Experimental, United States

R. Cordo-Russo. Instituto de Biología y Medicina Experimental, United States

A. Dupont. Sanatorio Mater Dei, United States

M. María Florencia. Instituto de Biología y Medicina Experimental, United States

R. Schillaci. Instituto de Biología y Medicina Experimental, United States

Background Trastuzumab deruxtecan (T-DXd) administration improves response for patients with HER2-positive metastatic breast cancer (HER2+ BC). Unfortunately, 50% of patients relapse after 2 years. T-DXd resistance mechanisms are being explored. For trastuzumab we have shown that mucin 4 (MUC4) expression is an independent predictor of poor response in HER2+BC patients. MUC4 is upregulated by soluble TNF (sTNF) secreted by the tumor, confers resistance to trastuzumab by hiding its epitope on the HER2, reducing its binding and decreasing anti-tumor phagocytic function. In preclinical models of de novo trastuzumab-resistant tumors, combination of a sTNF blocking agent INB03, (DN), with T-DXd decreases tumor growth compared to T-DXd alone. To disclose the underlying mechanism, we studied whether DN improved internalization of T-DXd in tumor cells and modified the innate immune response to enhance T-DXd antitumor effects in a multiple HER2-targeted therapy-resistant model.

Methods Nude mice bearing HER2+MUC4+ JIMT-1 tumor, primary resistant to trastuzumab, pertuzumab and lapatinib, were treated with IgG 5 mg/kg, T-DXd 5 mg/kg (T-DXd 5), 2.5 mg/kg (T-DXd 2.5) or 1.25 mg/kg (T-DXd 1.25), DN 10 mg/kg or the combined therapies. T-DXd and IgG were administered i.v. on days 0, 7 and 14. DN was administered i.p. twice a week for 3 weeks. Tumor growth was monitored. Mitotic figures/field (mean) were analyzed in H&E tumor sections. Tumor-infiltrating macrophages were studied by flow cytometry. IFN γ was determined in tumor extracts by ELISA. Internalization of T-DXd in JIMT-1 cells was studied in a S1 Incucyte along 18h by Fab-rhodo red labeling.

Results T-DXd dose-response curves showed inhibition in tumor growth of 83%, 61% and 37% for T-DXd 5, 2.5 and 1.25 mg/kg treatment respectively compared with IgG-treated tumors. DN alone exhibited no antitumor activity. T-DXd+DN increased the antitumor effect by 10%, 33% and 97% for T-DXd dose of 5, 2.5 and 1.25 mg/kg respectively. Tumor growth inhibition of T-DXd 5 was similar to combination of T-DXd1.25+DN. Addition of DN did not have toxicity. DN increases IFN γ production in the TME of T-DXd treated tumors vs T-DXd alone and promoted macrophage recruitment to the tumor bed and polarization to the antitumor M1-like phenotype. Histopathological analysis of the tumor showed a significant decrease in proliferation in all the combined and in the T-DXd 5mg/kg (2.8-3.7 mitotic figures/field) vs IgG (6.0 mitotic figures/field). In vitro, JIMT-1 cells treated with DN internalized 40% more T-DXd than its vehicle-treated counterparts.

Conclusions Neutralizing sTNF with DN enhances T-DXd effect in a multiple HER2 targeted therapy resistant model of MUC4 expressing HER2+ BC. Combination of DN with T-DXd increases tumor response at all dose levels tested. The largest effect was seen at lower doses (T-DXd 1.25+DN), which mimicked the effect of 4 times the dose of T-DXd alone, suggesting significant synergy with DN as dose of T-DXd decreases. Combination of DN with T-DXd in MUC4 expressing HER2+ BC improves response to T-DXd alone by increasing T-DXd internalization and improving anti-tumor innate immune responses in the TME without increasing toxicity. The results suggest this combination should be investigated in clinical trials in patients who have MUC4 expressing tumors when T-DXd is started or become resistant to T-DXd therapy.

PO2-18-06

Targeting fibroblast growth factor receptor (FGFR1) expression through G-quadruplex stabilization inhibits metastatic breast cancer

Presenting Author(s) and Co-Author(s):

M. Safdar. Purdue University, United States

H. Lin. Purdue University, United States

S. Dagher. Purdue University, United States

J. Dickerhoff. Purdue University, United States

M. Ayers. Purdue University, United States

L. Solorio. Purdue University, United States

D. Yang. Purdue University, United States

M. Wendt. Purdue University, United States

S. Akhand. Abbvie, United States

Metastatic breast cancer (MBC) is the most advanced stage of breast cancer. Our understanding of the molecular mechanisms which drive MBC remain incomplete. Epithelial to mesenchymal transition (EMT) and mesenchymal to epithelial transition (MET) promote drug resistance and metastasis. It has been reported that fibroblast growth factor receptor 1 (FGFR1) plays a key role during the EMT:MET cycle. Furthermore, FGFR1 is amplified in 13% of primary and 20% of metastatic breast cancer patients. Therefore, optimizing inhibition of FGFR1 is crucial for the therapeutic targeting of the late stage breast cancer. First, we examined the efficacies of FGFR kinase inhibitors in the murine based dormant 4T07 tumor model. Inhibition of FGFR kinase activity leads to tumor growth inhibition but fail to eradicate dormant breast cancer cells. Therefore, we explored broader approaches to inhibit FGFR1 expression in addition to blockade of its kinase activity. G-quadruplex (G4) structures are secondary DNA structures commonly found upstream of transcriptional start sites (TSS) of oncogenes restricting their expression. Consequently, pharmacological stabilization of G4 structures within the promoters of cancer-related genes via use of small molecules has emerged as a promising therapeutic approach in cancer. Results herein demonstrate that the proximal promoter of FGFR1 contains sequences that form G4. Circular dichroism was used to verify formation of G4 in the FGFR1 proximal promoter. Importantly, use of the G4-binding compound CX-5461 stabilized the FGFR1 G4 structure, blocked the transcriptional activity of the FGFR1 proximal promoter and decreased FGFR1 expression. Therefore, we implemented the G4 stabilizers in FGFR1 expressing and metastatic drug-resistant BC cell lines. This approach results in dramatic downregulation of FGFR1 at the protein level after treatment with the G4 stabilizer. G4 stabilizing agents also interfere with ectopic FGFR1 expression and EMT-driven FGFR1 expression. Importantly, use of the G4-targeting compound CX5461 effectively blocked FGFR1 expression and inhibited FGFR1 downstream signaling, resulting in eradication of dormant breast cancer cells. Finally, in vivo application of CX5461 reduced FGFR1 expression, blocked pulmonary tumor formation and prolonged animal survival. In conclusion, consistent with the clinical observations our evaluation of FGFR kinase inhibitors validates the resistance to FGFR kinase inhibitors in MBC. Our findings indicate that targeting FGFR1 expression through G4 stabilization may be a potential strategy for MBC.

PO2-18-07

Ultrasound – guided Interstitial Laser therapy for Stage I Breast Cancer: a phase 2 trial

Presenting Author(s) and Co-Author(s):

D. Matsumoto. Hospital Israelita Albert Einstein, Sao Paulo, Sao Paulo, Brazil

s. Bromberg. hospital Israelita Albert Einstein, United States

M. corpa. Hospital Israelita Albert Einstein, United States

R. Garcia. Hospital Israelita Albert Einstein, United States

G. Mariotti. Hospital Israelita Albert Einstein, United States

M. Rudner. Hospital Israelita Alver Einstein, United States

A. Waitzberg. Universidade Federal de São Paulo, United States

A. Nazário. Universidade Federal de São Paulo, United States

G. Facina. Universidade Federal de Sao Paulo, United States

Background: Screening programs are changing the scope of breast cancer, with a growing number of patients diagnosed at a nearly stage. The current standard treatment (breast conservation and radiation therapy) offers an excellent prognosis for these patients. Besides tumor removal, other techniques can be used to destroy a mass in place. A range of minimally invasive techniques holds promise on local breast tumor ablation (i.e. thermotherapy, cryotherapy, and irreversible electroporation). Previous studies with Interstitial laser thermotherapy (ILT) for breast cancer report mean ablation rates between 33% to 87%. Most common cited causes for failure are equivocal tumor size estimation, inadequate technique and the learning curve. Objective: Improve the ILT technique and achieve better ablation rates through the evaluated procedure. Methods: A prospective study with 15 patients with Stage I invasive breast cancer, presented as a unique lesion as inclusion criteria was conducted. MRI and US were used to estimate the primary tumor volume and rule out multicentric/ multifocal disease. ILT ablation was performed using an Echolaser unit (Elesta) through percutaneous laser optical fibers with a US-guided insertion in the lesion center. All procedures were performed under local anesthesia and sedation. The post procedure image reevaluation included an immediate US after the ablation and a new MRI about 3 hours after the procedure. The definitive proposed surgical treatment was carried out 8-13 days after the ILT ablation. Results: Eighteen patients were included in the study, of whom 14 (with 15 lesions) completed the protocol. The mean tumor size measured by MRI was 13.7 (4-20) mm.

The mean treatment time was 10.1 minutes and all patients went home the same day, reporting only mild (78%) or moderate (22%) pain, controlled with analgesics.

The mean ablation index, evaluated by H&E and CK8/18, was 61,5% (0 -93%) and when only tumors under 15 mm were considered the mean ablation index was 75% (30%-93%).

The MRI performed after ablation procedure showed a large area of edema around the clip in all cases. The sensitivity and specificity to detect residual tumors were 1.0 and 0.84, respectively, when the residual tumors were larger than 15% of the original tumor size .
Conclusions: These preliminary results suggest that laser therapy can eliminate viable neoplastic tissue in vivo. To achieve better results, standardization in patient selection, power and energy applied, should be considered.

There are several advantages of ILT for breast cancer treatment, including preserving the structure and function of breast, no bleeding, no scarring and no radiation. More studies refining the technique should be conducted to allow the implementation of ILT as an alternative to surgical treatment in early breast cancer.

PO2-18-08

Identification of novel genetic/therapeutic vulnerabilities in breast cancer

Presenting Author(s) and Co-Author(s):

X. Wang. Mayo Clinic, Rochester, Minnesota, United States

M. Emch. Mayo Clinic, Rochester, Minnesota, United States

L. Voll. Mayo Clinic; College of Saint Benedict & Saint John's University, United States

R. Russell. Mayo Clinic; Hillsdale College, United States

E. Rodman. Mayo Clinic, United States

P. Beer. Step Pharma, United States

J. Hawse. Mayo Clinic, Rochester, Minnesota, United States

Background: Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among women worldwide. Triple negative breast cancer (TNBC) is an aggressive subtype that is defined by the lack of expression of estrogen and progesterone receptors in the absence of HER2 amplification or overexpression. TNBC represents 15-20% of all breast cancers and occurs more frequently in young premenopausal women. TNBC often ends with a poor clinical outcome due to high histological grade, rapid recurrence in many patients combined with few treatment options. These realities highlight the urgent need to identify novel therapeutics vulnerabilities that can be leveraged to improve TNBC patient outcomes.

Methods: We utilized the publicly available DepMap and Kaplan Meier datasets to identify essential genes that were unique to TNBC cells and whose expression levels were associated with worse patient outcomes. siRNA based approaches were used to confirm the relevance of top hits in mediating cancer cell phenotypes including viability, cell-cycle profiles and induction of apoptosis among others. A novel drug currently being developed was identified for the top hit in these studies and was subsequently employed in multiple in vitro approaches to characterize the mechanisms of action in TNBC as well as initial efficacy studies using clinically relevant ex vivo patient derived models.

Results: Using the DepMap database, we interrogated genome-wide sgRNA knockout screens conducted in over 40 breast cancer cell lines to identify specific genes whose expression was required for cell viability in TNBC cells, but not other breast cancer cell lines. This endeavor identified 6 genes (CTPS1, HUS1, PRKRA, RAD1, RAD9A and RHOA) that were preferentially essential in TNBC cells. Further profiling of these genes revealed that CTPS1 expression is higher in cancer relative to normal tissue and that its expression is further upregulated in chemotherapy- and PARPi-resistant models. Knockdown of CTPS1 in TNBC cells was shown to decrease cell proliferation and viability with no effects observed in estrogen receptor+ cell lines. Using a first-in-class, highly selective and orally bioavailable CTPS1 inhibitor (STP938) developed by Step-Pharma, we identified IC50s in the low nM range for many TNBC cell lines, including cell models that are resistant to existing standard-of-care therapies. Inhibition of CTPS1 was shown to arrest cells in S phase.

Conclusions: Our studies have identified CTPS1 as an essential gene in TNBC. CTPS1 encodes an enzyme responsible for the catalytic conversion of UTP (uridine triphosphate) to CTP (cytidine triphosphate), an essential step in the biosynthesis of nucleic acids. These findings are timely in light of the recent and ongoing development of the first-in-class CTPS1 inhibitor, STP938, for which first-in-human studies are underway for refractory B- and T-cell

lymphomas. Based on our initial studies using this drug, we provide pre-clinical evidence of its efficacy in multiple models of primary and advanced TNBC. Efforts are currently underway to move this work toward a clinical trial for TNBC patients.

PO2-18-09

A phase 3 randomized open-label study of extended adjuvant therapy with camizestrant vs standard endocrine therapy in patients with ER+/HER2- early breast cancer and an intermediate or high risk of recurrence (CAMBRIA 1)

Presenting Author(s) and Co-Author(s):

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

N. Niikura. Tokai University School of Medicine, Isehara-shi, Isehara, Kanagawa, Japan

P. Rastogi. UPMC Hillman Cancer Center and NRG Oncology, Pittsburgh, Pennsylvania, United States

K. Saini. Fortrea Inc., Durham, NC, USA, United States

I. Gioni. Late Development Oncology R&D, AstraZeneca, Cambridge, UK, United Kingdom

T. Klinowska. AstraZeneca, Cambridge, United Kingdom

I. Mayer. Late Development Oncology R&D, AstraZeneca, Gaithersburg, NJ, USA, United States

M. Stuart. Late Development Oncology R&D, AstraZeneca, Cambridge, UK, United Kingdom

E. Syta. Late Development Oncology R&D, AstraZeneca, Toronto, Canada, United States

A. Walding. Late Development Oncology R&D, AstraZeneca, Cambridge, UK, United Kingdom

T. Bachelot. Medical Oncology, Centre Léon Bérard, Lyon, France

Background: Definitive locoregional (surgery \pm radiotherapy) and standard adjuvant endocrine therapy (ET) (\pm chemotherapy or cyclin-dependent kinase 4/6 inhibitor [CDK4/6i]) can achieve cure in many patients (pts) with estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) early breast cancer (BC). Nevertheless, a significant proportion of pts with stage I-III disease will experience recurrence to metastatic, incurable disease (5- and 10-year cumulative incidences of recurrence of 8.3% and 14.0%, respectively). There is evidence that incorporating a more effective endocrine therapy after 2 years of standard adjuvant ET can result in clinical benefit for high-risk individuals.

Camizestrant is a next-generation oral selective ER degrader and pure ER antagonist. In SERENA-2, camizestrant 75 mg and 150 mg significantly prolonged progression-free survival vs fulvestrant in postmenopausal women with ER+/HER2- advanced BC with disease recurrence or progression after ET.

The CAMBRIA-1 study (NCT05774951) is evaluating the potential of extended adjuvant therapy with camizestrant to improve outcomes in pts with ER+/HER2- early BC with an intermediate or high risk of recurrence after definitive locoregional therapy and standard adjuvant ET.

Trial design: This phase 3 randomized, open-label study is enrolling women (pre- or postmenopausal) and men with ER+/HER2- (immunohistochemistry 0/1+/2+/in situ hybridization-negative) early BC who have completed definitive locoregional therapy and standard adjuvant ET (\pm CDK4/6i) for ≥ 2 and ≤ 5 years (+ 3 months) without disease recurrence. Pts must be considered at intermediate or high risk of recurrence based on clinical, biological, and genomic factors. Pts are randomized (1:1) to continue standard ET of the investigator's choice (tamoxifen or aromatase inhibitor \pm luteinizing hormone-releasing hormone [LHRH])

agonist) or camizestrant ± LHRH agonist for up to 60 months. The primary endpoint is invasive BC-free survival (STEEP 2.0 criteria). Secondary endpoints include invasive disease-free survival and distant relapse-free survival (STEEP 2.0 criteria), overall survival, safety, and health-related quality of life. Primary endpoint analysis will use a stratified log-rank test adjusting for stratification factors, assuming a two-sided significance level of 5%. Approximately 4300 pts will be randomized; enrollment is ongoing.

Clinical trial identification: NCT05774951

Editorial acknowledgment: Writing assistance was provided by Alison Lovibond, PhD, of BOLDSCIENCE Inc., funded by AstraZeneca.

Legal entity responsible for the study: AstraZeneca

Funding: This study was supported by AstraZeneca.

PO2-18-11

Short-term Pre-Operative Durvalumab (MEDI 4736) in early small triple negative breast cancer patients (POP-Durva)

Presenting Author(s) and Co-Author(s):

J. Ribeiro. Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France/Paris-Saclay University, Gustave Roussy, INSERM U981, PRISM Center, F-94805, VILLEJUIF France, United States

I. Pic. Paris-Saclay University, Gustave Roussy, INSERM U981, PRISM Center, F-94805, VILLEJUIF France, United States

Q. Blampey. Paris-Saclay University, Gustave Roussy, INSERM U981, PRISM Center, F-94805, VILLEJUIF France/ Paris-Saclay University, Centrale Supélec, Laboratory of Mathematics and Computer Science '6 (MICS), Gif-sur-Yvette, 91190 France, United States

E. Rassy. Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France, United States

N. Ibrahimi. Gustave Roussy, Direction de la Recherche Clinique, Bureau Biostatistique and Epidémiologie, F-94805, VILLEJUIF France, United States

L. Salabert. Institut Bergonié, Bordeaux, France, United States

O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France

M. Arnedos. Department of Medical Oncology, Institute Bergonié, Bordeaux, France, United States

S. Dogan. Paris-Saclay University, Gustave Roussy, INSERM U981, PRISM Center, F-94805, VILLEJUIF France, United States

K. Serhal. Gustave Roussy, Direction de la Recherche Clinique, Bureau Projets et Promotion, F-94805, VILLEJUIF France, United States

C. Mahaut. Gustave Roussy, Direction de la Recherche Clinique, Bureau Projets et Promotion, F-94805, VILLEJUIF France, United States

A. Viansone. Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France, United States

S. Laghouati. Gustave Roussy, Direction de la Recherche Clinique, Unité Fonctionnelle de Pharmacovigilance, F-94805, VILLEJUIF France, United States

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

C. Dutertre. Paris-Saclay University, Gustave Roussy, INSERM U981, PRISM Center, F-94805, VILLEJUIF France/Institut National de la Santé Et de la Recherche Médicale (INSERM) U1015, Equipe Labellisée—Ligue Nationale contre le Cancer, F-94805, VILLEJUIF France, United States

M. Lacroix-Triki. Gustave Roussy, Villejuif, France

J. Scoazec. Department of Pathology, Gustave Roussy Cancer Campus, Villejuif, France; Faculty of Medicine, Paris-Sud University, Kremlin-Bicêtre, France, United States

L. Derosa. Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France/Paris-Saclay University - Institut National de la Santé Et de la Recherche Médicale (INSERM) U1015, Equipe Labellisée—Ligue Nationale contre le Cancer, F-94805, VILLEJUIF France, United States

L. Zitvogel. Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France/Paris-Saclay University - Institut National de la Santé Et de la Recherche Médicale (INSERM) U1015, Equipe Labellisée—Ligue Nationale contre le Cancer, F-94805, VILLEJUIF France, United States

C. Balleyguier. Gustave Roussy, Université Paris-Saclay, Department of Radiology, Villejuif, F-94805, France, United States

N. Bercovici. Paris-Saclay University, Gustave Roussy, INSERM U981, PRISM Center, F-94805, VILLEJUIF France/12.13. Université Paris Cité, Institut Cochin, INSERM, CNRS, Paris, 75014 France, United States

P. Courneade. Paris-Saclay University, Centrale Supélec, Laboratory of Mathematics and Computer Science 6 (MICS), Gif-sur-Yvette, 91190 France, United States

S. Michiels. Gustave Roussy, Villejuif, France, United States

F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France

Background: Immune checkpoint inhibitors (ICIs) are one of the major therapeutic advancements in cancer treatment. Anti-programmed cell death protein 1 (Anti-PD1)/PD-L1 ICIs have improved progression-free survival in patients with metastatic triple negative breast cancer (TNBC) and pathologic complete response (pCR) and event-free survival in patients with early TNBC. Nevertheless, some patients treated with anti-PD(L)1 ICIs experience recurrence or do not achieve sustained clinical benefit. In addition, very interesting data show the existence of a subgroup of patients with exceptional tumour responses to monotherapy with anti-PD(L)1 ICIs. These exceptional responses are observed in various tumour types, such as colorectal or breast cancer. Although in colorectal cancer, the determinants for this extreme sensitivity to immunotherapy treatment are identified (existence of MSI) in breast cancer, this is not the case. There is still a lack of knowledge about predictive biomarkers and mechanisms of action for ICIs. **Trial Design:** POP-Durva (NCT05215106) is a prospective, one-arm-only study aiming at determining the pCR rate after two administrations of Durvalumab monotherapy in patients with stage I TNBC (ER < 1%, PR < 1%, HER2 negative) and TILs ≥ 5%, eligible for short-term treatment with durvalumab. Study treatment consists of two administrations of intravenous Durvalumab monotherapy, 10mg/kg, at two weeks intervals. After study treatment, patients will receive a standard treatment strategy (surgery or neoadjuvant systemic treatment) as per physician choice. The primary endpoint is the pCR rate after treatment with Durvalumab, defined as the absence of invasive disease in the breast and negative axillary nodes (ypT0/ypTis ypN0). Assessment of the primary endpoint will be performed at the surgery or at the biopsy at the end of treatment) for patients undergoing neoadjuvant treatment. For patients in whom neoadjuvant therapy is the first standard treatment strategy (i.e. after study treatment) a breast ultrasound-guided biopsy is mandatory at the end of the treatment visit. If the biopsy-proven residual disease is demonstrated, patients can receive standard neoadjuvant therapy at the discretion of the treating investigator. Patients with biopsy-proven residual disease will be considered as having no pCR. Those with a complete response may proceed directly to surgery. The expected pCR rate with Durvalumab monotherapy is 20%. The sample size of 195 patients will allow us to estimate this expected pCR rate with a 95% confidence interval of a precision of 6.2%. Secondary objectives are objective response rate and safety. Exploratory objectives are to: a. describe immune cell dynamics associated with exceptional responses to ICI (using spectral cytometry analysis), b. describe somatic genetic contributions to the determination of immune responsiveness (using whole exome sequencing (WES) and in a subset of patient's single-cell RNA-seq), c. characterize tumour cells – immune cells' interaction/spatial distribution (using imaging mass cytometry), d. explore the association between gut microbiome composition/signatures predictive of response to ICI (using 16s rRNA

sequencing) and e. identify predictive tissue/blood-based biomarkers of response and to anti-PD(L)1 ICIs therapy. A total of two dedicated FFPE samples and two fresh biopsies will be collected at the time of inclusion and at the end of treatment biopsy or on the surgical specimen. In addition, we will collect stool samples pre and at the completion of all Durvalumab treatments and blood samples at the time of inclusion, during treatment (before each Durvalumab administration) and at the end of treatment for serum and plasma extraction and whole blood to serve as a control for WES.

PO2-18-12

Updated Results of a Phase II Study: Neoadjuvant Inetetamab Combined with Pertuzumab, Paclitaxel and Carboplatin for Locally Advanced HER2-Positive Breast Cancer

Presenting Author(s) and Co-Author(s):

Y. Chai. Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China, United States

J. Liu. Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China, United States

M. Jiang. Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China, United States

M. He. Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China Country: China (People's Republic), United States

X. Wang. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

Y. Wang. Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China., United States

X. Yang. Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China., United States

J. Wang. Associate Chief Surgery, Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China., United States

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

Q. Li. Cancer Hospital Chinese Academy of Medical Sciences, United States

Background:

Inetetamab is a neotype HER2-targeted monoclonal antibody with amino acids modified Fc segment which optimizes the antibody-dependent cellular cytotoxicity effect. However, robust evidence evaluating the combination of inetetamab combined with pertuzumab, paclitaxel and carboplatin (TCbIP) for neoadjuvant therapy is still lacking. This study aimed to evaluate the efficacy and safety of TCbIP as a neoadjuvant therapy for patients with locally advanced HER2-positive breast cancer. We now present the updated results of this trial.

Methods:

This phase II trial included female patients with histologically confirmed stage IIA to IIIC HER2-positive primary invasive breast cancer. Eligible patients received TCbIP treatment every three weeks for a maximum of six cycles followed by surgery. The primary endpoint was pathologic complete response (pCR, ypT0/is ypN0) rate. Key secondary endpoints included near pCR (npCR, residual breast disease < 1cm) rate, objective response rate (ORR) and safety.

Results:

From November 2021 to July 2023, 40 patients were enrolled in the trial. One patient received one cycle of the study treatment but was lost to follow-up without surgery, and five patients received one cycle of the study treatment and were still undergoing treatment, leaving 34 patients in the intention-to-treat (ITT) population. Among these 34 patients (82.4% in stage III), 22 patients completed the study treatment and surgery (per-protocol [PP] population) and 12 patients were still undergoing neoadjuvant treatment. The ORR was 91.2% (31/34) in the ITT population and 86.4% (19/22) in the PP population. Among the 22 patients in the PP population, 12 patients (54.5%) achieved pCR, and 18 patients (81.8%) achieved npCR. The pCR rates for patients with hormone receptor (HR) negative and positive tumors were 80.0% (8/10) and 33.3% (4/12), respectively. The most common grade ≥ 3 adverse event was neutropenia (17.6%). No significant reduction in the left ventricular ejection fraction was observed in any patient.

Conclusions:

Neoadjuvant therapy with TCbIP demonstrated promising efficacy and manageable toxicity in patients with HER2-positive locally advanced breast cancer.

Registration number: NCT05749016 (www.clinicaltrials.gov).

PO2-19-01

A Single-Arm Prospective Study of the Neurocognitive Changes Occurring in Breast Cancer Patients on Aromatase Inhibitors. Is There a Difference Between Objective and Perceived Neurocognition?

Presenting Author(s) and Co-Author(s):

P. Ashok Kumar. SUNY Upstate Medical University, Syracuse, New York, United States

E. McDowell. SUNY Upstate Medical University, United States

A. Bubb. SUNY Upstate Medical University, United States

D. Huang. SUNY Upstate Medical University, United States

S. Sperry. SUNY Upstate Medical University, United States

S. Benjamin. SUNY Upstate Medical University, United States

A. Sivapiragasam. SUNY Upstate Medical University, United States

Background: Estrogen (ER) and Progesterone (PR) receptors are rich in regions of the brain involved in cognitive functions, like the hippocampus and cerebral cortex. Animal models have shown that estradiol regulates neurocognition and plays an important role in the normal brain development. Hormone positive (HR+) breast cancers (BC) comprise 70% of the disease and the standard of care in the post-menopausal group is the use of Aromatase Inhibitors (AI) for at least 5 years. While “chemo brain” is a well-recognized term, neurocognitive changes from estrogen inhibition by AI have not been clearly defined. As neurocognition is multi-faceted, information on specific aspects affected by AI use is unclear. We hope to answer this through our trial. Design: The study is a single arm, self-controlled prospective observational cohort study in which, post-menopausal BC patients who are to be started on AIs will undergo a battery of neurocognitive tests just before starting AI, at 6 months and at 12 months after being on AI. The changes at 6 and 12 months will be compared to baseline. The tests will involve objective [Hopkins verbal learning test revised (HVLТ), Controlled Oral Word Association Test from Multilingual Aphasia Examination, Trial Making Test A and B, and Recall and Recognition of Word List encoded from the HVLТ] and subjective/patient-reported [The Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog)] components. Tests for anxiety [Generalized Anxiety Disorder (GAD)–7], depression [Patient Health Questionnaire (PHQ)-9] and working memory (Working Memory Tasks from the Wechsler Adult Intelligence Scale) will also be assessed. While the objective tests involve providing patients with specific instructions and asking them to complete the tasks, the FACT Cog questionnaire uses a self-reported 37-item questionnaire enabling assessment of their perceived symptoms. The tests have been summarized in the table. Eligibility criteria: ER/PR+ post-menopausal BC and DCIS patients who are English speaking and are planning to start AIs will be included. Patients who have received hormonal therapy or chemotherapy in the past, those who are scheduled to receive chemotherapy, those who have undergone Whole brain Radiation therapy (RT), those with a premenopausal status, and those having comorbid conditions that could affect cognitive functioning (like any form of dementia or brain metastasis) will be excluded. Specific aims: Our aim is to see if there are progressive neurocognitive changes compared to an age-appropriate baseline and to see if changes to both objective and perceived cognitive changes occur over the course of AI use, in post-menopausal HR+ BC patients. Statistical methods: The T-test and McNemer test will be used. The normal values provided from the test may be used as a standard to justify normal or abnormal values from the collected data. Therefore, a percentage of normal (or abnormal) subjects in each time point can be derived and compared using the McNemar's test. Present accrual and target accrual: 4 patients have been accrued as of June

2023 with a target accrual of 80 patients [80% power to detect a significant change, at a p of 0.05]. Contact information for people with a specific interest in the trial: Dr Abirami Sivapiragasam (abisiva2019@yahoo.com), Dr Sam Benjamin (benjamis@upstate.edu), Dr Prashanth Ashok Kumar (ashokkup@upstate.edu), Amy Bubb (bubbam@upstate.edu).
 Summary of the neurocognitive tests employed in the trial.

S No	Test
Objective	
1	HVLT
2	Controlled Oral Word Association Test from the Multilingual Aphasia Examination
3	Trail Making Test A and B
4	Recall and Recognition of Word List encoded from the HVLT
Subjective	
1	The FACT-Cog questionnaire
Anxiety/Depression	
1	GAD7
2	PHQ9
Memory	
1	Digit Span and Letter-Number Sequencing subtests - Working Memory Tasks from the Wechsler Adult Intelligence Scale – Fourth Edition

PO2-19-02

NRG-BR009: Phase III Trial Evaluating Addition of Adjuvant Chemotherapy to Ovarian Function Suppression + Endocrine Therapy in Premenopausal Women with pN0-1, HR+/HER2- Breast Cancer and Oncotype Recurrence Score ≤ 25 (OFSET)

Presenting Author(s) and Co-Author(s):

E. Mamounas. NSABP Foundation and Orlando Health Cancer Institute, Orlando, FL, USA, Windermere, Florida, United States

G. Tang. NRG Oncology Statistics and Data Management Center Department of Biostatistics, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

S. Puhalla. UPMC Hillman Cancer Center, United States

S. Swain. Georgetown University Medical Center, Lombardi Comprehensive Cancer Center and MedStar Health, Washington, DC, USA, United States

P. Ganz. UCLA Jonsson Comprehensive Cancer Center, and UCLA Fielding School of Public Health, Los Angeles, California, United States

N. Henry. University of Michigan Medical School, United States

R. Cecchini. University of Pittsburgh, Pittsburgh, Pennsylvania, United States

S. Reid. Vanderbilt-Ingram Cancer Center, United States

P. Rastogi. NSABP/NRG Oncology and UPMC Hillman Cancer Center/University of Pittsburgh, United States

C. Geyer. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

J. White. Ohio State University, Columbus, Ohio, United States

A. Clark. University of Pennsylvania, United States

T. Haddad. Mayo Clinic, Rochester, Minnesota, United States

G. Vidal. The West Clinic, Germantown, United States, United States

N. Wolmark. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

Background: Identifying pts with HR-positive/HER2-negative breast cancer (BC) who benefit from adjuvant chemotherapy (ACT) has been a major research focus over the past 20 years. Development and clinical application of genomic classifiers such as the 21-gene recurrence score (RS) has contributed to the biologic understanding of BC and has refined pt selection for ACT. The TAILORx and RxPONDER clinical trials demonstrated that RS identifies many postmenopausal pts with node-negative and node-positive BC and RS < 25, who do not benefit from the addition of ACT to endocrine therapy (ET). However, both trials also showed that certain subsets of premenopausal pts (node-negative/high clinical risk/RS 16-20, node-negative/RS 21-25, and node-positive/RS < 25) benefited from the addition of ACT to ET. Most premenopausal pts in these two trials did not receive ovarian function suppression (OFS) as part of their ET regimen. Given the observed benefit from OFS in high-risk premenopausal pts with HR-positive/HER2-negative BC in the SOFT and TEXT trials, many questioned whether all or part of the observed ACT benefit in the TAILORx/RxPONDER trials may have been the result of chemotherapy-induced OFS. To address this question, OFSET is a Phase III, multicenter clinical trial evaluating the addition of ACT to OFS+ET vs. OFS+ET alone. Methods: We hypothesize that the addition of ACT to OFS+ET is superior to OFS+ET in improving invasive breast cancer-free survival (IBCFS) among premenopausal, early-stage BC pts with

HR-positive/HER2-negative tumors, and a 21-gene RS between 16-25 (for pN0 pts) and 0-25 (for pN1 pts). Secondary objectives include invasive disease-free survival (IDFS), overall survival (OS), distant recurrence-free interval (DRFI), breast cancer-free interval (BCFI), and health-related quality of life (HRQOL). Eligible pts must be node-negative with RS 16-20 (plus high clinical risk), or RS 21-25, or have 1-3 positive nodes with RS < 25. Stratification is by nodal status/RS status (pN0 RS 16-25 vs pN1 RS 0-15 and pN1 RS 16-25), intent to receive CDK4/6 inhibitor (yes; no), and age (18-39 vs ≥40). Pts are randomized after surgery to either OFS+ET or ACT followed by OFS+ET. ET is an aromatase inhibitor per investigator discretion, but tamoxifen is allowed if pts do not tolerate the AI or if OFS is incomplete. Radiation therapy will be administered per investigator discretion according to protocol guidelines. The HRQOL sub-study will assess differences in severe menopausal symptoms, measured by the FACT ESS-19 score, between the arms, as well as increased pain severity (PROMIS) during ACT+OFS+ET compared to OFS+ET. Blood and tumor specimens will be collected for future research. The accrual of 3,960 pts is anticipated to be completed in seven years and seven mos. Based on data from NSABP B-28 and RxPONDER, the 5-year IBCFS of pN1 pts on the ACT+OFS+ET arm is estimated at 92.3%. Based on data from TAILORx, the 5-year IBCFS of pN0 pts on the ACT arm is ~95%. Assuming 56% of the pts to be pN0 and 44% pN1, a 0.5% annual loss-to-follow-up rate, the definitive analyses to detect a hazard ratio: 0.75 with ACT+OFS+ET vs. OFS+ET, with one-sided alpha of 0.025 and 80% power will require 380 IBCFS events, which are expected to occur ~11 years after study initiation. The OFSET study is expected to be activated in the third quarter of 2023. Current accrual (06-19-2023) is 0/3,960 Support: U10CA180868, U10CA180822, UG1CA189867, U24CA196067. NCT05879926.

PO2-19-03

Phase 2 study of response-guided neoadjuvant sacituzumab govitecan in patients with localized breast cancer (NeoSTAR)

Presenting Author(s) and Co-Author(s):

L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

A. Garrido-Castro. Dana-Farber Cancer Institute, and Harvard Medical School, Brookline, Massachusetts, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Tung. Beth Israel Deaconess Medical Center, Boston, United States

R. Abelman. Mass General Cancer Center/Dana-Farber Cancer Institute, Boston, Massachusetts, United States

L. Ryan. Cancer Center, Massachusetts General Hospital, United States

M. Moran. Dana-Farber Cancer Institute, United States

E. Mittendorf. Dana Farber Cancer Institute, Boston, Massachusetts, United States

L. Ellisen. Massachusetts General Hospital, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background: Optimizing treatments for localized breast cancer is key to preventing metastatic recurrences and reducing mortality. Sacituzumab Govitecan (SG) is a novel antibody-drug conjugate in which the topoisomerase 1 inhibitor SN-38 (the active metabolite of irinotecan) is coupled to a humanized monoclonal antibody targeting the antigen Trop-2, which is highly expressed in triple negative breast cancer (TNBC). SG is FDA approved for patients with metastatic hormone receptor-positive (HR+) and TNBC. However, efficacy in localized BC is not known. The NeoSTAR clinical trial is evaluating SG in the neoadjuvant (NA) setting for participants with localized breast cancer. Cohort A1 evaluating NA SG monotherapy in localized TNBC is completed, and now cohorts A2 (SG + pembrolizumab (P) for TNBC), B1 (SG monotherapy for HR+ BC), and C (SG + P for HER2- inflammatory breast cancer (IBC)) are enrolling.

Trial design: This is a single-arm phase II study of NA SG or SG + P with multiple cohorts across different breast cancer subtypes. In all cohorts, SG is administered via an IV infusion on days 1 and 8 of each 21-day cycle at a starting dose of 10 mg/kg for 4 cycles. For cohorts A2 and C, pembrolizumab is given on day 1 of each cycle. For A2 and B1, after 4 cycles, participants who have biopsy-proven residual disease will have the option to receive additional standard NA therapy at the discretion of the treating physician and subsequently proceed to surgery. Those with a complete response on imaging may proceed directly to surgery. If pathological complete response (pCR) is achieved after 4 cycles of SG + P, participants on A2 will remain on study and receive adjuvant weekly paclitaxel and carboplatin for 12 weeks along with continuation of P to complete a total of one year of the PD-1 inhibitor; participants on B1 will receive adjuvant therapy at the discretion of the treating physician, with the option to continue P to complete a total of one year. On cohort C, after 4 cycles of SG + P, dose-dense doxorubicin + cyclophosphamide + P for 4 cycles will be given before considering surgery. A baseline research biopsy is required for all cohorts, as well as tissue collection following

treatment with SG (either at surgery or via biopsy prior to additional NA therapy).

Eligibility criteria: Participants ≥ 18 years of age with previously untreated localized breast cancer as determined by the local institution will be enrolled. For A2, participants must either have a primary tumor >2 cm or be node positive. For B1, participants with anatomic clinical stage II-III breast cancer with primary tumor > 1.5 cm and high genomic risk are eligible. For the IBC cohort (C), participants with T4d and any N are eligible. An ECOG performance score of 0 or 1, and adequate bone marrow, hepatic, and renal function is required.

Study Objectives: The primary objective is to assess the pCR rate in breast and lymph nodes (ypT0/isN0) with SG + P (A2), SG (B1), or SG + P followed by AC + P (C). Secondary objectives include assessment of overall response rate, evaluation of the safety and tolerability of SG or SG + P (CTCAE v5.0), event-free survival (EFS), and quality of life (EORTC QLQ-C30). Exploratory objectives include assessment of potential predictive biomarkers, including Trop-2 expression, DNA damage response markers and immunological markers, as well as changes in cell free DNA with SG.

Statistical methods: The primary analysis is based on the estimated pCR rate with SG or SG + P and will be provided as a proportion (with two-sided 95% confidence interval). Each cohort will follow a Simon two-stage design. EFS will be analyzed using Kaplan-Meier methods and descriptive statistics.

Target Accrual: 50 participants (A2), 56 participants (B1), 39 participants (C)

Contact: Dr. Laura Spring (LSpring@mgh.harvard.edu)

Clinicaltrials.gov #: NCT04230109

PO2-19-04

Trial in Progress: The REJOIN Trial to Use Exercise and Education to Relieve Joint Pain in Older Breast Cancer Survivors Taking Aromatase Inhibitors

Presenting Author(s) and Co-Author(s):

S. Bluethmann. Wake Forest University, Winston-Salem, North Carolina, United States

P. Newman. Penn State College of Medicine, Hershey, Pennsylvania, United States

C. Truica. Penn State Cancer Institute, United States

N. Olsen. Penn State College of Medicine, United States

H. Klepin. Wake Forest School of Medicine, Winston-Salem, NC, Winston-Salem, North Carolina, United States

Background: Physical activity (PA) is a recommended part of breast cancer survivorship. PA promotes survival and mitigates symptoms in older breast cancer survivors (BCS), especially in reducing joint pain associated with Aromatase Inhibitors (AIs). The purpose of the study is to test if a self-management intervention (including education and exercise instruction) improve joint pain management better than standard care.

Trial Design: This two-armed randomized controlled pilot trial (NCT03955627) includes insufficiently active BCS, 60 years and older, diagnosed with stage I-III hormone-sensitive breast cancer, who have completed primary cancer treatment and are within 6 months of initiating AIs. We adapted an evidence-based PA program for older adults (Fit and Strong!) that includes bi-weekly, supervised exercise sessions plus education (90 minutes total). The 16-week, evidence-based intervention program includes: 8-weeks of supervised sessions delivered remotely plus 8-weeks of self-guided home sessions with periodic phone coaching. We are conducting select geriatric assessments (e.g., cognitive assessment, polypharmacy) plus measurements of exercise (both self-reported and objectively measured by accelerometer), joint pain (brief pain inventory), and AI adherence (confirmed by self-report and prescription records) assessed four times (baseline, 4, 6 and 12 months).

Eligibility Inclusion criteria: • Female, aged ≥ 60 years at enrollment • Planning to initiate (or are < 24 weeks from initiating) AIs • Diagnosed stages I-III breast cancer • ER+ tumor (at least 5% of cells) • Completed surgery, radiation and/or chemotherapy • Independent ambulator (verified by treating clinician/staff) • Physician approval to start an exercise program • Insufficiently active (less than 150 minutes per week of moderate intensity activity or less than two sessions per week of strength training) • Able to complete surveys and forms/ understand English • Agree to random assignment to treatment or control group • Can commit to 8 weeks, bi-weekly classes offered by Zoom video and 8 Weeks of at-home exercise. • Must have internet access or data plan to support video conferencing software • Minimum cognitive impairment (verified by cognitive screening questions administered by phone)

Specific Aims: The primary aim is to test the efficacy of a self-management intervention (exercise plus education) on AI-associated arthralgia. Hypothesis: Participants in the treatment group will report less pain than the control group.

--A secondary aim is to test the effect of the pilot intervention on adherence to AIs. Hypothesis: Participants in the treatment group will report better AI Adherence than controls.

Statistical Methods: We will use the Wilcoxon-Mann-Whitney t-test to assess the effect size from the start to the end of the trial, assuming a power calculation of 80%, a two-sided alpha of

10%, and a pooled standard deviation of one between the outcomes of the two groups (usual care and treatment) being compared. Present Accrual and Target Accrual REJOIN enrolled 12 participants in 2022, but two withdrew after randomization. We now have data on 10 participants with a target accrual of 24 overall. The original 12 were accrued at Penn State College of Medicine. We subsequently opened a second site at Wake Forest University and are recruiting the remaining participants.

Contact information: For more information about REJOIN, please contact the study director, Dr. Shirley Bluethmann at sblueth@wakehealth.edu or the REJOIN project manager, Angela Grubb, at agrubb@wakehealth.edu

PO2-19-05

Randomized Phase II trial evaluating three anti-diarrhoeal prophylaxis strategies in patients with HER2+ / HR+ early breast cancer treated with extended adjuvant neratinib (DIANER GEICAM/2018-06)

Presenting Author(s) and Co-Author(s):

M. Gil-Gil. Institut Català d'Oncologia, Insitut d'Investigació Biomèdica Bellvitge. GEICAM Spanish Breast Cancer Group, United States

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

E. Carrasco. GEICAM Spanish Breast Cancer Group, Spain

E. Galve. Hospital Universitario de Basurto, United States

N. Martínez-Jáñez. Medical Oncology Hospital Universitario Ramón y Cajal. Madrid. Spain. GEICAM Spanish Breast Cancer Group., TRES CANTOS, Madrid, Spain

S. González-Santiago. Hospital Universitario San Pedro de Alcántara, Cáceres, Spain

B. Adamo. Medical Oncology Department, Hospital Clínic de Barcelona ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain, Catalonia, Spain

M. Valero. Hospital Quirónsalud Sagrado Corazón, Sevilla. GEICAM Spanish Breast Cancer Group, Madrid. Spain., United States

C. Martínez. ALTHAIA Xarxa asistencial de Manresa, Barcelona, Spain. GEICAM Spanish Breast Cancer Group, Madrid. Spain., United States

A. Guerrero. Fundación Instituto Valenciano de Oncología (FIVO). GEICAM Spanish Breast Cancer Group., Valencia, Comunidad Valenciana, Spain

S. Antolin Novoa. Complejo Hospitalario Universitario A Coruña (CHUAC). GEICAM Spanish Breast Cancer Group., Spain

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

I. Blancas. Medical Oncology Dept, University Hospital San Cecilio, Granada, Spain

R. Andrés. Hospital Clínico Universitario Lozano Blesa. GEICAM Spanish Breast Cancer Group., Spain

J. Alonso-Romero. Hospital Clínico Universitario Virgen de la Arrixaca. GEICAM Spanish Breast Cancer Group., United States

A. Vethencourt. Institut Català d'Oncologia, Oncology Department, Barcelona, Spain. Insitut d'Investigació Biomèdica Bellvitge IDIBELL, Barcelona, Catalonia, Spain

J. Chacón. Hospital Universitario de Toledo. GEICAM Spanish Breast Cancer Group., Spain

N. Chavarría. Hospital Universitario de Jerez de la Frontera, Cádiz. GEICAM Spanish Breast Cancer Group, Madrid, Spain, United States

E. Espinosa. Hospital Universitario La Paz, Madrid. GEICAM Spanish Breast Cancer Group, Madrid, Spain, United States

B. Hernando. Hospital Universitario de Burgos. GEICAM Spanish Breast Cancer Group, Spain

E. Adrover. Complejo Hospitalario Universitario de Albacete, United States

F. Rojo. The Autonomous University of Madrid, Spain

M. Casas. GEICAM Spanish Breast Cancer Group, Spain

L. McCulloch. Puma Biotechnology Inc., South San Francisco, California, USA, United States

J. Vedovato. Pierre Fabre Medicament, Boulogne-Billancourt, France, United States

Background: Neratinib (NER), and irreversible pan-HER tyrosine kinase inhibitor, is approved for the extended adjuvant treatment of HER2+/HR+ early breast cancer (EBC) patients within 1 year of trastuzumab (T)-based therapy completion. The ExteNET trial showed that the extended adjuvant NER compared with placebo modifies the risk of recurrence by an absolute rate of 2.5% at 5 years in HR+/HER2+ patients (Martin et al., 2017). However, without prespecified prophylaxis, diarrhoea was the most common reason for NER discontinuation in the first three cycles in said study.

The CONTROL trial evaluated effectiveness of different anti-diarrhoeal strategies showing a reduction of severe diarrhoea and early discontinuation when indirectly compared to ExteNET (Chan et al., 2022). DIANER (NCT05252988) evaluates the 3 best reported anti-diarrhoeal strategies from CONTROL in patients receiving NER as per European approved label.

Trial design and patients: DIANER is an international, multicenter, controlled, randomized, phase II study. Patients with HER2+/HR+ EBC (stage IB-IIIC) who completed prior neo/adjuvant T-based therapy within 2 weeks and 1 year will be included and randomized 1:1:1 to 3 treatment arms. Arm A: NER (240 mg/day[d] x 1 year) + loperamide (12 mg/d x 14 d → 8 mg/d till end of cycle 2 → as needed [PRN]), Arm B: NER dose escalation (120 mg/d x 7 d → 160 mg/d till d 14 → 240 mg/d x 13 cycles) + loperamide PRN, and Arm C: NER (like Arm A) + loperamide (12 mg/d x 14 d → 8 mg/d till end of cycle 1 → PRN) + colesevelam (3,750 mg/d x 28 d). Patients are stratified by menopausal status and prior anti-HER2 therapy (T versus T + pertuzumab).

Specific aims: Primary objective is incidence of NER discontinuations due to diarrhoea in the first 3 cycles. Secondary objectives are: incidence of NER discontinuations; AEs and hospitalizations; duration, severity, and treatments for diarrhoea; NER exposure; and health-related quality of life (HRQoL) using FACT B and EQ5D-5L. Exploratory objectives include HRQoL using STIDAT; minimal residual disease and molecular alterations.

Statistical methods: A maximum of 315 pts (105 per arm) will be needed using a Simon's optimal two-stage design with the hypotheses of a desirable early discontinuation rate of 5% (H1) versus an undesirable early discontinuation rate of 13% (H0). In the first stage, arms with ≥ 4 pts discontinuing due to diarrhoea in the first 3 cycles, will be closed for enrolment.

The 2-sided 90% confidence intervals using the method described by Koyama et al. (Koyama and Chen 2008) will be provided for the primary endpoint at the end of the 2nd stage of the Simon 2-stage design.

Present accrual and target accrual: DIANER will take place in 81 sites in 5 European countries. As of Jul 10/2023 the study is open in 52 sites in Spain with 80 randomized patients.

Contact information for people with a specific interest in the trial:

Evelia Cortazar (Geicam PM): ecortazar@geicam.org

PO2-19-06

An Open-label, Interventional, Multicenter Study of Trastuzumab Deruxtecan Monotherapy in Patients With Unresectable and/or Metastatic HER2-Low or HER2 Immunohistochemistry 0 Breast Cancer: DESTINY-Breast15

Presenting Author(s) and Co-Author(s):

S. Modi. Memorial Sloan Cancer Center, New York, New York, United States

R. Salgado. GZA-ZNA-Hospitals, Antwerp, Belgium; Peter Mac Callum Cancer Centre, Temse, Belgium

V. Guarneri. Department of Surgery, Oncology and Gastroenterology, University of Padua; Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Veneto, Italy

D. Alagappan. Daiichi Sankyo, Inc., United States

N. Dennis. Daiichi Sankyo Oncology France, United States

A. Hanlon Newell. Daiichi Sankyo, Inc., United States

A. Boran. Daiichi Sankyo, Inc., United States

O. Morsli. Daiichi Sankyo, Inc., United States

A. Llombart-Cussac. Arnau de Vilanova Hospital, Valencia, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US, Comunidad Valenciana, Spain

Background

Approximately 50% of all breast cancer (BC) tumors express low levels of HER2, defined by HER2 immunohistochemistry (IHC) scores of 1+ or IHC 2+/in situ hybridization negative (ISH-), and are referred to as HER2-low BC. Trastuzumab deruxtecan (T-DXd), a HER2-directed antibody-drug conjugate, has been approved in the United States, European Union, and other countries for the treatment of adult patients with unresectable or metastatic HER2-low BC (IHC 1+ or IHC 2+/ISH-), regardless of hormone receptor (HR) status, who previously received chemotherapy in the metastatic setting or who have developed disease recurrence within 6 months of completing adjuvant chemotherapy. The DESTINY-Breast04 trial that formed the basis of T-DXd approval in HER2-low BC included only 63 patients who were HR-negative and patients with HER2 IHC 0 status were not enrolled. However, the phase 2 DAISY trial demonstrated clinically meaningful activity of T-DXd in patients with HER2 IHC 0 BC. Along with HER2 status, HR-positive or HR-negative tumor status could confer variation in prognosis and sensitivity to systemic therapy. Few targeted agents are available for patients with HR-negative, HER2 IHC 0 metastatic BC, particularly for patients without pathogenic BC gene mutations or programmed cell death ligand 1 expression. Therefore, there is an unmet medical need for therapeutic treatment options in this patient population.

Study Description

DESTINY-Breast15 is a multicenter, open-label, single-arm, phase 3b trial designed to evaluate the efficacy and safety of T-DXd in patients with HR-positive or HR-negative unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2 IHC 0 BC who received 1 or 2 lines of prior therapy in the metastatic setting, including (but not limited to) targeted agents or endocrine therapy per cohort. Patients must have an ECOG PS score of 0 or 1, have never previously been HER2-positive (IHC 3+ or IHC 2+/ISH+), and have never previously received anti-HER2 therapy in the metastatic setting. At least 250 patients will be enrolled from approximately 80 sites in Belgium, Brazil, China, Ireland, Italy, Netherlands, Portugal, Spain, and the United

States to receive T-DXd and will be assigned to 1 of 4 cohorts according to their HR and HER2 status (tested per local practice in accordance with ASCO/CAP 2018 guidelines). The 4 cohorts are cohort 1, HR-negative, HER2-low ($n \approx 100$); cohort 2, HR-negative, HER2 IHC 0 ($n \approx 50$); cohort 3, HR-positive, HER2-low ($n \approx 50$); and cohort 4, HR-positive, HER2 IHC 0 ($n \approx 50$). Cohort 3 will specifically recruit patients with rapid disease progression, defined as recurrent disease < 2 years from starting adjuvant endocrine therapy, progression within 12 months of completing adjuvant CDK4/6 inhibitor, or progression within 12 months of starting CDK4/6 inhibitor therapy in the metastatic setting. T-DXd will be administered at a dose of 5.4 mg/kg intravenously once every 3 weeks until disease progression, unacceptable toxicity, or 2 years after the first dose of T-DXd. The primary end point is time from the start of T-DXd treatment to initiation of subsequent anticancer treatment or death. Secondary end points are real-world progression-free survival (defined as time from the date of first administration of T-DXd to date of first observed instance of disease progression per RECIST version 1.1 or death from any cause), time to treatment discontinuation or death, objective response rate per RECIST version 1.1, safety, and patient-reported quality-of-life–related outcomes. Time-to-event endpoints will be evaluated using Kaplan-Meier methods.

PO2-19-07

PROOFS – Pre-/perimenopausal patients with HR+/HER2- EBC with intermediate to high clinical and low genomic risk, treated by endocrine treatment (ET) plus ovarian function suppression (OFS) or chemotherapy followed by ET

Presenting Author(s) and Co-Author(s):

R. Wuerstlein. Breast Center, Dept. OB&GYN and CCC Munich, LMU University Hospital, Munich, Germany

L. Fischer. Breast Center, Municipal Hospital Holweide, Cologne, Cologne, Germany

N. Harbeck. University of Munich, Munich, Bayern, Germany

M. Graeser. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; Department of Gynecology, University Medical Center Hamburg, Moenchengladbach, Nordrhein-Westfalen, Germany

U. Nitz. West German Study Group and Breast Center Niederrhein, United States

M. Christgen. Medizinische Hochschule Hannover, Hannover, Niedersachsen, Germany

S. Kuemmel. West German Study Group, Moenchengladbach, Germany; Breast Unit, Kliniken Essen-Mitte, Essen, Germany; Charité - Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany

C. zu Eulenburg. West German Study Group, Moenchengladbach, Germany; Department of Medical Biometry and Epidemiology, University Medical Center Hamburg, Hamburg, Germany

M. Warm. Breast Center, Municipal Hospital Holweide. Cologne, Cologne, Germany

O. Gluz. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; University Clinics Cologne, Moenchengladbach, Nordrhein-Westfalen, Germany

Background During the past years, clinical routine has shifted away from relying solely on clinicopathologic factors toward increasing use of multigene expression assays in guiding treatment decisions regarding adjuvant chemotherapy (CT) for hormone receptor-positive (HR+), HER2-negative (HER2-) early breast cancer (EBC) with 0 to 3 positive lymph nodes. In case of a low genomic risk, there is strong consensus in favor of endocrine treatment (ET) alone for postmenopausal patients, regardless of clinical risk (supported by data from planB, ADAPT, RxPonder, TailorX, MINDACT). However, there is still uncertainty regarding optimal therapy for pre- and perimenopausal patients with a similar clinical/genomic risk profile. Since the observed benefit of CT in this patient group may be partly attributable to CT-induced ovarian function suppression (OFS), some of these patients could be spared CT by adding OFS to endocrine therapy. The West German Study Group (WSG) initiated the PROOFS-registry to create a real-world database on how to optimally treat these patients. Eligibility Criteria PROOFS (NCT05792150) aims at the long-term follow up of pre- or perimenopausal patients with HR+/HER2- EBC with an intermediate to high clinical risk of recurrence and low genomic risk measured by MammaPrint(R). Additional endocrine response assessment (Ki67) after a short preoperative endocrine therapy is encouraged. Up to 25% of the study population may have node-positive disease. Participants undergo standard-of-care treatment at physician's discretion and according to clinical routine, which may include CT neoadjuvant or adjuvant + ET, ET + OFS in premenopausal, or ET +/- OFS in perimenopausal women. Specific Aims PROOFS aims to give insights in the real-world use of OFS and to confirm an excellent outcome in pre-/perimenopausal women with HR+/HER2- early BC with an intermediate to high clinical risk of recurrence and low genomic risk treated by ET +/- OFS alone (without CT). In

addition, quality of life is captured. **Statistical Methods** The primary objective is to demonstrate the 5-year distant recurrence-free interval (dRFI) in patients treated by ET +/- OFS alone. The null hypothesis $H(0)$ is: 5-year dRFI < 92%. Secondary endpoints for all patients are 5- and 10-year dRFI, distant disease-free survival (dDFS), overall survival (OS), breast cancer-free interval (BCFI), quality of life (QLQ BR23 and QLQ-C30) and therapy adherence. Cox regression models, Kaplan-Meier method and log-rank tests will be applied for survival analysis. Linear mixed models will be utilized to quantitatively describe the course of quality of life-scores as well as therapy adherence, and to conduct group comparisons. **Present and Target Accrual** The study is open for recruitment of 1500 patients (approximately 20% receiving CT and 80% receiving ET +/- OFS) at up to 100 centers in Germany (June 2023: 24 open for recruitment).

Funding

AGENDIA N.V., Amsterdam

Contact Information

rachel.wuerstlein@med.uni-muenchen.de

PO2-19-08

INAVO121: Phase III study of inavolisib + fulvestrant vs alpelisib + fulvestrant in patients with hormone receptor-positive, HER2-negative, PIK3CA-mutated locally advanced or metastatic breast cancer

Presenting Author(s) and Co-Author(s):

D. Juric. Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

G. Bianchini. IRCCS Ospedale San Raffaele, Milan, Lombardia, Italy

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

W. Jacot. Institut du Cancer de Montpellier, Université de Montpellier, INSERM U1194, Paris, Montpellier, Languedoc-Roussillon, France

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

V. Craine. F. Hoffmann-La Roche Ltd, Basel, Switzerland, Switzerland

K. Hutchinson. Genentech, Inc., South San Francisco, United States, United States

A. Flechais. F. Hoffmann-La Roche Ltd, Basel, Switzerland, Switzerland

E. Thanopoulou. Roche Products Limited, Welwyn Garden City, UK, United Kingdom

N. Harbeck. University of Munich, Munich, Bayern, Germany

BACKGROUND

Standard-of-care (SoC) endocrine therapy (ET) for patients (pts) with hormone receptor-positive, HER2-negative, PIK3CA-mutated locally advanced or metastatic breast cancer (HR+, HER2-, PIK3CA-mut LA/mBC) was transformed by combinations with cyclin-dependent kinase 4/6 inhibitors (CDK4/6is); a CDK4/6i-based combination is approved in high-risk early BC.

However, in most pts, mechanisms of resistance that emerge during or after treatment with a CDK4/6i and ET combination lead to relapse/disease progression. Dysregulating mutations in PIK3CA, occurring in ~40% of HR+, HER2- BCs, represent a common mechanism of resistance to CDK4/6is and ET combinations. Alpelisib (ALP; a selective PI3K α inhibitor; PI3K α i) + fulvestrant (FUL) is approved for pts with HR+, HER2-, PIK3CA-mut LA/mBC, but its widespread implementation in clinical practice has been challenging. As such, there is a significant need to develop PI3K α is with a better therapeutic index. Inavolisib (INAVO) is a highly potent and selective PI3K α i that also facilitates the degradation of mutated PI3K α isoform. INAVO has demonstrated manageable safety/tolerability, alone and in combination with SoC treatments in HR+, HER2-, PIK3CA-mut LA/mBC. Moreover, an ongoing Phase I trial showed that INAVO + FUL elicited encouraging preliminary antitumor activity in heavily pretreated pts, including a CDK4/6i-based regimen.

TRIAL DESIGN

INAVO121 is a Phase III, randomized, open-label study. Pts are randomized 1:1 to receive INAVO (9 mg oral daily; PO QD) + FUL (500 mg intramuscularly on Days [D] 1 and 15 of Cycle 1, then D1 of subsequent cycles), or ALP (300 mg PO QD) + FUL. Randomization is stratified by visceral disease (yes vs no) and prior CDK4/6i therapy (adjuvant vs metastatic setting). Pts will receive treatment until disease progression or unacceptable toxicity.

ELIGIBILITY CRITERIA

Pts have HR+, HER2-, PIK3CA-mut LA/mBC (confirmed by circulating-tumor DNA or tumor tissue), adequate hematologic and organ function, and disease progression after or during treatment with a CDK4/6i-based regimen. Up to two prior lines of systemic therapy in LA/mBC, including one line of chemotherapy, are allowed.

AIMS

The primary endpoint is progression-free survival (PFS) by blinded independent central review (BICR). Secondary endpoints include overall survival, BICR-objective response rate, BICR-best overall response, BICR-duration of response, BICR-clinical benefit rate, safety, tolerability, pt-reported outcomes, and pharmacokinetics.

STATISTICAL METHODS

A stratified log-rank test at an overall 0.05 significance level (two-sided) will be used for the primary endpoint analysis. Median PFS will be estimated using Kaplan–Meier methodology. An independent data monitoring committee will be in place for safety and efficacy.

ACCRUAL

The study is open for enrollment and has randomized four pts; the study is targeting 400 pts at ~200 sites globally.

CONTACT INFORMATION

For more information or to refer a patient, email global.roche.genentechtrials@roche.com or call 1-888-662-6728 (USA only).

Clinicaltrials.gov number NCT05646862.

This abstract was originally presented at ASCO 2023 (TPS1123).

PO2-19-09

INAVO122: a Phase III study of maintenance inavolisib or placebo + pertuzumab + trastuzumab following induction with pertuzumab + trastuzumab + a taxane in patients with PIK3CA-mutated, HER2-positive advanced breast cancer

Presenting Author(s) and Co-Author(s):

S. Swain. Georgetown University Medical Center, Lombardi Comprehensive Cancer Center and MedStar Health, Washington DC, USA, United States

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

R. Basho. The Lawrence J. Ellison Institute for Transformative Medicine, Los Angeles, USA, Los Angeles, California, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

N. Harbeck. University of Munich, Munich, Bayern, Germany

C. Huang. National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, Taipei, United States

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

J. Chen. Oncology Biomarker Development, Genentech, Inc., South San Francisco, USA, United States

V. Henschel. Product Development Data Science, F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States

S. Warburton. Oncology and Hematology, Roche Products Limited, Welwyn Garden City, UK, United States

F. Amair-Pinedo. Product Development Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

Background

The PI3K pathway plays a crucial role in HER2 signaling. Somatic mutations of PIK3CA, the gene that encodes the PI3K p110 α subunit, may induce resistance to HER2-targeted therapies and are associated with poorer clinical outcomes (Swain SM, et al. SABCS 2022; P2-11-07). Inavolisib, a potent p110 α -selective inhibitor that induces degradation of mutant p110 α , has shown antitumor activity in PIK3CA-mutated HER2-positive breast cancer (HER2+ BC) and long-term tolerability with early intervention for common on-class toxicities, including hyperglycemia, diarrhea, and stomatitis (Bedard P, et al. ASCO 2022; 1052). The current study will assess the efficacy and safety of maintenance inavolisib + fixed-dose combination of pertuzumab + trastuzumab for subcutaneous injection (PH FDC SC) after first-line induction treatment in patients with PIK3CA-mutated, HER2+, advanced BC (aBC).

Trial design

INAVO122 is a multicenter, randomized, international, double-blind, placebo-controlled study.

Patients will be enrolled for: first-line induction treatment if they are receiving/will receive PH + a taxane; or maintenance treatment completing induction treatment. In the maintenance phase, patients will be randomized 1:1 to receive inavolisib (9 mg orally once daily; Days 1–21 of 21-day cycles) + PH FDC SC (every 3 weeks), or placebo + PH FDC SC. Study treatment will continue until disease progression, unacceptable toxicity, death, consent withdrawal, or at the investigator's discretion.

ELIGIBILITY

Enrolled patients must have centrally determined HER2+, PIK3CA-mutated tumors, with documented hormone receptor status per local assessment, and be disease-free for ≥ 6 months from completion of neoadjuvant/adjuvant systemic non-hormonal treatment. They must not have received any treatment for aBC prior to induction, and, at screening, fasting glucose must be < 126 mg/dL and HbA1c $< 6.4\%$. To be randomized, patients must have completed induction therapy per standard of care without progression of disease and show left ventricular ejection fraction $\geq 50\%$.

AIMS

The primary endpoint is investigator-assessed progression-free survival. Secondary endpoints are overall survival; investigator-assessed objective response rate, duration of response, clinical benefit rate, and time to second disease progression; health-related quality of life; safety; and pharmacokinetics.

STATISTICAL METHODS

The primary endpoint analysis will utilize a two-sided stratified log-rank test at a two-sided significance level of 5%. A stratified Cox proportional hazards model will be used to estimate the hazard ratio between the two treatment arms and its 95% confidence intervals.

ACCRUAL

Target randomization is ~230 patients; recruitment began in July 2023.

CONTACT INFORMATION

For more information or to refer a patient, email global.roche.genentechtrials@roche.com or call 1-888-662-6728 (USA only).

Clinicaltrials.gov number NCT05894239.

PO2-19-10

CAPItello-292 Phase 3: An open-label, randomized study of capivasertib, fulvestrant, and investigator's choice of CDK4/6 inhibitor (palbociclib or ribociclib) in HR+/HER2– advanced breast cancer

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

J. Collins. AstraZeneca, Gaithersburg, USA, United States

C. D'Cruz. Oncology R&D, AstraZeneca, Waltham, Massachusetts, United States

C. Gresty. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

R. Sommariva. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

D. Sudhan. Research and Early Development, Oncology R&D, AstraZeneca, Waltham, Massachusetts, United States

C. Miller. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

J. Ha. AstraZeneca, Cambridge, UK, United Kingdom

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

Background: Overcoming resistance to endocrine therapy in advanced breast cancer (ABC) is a major challenge, and there remains an unmet need for safe and efficacious treatment options. AKT pathway activation is implicated in resistance to endocrine therapy and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) ABC. In the Phase 3 CAPItello-291 study, capivasertib (a potent inhibitor of all three AKT isoforms) plus fulvestrant significantly improved progression-free survival (PFS) versus fulvestrant in patients with aromatase inhibitor-resistant HR+/HER2– ABC. Simultaneous inhibition of the AKT and CDK4/6 pathways may delay CDK4/6 inhibitor resistance or re-sensitize tumors to endocrine therapy plus CDK4/6 inhibitors, leading to improved clinical outcomes. CAPItello-292 is an ongoing Phase 1b/3 study examining the efficacy and safety of adding capivasertib to fulvestrant plus a CDK4/6 inhibitor in HR+/HER2– ABC. Phase 1b has previously confirmed the recommended Phase 3 dose (RP3D) in combination with palbociclib to be tolerable with preliminary signals of clinical activity; determination of the RP3D in combination with ribociclib is currently being explored.

Trial design: The Phase 3 component of CAPItello-292 is an open-label, randomized study assessing the efficacy of the addition of capivasertib to fulvestrant and the investigator's choice of CDK4/6 inhibitors (either palbociclib or ribociclib) in patients with HR+/HER2– ABC following recurrence or progression on or within 12 months of the end of (neo)adjuvant endocrine therapy (HER2– defined as immunohistochemistry [IHC] 0, or 1-positive or IHC2-positive/in situ hybridization-negative). Approximately 628 patients will be randomized 1:1 to receive capivasertib (400 mg, oral twice daily, 4 days on and 3 days off) plus fulvestrant (500 mg intramuscularly every 28 days plus loading dose on cycle 1, day 15) and investigator's choice of CDK4/6 inhibitor (125 mg palbociclib once daily for 21 days of each 28-day cycle or ribociclib at the determined RP3D) or fulvestrant plus investigator's choice of CDK4/6 inhibitor alone. Patients will be treated until disease progression, unacceptable tolerability, or withdrawal of consent. Treatment beyond progression is permitted for patients with clinical benefit at the investigator's discretion.

The primary endpoint is PFS (by blinded independent central review [BICR]). The secondary endpoints include PFS in patients with AKT pathway-altered tumors, overall survival, time to second progression or death, objective response rate, duration of response, clinical benefit rate (all by BICR), physical functioning, global health status/quality of life and safety.

The study plans to enroll patients from 23 countries and is planned to start at the end of 2023.

Clinical trial identification: NCT04862663.

Funding: CAPItello-292 is supported by AstraZeneca

Editorial acknowledgment: AstraZeneca-funded medical writing support was provided by Suzanne Patel, Ph.D., from BOLDSCIENCE Inc.

Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

PO2-19-11

NOBLE – Neoadjuvant Olaparib and Durvalumab for patients with BRCA-associated TripLE Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

E. Buhner. EORTC, United States

E. Xenophontos. European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium, Brussels, Belgium

A. Hamy-Petit. Institut Curie, United States

J. Casas-Martin. European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium, Brussels, Belgium

C. Callens. INSTITUT CURIE, Paris, France

T. Meyskens. AZ Klina, Brasschaat, United States

C. Poncet. European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium, Brussels, Belgium

A. Lanzi. Institut Curie, United States

E. Brain. European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium, United States

Background The standard of care for patients with early triple-negative breast cancer (TNBC) is neoadjuvant chemotherapy followed by surgery. Recently, immune checkpoints inhibitors (ICI) added to neoadjuvant chemotherapy have shown efficacy. Among TNBC, BRCA mutations and other homologous recombination deficiency (HRD) signals are relatively frequent. As opposed to other types of breast cancer, TNBC show a high neoantigen load, a large number of tumour infiltrating lymphocytes (TILs), and a high PD-L1 expression. In BRCA/HRD breast cancer, PARP inhibitors (PARPi) exhibit a distinct anticancer activity. In addition, they show immunomodulatory effects by promoting PD-L1 expression and DNA damage, increasing neoantigen load. Chemotherapy-free regimens combining PARPi and ICI result in promising synergistic activity as shown in the metastatic setting, supporting investigation in the neoadjuvant setting. Trial design NOBLE is an EORTC phase 2, randomized, international, multicentre, open label, clinical trial. Eligible patients will undergo central screening for tumoral BRCA/HRD (Institute Curie, 455 patients), 152 patients will be randomized 1:1 between olaparib vs olaparib and durvalumab for 4 cycles (16 weeks) of neoadjuvant treatment. Thereafter, patients will undergo surgery. All patients will be followed-up to 2 years (y) after surgery. The trial will be conducted in 3 steps (screening/randomization): Step 1 – Feasibility (60/20): to assess the central testing failure rate, the turn-around time for central testing and the prevalence of tBRCA/HRD; Step 2 (193/64) – Futility; and Step 3 (202/152) – Expansion of recruitment. The primary endpoint is the rate of pathologic complete response (pCR) at the time of surgery, defined as ypT0/is ypN0. Secondary endpoints are response based on RECIST v1.1, surgery rate, 2-y event-free-survival, 2-y overall survival, safety, and quality of life. The study is expected to be activated in early autumn 2023 and the primary endpoint will be available approximately 5 years after the screening of the first patient. Main inclusion criteria

- Histologically confirmed primary TNBC, defined as:
 - - ER and PgR \leq 10%
 - - HER2-negative per ASCO CAP guidelines
 - Stage T1c-T2 N0-N1 M0

- BRCA mutation and/or HRD based on methylation as determined by central testing
- ECOG status 0-1
- Written informed consent
- Age ≥ 18 years
- No prior systemic therapy nor surgery for the current

Main exclusion criteria

- Previous treatment with a PARPi or an immune-checkpoint inhibitor
- History of previous invasive breast cancer
- Bilateral and/or multifocal and/or multicentric BC
- Autoimmune or inflammatory disease

Specific aims The aim of this study is to provide a safe and effective neoadjuvant treatment free of chemotherapy to a distinct subpopulation among patients with TNBC. We will evaluate the pCR after neoadjuvant treatment with olaparib alone and with olaparib in combination with durvalumab in patients with TNBC showing a BRCA1/2 mutation or HRD based on methylation.

Statistical methods The sample size was calculated based on the minimax Simon two-stage design including an interim analysis for futility of the primary endpoint. Decision rules are pre-specified in the study protocol. Each treatment arm will be analyzed independently. There will be no formal comparison between the two experimental treatment arms. A minimization technique will be used for random treatment allocation stratifying for the type of HRD alteration, PD-L1 expression level and for TILs.

Accrual We expect to start recruiting in September 2023. We aim to screen 455 patients to randomize 152 patients. Contact information for people with a specific interest in the trial

- Etienne Brain (study coordinator): etienne.brain@curie.fr
- Anne-Sophie Hamy-Petit (study co-coordinator): anne-sophie.hamy-petit@curie.fr

PO2-19-12

Enhancing skin appearance and quality of life in breast cancer survivors on aromatase inhibitor therapy

Presenting Author(s) and Co-Author(s):

L. Cornell. Mayo Clinic Florida, Jacksonville, Florida, United States

L. Tolaymat. Mayo Clinic Florida, United States

P. Advani. Mayo Clinic, United States

S. Chumsri. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

P. Thais. Mayo Clinic Florida, United States

Background: Post-menopausal women with estrogen receptor positive breast cancer (BC) are typically prescribed endocrine therapy with an aromatase inhibitor (AI) for 5-10 years following BC diagnosis. AIs have multiple established side effects related to estrogen deprivation including vasomotor symptoms, vaginal dryness, and accelerated bone thinning. Many patients also complain about the impact of AIs on skin quality; however, limited data currently exists, particularly with objective measurements of skin quality. Canfield Sciences VISIA-CA is a device that can be used to objectively measure skin changes using patented comparison to norms analysis with a skin feature database to grade the skin relative to others in the same age and skin type. Herein, we aim to evaluate changes in skin quality with the Canfield Sciences VISIA-CA Device after initiation of AI therapy and investigate potential benefits of skincare intervention. **Trial Design:** This is a pilot study aiming to describe changes in skin quality after initiation of AI therapy in BC survivors through use of VISIA-CA technology and patient reported outcome measures. This study will allow us to collect data and identify the trend (if any) for a future larger study. Patients who consent for participation are given a baseline survey to assess self-reported quality of life, perception of skin quality, and self-image prior to initiation of AI. Patients also receive baseline skin measurement with the VISIA-CA device and facial skin photography. Baseline skincare regimen is documented. Any patients on prescription tretinoin products at time of baseline assessment are excluded from the study. Patients return 6 months after initiation of AI for follow-up surveys, updated VISIA-CA measurement, and facial skin photography. Patients then meet with a Mayo Clinic Cosmetic Center aesthetician for skincare intervention with recommended topical treatments including daily facial cleanser, exfoliator, toner, hydrating crème, and retinol-based product. Patients return for additional visits with updated survey, VISIA-CA measurement, and facial skin photography at 1 month, 3 months, and 6 months after skincare intervention. Patients are asked to complete skincare compliance diary to document adherence on a weekly basis. **Eligibility Criteria:** Post-menopausal patients with newly diagnosed ER-positive BC at Mayo Clinic Florida are identified for participation in the study prior to beginning AI therapy. **Specific Aims:** 1.) Evaluate the incidence and severity of skin changes after initiation of AI therapy in BC survivors through use of Canfield Sciences VISIA-CA technology, facial skin photography, and validated patient reported outcome measures. 2.) Assess for objective improvements in skin quality measurements after skincare intervention including a retinol-based product **Statistical Methods:** Continuous variables will be summarized as mean (standard deviation) or median (range) and categorical variables will be reported as frequency (percentage). The changes of skin measurement and patient reported outcome measurements will be calculated and summarized for the following time frames: 1) from initiation of AI therapy to 26 weeks after 2) from the initiation of skincare intervention and 4 weeks, 12 weeks, and 26 weeks after. Appropriate statistical plots will be used to illustrate the change. **Target Accrual:** 50 patients.

Schedule of Events

Tests and Procedures	Baseline	Month 6	Month 7	Month 9	Month 12
Window (from initiation of AI)	Prior to AI initiation	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days
Review of Eligibility Criteria	X				
Medical History / Demographics	X				
Skin Satisfaction Survey	X	X	X	X	X
Rosenberg Self-Esteem Scale	X	X	X	X	X
Skin measurements with the VISIA-CA device	X	X	X	X	X
Facial skin photography	X	X	X	X	X
Skincare Intervention -Daily facial cleanser -Exfoliator -Toner -Hydrating crème -Retinol-based product		X			
Skincare Compliance Diary Review			X	X	X

PO2-20-01

The STOP-HER2 Trial: A Phase 2 Study of Stopping Trastuzumab - Outcomes in Patients with HER2+ Metastatic Breast Cancer (TBCRC 062)

Presenting Author(s) and Co-Author(s):

H. Parsons. Dana Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States

S. Morganti. Dana-Farber Cancer Institute; Harvard Medical School; Broad Institute of MIT and Harvard, United States

K. Smith. Johns Hopkins University School of Medicine, United States

V. Attaya. Dana-Farber Cancer Institute, United States

E. Kallfelz. Dana-Farber Cancer Institute, United States

M. DeMeo. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. LaScala. Patient Advocate, Wilmington, Delaware, United States

S. Mertz. University of Chicago School of Medicine, United States

T. Pollastro. University of Washington, Mercer Island, Washington, United States

P. Spears. University of North Carolina, Chapel Hill, United States

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

C. Dang. Breast Medicine Service, Memorial Sloan-Kettering Cancer Center, United States

S. Dent. Duke University, Durham, North Carolina, United States

A. Elkhanany. Baylor College of Medicine, Houston, TX, Houston, Texas, United States

W. Gwin. University of Washington School of Medicine, United States

C. O'Sullivan. Mayo Clinic, Rochester, MN, USA, ROCHESTER, Minnesota, United States

K. Miller. Indiana University, United States

S. Nunnery. Vanderbilt University Medical Center, United States

E. Walsh. Georgetown University Hospital, United States

A. Storniolo. Indiana University School of Medicine, Indianapolis, Indiana, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Wolff. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

M. Rimawi. Baylor College of Medicine, Houston, Texas, United States

I. Krop. Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

BACKGROUND:

Anti-HER2 therapies have transformed the trajectory for patients with HER2-positive (HER2+) MBC. A subset of patients with HER2+ MBC do exceptionally well and remain on maintenance

anti-HER2 therapy for many years. However, current therapy is non-curative and patients are treated indefinitely. While these therapies often are well-tolerated, they may cause significant toxicities, are expensive, and typically require frequent infusion and provider visits. Case reports and retrospective series demonstrate that some patients may do well after stopping anti-HER2 treatment. We currently lack prospective data on the likelihood of clinical impact of successful treatment discontinuation, outcomes among patients who progress and restart HER2-directed therapy, and tools to predict who may safely stop therapy.

In this study, we will enroll pts with an exceptional response to anti-HER2 therapy. Pts may elect to either continue or stop anti-HER2 therapy and will be followed clinically and radiographically on a protocol-specified schedule. Considering the central role of patients in choosing the study intervention arm, and the unique nature of stopping therapy as a treatment intervention, patient advocates have been deeply involved in the study design to ensure patient concerns are being heard and addressed. We will retrospectively assess minimal residual disease (MRD), measured in plasma, as a biomarker of ongoing response, in a step toward shifting the treatment paradigm for pts with HER2+ MBC.

METHODS:

STOP-HER2 is a prospective, non-randomized, phase II, multicenter study of either continuation (cohort 1) or cessation (cohort 2) of anti-HER2 therapy in exceptional responders with HER2+ MBC. Eligible patients must have biopsy-proven HER2+ MBC by ASCO/CAP guidelines and must have been receiving first-line anti-HER2 therapy for MBC for at least 3 years without evidence of progressive disease (PD) as determined by the treating investigator. Patients with prior brain-only PD or oligo-PD outside the brain are eligible at least 2 years after local treatment to the central nervous system (CNS) and in absence of subsequent PD. Up to fifty-two participants will be enrolled into cohort 2, and an additional thirty participants enrolled into the cohort 1, at 10 US sites within the Translational Breast Cancer Research Consortium. Co-primary endpoints are the 1-year progression-free survival (PFS) in cohorts 2 and 1, separately. Secondary endpoints include the clinical benefit rate upon re-initiation of anti-HER2 therapy for patients in cohort 2 experiencing PD after treatment discontinuation; and 3-year overall survival in both cohorts. Correlative endpoints include MRD status at baseline and the correlation between MRD dynamics and outcomes. Patient-reported outcomes will be collected and analyzed, including quality of life, illness intrusiveness, financial toxicity, anxiety, and decision regret. The study will use a two-stage design to assess the primary objective of estimating the rate of participants who are free of progression at one year after discontinuing anti-HER2 therapy. If 50% or less are free of progression at one year, stopping HER2 therapy would not be considered a viable treatment plan (null hypothesis). The study is designed to have 80% power to reject the null hypothesis at the 10% type I error rate when 68% of exceptional responders are free of progression at one year after stopping HER2 therapy. STOP-HER2 began enrollment in Q2 2023 (NCT05721248).

PO2-20-02

A Phase 3 study of gedatolisib plus fulvestrant with and without palbociclib in patients with HR+/ HER2- advanced breast cancer previously treated with a CDK4/6 inhibitor plus a non-steroidal aromatase inhibitor (VIKTORIA-1)

Presenting Author(s) and Co-Author(s):

S. Hurvitz. Fred Hutchinson Cancer Center, Seattle, Washington, United States

F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France

M. Cristofanilli. Weill Cornell Medicine, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

A. Giordano. Dana Farber Cancer Institute, Harvard University, Boston, MA, United States

H. Han. H. Lee Moffitt Cancer Center, Tampa, Florida, United States

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

R. Wesolowski. James Cancer Hospital and the Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

I. Gorbachevsky. Celcuity, Inc., Minneapolis, MN, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

Patients who receive frontline CDK4/6 inhibitor (CDK4/6i) therapy eventually experience disease progression. Resistance to CDK4/6i is likely a transient adaptive mechanism that may be reversed by inhibition of the PI3K/mTOR pathway. Thus, combination of CDK4/6i and PI3K/mTORi after disease progression on CDK4/6i could restore sensitivity to CDK4/6i and prevent activation of the PI3K/mTOR pathway. This hypothesis was evaluated in a Phase 1b study (Layman SABCS 2021) of gedatolisib (geda), a potent inhibitor of PI3K and mTOR. Subjects with HR+/HER2- ABC treated with prior CDK4/6i received geda (180 mg IV weekly for 3 weeks, then one week off) with palbociclib (P) and fulvestrant (F). Median PFS was 12.9 months with 63% overall response rate. Efficacy was observed regardless of PIK3CA mutation status (Wesolowski SABCS 2022). Geda was well tolerated, with few discontinuations due to treatment-related adverse events (4%). The most common AE was stomatitis; hyperglycemia of any grade occurred in 26% of patients. This preliminary data, dosing schedule, and study population characteristics form the basis for the Phase 3 trial, VIKTORIA-1.

This Phase 3 multinational clinical trial will evaluate geda and F with or without P in patients with HR+/HER2- ABC previously treated with any CDK4/6i in combination with a non-steroidal aromatase inhibitor (AI) therapy. Those without tumor PIK3CA mutations will be assigned to Study 1 (n=351) and randomized to Arm A (geda, P, and F), Arm B (geda and F), or Arm C (F). Those with PIK3CA mutations will be assigned to Study 2 (n=350) and randomized to Arm D (geda, P, and F), Arm E (alpelisib and F), or Arm F (geda and F). Key eligibility criteria include adults with confirmed metastatic or locally advanced breast cancer, any menopausal status, radiologically evaluable disease, and prior CDK4/6i treatment in combination with a non-steroidal AI. Prior hormonal therapy, including SERDs, is allowed. Key exclusion criteria include prior treatment with a PI3K, Akt, or mTOR inhibitor, prior treatment with chemotherapy for advanced disease, more than two lines of prior endocrine therapy, bone only disease with no

soft tissue components, active CNS metastases, and type 1 diabetes or uncontrolled type 2 diabetes.

The primary endpoint is PFS assessed by blinded independent central review per RECIST v1.1. Secondary endpoints included overall survival (OS), safety and tolerability, ORR, duration of response, time to response, CBR, quality of life, and pharmacokinetics. Enrollment is ongoing.

This trial abstract was previously presented at the 2022 San Antonio Breast Cancer Symposium, December 6-10, 2022.

PO2-20-03

VERITAC-3: A randomized phase 3 study, with a lead-in, of first-line vepdegestrant + palbociclib vs letrozole + palbociclib in estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer

Presenting Author(s) and Co-Author(s):

S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States
E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States
M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France
M. Danso. Virginia Oncology Associates, Norfolk and Virginia Beach, VA, USA, United States
S. Hurvitz. Fred Hutchinson Cancer Center, Seattle, Washington, United States
H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan
C. Chappey. Pfizer Inc., La Jolla, California, United States
D. Yang. Pfizer Inc., La Jolla, California, United States
J. Perkins Smith. Pfizer Inc., New York, New York, United States
Y. Liu. Pfizer Inc, San Diego, California, United States
Y. Zhang. Arvinas Operations, Inc., New Haven, Connecticut, United States
S. Anderson. Arvinas Operations, Inc., New Haven, Connecticut, United States
M. de Laurentiis. Istituto Nazionale Tumori "Fondazione Pascale", Italy

Background: Vepdegestrant (ARV-471) is a selective, orally administered PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader. In the phase 2 portion (VERITAC) of a first-in-human phase 1/2 study (NCT04072952), vepdegestrant 200 mg once daily (QD) was well tolerated and had clinical activity in heavily pretreated patients with ER+/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer and was selected as the recommended phase 3 dose (RP3D) for vepdegestrant monotherapy. A phase 1b cohort of the phase 1/2 study is evaluating the safety and clinical activity of vepdegestrant plus palbociclib in patients with ER+/HER2– breast cancer after prior endocrine-based therapy; prior cyclin-dependent kinase (CDK)4/6 inhibitor therapy was permitted. Preliminary results showed encouraging activity for the combination based on clinical benefit rate (CBR; rate of confirmed complete response, partial response, or stable disease ≥ 24 weeks); an increase in palbociclib exposure was observed relative to historical palbociclib pharmacokinetic data and was accompanied by a higher incidence of grade 3/4 neutropenia compared with prior palbociclib and endocrine therapy combination studies, which was managed by monitoring and standard palbociclib dose modifications. The global, randomized phase 3 VERITAC-3 study (NCT05909397) will compare the efficacy and safety of vepdegestrant plus palbociclib vs letrozole plus palbociclib as first-line treatment for patients with ER+/HER2– advanced breast cancer. An open-label study lead-in (SLI) will evaluate the safety and tolerability of vepdegestrant 200 mg QD plus 2 doses of palbociclib (100 mg QD and 75 mg QD) in patients with ER+/HER2– advanced breast cancer to select the RP3D of palbociclib for this combination.

Trial Design: Approximately 50 and 1130 patients will be enrolled in the SLI and the phase 3 parts of the study, respectively. Eligible patients (aged ≥ 18 years) must have histologically or cytologically confirmed ER+/HER2– locoregionally recurrent or metastatic breast cancer, with no prior treatment in the advanced setting, and no prior treatment in any setting with CDK4/6

inhibitors, vepdegestrant, fulvestrant, elacestrant, or other investigational agents (including novel endocrine therapy, selective ER degraders, selective ER covalent antagonists, and complete ER antagonists). Patients with measurable disease per RECIST v1.1 or nonmeasurable bone-only disease are eligible. Patients with disease recurrence during or ≤ 12 months after completion of adjuvant endocrine therapy are excluded. For the SLI, patients are randomized 1:1 to receive vepdegestrant 200 mg QD in combination with palbociclib 100 mg QD or 75 mg QD and are treated in 28-day cycles with vepdegestrant given continuously and palbociclib given for 21 days followed by 7 days off treatment. The objective of the SLI is to identify the RP3D of palbociclib in combination with vepdegestrant, which will be determined through the primary outcome measures of incidence of grade 4 neutropenia, study drug dose reduction, and study drug discontinuation within the first 4 cycles of treatment. Secondary outcome measures include safety, antitumor activity (objective response rate, CBR, and duration of response), and plasma concentrations of study drugs. In the planned phase 3 portion of the trial, patients will be randomized to vepdegestrant plus palbociclib or letrozole plus palbociclib. The primary efficacy endpoint of the phase 3 portion is progression-free survival based on blinded independent central review. Enrollment began June 2023 and is ongoing.

PO2-20-04

TACTIVE-U: phase 1b/2 umbrella study of vepdegestrant, a PROteolysis TARgeting Chimera (PROTAC) estrogen receptor (ER) degrader, combined with other anticancer treatments in ER-positive advanced or metastatic breast cancer

Presenting Author(s) and Co-Author(s):

C. Isaacs. Georgetown University, United States

K. Jerzak. Sunnybrook Health Sciences Centre, United States

J. Hilton. The Ottawa Hospital Cancer Centre, United States

J. Guimarães. Sherbrooke University and Integrated University Health and Social Services Center (CIUSS) of Saguenay-Lac-Saint-Jean, Quebec, Canada

R. Layman. The University of Texas MD Anderson Cancer Center, United States

D. Lu. Pfizer, United States

G. Mo. Pfizer Inc., La Jolla, California, United States

A. Calella. Pfizer Srl, Milan, Italy

O. Valota. Pfizer Srl, Milan, Italy

S. Anderson. Arvinas Operations, Inc., New Haven, Connecticut, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

Background: Vepdegestrant (ARV-471), an oral PROTAC ER degrader, was well tolerated and showed evidence of clinical activity in the first-in-human phase 1/2 study in heavily pretreated patients with ER+/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (NCT04072952). The cyclin-dependent kinase (CDK)4/6 inhibitors abemaciclib and ribociclib are approved in combination with an aromatase inhibitor or fulvestrant, or as monotherapy (abemaciclib), for ER+/HER2- advanced or metastatic breast cancer. In preclinical studies, vepdegestrant combined with abemaciclib or ribociclib showed evidence of synergistic interactions in ER+ breast cancer cells and greater tumor growth inhibition in a xenograft breast cancer model compared with fulvestrant in combination with these agents. Inhibitors targeting different CDKs, such as samuraciclib (oral CDK7 inhibitor), are in clinical development for solid tumors. The open-label, phase 1b/2 TACTIVE-U umbrella study will evaluate the safety, efficacy, and pharmacokinetics of vepdegestrant in combination with other anticancer treatments in patients with ER+ advanced or metastatic breast cancer. Vepdegestrant is being evaluated in combination with abemaciclib (sub-study A; NCT05548127), ribociclib (sub-study B; NCT05573555), and samuraciclib (sub-study C).

Trial Design: Patients eligible for current sub-studies of TACTIVE-U are aged ≥ 18 years, have histologically or cytologically confirmed ER+/HER2- advanced or metastatic breast cancer not amenable to surgical resection, and have received prior therapy for advanced or metastatic disease, including any CDK4/6 inhibitor-based regimen in any setting. In each sub-study, patients will receive vepdegestrant orally once daily (QD) continuously in a dose escalation/de-escalation approach. Abemaciclib will be given orally twice daily continuously in sub-study A, ribociclib will be given orally QD for 21 days followed by 7 days off treatment in sub-study B, and samuraciclib will be given orally QD continuously in sub-study C. For all sub-studies, the primary endpoint of the phase 1b portion is dose-limiting toxicities to determine the recommended phase 2 dose of vepdegestrant in combination with the other anticancer treatment. Secondary endpoints of phase 1b are antitumor activity (objective response, clinical benefit rate [CBR], and duration of response [DOR]), progression-free survival (PFS), safety

(type, frequency, and severity of adverse events and laboratory abnormalities), and plasma concentrations of study drugs. The phase 2 portion of each sub-study will further evaluate the antitumor activity of the combinations; the primary endpoint is objective response and secondary endpoints include antitumor activity (CBR and DOR), PFS, overall survival, safety, plasma concentration of study drugs, and changes in circulating tumor DNA. Future combination sub-studies will be included in TACTIVE-U.

PO2-20-05

Onco-Genome Brazil: Mapping Breast and Prostate Cancer in the Brazilian Public Health System

Presenting Author(s) and Co-Author(s):

J. Schuch. Hospital Moinhos de Vento, Brazil

C. Bordignon. Hospital Moinhos de Vento, Brazil

M. Rosa. Hospital Moinhos de Vento, Brazil

A. de Baumont. Hospital Moinhos de Vento, Brazil

M. Bessel. Hospital Moinhos de Vento, Brazil

G. Macedo. Hospital Moinhos de Vento, Brazil

D. Rosa. Hospital Moinhos de Vento, Brazil

Background: Breast and prostate cancers are the most common malignancies diagnosed in women and men respectively, and present with great clinical heterogeneity, even in tumors with the same phenotypic characteristics. Somatic and germline molecular alterations in DNA may have prognostic and predictive impact, influencing response to therapies and overall survival. In addition, the evaluation of germline mutations can help identify individuals and families at higher risk for developing cancer. Aims: Our aim is to characterize the somatic and germline genomic landscape of women with locally advanced HER2-positive breast cancer and men with metastatic prostate cancer from Brazil. Secondly, we aim to identify genetic variants associated with tumor prognosis and treatment response, identify patients carrying pathogenic alterations in cancer-predisposing genes, and characterize the genetic ancestry of the population included in the study. Trial design: This observational multicenter cohort study (NCT05306600) will include 550 adult patients from the five macro-regions of Brazil, divided into two arms: 1) breast cancer and 2) prostate cancer. Clinical and pathological data will be collected, as well as DNA samples from peripheral blood and tumor tissue. Whole-exome sequencing (WES) will be performed to identify variants that may be drivers and/or actionable in a specific patient or tumor. These variants will be interpreted and classified according to their population frequencies, in silico predictors, functional studies, and literature data, following international guidelines proposed by expert societies. This trial is supported by the Ministry of Health in Brazil and includes patients of the Public Health System. Eligibility criteria: In arm 1, the inclusion criteria are patients with a histological diagnosis of breast carcinoma with overexpression of HER-2, clinical stage II or III, and undergoing neoadjuvant treatment with chemotherapy plus trastuzumab. In arm 2, the criteria are patient with histological diagnosis of prostate adenocarcinoma, currently in clinical stage IV. Patients without availability of biological material collection are excluded from the study, as well as patients in whom there was no central confirmation of required histology. Statistical methods: Univariate and multivariate analyses will be conducted to evaluate the possible effect of specific genes or mutations on the investigated outcomes, including tumor prognosis and treatment response. Discussion: Currently, 265 participants have already been included in the study, 150 in arm 1 and 115 in arm 2. This trial will contribute to the construction of a robust database that should provide a better understanding of the genomic profile of patients with breast and prostate cancer in Brazil. For more information about the trial, please contact Daniela Rosa (daniela.rosa@hmv.org.br).

PO2-20-06

Using the Australian Cardio-Oncology Registry to study long-term cancer therapy related cardiac dysfunction in adult oncology patients – The Chris O'Brien Lifehouse experience

Presenting Author(s) and Co-Author(s):

J. Finney. Chris O'Brien Lifehouse, Camperdown, New South Wales, Australia, United States

B. Felmingham. Murdoch Children's Research Institute, Melbourne, Australia, United States

S. Kumar. Department of Oncology, University of Cambridge, United States

A. Mahmood. Chris O'Brien Lifehouse, Camperdown, New South Wales, Australia, United States

L. Horvath. Chris O'Brien Lifehouse, Camperdown, New South Wales, Australia, United States

D. Celermajer. Department of Cardiology, RPA Hospital, Camperdown, New South Wales, Australia, United States

R. Conyers. Children's Cancer Centre, The Royal Children's Hospital, Melbourne, Australia, United States

Background

Cancer therapy related cardiac dysfunction (CTRCD) is a significant side effect of several chemotherapies, targeted agents, and immunotherapies integral to treatment. Anthracyclines are an example of a commonly used chemotherapy drug class that can cause irreversible early and late onset heart failure. CTRCD often leads to dose reductions and treatment delays or cessation, limiting treatment success and contributing to increased mortality and life-long morbidity in oncology survivors. In Australia, there are currently no multi-centre, longitudinal studies examining CTRCD in adult oncology patients.

Trial design

The Australian Cardiology-Oncology Registry (ACOR) is a prospective observational non-interventional study involving 14 sites across Australia. Patient information is obtained from hospital medical records and de-identified upon entry into the registry. Patient demographics, medical history, cancer diagnosis, treatment, cardiac evaluations, and the management of demonstrated CTRCD are recorded. Data is collected at baseline (prior to treatment), and then at six-monthly intervals thereafter. Additionally, patients who develop anthracycline-induced cardiotoxicity (ACT) will be asked to participate in the biobanking study, which will involve a one-off 12mL peripheral blood draw that will be processed at an external site for whole genome exome sequencing and the development of pluripotent derived stem cell cardiomyocytes.

Eligibility criteria

Inclusion Criteria

- Adult oncology patients (>18+ years of age) treated with cardiotoxic therapies within the last 5-years

Exclusion Criteria

- Diagnosis of Trisomy 21
- Patients being treated with palliative intent

Specific aims

Chris O'Brien Lifehouse aims to use the ACOR to explore the epidemiology, clinical

presentation, and management of CTRCD amongst adult oncology patients receiving cardiotoxic therapies. In addition, a biobanking sub-study will attempt to identify gene polymorphisms predisposing individuals to developing ACT. It is hoped that such longitudinal data collection can lead to the introduction of an ACT susceptibility genetic screening test allowing for the inclusion of patient risk stratification prior to anthracycline exposure in routine cancer treatment.

Statistical methods

Descriptive statistics will be used for variables for quantitative analysis. Kaplan Meier analyses will be used for survival curves, freedom from cardiac failure since enrolment and freedom from arrhythmia since enrolment. An annual report will be produced.

Present accrual and target accrual

At the time of submission, 224 adult oncology patients have been recruited to the ACOR via Chris O'Brien Lifehouse with the opening of the biobanking sub-study currently in progress. The ACOR anticipates with full registered site capacity to capture 600 patients annually.

PO2-20-07

A case report of a severe cutaneous adverse event in triple negative breast cancer treated with chemoimmunotherapy

Presenting Author(s) and Co-Author(s):

A. Zhang. Case Western Reserve University/University Hospitals, United States

M. Beveridge. Case Western Reserve University/University Hospitals, United States

B. Moftakhar. Case Western Reserve University/University Hospitals, United States

Introduction Cutaneous adverse events related to immune checkpoint inhibitors (ICI) are common and most are mild. However, numerous case reports have documented severe ICI-related skin-toxicities such as Stevens-Johnsons Syndrome (SJS) most commonly among patients with melanoma and lung cancer as immunotherapy has now become a mainstay of treatment in these tumors. The use of ICIs in breast cancer treatment has only recently become standard of care for treatment of metastatic and high risk early-stage triple negative breast cancer with the publication of two landmark clinical trials, KEYNOTE-355 and KEYNOTE-522, respectively. While these trials report low rates of severe skin reactions, little is known about ICI-related severe skin toxicities in patients with breast cancer.

Case description A 58-year-old female with clinical stage IIB (cT2N0M0) triple negative breast cancer was undergoing neoadjuvant treatment with pembrolizumab, an anti-programmed death (PD-1) monoclonal antibody, coupled with a chemotherapy back-bone of 12 weekly treatments of carboplatin and paclitaxel followed by 4 cycles of doxorubicin and cyclophosphamide. She developed an erythematous and itchy rash on the right breast and axilla approximately 61 days into her treatment course after having received her fourth dose of pembrolizumab. Over the next 10 days, she developed progression of the rash with painful red papules coalescing into reticulated plaques and dusky blistering of the skin involving the right arm, axilla, abdomen, inguinal folds, thigh, and back, totaling < 10% total body surface area. Notably, the rash did not have mucosal involvement. She was hospitalized for close monitoring and treatment.

A punch biopsy of the rash revealed interface dermatitis with areas of full thickness skin necrosis consistent with erythema multiforme, SJS, toxic epidermal necrolysis (TEN), or a fixed drug eruption. Her skin continued to slough in the distribution of rash and a diagnosis of SJS was made. The patient had no response to initial treatment with high dose steroids. Cyclosporine was added, resulting in rapid improvement of her rash.

The patient's neoadjuvant treatment was stopped given the grade 3 SJS she experienced. Despite this truncated neoadjuvant treatment, she had excellent clinical response as her tumor was no longer palpable. She proceeded with a partial mastectomy and sentinel lymph node biopsy. Pathology revealed a pathological complete response. She did not receive any further systemic therapy in the adjuvant setting. Three months later, she was evaluated in clinic without evidence of SJS on physical exam. She was rapidly tapered off cyclosporine over one week without recurrence of her rash.

Discussion Severe cutaneous adverse events related to ICIs remains an emerging area of study. In SJS, drug-specific CD8+ T lymphocytes utilize granulysin to mediate keratinocyte apoptosis. It is hypothesized that the blocking of the PD-1/PD-L1 interaction by ICIs results in the disruption of T-cell homeostasis leading to self-directed cytotoxic and inflammatory reactions and ultimately epidermal detachment. In contrast, Molina et al 2020 postulate that such ICI-related skin reactions may represent a separate clinical entity from SJS. In their case report of seven patients, they propose the term "progressive immunotherapy-related

mucocutaneous eruption" (PIRME), which the authors suggest is characterized by delayed symptom onset, mild initial presentation, rare ocular involvement, benign clinical course, and favorable treatment response. Further characterization of ICI-related cutaneous adverse events is needed to understand the disease course, optimal treatment, and importantly, implications for re-challenging patients with immunotherapy. Clinicians taking care of breast cancer patients treated with ICIs need to be educated to recognize the associated skin toxicities as patients can rapidly worsen without appropriate treatment.

PO2-20-08

Metastatic Lung Cancer Masquerading as Metaplastic Breast Cancer

Presenting Author(s) and Co-Author(s):

T. Pai. Mayo Clinic, United States

M. Wasserman. Mayo Clinic, United States

J. Lewis. Mayo Clinic, United States

M. Komforti. Mayo Clinic, United States

J. Jakub. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

A. Lee. Mayo Clinic, United States

Y. Lou. Mayo Clinic, United States

P. Advani. Mayo Clinic, United States

R. Rao. Mayo Clinic, Jacksonville, United States

Background Metaplastic breast carcinoma (MBC) is an unusual malignancy that presents a diagnostic challenge due to the presence of varying cytomorphologies that can be seen in benign and malignant tumors. We posit that metastatic disease to the breast, itself an uncommon entity, should be considered in the differential diagnosis of MBC. We report a unique case of metastatic non-small cell lung cancer (NSCLC) with an actionable driver mutation that presented as a symptomatic breast mass and was initially considered to represent MBC. Report A 74-year-old woman with a 22-pack-year smoking history presented to the breast clinic complaining of a palpable left breast mass that had grown rapidly over the previous month. Ultrasound-guided biopsy of the breast mass revealed high-grade poorly differentiated carcinoma. On immunohistochemical (IHC) evaluation, tumor cells were strongly positive for epithelial markers CAM5.2 and keratin AE1/AE3, weakly positive for breast cancer (BC) marker TRPS1, and negative for BC marker GATA3, squamous cell carcinoma markers p63 and CK5, and melanoma marker SOX10. Metaplastic triple-negative BC was diagnosed. However, concern remained for metastasis from a non-breast primary tumor due to the patient's constitutional symptoms such as fatigue, night sweats, and 60-pound unintentional weight loss over the previous year, as well as interval development of a suspicious nodular rash on her right upper extremity. An FDG-PET-CT was obtained and demonstrated a hypermetabolic left lung consolidation (maximum SUV 33.3) measuring 7.2 cm, pulmonary nodules, and extensive thoracic lymphadenopathy. Due to rising suspicion for a primary lung tumor, additional IHC staining on the original breast biopsy was requested. Tumor cells were positive for TTF-1, consistent with metastatic lung adenocarcinoma. Tissue next-generation sequencing (NGS) identified a MET exon 14 skipping mutation, making the patient eligible for treatment with capmatinib, a first-line kinase inhibitor targeted therapy for metastatic NSCLC. At the time of this report, the patient has completed a course of palliative stereotactic body radiation therapy to the left lung and started capmatinib 400 mg BID, which she is tolerating well. Her first restaging scans after treatment initiation will be obtained one week after the time of this report. Conclusion In the absence of heightened suspicion for a non-breast primary tumor, our patient had initially received a diagnosis of triple-negative MBC. This diagnosis would have exposed her to increased treatment-related toxicities from cytotoxic chemotherapy and poor prognosis from MBC without survival benefit from targeted therapy for NSCLC. We advocate for the use of supplemental body imaging, expert and comprehensive IHC evaluation, and multidisciplinary discussion in cases of MBC and undifferentiated breast malignancy to

facilitate accurate diagnosis and treatment.

PO2-20-09

Hiding in plain sight: A heterogeneous response in a patient with metastatic HR+/HER2- breast cancer

Presenting Author(s) and Co-Author(s):

N. Priedigkeit. Dana-Farber Cancer Institute / Broad Institute of MIT and Harvard, Boston, Massachusetts, United States

J. Brock. Brigham and Women's Hospital, United States

O. Cunningham. Dana-Farber Cancer Institute, United States

M. Skeffington. Dana-Farber Cancer Institute, United States

M. Hughes. Dana Farber Cancer Institute, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

S. Lester. Harvard Medical School / Brigham and Women's Hospital, United States

H. Parsons. Dana Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

INTRODUCTION: Metastatic breast cancer is an infamously heterogeneous disease—characterized by a range of clinical presentations and treatment responses. In light of this heterogeneity, ASCO guidelines recommend patients with new, accessible metastatic tumors undergo a biopsy to inform treatment decisions. Here, we present a patient with HR+/HER2- disease with a long history of unusually heterogeneous responses—and a repeat metastatic biopsy that provided an answer.

CASE: A 55-year-old woman presented for consultation of treatment-refractory metastatic breast cancer. She was originally diagnosed with a right-sided Stage III HR+/HER2- invasive ductal carcinoma (IDC) at the age of 33. Upon staging, she was incidentally found to have a right lower-lobe lung carcinoid tumor that was removed by lobectomy. She underwent a partial mastectomy, axillary lymph node dissection, followed by adjuvant chemo- and radiation therapy. She tolerated one week of tamoxifen which was discontinued due to adverse effects. Fifteen years later, screening mammography revealed a suspicious lesion in the right breast—biopsy consistent with a new IDC. She underwent bilateral mastectomies which showed a pT1cNxM0 G2 IDC with associated DCIS (ER+/PR+/HER2 IHC 2+, FISH-negative, Oncotype RS 12). Genetic testing was negative. The patient trialed adjuvant tamoxifen, which was discontinued due to repeat adverse effects. Two years later, rising tumor markers prompted restaging scans that demonstrated an enlarging liver lesion. Liver biopsy was consistent with metastatic adenocarcinoma of the breast (ER+/PR+/HER2 IHC 0), GATA3 positive. Patient was started on letrozole with lupron and palbociclib with disease control for two years until progression in the bone, prompting a switch of letrozole to fulvestrant with continued palbociclib. Her disease was stable for two additional years until progression of multiple liver lesions. She was then started on single-agent paclitaxel. At this point, she was seen in our office for consultation and next-line therapy options. Repeat staging scans showed heterogeneous response in the liver with overall progression. ctDNA testing revealed a mutation in MEN1 (p.Q354*, 2.8% VAF) without other actionable alterations. Patient opted to enroll into a clinical trial of an experimental ER-antagonist but experienced progression of her liver lesions on first staging scans. A second liver biopsy was performed on a progressive lesion which showed ER-/PR-/HER2- disease. She opted to enroll into a Phase 1b/2 trial with sacituzumab govitecan-hzyi in combination with a PARPi. Staging scans again showed a mixed

response in the liver. Given a history of mixed responses and discordant receptor staining, the differential diagnosis included loss of hormone receptor expression in the breast carcinoma versus metastases from an occult neoplasm. Additional immunohistochemical studies were performed on a subsequent liver biopsy showing positivity for chromogranin, synaptophysin, and INSM1, and negative results for ER, PR, GATA3, and TRPS1. Next-generation sequencing of the progressive lesion revealed a MEN1 SNV (p.Q354*, VAF 82%) as well as loss of 11q (MEN1 locus) suggestive of biallelic loss of MEN1—providing molecular evidence of a metastatic carcinoid tumor. A history of mixed response in the liver was concluded to be two coexisting neoplasms—a metastatic HR+/HER2- breast cancer as well as a late recurrence of a right-lower lobe carcinoid tumor from 22 years prior.

DISCUSSION: The unanticipated discovery of an occult, coexisting neoplasm in the setting of a metastatic HR+/HER2- breast cancer illustrates the value of meticulous pathological review, repeat molecular testing and the use of next-generation diagnostic tools such as tumor sequencing in the advanced setting—particularly when a clinical story defies conventional expectations—to personalize care and optimize oncologic management in the face of complex biology.

PO2-20-10

Exceptional long-term disease control on pembrolizumab monotherapy in a patient with TMB-high PMS2-mutated MMR-deficient triple negative breast cancer brain metastasis

Presenting Author(s) and Co-Author(s):

J. Cha. University of California, San Francisco, Boston, Massachusetts, United States

A. Grinshpun. Dana-Farber Cancer Institute, and Harvard Medical School, United States

L. Buckley. Dana-Farber Cancer Institute, United States

B. Alexander. Foundation Medicine, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

Introduction The brain is among the most common sites of breast cancer (BC) spread. Prognosis of BC brain metastasis (BCBM) differs by receptor subtype, with poorest median overall survival (OS) for triple-negative (TN) BCBM at under 5 months. Though treatment guidelines have evolved in recent years, most strategies have focused on local therapies including surgery and stereotactic radiotherapy (SRT), rather than on systemic agents. The 2020 FDA approval of pembrolizumab (pembro) for patients (pts) with metastatic high-tumor mutational burden (TMB-h, ≥ 10 mutations/megabase) solid tumors, agnostic of primary site, combined with clinical trials in melanoma reporting efficacy of immune checkpoint inhibitors (ICI) against BM, suggest a potential use of ICI for pts with TMB-h BCBM. Results of the TAPUR study supported modest therapeutic benefit of pembro for 28 pts with metastatic BC selected for TMB-h, with median OS of 30.6 weeks, but did not include pts with active BCBM. TMB-h is uncommon in BC, and further genomic signatures remain to be elucidated to identify pts with BCBM responsive to ICI. We present a remarkable case of a pt with Lynch Syndrome (LS) due to a germline PMS2 mutation, who developed TMB-h, mismatch repair (MMR)-deficient TN BCBM, and has maintained stable disease for over 6 years on pembro monotherapy. **Case description** A 62-y.o. woman underwent screening mammography that identified a right breast mass. Pt has a family history of a mother with uterine and pancreatic cancer, and father with bladder cancer. Biopsy confirmed invasive ductal carcinoma (IDC), grade 1 (G1), ER/PR-positive, HER2 score 0. She underwent partial mastectomy, axillary dissection, radiation, and received adjuvant anastrozole. Three years later, while still on anastrozole, she presented with a 6 cm right breast mass. Mastectomy disclosed G3, ER/PR-negative, HER2-positive (3+, Her2:CEP17 ratio 5.6) IDC. She received adjuvant chemotherapy (AC-T) and 1 year of trastuzumab. Seven years later, pt presented with headaches and word finding difficulties. MRI identified a 3.6 cm frontal mass, which biopsy revealed as TN BCBM. Systemic imaging ruled out distant metastases. Pt proceeded with SRT and exemestane (despite receptor staining ER- in case of a possible false negative result). Despite radiotherapy, pt had BCBM progression within the same year with the largest mass diameter grown to 4.8 cm. Resection (followed by SRT) identified the dominant histology as G3 TNBC. Following transition of care to our institution, germline testing revealed a pathogenic mutation in PMS2 (c943C >T). Tumor sequencing of the resected brain metastasis showed TMB of 48 and MMR deficiency. Therefore, systemic therapy with pembro monotherapy was initiated and maintained with good tolerability. Two years later, concern for progression from rising tumor markers led to addition of concurrent carboplatin/gemcitabine for 5 cycles. Imaging and tumor markers stabilized, and pt returned to pembro monotherapy. Today, 3 years later, and over 6.5 years after initial TN BCBM diagnosis, pt continues to have stable disease on pembro with an

excellent performance status (ECOG 0) and no evidence of intracranial or extracranial progression. Discussion We document an exceptional case of prolonged benefit to pembro in a pt with TMB-h PMS2-mutated MMR-deficient TN BCBM. This case highlights two major pragmatic points to clinical practice; (i) the significance of germline testing in all pts with metastatic BC, and (ii) the impact of molecular testing of tumor tissue to identify rare alterations which may have dramatic effects on pt outcomes. Altogether, this case is a remarkable addition to growing evidence that TMB could be a biomarker for predicting response to ICI therapy and provides an example of ICI efficacy in the setting of BCBM. Further research on additional genomic, clinical, and pathologic features associated with ICI responsiveness is warranted for greater precision in BCBM management.

PO2-20-11

Safety and efficacy of KEYNOTE-522 in combination with anti-retroviral therapy in a patient with HIV and triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

S. Haddad. Department of Medicine, Graduate Medical Education, Brown University/Kent Hospital, Warwick, RI, USA, East Providence, Rhode Island, United States

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

M. Hadfield. Division of Hematology and Medical Oncology, Lifespan Cancer Institute and Legorreta Cancer Center, Warren Alpert Medical School of Brown University, Providence, RI, USA, United States

Y. Wang. Department of Pathology and Laboratory Medicine, Rhode Island Hospital and Lifespan Medical Center, Warren Alpert Medical School of Brown University, Providence, RI, USA, United States

C. Taneja. Department of Surgery, Rhode Island Hospital, Lifespan Cancer Institute, Brown University Warren Alpert Medical School, Providence, RI, USA, United States

K. Leonard. Department of Radiation Oncology, Rhode Island Hospital, Lifespan Cancer Institute, Brown University Warren Alpert Medical School, Providence, RI, USA, United States

M. Sanchez. Department of Infectious Disease & Immunology, Rhode Island Hospital and Lifespan Medical Center, Providence, RI, USA, United States

R. Ward. Rhode Island Medical Imaging and Department of Radiology, Rhode Island Hospital and Lifespan Medical Center, Warren Alpert Medical School of Brown University, Providence, RI, USA, United States

A. Lourenco. Rhode Island Medical Imaging and Department of Radiology, Rhode Island Hospital and Lifespan Medical Center, Warren Alpert Medical School of Brown University, Providence, RI, USA, United States

M. Fenton. Division of Hematology and Medical Oncology, Lifespan Cancer Institute and Legorreta Cancer Center, Warren Alpert Medical School of Brown University, Providence, RI, United States

Introduction:

Triple-negative breast cancer (TNBC) is a subtype of breast cancer (BC) that does not express estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER-2), accounting for about 15% of all BC. TNBC is more aggressive than other BC with a higher risk of recurrence and mortality. The current standard of care for high-risk, early-stage TNBC based on the KEYNOTE-522 trial is neoadjuvant multidrug chemotherapy (paclitaxel and carboplatin [TCb] weekly x 12 weeks and doxorubicin and cyclophosphamide [AC] Q3 weeks) with pembrolizumab (P). The trial demonstrated patients who received chemotherapy plus P had a higher pathological complete response and event-free survival compared to patients who received chemotherapy plus placebo. However, the trial excluded patients with any autoimmune disease requiring treatment within 2 years, a diagnosis of immunodeficiency or steroids within 7 days before the first treatment, or a known history of human immunodeficiency virus (HIV). While limited data exist on immune checkpoint inhibitors (ICI) in patients with immunodeficiencies, subsequent data demonstrate that patients with HIV have similar efficacy and immune-related adverse events (irAE) compared to patients without HIV, and 2017 consensus recommendations encouraged broader eligibility in clinical trials to

include patients with HIV. We present one of the first reported clinical cases of a patient with HIV diagnosed with stage IIB TNBC, treated per KEYNOTE-522 and anti-retroviral therapy (ART).

Clinical Case:

A 55-year-old female with a medical history significant for HIV, self-detected a mass in her left breast. Diagnostic imaging demonstrated a suspicious 4.0 cm mass in the left breast without adenopathy. An ultrasound-guided biopsy of the mass revealed grade 3 invasive ductal carcinoma with ER 0%, PR < 1%, and HER-2 1+. The clinical stage was cT2N0M0, prognostic stage IIB. Genetic testing was positive for germline BRCA2 pathogenic variant. HIV PCR < 20 copies/mL and CD4 count 1.298 K/uL prior to neoadjuvant chemotherapy. The patient was adherent to HIV ART with bicitgravir, emtricitabine, and tenofovir alafenamide. The patient received KEYNOTE-522, including 11 cycles of TCb-P, followed by four cycles of AC-P. Following neoadjuvant treatment, the patient underwent a left segmental mastectomy and sentinel lymph node biopsy and achieved a pathological complete response. She completed left whole breast radiation (RT) with 3DCRT plus 3DCRT tumor bed boost to a total dose of 48.06 cGy and one-year of adjuvant P.

Treatment-related adverse events included grade 4 febrile neutropenia after cycle one AC without growth factor, requiring a 5-day hospitalization; and grade 3 peripheral neuropathy, resulting in discontinuation of week 12 of TCb. The patient also developed paronychia, and a pulmonary embolism after week 11 of TCb. She had no irAE. Radiation-related adverse events included grade 1 left breast dermatitis and fatigue and mild left breast soreness.

Discussion:

Among the subset of patients diagnosed with TNBC, the percentage of patients with HIV or immunodeficiency receiving active BC treatment is low. Safety and efficacy data for novel cancer therapeutics including ICI are limited since historically patients with HIV and other immunodeficiency states were excluded from trials. Anti-PD-1 ICI has become a key part of the standard of care for the treatment of breast cancer. Patients with HIV experience rare infectious complications and have a life expectancy near the general population with ART. We support the inclusion of patients with HIV in future clinical trials for TNBC and/or ICI and recommend treatment of patients with HIV and TNBC per standard of care in multi-disciplinary collaboration with HIV clinicians.

PO2-20-12

Breast Implant-associated Squamous Cell Carcinoma

Presenting Author(s) and Co-Author(s):

F. Azad. University at Buffalo, United States

A. Siva. University at Buffalo, United States

P. Patel. University at Buffalo, United States

C. Miranda. University at Buffalo, United States

M. Gravina. University at Buffalo, United States

A 54-year-old female with a history of bilateral breast implants presented with intermittent left breast pain for 6 months. She first had bilateral breast implants placed in 1996 and had no reported issues until 2010, when she had bacteremia and seeding infection with subsequent removal of both implants. She then had a second set of silicone-based implants placed in 2012 with no issues for 10 years. Family history was negative for breast cancer or any other malignancy. She had no prior smoking history. Vital signs and laboratory values were unremarkable. On exam, the left breast appeared larger than the right, dense, thickened, and slightly edematous. No lymphadenopathy was palpated. Both mammogram and ultrasound of bilateral breasts, done at the onset of her pain, were normal. Given the patient's symptoms, an MRI of the breasts was done, with findings concerning an infection or lymphoma. It revealed an irregular fluid collection in the left breast. The fluid collection was rim-enhancing with frond-like areas of enhancing tissue, extending through the inferior aspect of the capsule into the subcutaneous tissue of the lower outer quadrant of the left breast. Enhancement and edema extended off of the superior and posterior aspect of the prosthesis into the pectoralis muscle. It was particularly prominent along the medial aspect of the prosthesis where it extended in the chest wall between the sternum and the costal cartilage. There were 3 mildly enlarged left intramammary lymph nodes measuring up to 7 mm in short axis, with diffuse edema seen within the breast. No axillary adenopathy was seen in the MRI. She was referred to surgery and had both right and left breast implants removed, and a left breast JP drain was placed. The pathology from the left breast capsule excision revealed squamous cell carcinoma, well-differentiated and invasive, associated with a scar and extending to the surgical margin. She was diagnosed with a rare case of breast implant-associated squamous cell carcinoma (BIA-SCC). Subsequent staging imaging showed postsurgical inflammatory changes with no nodal metastatic disease. She continued to follow up outpatient with plans of multidisciplinary meeting to discuss long-term treatment options. Most patients undergoing breast augmentation experience no serious complications. Previously, rare incidences of breast-implant-associated anaplastic large cell lymphoma (BIA-ALCL) had been reported, with 1234 cases as of 2022. More recently, cases of BIA-SCC have been seen. Primary SCC of the breast is extremely rare in both augmented and non-augmented women. 19 cases of BIA-SCC are reported in the literature as of 2022, all seen in females, typically arising from capsular tissue around the breast implant. It is a rare and potentially aggressive malignancy, with unclear etiology and undefined therapy regimen due to a paucity of data. Suggested treatments include resection with a negative margin, although this could require an extensive and complex reconstruction, including plastic surgery soft tissue coverage of the resection defect. Definitive radiation to obtain local control can be considered in an organ-sparing approach. Consideration can also be given to either chemosensitization with agents such as cisplatin or combining radiation with immunotherapy.

PO2-21-01

Granular Cell Tumors of the Breast: A Case Series

Presenting Author(s) and Co-Author(s):

S. Kochi. Georgetown School of Medicine, United States

M. Karsten. Georgetown School of Medicine, United States

M. Masanam. Medstar Georgetown University Hospital, United States

T. Thorson. Medstar Georgetown University Hospital, Department of Breast Surgery, United States

R. Derakhshandeh. Medstar Georgetown University Hospital, Department of Pathology, United States

P. Wehner. Medstar Georgetown University Hospital, Department of Breast Surgery, United States

L. De La Cruz. Medstar Georgetown University Hospital, Department of Breast Surgery, United States

J. Son. MedStar Georgetown/MedStar Montgomery, North Bethesda, Maryland, United States

Objective: Granular cell tumors (GCT) of the breast are rare, Schwann-cell derived tumors that are largely benign in nature, but may present with malignant characteristics in 1-2% of cases. There are few reports highlighting the clinical presentation, cytologic differences, operative management and clinical outcomes of patients with these benign versus malignant GCTs. Here, the authors report the clinical course of 9 patients identified with either benign or malignant GCT of the breast. **Methods:** The medical records for a total of 9 patients treated for histologically confirmed GCT of the breast between March 2015 and May 2023 at our institution were retrospectively reviewed. Clinical data, imaging findings, immunohistochemical markers, surgical interventions, and clinical follow-up data were collected and analyzed. **Results:** All patients were female, with a mean age of 46 years (Range: 29-61). 5 (56%) patients presented with left-sided lesions with an average maximum dimension of 1.1 cm (SD: 0.7 cm). All 9 (100%) tumors were positive for S100, 4 (44%) were positive for CD68, and 3 (33%) were positive for Inhibin. 4 (44%) patients underwent local mass excision, 3 (33%) underwent lumpectomy, 1 (11%) underwent lumpectomy with sentinel lymph node biopsy, and 1 (11%) underwent partial mastectomy with sentinel lymph node biopsy. There were no perioperative complications nor complications noted at postoperative follow up visits. 1 patient (11%) had 2 recorded recurrences of GCT after the initial breast mass excision, with each tumor exhibiting different positive immunohistochemical markers. 1 (11%) patient had a previous history of breast cancer at time of GCT diagnosis, and 1 (11%) patient had concurrent breast malignancy with the granular cell tumor being in the lymph node of the same breast. **Conclusions:** Granular cell tumors of the breast are rare Schwann cell derived tumors that often present near breast scar tissue as spiculated, ill-defined masses with microcalcifications on radiologic imaging, mimicking breast malignancy, leading to overtreatment. This study found that for GCTBs that present in lymph nodes, regardless of low malignant potential seen histologically, there was a higher risk of recurrence, and may require further workup and close follow up after wide local excision. For all other granular cell tumors presenting with normal appearing lymph nodes on imaging, a local mass excision was adequate in management, with low risk of recurrence or malignant potential. Future studies should be performed analyzing long-term follow up for these patients to determine risk of recurrence over longer periods of time, and risk for breast malignancy.

Granular Cell Tumor Characteristics

Patient	Age	Laterality	Location	Maximum Dimension (cm)	Positive Immunohistochemistry
1	29	Left	2 o'clock	1.5	S100, CD68, Calretinin, Inhibin, and NSE
2	54	Left	8 o'clock	0.8	S100, Vimentin
3	51	Right	7 o'clock	0.5	S100, Calretinin, and CD68
4	33	Left	8 o'clock	1.1	S100 and Inhibin
5	32	Right	11 o'clock	0.5	S100 and CD68
6	43	Left	2 o'clock	0.9	S100
7	61	Right	9 o'clock	2.8	S100, CD68, SOX10, and Inhibin
8	56	Right	12 o'clock	0.5	*IHC not available from outside report*
9	59	Left	10 o'clock	1.7	S100, CD68

Tumor characteristics including laterality, tumor location, maximum dimension in centimeters, and positive immunohistochemistry markers were shown for each patient.

PO2-22-02

Characterization of peripheral T-cell dynamics in the patients with bone metastasis from breast cancer following stereotactic body radiotherapy

Presenting Author(s) and Co-Author(s):

S. Jeon. Department of Radiation Oncology, Seoul National University Bundang Hospital, United States

E. Shin. Korea Advanced Institute of Science and Technology, United States

I. Kim. Department of Radiation Oncology, Seoul National University Bundang Hospital, Seongnam, Korea, Republic of Korea

Purpose: Preclinical studies suggest that radiotherapy (RT) elicits various effects on antitumor T-cell responses. However, systemic T-cell responses upon RT in real-world cancer patients, including those with metastatic breast cancer, are poorly characterized. This study aims to investigate the detailed dynamics of peripheral T cells upon stereotactic body radiotherapy (SBRT) in metastatic breast cancer patients. **Methods:** Peripheral blood samples of 32 prospectively recruited patients who received SBRT to bone metastasis of breast cancer, which were acquired at pre-SBRT (W0), 1 week after SBRT (W1), and 4 weeks after SBRT (W4), were analyzed using multi-color flow cytometry and cytometric bead array. Most patients (n = 30) received SBRT of 1 fraction (n = 16) or 3 fractions (n = 14). We also performed a subgroup analysis of 22 patients who did not start a new systemic therapy within 1 month before SBRT (new systemic Tx >1mo) to exclude the effects of systemic therapies. **Results:** Peripheral PD-1+ CD8+ T cells, which are enriched for tumor-specific clonotypes, were activated with increased expression of Ki-67 at W1 compared to W0. Expression of Ki-67 on PD-1+ CD8+ T cells remained higher at W4 than W0, although it was not statistically significant. Moreover, expressions of Ki-67 and CTLA-4 on circulating regulatory T (TREG) cells were increased at W1 compared to W0. The suppressive (Foxp3hiCD45RA-) TREG cells also exhibited enhanced expressions of Ki-67 and CTLA-4 at W1. We defined immunologic responders (ImmRs) as patients with Ki-67 expression on PD-1+ CD8+ T cells at W1 greater than 1.5-times of W0, and otherwise immunologic non-responders (ImmNRs). Notably, fold changes in expressions of Ki-67 and CTLA-4 on TREG cells and proportion of suppressive TREG cells among total TREG cells at W1 over W0 were higher in ImmRs than ImmNRs. Similar phenotypical changes of T cells were observed in the subgroup analysis of the patients with new systemic Tx >1mo. The peripheral T-cell changes were not significantly different between the dose-fractionation schedules (1 fraction vs. 3 fractions) nor molecular subtypes of cancer. In patients with new systemic Tx >1mo, plasma level changes of TGF- β 1, sCTLA-4, and s4-1BB at W1 compared to W0 were significantly higher in ImmRs compared to ImmNRs, while only change of s4-1BB was associated with the immunologic response. **Conclusions:** Our results suggest that circulating PD-1+ CD8+ T cells are activated upon SBRT. However, SBRT also results in the activation of circulating TREG cells, which was more prominent in patients with a significant activation of circulating PD-1+ CD8+ T cells. Alterations in plasma levels of TGF- β 1, sCTLA-4, and s4-1BB are associated with the peripheral T-cell responses. Dose-fractionation schedule is not associated with the peripheral T-cell responses. Work supported by grants from the National Research Foundation of Korea (NRF-2023R1A2C3003782)

PO2-22-03

Reirradiation for locally recurrent breast cancer: a long-term single centre experience

Presenting Author(s) and Co-Author(s):

J. Baude. Institut Curie, France

R. Dendale. Institut Curie, France

A. Fourquet. Institut Curie, France

Y. Kirova. Institut Curie, Paris, Ile-de-France, France

Background:

About 10–15% of patients with breast cancer will eventually develop an ipsilateral breast recurrence. The management of cancer relapse in previously irradiated tissues is a challenging therapeutic issue, and data on breast re-irradiation are currently lacking. Hence, the aim of this work was to report our experience with breast re-irradiation for non-metastatic recurrent breast cancer.

Material and Methods:

All patients who underwent a breast or chest wall re-irradiation in the Institut Curie, Paris, France between 2003 and 2019 were identified. Those who underwent re-irradiation only in other volumes than the ipsilateral breast were excluded. Local recurrence-free (LRFS), overall survival (OS), disease-specific survival (DSS), progression-free survival (PFS), and metastasis-free survival (MFS) were evaluated. Physician-reported acute and late toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Results:

Between 2003 and 2019, 21,372 patients underwent a breast irradiation in our institution. Of these, 453 received a new irradiation to the contralateral breast and/or lymph nodes, 105 to the homolateral lymph nodes without breast/chest wall re-irradiation and 28 received a second course of radiotherapy (RT) to the homolateral breast. These 28 patients were included in this study. Median follow up after re-irradiation was 45.5 months (IQR 33.5-79.75 months). The median age at the time of second breast RT was 63 years (IQR, 49-78). The median RT dose to the breast/chest wall was 60 Gy (interquartile range (IQR) 50-66 Gy) for the first irradiation and 48 Gy (IQR 30-50 Gy) for the second. The median cumulative dose was 100 Gy (IQR 92-114 Gy). The median time between the two courses of RT was 47 months (IQR 22.75-109.5 months). Eighteen (64%) patients were treated with a curative intent and 10 (36%) for palliative purposes. Ten (36%) had a macroscopic breast residue at re-irradiation. The second RT course was performed with electrons, photons and a combination of both in 13 (46%), 8 (29%) and 6 (21%) patients, respectively. At 2 years, LRFS, OS, DSS, PFS and MFS were respectively 59%, 79%, 82%, 50% and 75% in the whole cohort. 2-year-LRFS (72% vs 31%, $p=0.02$), OS (94% vs 50%, $p<0.01$), DSS (94% vs 56%, $p<0.01$) and PFS (61% vs 20%, $p=0.02$) differed significantly between patients treated in a curative or in a palliative intent, but not MFS (78% vs 69%, $p=0.77$). Among patients, 8 (29%) remained relapse-free 5 years after the second course of RT. Only one patient experienced an acute grade 3 adverse event (dermatitis), and 1 presented a late grade 3 one (skin fibrosis). One patient with major cardiovascular risk factors died of myocardial infarction 13 months after the second left breast irradiation.

Conclusion:

Breast or chest wall re-irradiation appears to be feasible with good disease control in patients treated with a curative intent, and acceptable toxicity rates. In addition, a significant number of

patients were disease-free 5 years after the second course of RT. Prospective larger data with longer follow-up are needed to confirm these findings.

PO2-22-04

Median Five-Year Follow-Up Results from the Multi-Institution Trial for the Treatment of Early-Stage Breast Cancer Using Intra-Operative Electronic Brachytherapy

Presenting Author(s) and Co-Author(s):

B. Schwartzberg. Schwartzberg Center for Minimally Invasive Breast Surgery, Santa Rosa, California, United States

A. Syed. MemorialCare Health System, Long Beach, California, United States

A. Bhatnagar. Cancer Treatment Services of Arizona, Casa Grande, Arizona, United States

S. Rahman. Diablo Valley Oncology Hematology Medical Group, Pleasant Hill, California, United States

V. Jones. City of Hope, California, United States

A. Chang. Revlon/UCLA Breast Center, Los Angeles, California, United States

T. Cockerham. Sarah Cannon Cancer Center at Parkridge Medical Center, Chattanooga, Tennessee, United States

V. Osborn. Exeter Hospital, Exeter, New Hampshire, United States

R. Cohen. Sentara Northern Virginia Medical Center, Woodbridge, Virginia, United States

C. Hodge. Advent Health Florida Hospital, Orlando, Florida, United States

C. Lopez-Penalver. Miami Cancer Institute at Baptist Health, Inc., Miami, Florida, United States

B. Chakravarthy. Vanderbilt University Medical Center, Nashville, Tennessee, United States

W. Dooley. OU Health University of Oklahoma Medical Center, Oklahoma City, Oklahoma, United States

C. Madu. Staten Island University Hospital, Staten Island, New York, United States

A. Okabe. MedStar Franklin Square Medical Center, Baltimore, Maryland, United States

M. Farha. MedStar Good Samaritan Hospital, Baltimore, Maryland, United States

A. Madrigano. Rush University Medical Center, United States

C. Morrison. University of Arizona Medical Center, Tucson, Arizona, United States

G. Neuner. Greater Baltimore Medical Center, Baltimore, Maryland, United States

C. Wengler. Cleveland Clinic Martin Health, Stuart, Florida, United States

S. David. Monash Health/ Peter MacCullum Centre, Melbourne, Victoria, Australia

K. Toosie. Tri City Medical Center, Oceanside, California, United States

B. Stephens. Lutheran Health Network, Fort Wayne, Indiana, United States

Background: An IRB-approved single arm prospective multi-institution trial was designed to determine the efficacy and outcome of single fraction 20 Gy intra-operative radiation therapy (IORT) using disposable balloon electronic brachytherapy at the time of breast conserving surgery for early-stage breast cancer (women at least 40 years old, infiltrating ductal carcinoma [IDC] or ductal carcinoma in situ [DCIS], single lesion no larger than 3 cm, pN0). Ipsilateral breast tumor recurrences (IBTR) at median 5-year follow-up, the primary protocol endpoint of the trial, would be analyzed with outcomes compared to reported whole breast radiation therapy (WBRT) results. Methods: Between May 2012–July 2018, 1199 enrolled breast cancer patients at twenty-six national and international institutions were successfully treated per protocol with lumpectomy plus single 20 Gy fraction IORT using disposable balloon electronic brachytherapy.

Data collection and retrospective chart review included demographics, treatment, histopathology, toxicity, IBTR (defined as recurrence in the lumpectomy cavity/index quadrant), and survival. Results: All subjects were successfully treated with a single 20 Gy fraction of IORT. IORT cohort characteristics of the treated subjects are summarized in Table 1. Sixty-six (5.5%) patients received subsequent unplanned risk-adjusted WBRT. At median 5.0-year follow-up (range 0.5 – 9 years), there were 42 (3.50%) IBTR. The original mean tumor size of patients with IBTR was 13.6mm (range 0.03 - 30mm). The mean time to IBTR was 47.6 months (range 12 – 98 months). There were 30 IBTR in patients originally diagnosed with IDC, and 12 IBTR among patients originally diagnosed with DCIS. Three patients originally diagnosed with IDC recurred as DCIS, while 4 patients with DCIS recurred as IDC. The remainder recurred with the same pathology as their original diagnoses. Sorting by 2017 ASTRO accelerated partial breast irradiation (APBI) criteria, there were 25 IBTR in patients categorized immediately following lumpectomy plus IORT as Suitable, 12 IBTR among patients categorized immediately following lumpectomy plus IORT as Cautionary, and 5 IBTR in patients categorized immediately following lumpectomy plus IORT as Unsuitable. Nine (0.75%) patients experienced new ipsilateral primary breast cancers, with 8 classified as Suitable and one as Cautionary using post-lumpectomy plus IORT ASTRO APBI criteria. Seventeen (1.4%) patients experienced acute serious adverse events (SAEs). These included 5 wound infections, 4 hematomas, 2 skin ulcerations, 2 cellulitis, 2 seromas, 1 skin necrosis, and 1 wound dehiscence. All SAEs resolved within 6 months of IORT. One patient died of breast cancer metastases at 3-year follow-up. One patient who was diagnosed with IBTR at 3-year follow-up died 3 years later from dementia. There were 45 unrelated patient deaths. Conclusions: At median 5.0-year follow-up, the 1199 early-stage breast cancer patients successfully treated in this multi-institution trial with a single 20 Gy fraction of IORT to the lumpectomy cavity at the time of partial mastectomy experienced an IBTR of 3.50%. This recurrence rate is acceptable when compared to the 0.9% - 2.5% IBTR reported for WBRT, given the benefits of IORT (convenience, decreased exposure to XRT, better cosmetic outcome, patient preference).

Table 1. IORT cohort characteristics

IORT Cohort Characteristics	
Mean Age (range)	66 years (ages 41-93)
Ethnicity	
Caucasian	962 (80.2%)
African American	82 (6.8%)
Hispanic	84 (7.0%)
Asian	43 (3.6%)
Native American	7 (0.6%)
Other/unknown	21 (1.8%)
Mean tumor size (range)	11.5mm (0.03-90)
Tumor type at lumpectomy	
IDC	964 (80.4%)
DCIS	223 (18.6%)
Other	12 (1.0%)
2017 ASTRO APBI categories (post-lumpectomy plus IORT)	
Suitable	890 (74.2%)
Cautionary	187 (15.6%)
Unsuitable	122 (10.2%)

PO2-22-05

A prospective phase I-II study of hypofractionated accelerated breast and nodal intensity modulated radiation therapy delivered in the prone position

Presenting Author(s) and Co-Author(s):

J. Purswani. New York University Grossman School of Medicine, New York, United States

O. Maisonet. New York University Grossman School of Medicine, United States

J. Xiao. New York University Grossman School of Medicine, United States

J. Teruel. New York University Grossman School of Medicine, United States

C. Hitchen. New York University Grossman School of Medicine, United States

X. Li. New York University Grossman School of Medicine, United States

J. Goldberg. New York University Grossman School of Medicine, United States

C. Perez. New York University Grossman School of Medicine, United States

S. Formenti. Weill Cornell Medical Center, United States

N. Gerber. New York University Grossman School of Medicine, United States

Background In patients with breast cancer, prone radiotherapy (RT) has been shown to reduce heart and lung dose. Routinely used for whole breast (WB) RT, its use to treat regional lymph nodes (LNs) is not widespread. **Methods** In this phase I-II study (NCT02308488) patients treated with lumpectomy or mastectomy with 1-5 pathologically involved LNs underwent WBRT or post-mastectomy RT plus regional nodal RT using IMRT to the supraclavicular and level III axillary LNs. The prescription was 40.5Gy in 15 daily 2.7Gy fractions with a daily concomitant 0.5Gy tumor bed boost. Patients who underwent sentinel LN biopsy (SLNB) alone (no axillary dissection) had the level I-II axilla included in the RT field. The primary endpoints were incidence of >grade 2 acute toxicity per CTCAE v 3.0 and dosimetric feasibility. The secondary endpoint was late toxicity. Clinical outcomes were local recurrence (LR), disease free survival (DFS), distant recurrence free survival (DRFS) and overall survival (OS). Coverage constraints included planning target volume [PTV] V48Gy \geq 98%, PTV breast V40.5Gy \geq 95% and PTV nodes V38.5Gy \geq 95%. Normal tissue constraints included heart V5Gy < 5%, ipsilateral lung V10Gy < 20%, contralateral lung V5Gy < 15%, ipsilateral brachial plexus (BP) maximal dose (Dmax) < 42Gy, spinal cord Dmax \leq 37.5Gy, thyroid contralateral lobe Dmax \leq 15Gy, esophagus V30Gy < 50% and Dmax \leq 40.5Gy. **Results** From 2011-2016, 97 patients with stage IB-IIA breast cancer were enrolled. 66 underwent lumpectomy and 31 underwent mastectomy. 16 had SLNB alone. There were no grade 3 acute toxicities meeting the primary toxicity endpoint. Common acute low-grade toxicities included fatigue (grade 1: 65 [66.3%]; grade 2: 7 [7.1%]), esophagitis (grade 1: 7 [7.1%]; grade 2: 10 [10.2%]), dermatitis (grade 1: 82 [83.7%]; grade 2: 7 [7.1%]). At median and maximum follow up of 8.02 (IQR: 3.31) and 13.3 years, respectively, there were 2 LRs (2.1%). 8-year DRFS, DFS and OS were 88.1% (95% CI 81.3%, 95.4%), 85.7% (95% CI 78.4%, 94.6%) and 90.5% (95% CI 84%, 97.6%), respectively. Clinician-rated cosmesis (n=64) was excellent/good in 67.2% of cases and fair/poor in 6.3%. Patient-rated cosmesis (n=47) was excellent/good in 91.5% and fair/poor in 8.5%, with patients rating themselves more favorably than their physicians (p=0.0014). The incidence of maximum grade 1, 2 and 3 late toxicities were 49 (62.8%), 15 (19.2%), and 3 (3.8%), respectively. This included 2 grade 3 asymmetries, 1 grade 3 pigmentation change, and 1 grade 2 pneumonitis. There was no brachial plexopathy. Among the 28 patients who underwent reconstruction, 17 were implant-based and 11 were autologous. Of the implant-based, 9 underwent RT to the tissue expander and 8 to the permanent implant. 11/28 patients had long-term plastic surgery

follow up. There were 3 hospitalizations with reoperation post-RT (1 unplanned revision, 1 implant removal for threatened exposure, and 1 excision of fat necrosis). There was 1 incident of wound infection/ cellulitis. With regard to dosimetric constraints, 54.3% of plans (95% CI 43.6%, 64.8%) met all constraints. 92% (95% CI 83%, 97%), 98% (95% CI 93%, 100%) and 89% (95% CI 80%, 94%) met the PTV tumor V48Gy, PTV breast V40.5Gy, and PTV nodes V38.5Gy coverage constraints, respectively. Heart, contralateral lung, spinal cord, and esophagus constraints were met by all patients. 95% (95% CI 88.6%, 98.4%) met the ipsilateral lung V10Gy and 99% (95% CI 94%, 100%) met the thyroid contralateral lobe constraint. The BP constraint was met in 73% (95% CI 63.0%, 81.0%) of plans with a mean increase of 1.61 Gy (SD 1.96 Gy) over target. Conclusion Toxicity was low and outcomes were excellent in this prospective trial of hypofractionated regional nodal RT in the prone position. Dosimetric constraints were only met in 54% of plans with the nodal coverage and the BP constraint as the most frequently unmet. These constraints may need to be modified and/or techniques refined to optimize hypofractionated prone nodal RT.

PO2-22-06

MRI response Assessment of Single Fraction Pre-operative Stereotactic Radiotherapy: Preliminary results

Presenting Author(s) and Co-Author(s):

B. Dogan. UT Southwestern Medical Center, Dallas, Texas, United States

S. Sahoo. University of Texas Southwestern Medical Center, United States

M. Leitch. UTSW Medical Center, United States

P. Alluri. UTSW, United States

R. Timmerman. UTSW, United States

D. Farr. UT Southwestern Medical Center, United States

A. Rahimi. University of Texas Southwestern Medical Center, Dallas, Texas, United States

Background: Pre-operative stereotactic breast irradiation (SPBI) improves targeting precision and has the potential to decrease treatment-related toxicity while downstaging or eliminating cancer. Accurate pCR prediction may allow omission of surgery. We are reporting initial interim results of the performance of multiparametric breast MRI in identifying pathologic response rate after single-fraction pre-operative SPBI in early stage estrogen receptor-positive (ER+), HER-2 negative breast cancer. Methods: In an ongoing single center prospective single-arm trial 22 patients with ER+/HER2-negative, cN0, unifocal, invasive breast cancer ≤ 3 cm underwent single-dose ablative SPBI, followed by definitive surgery per standard of care. Residual disease vs complete imaging response to SPBI was assessed on baseline and post-SPBI/pre-operative breast MRI. Pathologic response was categorized using MDACC Residual Cancer Burden (RCB) Categories. Wilcoxon rank sum test was used to assess the correlation of pathologic complete response (pCR) or RCB status on final path with MRI lesion size, volume, diffusion weighted imaging apparent diffusion coefficient (ADC) value, and when available, presence of residual enhancement on pre-operative MRI. MRI volume and ADC values were obtained using a dedicated CAD software. Area under the receiver operating Curve(AUC) was constructed to assess the diagnostic performance of pre-operative MRI on predicting pathologic response. Results Mean patient age was 64.9 (SD ± 7.3) years, tumor diameter 1.2(± 0.6) cm, pre-SPBI volume 6.4 ± 9.1 cm³, post SPBI volume 1.8 ± 5.6 cm³, ADC 0.91 $\times 10^{-3}$ mm²/s. At surgical pathology, 6(27.2%) achieved pCR/RCB-0, 9(41%) RCB-I, 7(31.8%) RCB-II. Mean baseline MRI size (1.2 ± 0.7 vs 1.3 ± 0.6 , p=0.88), enhancement volumes (6.0 ± 6.2 vs 7.9 ± 9.9 cm³, p=0.59), DWI ADC values (1.1 ± 0.3 vs 0.9 ± 0.2 mm²/s, p=0.48) were not significantly different between tumors that showed pCR vs RCB I-II at surgical pathology. Time elapsed from SBRT to surgery were significantly longer in patients with pCR (264.3 ± 74.2 vs 183.7 ± 68.3 days, p=0.04) On pre-op MRI, mean enhancement volume was smaller in cancers that had pCR, however it did not reach significance (0.1 ± 0.1 vs 2.1 ± 6.0 cm³, p=0.2). Of 18 patients with available pre-operative MRI, residual enhancement was present in 7, of these 6/7(87%) had RCB I-II, and 1/7(13%) RCB-0 at surgical pathology. Conversely, in 11 patients with no residual enhancement on MRI, pathology showed pCR/RCB-0 in 5(45.5%), while 6(54.5%) had RCB I or II. Presence of residual enhancement on pre-operative MRI had an AUC of 0.68 (95%CI 0.43; 0.93, p=0.2) in predicting residual cancer after SPBI. Conclusion: Detecting residual enhancement on pre-operative MRI is a strong indicator of residual disease after SPBI, while lack of enhancement is not a reliable predictor of pCR. Our preliminary results do not indicate an association between baseline MRI enhancement volume, DWI ADC and pathologic

response.

PO2-22-08

Nipple areolar complex changes after breast-conserving surgical therapy and periareolar mastopexy: a three-dimensional Surface Analysis

Presenting Author(s) and Co-Author(s):

T. Peter. Breast Center, Department of Obstetrics and Gynecology, LMU University Hospital, Germany, United States

K. Koban. Department Hand-, Plastic- and Aesthetic Surgery, United States

D. Ehrl. Department Hand-, Plastic- and Aesthetic Surgery, United States

P. Geiger. Breast Center, Department of Obstetrics and Gynecology, LMU University Hospital, Germany, United States

N. Harbeck. University of Munich, Munich, Bayern, Germany

S. Kahlert. Breast Center, Department of Obstetrics and Gynecology, LMU University Hospital, Germany, United States

C. Luczak. Breast Center, Department of Obstetrics and Gynecology, LMU University Hospital, Germany, United States

J. Schmid. Breast Center, Department of Obstetrics and Gynecology, LMU University Hospital, Germany, United States

R. Wuerstlein. Breast Center, Dept. OB&GYN and CCC Munich, LMU University Hospital, Munich, Germany

F. Hagemann. Breast Center, Department of Obstetrics and Gynecology, LMU University Hospital, Germany, United States

Objectives: The position and configuration of the nipple-areolar complex (NAC) have a high impact on satisfaction (objective and subjective) after breast-conserving therapy (BCT). The aim of this study is to objectively measure the changes in the NAC after breast conservation surgery by the use of the 3D whole body scanner and compare its results with the outcome reported by the patients. This will support further patients and help physicians to tailor their technique prior to breast-conserving surgery. **Methods:** In a unicentric pilot project 6 months after BET with periareolar mastopexy and adjuvant radiation between 2019 and 2022, 38 women were studied. The mean age was 56.3 ± 11.6 and BMI was 24.6 ± 4.5 kg/m². Objective 3D parameters were collected using the Vectra Whole Body Surface Imaging System (WB360) based on breast and NAC dimensions. In addition, the patients received the BCT module and the mastopexy module items about satisfaction with the NAC from the BREAST Q questionnaire. **Results:** In a group of 38 women, BCT with periareolar mastopexy and irradiation showed a small but significant change in NAC position and shape (see Table 1). This small change is matched by the high satisfaction with the nipple and areola surveyed in the BREAST-Q questionnaire. More than 66% of the women were rather satisfied or very satisfied. The BREAST-Q results from the Items about satisfaction with the nipple and areola are shown in Table 2. However, 34% of participants reported being somewhat dissatisfied to very dissatisfied with the symmetry of placement. This could be due to a significant cumulative small change in nipple-sternal notch distance and nipple-midline distance. No significant difference was found when measuring the nipple-inframammary fold distance ($p=0.649$). The absolute difference was of 0.13 ± 1.22 mm. The change in breast diameter was of 0.55 ± 1.54 mm (relative $2,75 \pm 7.95\%$). There was also no significance ($p=0.042$). This indicates that after BCT, the nipple-inframammary fold distance and breast diameter did not change significantly. Breast volume decreases insignificantly by 49.2 ± 136.1 cc (relative $12,96 \pm 33.51$) on the operated

side ($p=0.009$). In particular, a difference in vertical diameter of the NAC of $-4,79$ mm ($14,27\%$) was observed between the non-operated and the operated breast ($p=0.005$ by Wilcoxon-test). The BREAST-Q BCT Module consists of 8 domains. The higher the score, the higher the satisfaction with the questioned item. In our sample of 38 women, satisfaction with the surgeon(s) was highest (BREAST-Q score of $83,97 \pm 19,12$). The mean Q score for satisfaction with "psychosocial well-being" is $67,47 \pm 22,03$. For the item "sexual well-being", only 35 women answered sufficient questions and the mean Q score was $54,42 \pm 16,43$. "Satisfaction with breast" had a Q-score of $61,03 \pm 19,36$. The questions about "physical well-being" had a mean of $70,11 \pm 16,69$. The Q-score for "satisfaction with medical team", "with office staff", and "with information" can be seen in Table 3. Conclusions: In a nutshell, the conclusion of this study is that the Vectra XT 3D-Imaging is a useful tool to assess the cosmetic outcome in terms of NAC position and shape. Hence, it is a helpful tool to support the planning of the surgery and may have a positive impact on the outcome. Postoperatively, there was only a slight change in the NAC dimension and position compared with intraoperative planning. The 3D Surface Analysis is most useful in assessing the quality of reconstruction after BCT and additionally the NAC is therefore an important factor for patient satisfaction. Results of a multicenter study are pending.

Table 1: Descriptive statistic and Wilcoxon-test Results from the measures from the Breast and from NAC Dimension and Position (n=38)

	Breastside	Mean	Absolute Difference	Relative Difference (%)	Z	p-value
Vertical Diameter of the NAC (mm)	operated	46,715 (10,342)	-4,790 (9,579)	-14,27 (22,98)	-2,821	0,005
	not operated	41,925 (10,258)				
Horizontal Diameter of the NAC (mm)	operated	42,882 (9,721)	-4,143 (7,017)	-12,26 (18,85)	-3,111	0,002
	not operated	38,739 (8,605)				
Breastvolume (cc)	operated	316,5 (194,0)	49,2 (136,1)	12,96 (33,51)	-2,618	0,009
	not operated	365,6 (178,8)				
Distance sternal notch to nipple (mm)	operated	21,4 (3,4)	1,47 (1,67)	6,27 (6,68)	-4,625	<0,001
	not operated	22,9 (3,5)				
Distance nipple to inframammary fold (mm)	operated	7,3 (1,5)	0,13 (1,22)	0,27 (17,77)	-0,456	0,649
	not operated	7,5 (1,5)				
Breastdiameter (mm)	operated	16,4 (2,0)	0,55 (1,54)	2,75 (7,95)	-2,029	0,042
	not operated	17,0 (2,3)				
Distance nipple to midline (mm)	operated	10,8 (1,5)	0,72 (1,46)	5,23 (12,47)	-3,025	0,002
	not operated	11,5 (1,8)				

The 3D Measures from the Breast and from NAC Dimension and Position

Table 2: Results from the BREAST-Q mastopexy modul about satisfaction with the nipples (n=38)

		high	low	lined up	shape	look	sensation
Response	very dissatisfied	2	3	2	2	2	2
	somewhat dissatisfied	1	10	3	6	8	8
	somewhat satisfied	21	11	19	14	18	18
	very satisfied	14	14	14	16	10	10

Satisfaction with the nipples

Table 3: Results from the BREAST-Q BCT Modul after BCT and periareolar mastopexy und adjuvant radiation (n=38)

	n	Mean	Standard Deviation
Psychosocial well-being	38	67.47	22.032
Sexual well-being	36	54.42	16.436
Satisfaction with breast	38	61.03	19.357
Physical well-being	38	70.11	16.686
Satisfaction with Information	38	72.08	19.205
Satisfaction with surgeon	38	83.97	19.123
Satisfaction with medical team	38	81.03	23.231
Satisfaction with office staff	38	83.24	23.586

BREAST-Q Scores

PO2-22-09

The impact of blood loss and blood pressure management in DIEP flap surgery– a retrospective analysis of 206 patients

Presenting Author(s) and Co-Author(s):

H. Fritsch. St. Franziskus Hospital Münster, United States

C. Schreiber. Universität Köln, United States

W. Malter. Universitätsklinikum Köln, United States

M. Warm. Breast Center, Municipal Hospital Holweide. Cologne, Cologne, Germany

M. zinser. Universitätsklinikum Köln, United States

A. bach. St. Antonius Hospital Eschweiler, United States

C. Eichler. St. Franziskus Hospital Münster, United States

Introduction:

Autologous breast reconstruction using the deep inferior epigastric perforator flap has excellent success rates and a natural aesthetic result. Therefore, this method and its management are of great importance in modern oncoplastic surgery. In particular, women who have undergone radiation therapy after mastectomy benefit from this satisfactory and usually uncomplicated method of breast reconstruction. To achieve a desirable outcome, the effects of blood loss and blood pressure management may play an important role. In this analysis, we hypothesize that neither postoperative blood pressure management (using catecholamines) nor the amount of blood loss (defined by the median hemoglobin level difference) will worsen the surgical outcome or increase the complication rate.

Patients and Methods:

We performed a multicenter, multisurgeon retrospective analysis with the following primary end points: intraoperative blood loss and postoperative blood pressure management. Secondary endpoints included serious complications including flap loss and minor complications. Patients (n=194) were included from 2014-2018 at St. Antonius Hospital in Eschweiler and from 2016 to July 2018 at the Cologne Municipal Breast Cancer Center in Holweide. Patients underwent either unilateral (n=180) or bilateral (n=13) breast reconstructions with DIEP flaps, resulting in a total of n=206 cases. The subgroup regarding blood pressure management was defined by cohorts with or without catecholamine administration and included all n=206 cases. Blood loss was defined by median hemoglobin level difference and could be calculated in n=199 cases. The cohorts of the two subgroups were comparable.

Results:

Six flap losses were detected in a total of 206 cases (2.9%). The distribution of flap losses in the blood pressure management subgroup was not statistically significant ($p=.67$), while the test was not available for the blood loss subgroup.

Furthermore, the analysis showed that there were no significant differences in the rates of overall complications related to the amount of blood loss intraoperatively ($p=.06$) or blood pressure management postoperatively ($p=.19$).

Conclusion:

DIEP flap surgery is a safe method for autologous breast reconstruction, independent of blood loss and blood pressure management.

PO2-22-10

Surgical outcomes after neoadjuvant chemotherapy with and without immunotherapy in patients with triple negative breast cancer

Presenting Author(s) and Co-Author(s):

A. Coste Holt. UCLA, United States

M. Berkowitz. UCLA, United States

N. McAndrew. UCLA David Geffen School of Medicine, United States

C. Smith. UCLA, United States

J. Baker. UCLA, United States

N. Kapoor. UCLA, United States

Background: The KEYNOTE-522 trial demonstrated that the addition of neoadjuvant pembrolizumab to neoadjuvant chemotherapy (NAC) for the treatment of early-stage triple negative breast cancer (TNBC) significantly improves rates of both pathologic complete response (pCR) and event-free survival. The impact of adding immunotherapy to NAC on surgical outcomes, however, is unknown. The purpose of this study is to compare 90-day surgical complication rates and timing to subsequent adjuvant therapy of patients undergoing neoadjuvant chemotherapy for stage I-III TNBC with and without immunotherapy.

Methods: Patients treated at University of California, Los Angeles with neoadjuvant therapy for TNBC between 2018-2022 were identified retrospectively. Patient comorbidities, tumor characteristics, type of surgery, 90-day postoperative minor and major complications, timing to adjuvant therapy, and oncologic outcomes were reviewed and analyzed. Major complications were defined as those requiring reoperation or hospitalization.

Results: A total of 44 patients were included, 15 patients received neoadjuvant chemotherapy with immunotherapy (NAC-I) and 29 patients received neoadjuvant chemotherapy alone (NAC). There was no difference in patient comorbidities between the groups. Compared to the NAC group, significantly more patients in the NAC-I group had stage II or III tumors (58.6% vs. 86.7%, respectively, $p=0.028$). 73% of patients in the NAC-I group underwent mastectomy compared to only 44% of patients in the NAC group ($p=0.111$). In total, 23 patients underwent reconstruction with mastectomy, 6 patients underwent immediate DIEP flap (4 in NAC-I group and 2 in NAC group) and 17 underwent immediate tissue expander (7 in NAC-I and 10 in NAC group). 80% of patients in the NAC-I experienced a pCR compared to only 44% in the NAC group ($p=0.026$). A total of 15 patients (34.1%) experienced surgical complications and there was no significant difference in the complication rate between the groups ($p=0.552$). Five patients (33%) in the NAC-I group experienced minor complications of seroma requiring aspiration ($n=4$), cellulitis requiring antibiotics ($n=1$), or wound dehiscence requiring local wound care ($n=2$). No patients in the NAC-I group had major complications. Ten patients (33%) in the NAC group experienced complications, including 6 minor complications and 4 major complications including postoperative bleeding or flap necrosis requiring unplanned return to surgery or hyperbaric oxygen treatment. On multivariable regression analysis, controlling for patient characteristics, tumor stage, and preoperative immunotherapy, only younger age was a statistically significant variable associated with increased risk of surgical complications ($p=0.012$). Median time to adjuvant therapy, including radiation and/or systemic therapy, was similar between NAC-I and NAC groups, at 32 and 36 days, respectively ($p=0.37$). In the NAC-I group, 14 patients (93.3%) had adjuvant systemic therapy including pembrolizumab alone

(n=12), pembrolizumab with olaparib (n=1) or capecitabine alone (n=1). In the NAC group, 11 patients (37.9%) underwent adjuvant systemic treatment including chemotherapy with either capecitabine (n=1), pembrolizumab (n=1), or olaparib (n=2); or single agent capecitabine (n=6) or olaparib (n=1).

Conclusions: Despite patients in the NAC-I group having more advanced stage tumors and undergoing more extensive surgery and reconstruction compared to those in the NAC alone group, a significantly higher rate of surgical complications was not observed in the NAC-I group and there was no significant difference in time to adjuvant therapy between the two groups. Similar to results from the KEYNOTE-522 trial, more patients in the NAC-I group experienced a pCR compared to NAC alone. Larger studies are needed to continue to assess and optimize the surgical safety of neoadjuvant immunotherapy with chemotherapy in patients with TNBC.

PO2-22-11

'A sledgehammer to crack a nut' or 'the safer option'? Understanding decision making for and against oncoplastic breast conserving surgery as an alternative to mastectomy in women with early breast cancer: The UK ANTHEM study

Presenting Author(s) and Co-Author(s):

C. Davies. Bristol Medical School, United States

C. Conefrey. Bristol Medical School, United States

N. Mills. Bristol Medical School, United States

P. Fairbrother. Independent Cancer Patients' Voice (ICPV), United States

C. Holcombe. Liverpool University Hospital NHS Foundation Trust, United States

L. Whisker. Nottingham Breast Unit, United States

J. Skillman. Coventry and Warwickshire NHS Trust, United States

P. White. University of West of England, United States

D. MacMillan. Nottingham Breast Unit, United States

C. Comins. University Hospitals Bristol and Weston NHS Foundation Trust, United States

W. Hollingworth. Bristol Medical School, United States

S. Potter. Bristol Medical School, United States

Background: Oncoplastic breast conserving surgery (OPBCS) may allow women with breast cancer to avoid mastectomy, but many women continue to choose more extensive surgery even when breast conserving options are offered. Reasons for women's procedure choices are unclear. The UK prospective multicentre ANTHEM study (ISRCTN18238549) aimed to explore the feasibility of undertaking a large-scale multicentre study comparing the clinical and patient-reported outcomes of OPBCS as an alternative to mastectomy in women offered both options. The qualitative phase of the study aimed to use semi-structured interviews to explore women's perceptions of choice and to understand factors influencing decision making for and against OPBCS in early breast cancer. Methods: Women offered OPBCS as an alternative to mastectomy were eligible to participate in the ANTHEM study. Participants underwent their surgical procedure of choice and were followed up for 12 months. Semi-structured interviews were conducted with a purposive sample of women who elected to undergo either OPBCS or mastectomy with or without immediate breast reconstruction (IBR) at multiple UK centres to explore perceptions of choice, rationale for decision-making, and factors influencing procedure choice. Thematic analysis was used to explore the qualitative interview data. Sampling, data collection and analysis were undertaken concurrently and iteratively until data saturation was achieved. Results: Twenty-seven women from 12 UK breast units were interviewed. Of these, 12 elected to have OPBCS with volume displacement (n=7) or replacement procedures (n=5) and 15 chose mastectomy with (n=10) or without (n=5) IBR. Overwhelmingly, women's decisions were guided by their surgical teams and their understanding and interpretation of the information they received from them. Indeed, although provision of choice was a pre-requisite for study entry, almost a third of women didn't feel they had been offered meaningful choice as their surgeon recommended either OPBCS or mastectomy for them. Several women described how choice was unexpected as they had automatically assumed that they would need a mastectomy and expressed delight at being offered OPBCS as an alternative. Having choice and needing to make a decision about surgery, however, was a difficult experience for some women who reported finding the process challenging. Decision-making for and against OPBCS was underpinned by women's perceptions of three key inter-related factors based on the

information they received from their surgical teams: i) the effectiveness of OPBCS at removing all the cancer; ii) perceived longer term oncological safety and iii) practical issues. Almost all women described concerns about whether all the cancer would be removed by OPBCS, the need for further surgery for involved surgical margins and anxieties about cancer recurrence over time. Women who felt reassured that OPBCS was oncologically safe were happy to accept this option. Women who remained very anxious about incomplete excision and cancer recurrence were more likely to opt for mastectomy as a 'safer' option. Practical issues such as the perceived magnitude of the surgery and duration of the recovery were also important with many women choosing OPBCS as a less invasive or radical option than mastectomy. While many women described preferring to keep their breast and maintaining their femininity, only a minority of women referred to the cosmetic benefits of OPBCS as influencing their decision-making. Conclusions: Women's decision-making for OPBCS vs mastectomy for breast cancer is complex and heavily influenced by the attitudes and beliefs of their surgical team. Adequate, high-quality, accurate information about surgical options including appropriate reassurance about the short- and long-term oncological safety of OPBCS is vital if women are to make fully informed decisions and feel confident avoiding mastectomy if this is an option for them.

PO2-22-12

Patient-reported outcomes 3 and 18 months after prepectoral implant-based breast reconstruction: Results from the UK Pre-BRA multicentre prospective cohort study

Presenting Author(s) and Co-Author(s):

L. Johnson. Bristol Medical School, United States

K. Harvey. Bristol Medical School, United States

P. Sinai. Bristol Medical School, United States

N. Mills. Bristol Medical School, United States

P. White. University of West of England, United States

C. Holcombe. Liverpool University Hospital NHS Foundation Trust, United States

S. Potter. Bristol Medical School, United States

Background: Prepectoral implant-based reconstruction (PPBR) with and without mesh is becoming the standard of care for prosthetic reconstruction in the UK. In addition to being easier and quicker to perform, the procedure is perceived to be associated with better patient-centred outcomes including decreased post-operative pain, avoidance of animation deformity and improved cosmesis. Evidence to support these benefits, however, is lacking. The UK PreBRA prospective multicentre cohort study (ISRCTN11898000) aimed to assess patient-reported outcomes (PROs) before and 3 and 18 months following PPBR to provide much needed evidence to support the effectiveness of the technique.

Methods: Women aged 18 or over undergoing mastectomy for breast cancer or risk-reduction who opted to have PPBR between July 2019 and December 2020 were eligible to participate in the study. Demographic, operative, oncology and three-month complication data were collected. Participants were asked to complete the validated BREAST-Q questionnaire at before surgery and at 3 and 18 months following the procedure. Questionnaires were scored according to the developers' instructions and scores compared over time. Exploratory analysis of covariance, adjusting for baseline scores was performed to explore factors impacting PROs following PPBR.

Results: 347 women underwent PPBR at 40 centres across the UK. Of these, 334 (96.3%) completed PROMs at baseline with 237 (68.3%) completing at least two of the three main BREAST-Q scales at both 3 and 18 months. The median age of the cohort was 49 (range 23-74). Most women (n=291, 87.1%) had mastectomy for malignancy with a quarter (n=82, 24.6%) undergoing bilateral surgery. Approximately a fifth (n=68, 20.4%) had a body mass index >30 and 12% (n=40) were active smokers at the time of surgery. At 3 months, 68 (20.4%) had experienced a complication requiring readmission and/or re-operation and 27 (8.1%) experienced an implant loss.

In the cohort overall, women undergoing PPBR reported slight increases in their 'Satisfaction with Breasts' scores from baseline to 3 months after surgery but by 18 months, their scores had fallen below baseline values (Table 1). 'Physical well-being' scores decreased from baseline to 3 months but then remained stable. No changes were seen in 'Psychosocial well-being' scores across the three timepoints.

At 18 months, after adjusting for baseline BREAST Q scores, women having surgery for risk-

reduction reported scores that were 10-16 points lower than those having surgery for malignancy across all four main domains for the BREAST-Q. This exceeded the minimum clinically meaningful difference and was highly statistically significant. Women with high mastectomy weights (>600g) reported lower scores for 'Physical', 'Psychosocial' and 'Sexual' well-being but not 'Satisfaction with Breasts'. Smoking adversely impacted 'Psychosocial well-being' and 'Satisfaction with Breasts' and women with BMI >30 reported lower 'Physical well-being' scores at 18 months. Having a major complication requiring readmission/re-operation did not affect BREAST-Q scores, but when considered separately, implant loss dramatically impacted all BREAST-Q domains

Conclusions: Women having PPBR report short-term improvements in 'Satisfaction with Breasts' scores but these are not maintained over time and decrease to below baseline 18 months after surgery. 'Physical well-being' also decreased after PPBR despite no disruption to the pectoralis muscle. Women having surgery for risk-reduction reported the worse PROs. Further work is needed to establish the long-term patient-reported outcomes of PPBR and factors impacting these.

BREAST-Q domain	Mean score (95% confidence interval)		
	Pre-operative	3 months	18 months
Satisfaction with Breasts	63.8 (61.5-66.1)	66.3 (64.1-68.5)	60.9 (58.4-63.4)
Psychosocial Well Being	69.8 (67.8-71.9)	70.6 (68.0-73.2)	69.6 (66.9-72.4)
Sexual Well Being	58.2 (55.4-61.1)	51.9 (48.3-55.5)	48.1 (44.4-51.9)
Physical Well Being	82.8 (81-84.7)	73.5 (71.3-75.6)	74.7 (72.2-77.2)

PO2-23-01

Selective cavity margin shaving: effective method to maintain balance between cosmesis and negative margin in breast conserving surgery

Presenting Author(s) and Co-Author(s):

D. Kim. Soonchunhyang University Bucheon Hospital, United States

Z. Kim. Soonchunhyang University Bucheon Hospital, United States

S. Hur. Soonchunhyang University Bucheon Hospital, United States

C. Lim. Soonchunhyang University Bucheon Hospital, United States

Background: Breast conserving surgery (BCS), which became the mainstay of breast cancer surgery, both cosmesis and margin negativity are significant issues. Firstly, it is well known that negative resection margin is crucial for reducing local recurrence after BCS. Therefore, there has been numerous attempts to secure negative margin, such as specimen mammography, frozen section margin analysis, and cavity margin shaving. Regarding cosmesis, wider excision to secure negative margin could disrupt cosmesis especially in Asian patients with relatively smaller breast, and minimizing excision volume is necessary for optimal cosmetic outcome. Our center adopted the concept of selective cavity margin shaving (SCMS) to achieve negative margin while optimizing cosmetic result.

Method: 606 female patients with non-metastatic, unilateral breast cancer were prospectively collected and underwent BCS with SCMS from October, 2012 to December, 2020. The medical record was retrospectively reviewed, and we assessed positive margin rate and local recurrence. During BCS, the surgeon excised gross margin of 1~2cm around the cancer, and assessed the proximity of the margin through gross examination. If sufficient margin was not obtained, cavity shaving was performed in the close margin, while shaving from retrieved specimen was conducted on the sufficient margin side. Additionally, circumferential margin frozen analysis was carried out, and further excision was performed until a negative margin was achieved or when only focal DCIS involvement remained.

Result: The mean \pm SD age of the patients was 52.47 ± 9.92 years and mean follow-up period was 59.98 ± 26.59 months. 56 patients (9.24%) received neoadjuvant chemotherapy. 123 patients (20.29%) got positive margin for invasive cancer or DCIS in frozen section margin analysis and 97 patients (16.01%) underwent intraoperative re-excision. There was discordance between frozen and permanent section margin analysis in 48 patients (7.92%), and 7 patients (1.16%) underwent post-operative re-excision operation. Local recurrence occurred in 11 patients (1.82%), which is significantly lower compared to previously reported outcomes after BCS. Presence of lympho-vascular invasion, neoadjuvant chemotherapy, and margin involvement of invasive cancer in permanent section analysis were strongly related with local recurrence.

Conclusion: In conclusion, SCMS and frozen section margin analysis demonstrated low positive margin rate and reduced re-excision rate. The local recurrence was also lower compared to conventionally reported rate after BCS. Selective cavity margin shaving is an oncologically safer and effective surgical method with minimized cosmetic deformity.

Table 1. Baseline patient characteristics

Characteristics		N-606 (%)
Age (years)	Mean ± SD	52.47 ± 9.92
BMI (kg/m ²)	Mean ± SD	24.54 ± 3.84
Neoadjuvant chemotherapy	(+)	56(9.24%)
	(-)	550(90.76%)
	0	26(4.29%)
Pathologic stage	1	335(55.28%)
	2	223(36.80%)
	3	22(3.63%)
	0	29(4.79%)
T-stage	1	400(67.33%)
	2	167(27.56%)
	3	2(0.33%)
	0	498(82.18%)
N-stage	1	86(14.19%)
	2	14(2.31%)
	3	8(1.32%)
	<25%	35(5.78%)
Breast density	25-50%	123(20.30%)
	50-75%	269(44.39%)
	>75%	179(29.54%)
	(+)	182(30.03%)
Presence of microcalcification	(-)	424(69.97%)
	(+)	119(20.41%)
Extensive intraductal component	(-)	464(79.59%)
	(+)	499(82.34%)
HR	(-)	107(17.66%)
	(+)	104(17.16%)
HER2	(-)	502(82.84%)
	(+)	195(33.68%)
Ki-67 (20% cut-off)	(-)	384(66.32%)
	(+)	135(22.54%)
Lympho-vascular invasion	(-)	464(77.46%)

Table 1. Baseline patient characteristics

Table2. Univariate and multivariate analysis of factors associated with local recurrence

Factors	Univariate analysis		Multivariate analysis	
	Hazard ratio	P-value	Hazard ratio	P-value
Age	0.9386	0.1143		
BMI	1.0358	0.6785		
Neoadjuvant chemotherapy	11.5128	0.0008	28.7561	<0.001
Microcalcification	2.6706	0.1649	3.438	0.0889
Extensive intraductal component	2.3107	0.2515		
HR	0.2856	0.0863		
HER2	3.3021	0.1019		
Ki-67	>1000	0.9983	>1000	0.9976
Lympho-vascular invasion	3.2922	0.0920	9.4887	0.0017
Permanent margin positivity	DCIS	<0.001	<0.001	0.9993
	Invasive cancer	9.2976	0.0016	10.0943

Table2. Univariate and multivariate analysis of factors associated with local recurrence by Cox proportional hazard model.

PO2-23-02

Results of a prospective randomised multicentre study comparing indocyanine green (ICG) fluorescence combined with a standard tracer versus ICG alone for sentinel lymph node biopsy in early breast cancer: The INFLUENCE Trial

Presenting Author(s) and Co-Author(s):

V. Pitsinis. Ninewells Hospital and Medical School, Edinburgh, Scotland, United Kingdom

R. Kanitkar. Ninewells Hospital and Medical School, United States

A. Vinci. Ninewells Hospital and Medical School, United States

E. Elseedawy. NHS Tayside, United States

L. Canna. Cambridge University Hospitals, United States

J. Benson. Cambridge University Hospitals, United States

Background:

Use of fluorescence mapping for visualization of lymphatic and nodal tissue for sentinel lymph node biopsy (SNB) reveals high rates of identification (>98%). Studies combining ICG with either blue dye or radioisotope (RI) have shown high levels of concordance (>90%) and comparable performance parameters between ICG and standard tracers for SNB localization. ICG combines many advantages of blue dye and RI without the disadvantages of allergic reactions, staining of skin and surgical tissues along with handling and disposal of radioactivity materials. Moreover, magnetic tracers pose challenges of interference relating to surgical instrumentation and magnetic resonance imaging (MRI). The combination of ICG with a conventional tracer may represent a transition phase and this randomized study evaluates ICG as a sole tracer agent for SNB in early-stage breast cancer.

Methods:

In a prospective randomized study, 100 patients with unilateral clinically node negative tumours scheduled to undergo routine SNB for core-biopsy proven invasive breast cancer (≤ 5 cm) were identified at multidisciplinary meetings [non-invasive tumours excluded]. All patients had pre-operative axillary ultrasound and breast conserving surgery or mastectomy. Patients were recruited in two cohorts (n=50); cohort 1 was assigned to either ICG [2ml 0.5%] alone (n=25) or combined with RI [Technetium99 nanocolloid, 20MBq] (n=25). Cohort 2 received ICG alone (n=25) or combined with blue dye for SNB localization. The number of nodes whether blue, radioactive, fluorescent or a combination thereof were recorded. Lymphatic and nodal tissue was visualized with a fluorescent camera/detection system. Sensitivity of ICG alone and/or in combination with one or another standard tracer was calculated. The main objective was to assess the performance of ICG alone compared with a standard tracer combination in terms of rates of SNB identification along with procedural node positivity rates. Statistical analysis employed Chi-Square test, Fisher's Exact test, and logistic regression to determine differences between groups.

Results:

A total of 100 patients were randomized between March and December 2022 with 3 patients excluded from analysis (non-receipt of treatment allocation). Amongst evaluable patients (n=97), the overall SNB identification rate was 96.9% and by tracer category as follows: ICG alone = 97.9% (46/47); ICG + RI = 100% (25/25); ICG + blue dye = 92% (23/25). For cohort 1, the procedural node positivity rates were 17% for ICG alone and 18% for ICG + RI with corresponding figures of 12% for ICG alone and 20% for ICG + blue dye for cohort 2. Mean

procedural node retrieval per case was 2.5 in ICG alone Vs ICG + Blue Dye and 2.3 in ICG alone Vs ICG/RI cohorts. There were no significant differences ($p>0.05$) in performance of ICG alone or combined with a standard tracer, with ICG alone being non-inferior in terms of procedural and nodal detection rates. Similar conclusions were reached from a secondary analysis adjusting for BMI, age and mode of detection (screening/symptomatic).

Conclusion:

ICG fluorescence imaging permits real-time visualisation of lymphatics and gives an additional dimension to SNB that appears safe versus the competitive alternatives. These results confirm high sensitivity for fluorescence localisation alone for SNB with comparable performance to combined methods with blue dye or RI. The fluorochrome ICG is reliable as a sole tracer and avoids potential drawbacks of blue dye and RI including staining, allergic reactions, availability and costs.

PO2-23-03

Potential Candidates for Conservative Axillary Surgery after Neoadjuvant Chemotherapy

Presenting Author(s) and Co-Author(s):

B. Pereira Gonçalves. Instituto Português de Oncologia, United States

B. Costeira. Instituto Português de Oncologia de Lisboa, United States

C. Fernandes da Cunha. Instituto Português de Oncologia de Lisboa, United States

R. Oom. Instituto Português de Oncologia de Lisboa, United States

C. Costa. Instituto Português de Oncologia de Lisboa, United States

J. Vargas Moniz. Instituto Português de Oncologia de Lisboa, United States

N. Abecasis. Instituto Português de Oncologia de Lisboa (IPO), United States

C. Rodrigues dos Santos. Instituto Português de Oncologia de Lisboa, United States

BACKGROUND

Neoadjuvant chemotherapy (NAC) plays a crucial role in breast cancer treatment. Besides having prognostic relevance, this downstaging allows for more conservative breast surgery, now the standard of practice.

This strategy of de-escalation in axillary surgery after NAC is less established, especially in cN+ that turn into ycN0 tumors, where axillary lymph node dissection (ALND) or targeted ALND (TAD) with previous referencing of metastatic lymph combined with sentinel lymph node biopsy (SLNB) are options.

Assuming that nodal complete pathologic response (pCR) after NAC is dependent of tumor biology, we intent to identify molecular subtypes or biological factors associated with nodal pCR, and so identify which ones are the potential candidates for a more conservative axillary approach, such as SLNB.

METHODS

From 1st January of 2017 to 31st December of 2021, all patients with cN+, ypN+(sn) and cT4Nx invasive breast cancer, who were submitted to ALND after NAC at our center, were retrospectively evaluated. Nodal pCR defined by absence of axillary invasive disease.

RESULTS

591 patients were submitted to ALND after NAC during this 5-year period. Clinicopathological characteristics are described in table 1.

Overall nodal pCR rate was 39.8%. The greatest nodal pCR rate occurred in the Her2 type (66.2%), following luminal B Her2+ (56.4%), TN (54%) and at least luminal B Her2- (27.2%) and luminal A (20.5%) tumors - $p < 0.001$.

On univariate analysis, the subtypes Her2type (OR 3.400, 95%CI 1.974-5.855, $p < 0.001$), luminal BHer2+ (OR 2.237, 95%CI 1.431-3.497, $p < 0.001$) and TN (OR 2.011, 95%CI 1.303-3.103, $p < 0.002$) are all associated with higher rates of nodal pCR. On the other hand, luminal A (OR 0.346, 95%CI 0.195-0.617, $p < 0.001$) and luminal B Her2- subtypes (OR 0.384, 95%CI 0.271-0.545, $p < 0.001$) are associated with less nodal pCR. Ki67 (OR 1.027, 95%CI 1.020-1.035, $p < 0.001$) and tumoral pCR (OR 13.688, 95%CI 8.693-21.552, $p < 0.001$) are also associated with higher rates of nodal pCR. On multivariate analysis, the subtypes Her2type and

Luminal B Her2+ remain independently associated with nodal pCR – OR 2.417, 95%CI 1.078-5.549, p 0.032 and OR 2.080, 95%CI 1.005-4.304, p 0.049, respectively – as well as Ki67% (OR 1.019, 95%CI 1.009-1.030, p< 0.001) and tumoral pCR (OR 9.425, 95%CI 5.750-15.449, p< 0.001). When considering Ki67, TN tumors with Ki67≥50% are also identified as an independently associated factor with pCR – OR 4.946, 95%CI 1.190-20.559, p 0.028.

DISCUSSION AND CONCLUSION

The overall nodal pCR after NAC is around 40% and it clearly differs between molecular subtypes, being superior in the Her2type (66.2%), luminal B Her2+ (56.4%) and TN (54%) and at least 2 times inferior in luminal A (20.5%) and B Her2- tumors (27.2%). Data reveal Her2 expression (Her2type and luminal B Her2+) as an independent factor associated with higher nodal pCR rates, as well as the Ki67% and the tumoral pCR, consistent with tumor biology. In this series, the remaining molecular subtypes do not correlate in a consistent way with nodal pCR, but there's a trend for luminal A and B Her2- to influence it negatively, as opposed to TN, which appears to influence it positively. Besides that, the subgroup of TN tumors with high proliferative rates (Ki67≥50%,) appears to correlate with nodal pCR on multivariate analysis.

Parallel to tumoral pCR, nodal pCR can represent a chance to make axillary surgery more conservative. ALDN has a relevant morbidity and TAD, although less aggressive, requires a series of technical procedures that are usually difficult to perform in hospital facilities due to logistic constraints.

Recognizing the subtypes which have more consistent nodal pCR, the so-called “good responders”, can help to identify which ones are the potential candidates for a more conservative approach, as is SLNB. In this study, Her2+ tumors and eventually TN with high Ki67, appear as those with greater consistency in nodal pCR, being possible targets for this strategy.

Potential Candidates for Conservative Axillary Surgery after Neoadjuvant Chemotherapy

Clinicopathological characteristics		n 591
Female sex		586 (99.2%)
Age, years		54 (45-64)
Histology subtype	Ductal	541 (91.5%)
	Lobular	40 (6.8%)
	Others	10 (1.7%)
Molecular subtype	LumA	78 (13.2%)
	LumBHer2-	254 (43%)
	LumBHer2+	94 (15.9%)
	Her2 type	65 (11%)
	Triple negative (TN)	100 (16.9%)
Ki67, %		40 (25-66)
cT	1	43 (7.3%)
	2	260 (44.0%)
	3	133 (22.5%)
	4	155 (26.2%)
cN	cN+	555 (93.9%)
	cT4Nx	25 (4.2%)
	pN+(sn)	11 (1.9%)
Lymph nodes dissected		14 (10-18)

Table 1 - Clinicopathological characteristics

PO2-23-04

Magnetic Seeds, used to Locate the Metastatic Axillary Lymph Node placed before Neoadjuvant Chemotherapy for Breast Cancer Treatment, do not interfere the pre-surgical MRI Breast response assessment.

Presenting Author(s) and Co-Author(s):

M. Espinosa-Bravo. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Barcelona, Spain

J. Rivero Deniz. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

C. Morales Comas. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

J. de la Torre Fernandez de Vega. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

I. Vives Rosello. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

E. Esposito. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

V. Peg Camara. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

M. Rus Calafell. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

I. Miranda Gomez. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

C. Siso Raber. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

Background: Axillary management in clinically node-positive patients who converted to ycN0 after neoadjuvant chemotherapy (NAC) for breast cancer (BC) remains under research with the aim of de-escalation of axillary lymph node dissection (ALND). A magnetic seed is one of the several positive lymph nodes marking techniques used in targeted axillary dissection (TAD) for patients with cN1 breast cancer undergoing neoadjuvant systemic therapy. It has been criticized for its potential masking effect due to the artefact it produces in the MRI sequences used to assess a proper breast response. This study evaluates if the magnetic seeds placed before NAC for guided TAD have influenced in the breast MRI response assessments.

Methods: From October 2021 to June 2023, patients with cT0-4 cN1 breast cancer who were candidates for primary systemic treatment were prospectively recruited. Once a breast lesion and axillary node positivity were confirmed, a based hydrogel marker and a magnetic seed, respectively, were placed prior NAC. Once systemic treatment was completed, imaging techniques were used to assess the response, with MRI being the imaging technique of choice to assess breast response and axillary ultrasound the imaging technique of choice to assess axillary response. Surgical pathological confirmation of response in the axilla was by TAD, including sentinel lymph node and magnetic clipped node resection. Results: A total of 43 patients were included and their characteristics are shown in Table 1. In 16 patients (37%) the tumour was located in the upper outer quadrant (UOQ). In this group, the susceptibility artefact produced by the magnetic seed in the MRI created a black hole obscuring the axilla with a mean diameter of 69 mm (range: 57-76 mm). In no case did the halo interfere with the correct

MRI visualisation of the breast marker. By MRI, the mean distance of the artifact halo from the breast marker or residual breast lesion was 40 mm (range: 13-79 mm). Overall, complete radiological response (ycCR) was reported in 20 patients (46%), breast only in 21 (49%) and axilla only in 38 (88%) patients. In 5 patients, preoperative axillary ultrasound revealed residual axillary disease, confirmed by FNA, lead to direct ALND. In the remaining 38 patients the axillary TAD assessment was completed. In all cases, the magnetic clipped node was successfully surgically removed. Pathological complete response (pCR) was confirmed in 9 (21%), breast only in 11 (26%) and axilla only in 13 (30%) patients. MRI diagnostic performance in detecting residual breast disease after NAC was not altered by the magnetic clipped node artifact when comparing the tumour location in the UOQ to the other quadrants (AUC 0.764 vs. 0.702; p=0.698). Conclusions: Surgical axillary staging remains the most reliable method for assessing the axillary response after NAC. Target axillary dissection guided by magnetic seed placed before NAC is an effective and accurate technique. The artifact generated in the MRI does not interfere with the pre-surgical breast response assessment after neoadjuvant systemic treatment.

Table 1: Patients and tumor characteristics

	No. of patients (%)
Median age (years)	51 (range 27-87)
IHQ subtype	
Luminal A	6 (14%)
Luminal B HER2 neg	18 (42%)
Luminal B HER2 pos	7 (16%)
HER2 pos no luminal	5 (12%)
Triple negative	7 (16%)
Median BMI (Kg/m²)	25 (range 18-39)
Clinical tumor stage	
cT1	9 (21%)
cT2	27 (63%)
cT3	6 (14%)
cT4	1 (2%)
Clinical node stage	
cN1	40 (93%)
cN3	3 (7%)
Quadrant tumor localization	
Upper outer quadrant	16 (37%)
Other quadrant	27 (63%)
Breast surgery	
Lumpectomy	22 (51%)
Oncoplastic Surgery	9 (21%)
Mastectomy	12 (28%)
Axillary surgery	
TAD (SLN & clipped node)	38 (88%)
ALND	30 (70%)

PO2-23-05

Practice patterns and outcomes in the ongoing neoadjuvant ATNEC trial: node marking, response to NACT and breast conservation rates

Presenting Author(s) and Co-Author(s):

- A. Goyal. Royal Derby Hospital, United States
- A. Marshall. Warwick Clinical Trials Unit, University of Warwick, Coventry, England, United Kingdom
- S. Nicholls. Warwick Clinical Trials Unit, University of Warwick, United States
- N. Hammonds. University of Warwick, United States
- B. Elsberger. Aberdeen Royal Infirmary, United States
- D. Wheatley. Royal Cornwall Hospitals NHS Trust, Truro, England, United States
- J. Rose. NCRI Breast Clinical Studies Group, United States
- H. Edwards. Independent Cancer Patients' Voice, United States
- A. Shaaban. Queen Elizabeth Hospital, Birmingham, United States
- R. Butt. Mount Vernon Hospital, Northwood, United States
- G. Jackson. Mount Vernon Hospital, United States
- T. Homer. Health Economics Group, Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, United States
- L. Vale. Newcastle University, United States
- S. Ahmed. Leicester Royal Infirmary, United States
- S. Puri. Royal Derby Hospital, United States
- S. Gasson. Warwick Clinical Trials Unit, University of Warwick, United States
- J. Bruce. University of Warwick, United States
- H. Higgins. University of Warwick, United States
- J. Dunn. University of Warwick, Coventry, England, United Kingdom

Background

In ATNEC trial, cT1-3N1M0 patients receive NACT followed by SNB/TAD. If the sentinel nodes (SNs) have converted to benign (ypN0), patients are randomly assigned to Axillary Treatment vs no Axillary Treatment. The study promotes standardized node marking procedures and includes a radiotherapy quality assurance program.

Objectives – This study prospectively evaluates practice patterns, NACT response, adoption of node marking, rates of marked node identification, and breast conservation rates in the ongoing ATNEC trial across 70 centers in the UK. The trial aims to recruit 1900 patients.

Materials and Methods

Data from 196 randomized patients (median age: 54 [range: 28-79] years; median BMI: 26.5 [range: 17.6-51.1]) from December 2021 to June 28, 2023, across 70 UK centers were analyzed. These patients presented with cT1-3N1M0 breast cancer, received NACT, and exhibited no residual nodal disease (ypN0) on SNB/TAD.

Results

Among the randomised patients 54%(106) were post-menopausal, 71%(140) underwent breast

conserving surgery(BCS) and 29%(56) mastectomy. At presentation, 12% (23) had T3, 63% (124) had T2, and 23% (46) had T1 tumors. Grade 3 tumors accounted for 70% (138) of cases. Among the patients, 60% (117) were HER2 positive, 31% (61) were triple negative, and 9% (18) were HER2 negative (ER or PgR positive). Anthracycline and taxane-based NACT were administered to 57% (106), while 38% (71) received a platinum-containing regimen. During SNB/TAD, a median of 4 nodes (interquartile range, 3-5) were removed. Among 184 patients with node marking data, 74% (136) had the involved node marked.

The marked node was successfully removed in 94% (128) of these patients. Clip/coil only, Magseed and black dye were the commonest techniques used for node marking. The marked node was the sentinel node in 83% (106) of cases. Among 185 randomized patients with post-NACT response data, 68% (125) achieved a complete pathological response (pCR) in the breast, while 8% (15) had DCIS only and 22% (41) had invasive cancer. Among 105 patients with complete breast tumor response on imaging, 15% (16) had residual DCIS or invasive cancer. In the subset of patients with partial response or stable breast tumors on imaging (69 patients), 46% (32) had no residual tumor on histology (ypT0). Furthermore, 14% (26) exhibited partial or stable disease in the axilla on imaging but achieved complete pathological response on histology.

Conclusions

HER2-positive and triple-negative breast cancer cases predominate among patients undergoing NACT in the UK. Although 68% achieved a complete pCR (ypT0) in the breast, rates of BCS remain low. Notably, around 75% of randomized patients underwent node marking, with an intra-operative identification rate of 94%, demonstrating the successful implementation of node marking in the UK through the ATNEC trial.

PO2-23-06

Clinical study of stained region lymph node biopsy (SrLNB) in axillary surgery after neoadjuvant systemic therapy in patients with axillary lymph node positive breast cancer

Presenting Author(s) and Co-Author(s):

J. Wang. the First Affiliated Hospital of Nanjing Medical University, United States

R. Chen. the First Affiliated Hospital of Nanjing Medical University, United States

C. Li. the First Affiliated Hospital of Nanjing Medical University, United States

H. Zha. the First Affiliated Hospital of Nanjing Medical University, United States

Q. Zhu. the First Affiliated Hospital of Nanjing Medical University, United States

L. Huang. the First Affiliated Hospital of Nanjing Medical University, United States

X. Zha. the First Affiliated Hospital of Nanjing Medical University, United States

Background The probability of axillary lymph node converting from positive to negative after neoadjuvant systemic therapy (NST) for breast cancer patients is approximately 40%. A variety of axillary lymph node biopsy surgeries based on sentinel lymph node biopsy (SLNB) can help to omit axillary lymph node dissection (ALND). The common disadvantages, however, are mainly the restrictions, such as the need for strict regulation of the use of radiotracers, the high number of retrieved lymph nodes required, and the need to purchase ancillary equipment. The more restrictions there are, the more they limit the spread and availability of the technique and, more importantly, reduce the number of patients who will benefit. In fact, for patients with metastatic lymph nodes, the sentinel lymph nodes must be included in the lymph nodes that have metastasized. If these metastatic lymph nodes can be accurately marked and precisely retrieved after NST, it is possible to assess whether the axillary lymph nodes are converted from positive to negative without the need for SLNB. **Materials and methods** Breast cancer patients with pathologically confirmed axillary lymph node metastases who were receiving NST were recruited for this study. Before NST, carbon nanoparticles suspension injections were injected into the cortex of the pathologically confirmed metastatic lymph node to stain the region where the metastatic lymph node was located. The lymph nodes in the stained region were retrieved by stained region lymph node biopsy (SrLNB) during the axillary surgery, followed by ALND, without the use of SLNB. Finally, the identification rate and false-negative rate (FNR) of SrLNB were statistically analyzed according to pathology data. **Results** A total of 159 patients were successfully enrolled in this study between September 24, 2020 and December 2, 2022, with an axillary pCR rate of 40.9% (65/159). The identification rate of SrLNB was 100% (159/159), with an overall FNR of 5.3% (5/94). Subgroup analysis revealed that in the subgroups of 1, 2, 3 and ≥ 4 SrLN, the FNR was 0%, 0%, 0% and 8.9% (5/56), respectively, whereas in the cN1, cN2 and cN3 subgroups the FNR was 7.7% (3/39), 2.6% (1/38) and 5.9% (1/17), respectively. The FNR indexes were within the safety threshold of 10% in all subgroups. **Conclusion** SrLNB has a high identification rate and a low FNR and is useful for screening patients with positive to negative axillary lymph nodes for omitting ALND. srLNB requires only the use of an affordable and radiation-free carbon nanoparticles suspension injection for marking, making the whole technique simpler and easier to disseminate. The data from this study also suggest that SLNB may not be mandatory for axillary biopsy in patients with positive axillary lymph nodes undergoing NST.

Table 1. General characteristics of enrolled patients.

Characteristics (n=159)	Number of patients	%
Age (48.5 ± 10.3 years)		
< 50	82	51.6%
≥ 50	77	48.4%
Menstrual status at diagnosis		
Premenopausal	87	54.7%
Postmenopausal	72	45.3%
Clinically assessed breast tumor size at diagnosis (cT)		
cT1	8	5.0%
cT2	121	76.1%
cT3	26	16.4%
cT4	4	2.5%
Clinically assessed metastatic axillary lymph nodes by ultrasound (cN)		
cN1 (1-3)	68	42.8%
cN2 (4-9)	64	40.3%
cN3 (≥ 10)	27	17.0%
Molecular subtypes of breast tumor		
HR+ / HER2-	62	39.0%
HR+ / HER2+	38	23.9%
HR- / HER2+	32	20.1%
HR- / HER2-	27	17.0%
Types of axillary lymph node biopsy		
Fine needle aspiration	134	84.3%
Core needle biopsy	25	15.7%
Pathological response evaluation of breast tumor after NST		
Breast pCR (ypT0/is)	44	27.7%
Breast pPR	89	56.0%
Breast pSD	25	15.7%
Breast pPD	1	0.6%
Pathological staging of axillary lymph nodes after NST (ypN)		
ypN0	65	40.9%
ypN1	48	30.2%
ypN2	31	19.5%
ypN3	15	9.4%
Number of retrieved SrlLN		
0	0	0.0%
1	12	7.5%
2	34	21.4%
3	18	11.3%
≥ 4	95	59.7%

Table 2. Analysis of factors affecting axillary pCR rates.

Characteristics (n=159)	ypN0, n=65 (%)	ypN+, n=94 (%)	P value
Age (years)			
< 50	31 (37.8)	51 (62.2)	0.425
≥ 50	34 (45.4)	43 (54.6)	
Menstrual status at diagnosis			
Premenopausal	35 (40.2)	52 (59.8)	0.873
Postmenopausal	30 (41.7)	42 (58.3)	
Clinically assessed tumor size at diagnosis (cT)			
cT1	4 (50.0)	4 (50.0)	
cT2	51 (42.1)	70 (57.9)	0.364
cT3	10 (38.5)	16 (61.5)	
cT4	0 (0)	4 (100.0)	
Clinically assessed metastatic axillary lymph nodes by ultrasound (cN)			
cN1 (1-3)	29 (42.6)	39 (57.4)	0.881
cN2 (4-9)	26 (40.6)	38 (59.4)	
cN3 (≥ 10)	10 (37.0)	17 (63.0)	
Pathological response evaluation of breast tumor after NST			
Breast pCR (ypT0/is)	38 (86.4)	6 (13.6)	<0.001
Breast non-pCR	27 (23.5)	88 (76.5)	
Molecular subtypes of breast tumor			
HR+ / HER2-	8 (12.9)	54 (87.1)	
HR+ / HER2+	19 (50.0)	19 (50.0)	<0.001
HR- / HER2+	25 (78.1)	7 (21.9)	
HR- / HER2-	13 (48.1)	14 (51.9)	

Table 3. Analysis for the FNR of SrlLNB.

Characteristics	SrLN+ / non-	SrLN+ / non-	SrLN- / non-	SrLN- / non-	FNR (%)
	SrLN+	SrLN-	SrLN+	SrLN-	
All patients	65	24	5	65	5.3
Number of retrieved SrLN					
1	7	2	0	3	0
2	13	5	0	16	0
3	10	1	0	7	0
≥4	35	16	5	39	8.9
Clinically assessed metastatic axillary lymph nodes by ultrasound (cN)					
cN1 (1-3)	22	14	3	29	7.7
cN2 (4-9)	29	8	1	26	2.6
cN3 (≥10)	14	2	1	10	5.9

PO2-23-07

Three-dimensional navigated mass spectrometry for intraoperative margin assessment during breast cancer surgery

Presenting Author(s) and Co-Author(s):

M. Kaufmann. Queen's University, United States
A. Jamzad. Queen's University, United States
T. Ungi. Queen's University, United States
J. Rodgers. University of Manitoba, United States
T. Koster. Queen's University, United States
C. Yeung. Queen's University, United States
J. Ehrlich. Queen's University, United States
A. Santilli. Queen's University, United States
M. Asselin. Queen's University, United States
N. Janssen. Queen's University, United States
J. McMullen. Kingston Health Sciences Center, United States
K. Solberg. Kingston Health Sciences Center, United States
J. Cheesman. Kingston Health Sciences Center, United States
A. Di Carlo. Queen's University, United States
K. Ren. Queen's University, United States
S. Varma. Queen's University, United States
S. Merchant. Queen's University, United States
C. Engel. Queen's University, United States
G. Walker. Queen's University, United States
A. Gallo. Queen's University, United States
D. Jabs. Kingston Health Science Center, Kingston, Ontario, Canada
P. Mousavi. Queen's University, United States
G. Fichtinger. Queen's University, United States
J. Rudan. Queen's University, United States

Positive resection margins occur in approximately 25% of breast cancer (BCa) surgeries, requiring re-operation. Margin status is not routinely available during surgery; thus, technologies that identify residual cancer on the specimen or cavity are needed to provide intraoperative decision support that may reduce positive margin rates. Rapid evaporative ionization mass spectrometry (REIMS) is an emerging technique that chemically profiles the plume generated by tissue cauterization to classify the ablated tissue as either cancerous or non-cancerous, on the basis of detected lipid species. Although REIMS can distinguish cancer and non-cancerous breast tissue by the signals generated, it does not indicate the location of the classified tissue in real-time. Our objective was to combine REIMS with spatio-temporal navigation (navigated REIMS), and to compare performance of navigated REIMS with conventional histopathology examination (gold standard) to assess margin status (positive or negative) in patients undergoing surgery for BCa. A multivariate model was trained using pathology-validated mass spectra from ex vivo resection specimens from 11 patients, including

36 spectra from invasive cancer, and 118 spectra from normal breast adipose. This model was subsequently tested retrospectively on intraoperative data from 25 BCa cases that were conducted using navigated REIMS. Navigation was facilitated by an electromagnetic sensor placed on the cautery. To record the position of the tumor, a localization wire fitted with an electromagnetic sensor was placed into the tumor using ultrasound prior to surgery, and a 3D map of the tumor was created. This enabled real-time knowledge of the cautery position relative to the tumor during surgery. Spectra from the plume classified as BCa were mapped onto a display of the tumor region and compared with the pathology report. Our multivariate classifier exhibited >90% accuracy on cross-validation, driven by an elevated ratio of glycerophospholipid:triglyceride in cancer as compared with normal adipose. In the intraoperative testing cohort, 4/150 margins were assessed by pathology as positive, all of which were correctly identified by REIMS (Sensitivity=100%). Notably, two of these cases were positive for ductal carcinoma in situ. 146/150 margins were negative, of which 131/146 negative margins were consistent with histopathology (Specificity=90%). There were 13 negative margins that were determined to be positive by REIMS (false positive), of which 8 margins were noted as either 'close margins' (with cancer cells being detected within 1 mm of the inked margin on histopathology), or as high-density normal breast tissue. Other normal tissue such as skin and muscle also exhibited high phospholipid content but these spectra could be rationalized by relative distance from the tumor region using the navigation data and/or information provided by the surgeon in real-time. We have demonstrated the importance of spatio-temporal tracking and histopathology to validate intraoperative REIMS. Furthermore, we have shown the feasibility of navigated REIMS in identifying margins containing cancer in real-time during BCa surgery, where a wider excision may be desirable.

PO2-23-08

High intratumor heterogeneity induced PSME2 confers endocrine resistance via ER α PARylation in hormone receptor-positive and HER2-negative breast cancer

Presenting Author(s) and Co-Author(s):

L. Ge. Fudan University Shanghai Cancer Center, United States

Z. Wang. Fudan University Shanghai Cancer Center, United States

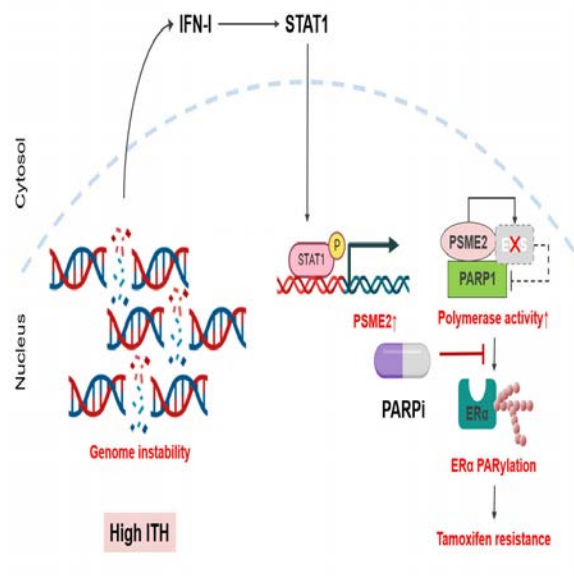
X. Jin. Fudan University Shanghai Cancer Center, United States

Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background: Hormone receptor-positive and HER2-negative breast cancer, characterized by its significant intratumor heterogeneity (ITH), poses increased recurrence, metastasis risk, and endocrine resistance. A comprehensive understanding of the genomic and biological characteristics underlying ITH is crucial for the development of effective therapeutic strategies. **Methods:** We leveraged the multiomics data from our large cohort of 381 hormone receptor-positive and HER2-negative breast tumors, supplemented with single-cell sequencing (scRNA-seq) data from 9 individual samples, to investigate ITH and its associated molecular features. Mechanistic investigations were conducted using Stable Isotope Labeling by Amino Acids in Cell culture (SILAC) proteomics, co-immunoprecipitation (Co-IP), Chromatin Immunoprecipitation followed by quantitative PCR (ChIP-qPCR), and dual-luciferase reporter assays. We specifically focused on the role of Proteasome activator subunit beta (PSME2), a potential regulator of drug resistance and metastasis. **Results:** We quantified the degree of ITH at sample level using multi-omics and scRNA-seq data and observed a correlation between higher ITH levels, increased genomic instability, upregulation of the STING type-I-interferon-dependent pathway, and poor efficacy of endocrine therapy. Both bulk and single-cell data revealed an enrichment of PSME2, associated with type-I interferon, in groups exhibiting high ITH. Patients with elevated PSME2 expression manifested a poorer prognosis and diminished responsiveness to endocrine therapy. Within the context of ITH, we discovered that IFN-I transcriptionally activated PSME2 via STAT1. Further investigation revealed a complex interplay among PSME2, PARP1, and EWS, wherein PSME2-mediated degradation of EWS relieved the transcriptional repression of PARP1, resulting in its overexpression. This series of events, orchestrated by PSME2, led to ER α PARylation and promoted tamoxifen resistance. In subsequent clinical translation studies employing mouse xenograft, patient-derived organoid (PDO), and patient-derived xenograft (PDX) models, we demonstrated that PARP1 inhibitors could effectively mitigate tamoxifen resistance induced by high PSME2 expression, providing new insights into therapeutic strategies. **Conclusions:** Our study highlights the importance of understanding ITH in hormone receptor-positive and HER2-negative breast cancer and identifies PSME2 as a key player in endocrine resistance and patient prognosis. The application of PARP1 inhibitors shows promise in improving treatment outcomes in tumors with elevated ITH and PSME2 expression.

Working Modle



PO2-23-10

Obesity May Modulate the Relationship Between High Mammographic Breast Density and Neoadjuvant Chemoresistance in Early Breast Cancer.

Presenting Author(s) and Co-Author(s):

A. Redfern. University of Western Australia, Perth, Western Australia, Australia

V. Agarwal. Fiona Stanley Hospital, Perth, Western Australia, Australia

E. Darcey. University of Western Australia, United States

L. Spalding. Harry Perkins institute for Medical Research, Perth, Western Australia, Australia

H. Martin. Fiona Stanley Hospital, Perth, Western Australia, Australia

J. Stone. University of Western Australia, Perth, Western Australia, Australia

Background - An inverse association has been described in a number of studies between mammographic breast density (MBD) and pathologic complete response (pCR) following neoadjuvant chemotherapy (NAC) for early breast cancer (BC), implicating high MBD in chemotherapy resistance. However, this effect has not been seen in all there is a paucity of data exploring whether this relationship extends the relationship beyond pCR to overall survival. This study aims to validate the relationship between MBD and pCR in patients undergoing NAC for early BC as well as to assess the relation of MBD with clinical complete response (cCR), relapse-free (RFS) and BC-specific survival (BCSS). Further, this study examines these associations stratified by body mass index (BMI).

Methods - MBD was measured in contralateral mammograms in 127 women before NAC, using Cumulus software. As the study spanned the transition period from film to digital mammography, film mammograms were digitised using a high-powered scanner and processed full-field digital mammograms were extracted from the imaging storage facility. Basic patient, tumour and treatment demographics were collated including BMI. Percent dense area (PDA) was correlated with patient and tumour characteristics, short-term (pCR/cCR incidences), and long-term chemotherapy outcomes (RFS and BCSS).

Results - Overall rates of cCR and pCR of 49% and 21% were observed across the whole cohort. Mean PDA was higher in those not undergoing cCR ($p=0.041$) and relapsing patients ($p=0.041$) but did not significantly vary by pCR or BC-deaths. As a dichotomous variable, high PDA relative to low PDA corresponded to lower cCR (40 v 58%, $p=0.027$), but no significant difference was seen for pCR (17.5 v 25.0%, $p=0.15$), BC relapse (38 v 30%, $p=0.15$) or BC-death (32 v 25%, $p=0.20$). High PDA (relative to low PDA) in patients with obesity (BMI $>30\text{kg/m}^2$) was associated with lower pCR (0% v 28.1%, $p=0.036$) and numerically higher relapse rates (56% v 28%, $p=0.063$) and breast cancer deaths (56 v 28%, $p=0.071$). No such relationship was observed in patients with a BMI $< 30\text{kg/m}^2$.

Conclusion - Higher MBD associated with lower cCR and higher relapse but not with pCR or BC death. The inferior outcomes with high MBD were confined to patients with obesity in our study. Further analysis of the relationship between MBD and outcomes, including by BMI, is warranted.

PO2-23-11

SMAD4 depletion contributes to endocrine therapy resistance by ERBB signaling in HR+HER2- breast cancer

Presenting Author(s) and Co-Author(s):

K. Li. The First Affiliated Hospital of Chongqing Medical University, United States

D. Shu. The First Affiliated Hospital of Chongqing Medical University, United States

H. Li. The First Affiliated Hospital of Chongqing Medical University, United States

Objectives: Endocrine therapy resistance is a significant clinical challenge for patients with estrogen receptor (ER)-positive breast cancer. Dysregulation of the ER and ERBB signaling pathways plays a key role in endocrine therapy resistance. However, it is unclear how these pathways are integrated during resistance development. SMAD4 is involved in multiple stages of tumorigenesis, but its role in endocrine resistance development remains elusive. Here, we aimed to investigate the role of SMAD4 in the development of acquired endocrine therapy resistance in ER-positive breast cancer. **Methods:** CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) screening was conducted to identify genes involved in regulating the sensitivity of T47D cells to 4-hydroxytamoxifen (OHT). Bioinformatics analysis was performed to explore the clinical significance of SMAD4. The differential expression of SMAD4 in cells before and after endocrine treatment was assessed by RT-qPCR and immunoblotting. Loss-/gain-of-function assays were conducted to validate the phenotype. RNA-seq and phenotype rescue experiments were used to explore the underlying mechanisms. Drug combination experiments were performed to assess the therapeutic effect on SMAD4-depleted cells. **Results:** CRISPR screening identified SMAD4 as a key determinant of endocrine therapy resistance. Bioinformatic analysis showed that SMAD4 expression was downregulated in breast cancer tissues and that low expression was associated with poor patient prognosis. Differential expression analysis after endocrine therapy treatment showed that endocrine therapy downregulated the expression of SMAD4. In vitro and in vivo models further demonstrated that SMAD4 downregulation leads to endocrine therapy resistance. Transcriptome sequencing analysis identified that the ER, ERBB and PI3K/Akt/mTOR signaling pathways were aberrantly activated upon SMAD4 depletion. Further analysis revealed that the PI3K/Akt/mTOR pathway may contribute to the regulation of ERBB on ER signaling to some extent. The aberrant activation of autophagy in phenotype rescue experiments was found to reduce the rescue effect of the combination of 4-hydroxytamoxifen (OHT) and lapatinib (LAPA). Finally, drug combination experiments verified that the combined use of OHT, LAPA and hydroxychloroquine (CQ) produced a synergistic effect in SMAD4-depleted cells. **Conclusions:** Taken together, our findings demonstrate that SMAD4 plays a crucial role in endocrine therapy resistance and suggest a reasonable treatment strategy for ER-positive breast cancer patients who are resistant to endocrine therapy.

PO2-23-12

Innovative Metastatic Breast Cancer Therapy, CBT300, Reverses Drug and Immune Resistance

Presenting Author(s) and Co-Author(s):

E. Stolarik. Creative BioTherapeutics, Gurnee, Illinois, United States

J. Zelek. Creative BioTherapeutics, Gurnee, Illinois, United States

M. Thigpen. Creative BioTherapeutics, Gurnee, Illinois, United States

A. Davidson. Creative BioTherapeutics, Gurnee, Illinois, United States

D. Davidson. Creative BioTherapeutics, Gurnee, Illinois, United States

For many patients with metastatic breast cancer (MBC), their disease is treatable but incurable. Although the rate of death from MBC has significantly decreased over the last 10 years due to early detection and new treatment options, MBC still accounts for over 40,000 deaths each year in the US that has been consistent for the past 30 years. Recently, it is estimated that 90% of those deaths were due to drug resistant recurrent disease. Nearly 45% of MBC deaths can be attributed to a subpopulation of patients with metastatic triple negative breast cancer (mTNBC). Despite MBC's initial sensitivity to chemotherapy, it often recurs at greater than 40% in stage I-III patients and greater than 80% in stage IV patients which have a dismal 5-year survival of 12%. African American women have a 40% greater incidence of death from MBC despite a 4% lower risk of diagnosis. Unfortunately, current therapies do little to reduce drug resistance and death for recurrent drug resistant MBC.

Currently, the only therapies approved by the FDA for recurrent TNBC patients are Keytruda plus chemotherapy and an Antibody Drug Conjugate (ADC) called Sacituzumab Govitecan. Keytruda (anti-PD-L1) is an immune checkpoint inhibitor (ICI) given with chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine plus carboplatin). The second recently approved therapy, Sacituzumab Govitecan (SG), is composed of an antibody to human trophoblast cell-surface antigen 2 (Trpo-2) coupled to SN-38 (topoisomerase I inhibitor). Although these results are very encouraging, the 80% of TNBC patients that either do not have high positive PD-L1 tumors, or don't respond to these therapies and become drug resistant suggests that most patients with TNBC will have recurrent disease with little or no hope for survival.

For contrast, our novel MBC therapy, CBT300, targets cell surface GRP78 that has been found in over 95% of MBC and in 93% of TNBC tumors. We can now show that inhibition of cell surface GRP78 can a) induce apoptosis of drug resistant TNBC cells in vitro and in vivo, b) eliminate drug resistance showing synergistic effects with chemotherapy in vitro and in vivo, c) decrease amount of chemotherapy in combination with CBT300 and d) reduce immune suppression. Recent publications show that GRP78 is found on many types of tumor cell surfaces but not on normal cell surfaces. In fact, tumor cell surface GRP78 (csGRP78) is important for many aspects of MBC development, including cell survival, proliferation, chemoresistance, angiogenesis, metastasis formation, immune suppression, and stem cell formation. Recently, it has been shown that increased cell surface GRP78 expression in TNBC patients was significantly associated with later stage, increased distant metastasis, increased aggressiveness, shorter disease-free survival, and decreased overall survival. In studies to help understand how cell surface GRP78 causes MBC progression and drug resistance, we discovered a novel GRP78 binding transmembrane protein on TNBC cells called Receptor Tyrosine Kinase Orphan Receptor-1 (ROR1). Using the GRP78 binding domain from ROR1 and a human Fc IgG1 domain, we created a biologic fusion protein that is a potent and cell

surface specific GRP78 inhibitor, CBT300. We now show that CBT300's elimination of cell surface GRP78 destabilizes and removes oncofetal proteins ROR1, Cripto-1, and checkpoint protein PD-L1 from tumor cell surfaces resulting in reversal of chemoresistance, reduction in immune suppression, inhibition of stem cell phenotype and increased tumor cell apoptosis. Since ROR1, Cripto-1 and PD-L1 are three of the major redundant pathways for tumor drug resistance, immune suppression and stem cell formation, the ability to inhibit all these pathways with CBT300, a single safe and very efficacious therapy, is very innovative and could be a significant advance for the treatment of MBC.

PO2-24-01

Kif11 Inhibition Preferentially Kills TP53-mutant Breast Cancer Cells

Presenting Author(s) and Co-Author(s):

A. Lanier. MD Anderson Cancer Center, Department of Clinical Cancer Prevention, United States

W. Tahaney. MD Anderson Cancer Center, United States

J. Qian. The University of Texas MD Anderson Cancer Center, United States

C. Moyer. University of Texas MD Anderson Cancer Center, Missouri City, Texas, United States

Y. Ma. MD Anderson Cancer Center, United States

B. Arun. UT MD Anderson Cancer Center, Houston, Texas, United States

A. Mazumdar. MD Anderson Cancer Center, Department of Clinical Cancer Prevention, United States

P. Brown. MD Anderson Cancer Center, Department of Clinical Cancer Prevention, United States

Background Triple-Negative Breast Cancer (TNBC) makes up 15-20% of breast cancer diagnoses and is more common in younger women, those with BRCA mutations, and Black patients. Furthermore, TNBCs are defined by their lack of expression of the targetable receptors: estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), and progesterone receptor (PR), resulting in few targeted therapy options for TNBC patients. One potential therapeutic target in TNBC is mutant p53, since 85-90% of TNBCs harbor TP53 mutations. However, the mutant p53 protein is challenging to target directly. Therefore, we have sought to identify survival pathways critical to TP53 mutant cells. Through a combined in vitro and in silico drug screen, we identified that the Kif11 inhibitor SB-743921 differentially kills TP53 mutant breast cancer cells compared to TP53 wild-type cells. Hypothesis

Based on this screening data, we hypothesized that Kif11 inhibition causes TP53 mutant cells to undergo mitotic catastrophe resulting in cell death due to failure of activation of p53-mediated cell cycle checkpoints. Methods

Clinical data was obtained from cBioPortal from the TCGA and METABRIC cohorts. Expression data analysis and survival analyses were performed using GraphPad Prism. Cell growth assays were conducted by seeding cells in 96 well plates, treating under designated conditions, then staining with Hoechst 33342 for cell counting on the ImageXpress Pico. Cell death was determined by co-staining with Hoechst 33342 and DRAQ7 followed by imaging and analysis on the ImageXpress Pico and by Annexin V and Propidium Iodide Staining followed by flow cytometry analysis. Cell cycle analysis was conducted following synchronization with Lovastatin and Mevalonate release followed by collection of samples, fixation, PI staining, and flow cytometry analysis. Immunofluorescence imaging was conducted by staining with anti-alpha-tubulin-AlexaFluor488 and DAPI and imaging at 20x and 63x on the ImageXpress PICO. In vitro expression experiments were carried out through qPCR and western blotting. < Results In human breast cancers, KIF11 is more highly expressed in TP53 mutant, as compared to wild-type breast cancers, and in TNBCs, as compared to other breast cancer subtypes.

Patients with tumors that had higher expression of Kif11 had poorer overall survival outcomes. Inhibition of Kif11 with the small molecule inhibitor SB-743921 induces greater death of TP53 mutant as compared to wild-type breast cancer cells. Kif11 inhibition leads to a cell cycle block in both TP53 mutant and wild-type cells, but TP53 mutant cells then die following this cell cycle block. Kif11 inhibition causes mitotic dysfunction, including monopolar spindle formation, in

mutant and wild-type cells, but greater incidence of spindle abnormalities and multinucleated cells in TP53 mutants. Introduction of a TP53 mutation into TP53 wild-type cells also induces cell death following Kif11 inhibition. Conclusions

The Kif11 mitotic kinesin is more highly expressed in TP53 mutant and triple-negative breast cancers than in TP53 wild-type breast cancers, and high expression is associated with poorer survival outcomes. In TP53 mutant cells, Kif11 inhibition results in mitotic dysfunction and cell death due to mitotic catastrophe. Acknowledgments

Research reported in this publication was supported by the John Charles Cain Endowment and the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Numbers TL1TR003169 and UL1TR003167. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We would also like to thank the MDACC NORTH Campus Flow Cytometry and Cellular Imaging Core Facility for their assistance.

PO2-24-02

Molecular characterization of primary tumors associated with various CTCs' subpopulation.

Presenting Author(s) and Co-Author(s):

M. Mego. Comenius University, Faculty of Medicine, United States

G. Minarik. Institute of Molecular Biomedicine, Faculty of Medicine, Comenius University, United States

M. Hucko. Slovak Academy of Sciences, United States

K. Kalavska. Comenius University, Faculty of Medicine, United States

M. Karaba. National Cancer Institute, United States

J. Benca. Comenius University, Faculty of Medicine, United States

T. Sedlackova. Institute of Molecular Biomedicine, Faculty of Medicine, Comenius University, United States

L. Kucerova. Faculty of Medicine, Comenius University, United States

J. Mardiak. Faculty of Medicine, Comenius University, United States

L. Klucar. Institute of Molecular Biology, Slovak Academy of Sciences, United States

Z. Cierna. Faculty of Medicine, Comenius University, United States

Background: Circulating tumor cells (CTCs) are prognostic in primary breast cancer (BC) patients and represent a heterogeneous population of cells with different phenotypes and biological value. However, molecular characterization of primary tumors associated with various CTCs' subpopulation is lacking. This study aimed to identify expression of genes associated with the presence of different CTCs subpopulations in primary BC patients using a comprehensive genomics approach. **Methods:** This prospective ongoing study included 312 patients (pts) with non-metastatic BC enrolled from March 2012 to February 2015. CTCs were detected on day -1 to 0 before surgery. Isolated peripheral blood mononuclear cells (PBMC) were depleted of hematopoietic cells using RosetteSep™ kit negative selection with anti-CD45 antibody. RNA extracted from CD45-depleted (CD45-) PBMC was interrogated for expression of EMT-inducing transcription factors (TWIST1, SNAIL1, SLUG, ZEB1) and epithelial (CK19) gene transcripts by quantitative reverse transcription-PCR. Expressions of gene transcripts in CD45- PBMC of patients were compared to those of CD45- PBMC of 60 healthy donors. Formalin-fixed paraffin-embedded tumor tissue was subject for gene expression analysis performed by HTG EdgeSeq Oncology Biomarker panel (HTG Molecular Diagnostics, Inc., Tucson, USA). **Results:** CTCs with epithelial phenotype (CTC_EP) were detected in 30 (9.6%) pts, CTC with EMT (epithelial-to-mesenchymal transition) were detected in 54 (17.3%), while blood of 79 (25.3%) pts exhibit at least one type of CTC. Patients with detectable CTC in peripheral blood had inferior disease-free survival compared to patients without detectable CTC (HR = 0.62, 95% CI 0.37-1.06, P=0.048). There was no association between epithelial CTCs and analysed patients/tumour variables. Genes expression analysis identified 7 differentially expressed genes in patients with the CTC_EP phenotype (CHGA, MESP1, COL2A1, MT2A, COMP, MMP7 and ORM2), 200 genes associated with CTC_EMT phenotype (top 10 genes included CHGA, CECR6, SMAD2, HUS1, FGF10, HNF1A, SEC61G, CDK4, CD44 and F3). Analysis identified that low expression of CHGA and MMP7 was consistently associated with any CTC subpopulations. **Conclusions:** In this study for the first-time revealed gene expressions associated with various CTC subpopulations. We suppose that these genes could represent potential therapeutic target aimed to inhibit metastatic cascade in

breast cancer.

PO2-24-03

Soluble E-cadherin promotes inflammatory breast cancer tumorigenesis via PDIA4-mediated suppression of ferroptosis

Presenting Author(s) and Co-Author(s):

X. Hu. MD Anderson cancer center, houston, Texas, United States

y. xiong. MD Anderson cancer center, United States

E. Villodre. MD Anderson Cancer Center, United States

J. Song. MD Anderson cancer center, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

W. Woodward. UT MD Anderson Cancer Center, Houston, Texas, United States

S. Krishnamurthy. MD Anderson cancer center, United States

j. Chen. MD Anderson cancer center, United States

B. Debeb. MD Anderson Cancer Center, United States

Xiaoding Hu^{1,6}, Yun Xiong², Emily S Villodre^{1,6}, Juhee Song³, Debu Tripathy^{1,6}, Wendy A Woodward^{4,6}, Savitri Krishnamurthy^{5,6}, Junjie Chen², Bisrat G Debeb^{1,6}

Departments of ¹Breast Medical Oncology, ²Experimental Radiation Oncology, ³Biostatistics, ⁴Breast Radiation Oncology, and ⁵Pathology and ⁶MD Anderson Morgan Welch Inflammatory Breast Cancer Clinic and Research Program, The University of Texas MD Anderson Cancer Center, Houston TX. Background: Inflammatory breast cancer (IBC) is an aggressive form of breast cancer known for its rapid progression and high metastatic potential without known distinctive drivers. Currently, there are no FDA-approved targeted therapies specifically for IBC patients, highlighting the urgent need for novel and effective treatments. Through our investigation of metastatic xenograft IBC sublines, we have identified soluble E-cadherin (sEcad), an extracellular proteolytic fragment of full-length E-cadherin, as a protein associated with IBC tumor progression. We hypothesize that sEcad promotes IBC tumorigenesis by suppressing ferroptosis. Methods: MDA-IBC3 (ER-/HER2+) and SUM149 (ER-/HER2-) IBC cell lines were used in this study. Stable overexpression of sEcad in IBC cell lines was achieved using lentiviral vectors. Cell death for ferroptosis was measured by propidium iodide staining using flow cytometry. Mass spectrometry and Bio-ID-based proteomics assays were used to identify sEcad-interacting proteins and potential mechanisms. For in vivo studies, control and sEcad -overexpressing SUM149 and MDA-IBC3 cells were injected into the cleared mammary fat pads of SCID/Beige mice and tumor growth was monitored via caliper measurements. Serum sEcad levels from IBC patients (n=301) were analyzed by ELISA. Results: High serum sEcad levels in IBC patients correlated with poorer OS (p=0.02) and earlier development of metastasis (p=0.006). Overexpression of sEcad in IBC cell lines enhanced cell proliferation and colony formation in vitro. Mice injected with sEcad-overexpressing SUM149 and MDA-IBC3 cells had significantly higher tumor growth rates compared to controls (SUM149: p=0.007; MDA-IBC3: p=0.006). Mechanistically, mass spectrometry and Bio-ID assays identified Protein Disulfide Isomerase Family A Member 4 (PDIA4) as a novel binding partner of sEcad, which was validated through co-immunoprecipitation. Additionally, sEcad increased the expression of PDIA4, an enzyme that plays a role in cellular redox regulation and protein folding. PDIA4 has been shown to regulate

key players of ferroptosis such as ATF4, SLC7A11. Our results showed that, compared to controls, sEcad-overexpressing IBC cells displayed significant resistance to ferroptosis inducers, including RSL3, FIN56, and sulfasalazine. Knockdown of PDIA4 in sEcad high-expressing cells significantly increased their sensitivity to ferroptosis-promoting drugs. Moreover, we found that PDIA4 regulates ATF4 to impact ferroptosis-mediated cell death in IBC cells. Conclusions: Our study shows that sEcad affects ferroptosis through PDIA4, impacting tumorigenesis in IBC. These findings uncover a novel and pivotal role for sEcad in IBC tumor growth and progression, providing new insights and potential therapeutic targets for IBC patients.

PO2-24-04

Exploring the role and therapeutic potential of Ubiquitin Specific Peptidase 11 (USP11) in estrogen receptor positive breast cancer

Presenting Author(s) and Co-Author(s):

R. Moore. Royal College of Surgeons in Ireland/ School of Pharmacy and Biomolecular Sciences, DUBLIN 2, Dublin, Ireland

A. Blümel. Royal College of Surgeons in Ireland/School of Pharmacy and Biomolecular Sciences, Ireland

E. Ward. Royal College of Surgeons in Ireland/School of Pharmacy and Biomolecular Sciences, Ireland

E. Sainsbury. Royal College of Surgeons in Ireland/ Tissue Engineering Research Group, Ireland

E. Conroy. UCD/Conway Institute, Ireland

F. O'Brien. Royal College of Surgeons in Ireland/ Tissue Engineering Research Group, Ireland

C. Curtin. Royal College of Surgeons in Ireland/ Anatomy and Regenerative Medicine, Ireland

S. Ali. Imperial College London/ Department of Surgery & Cancer, United Kingdom

H. McCarthy. pHion Therapeutics Ltd, United Kingdom

W. Gallagher. UCD/Conway Institute, Ireland

D. O'Connor. Royal College of Surgeons in Ireland/ School of Pharmacy and Biomolecular Sciences, Ireland

Dysregulated estrogen receptor (ER) function is a key feature of 70% of breast cancers. In this setting ER primarily functions as a growth-controlling transcription factor driving pro-tumorigenic properties, thus there is a need to identify novel modulators of ER transcriptional activity as alternative therapeutic options. Previously, we showed a significant association between high ubiquitin specific protease 11 (USP11) expression and poor survival in ER+ breast cancer patients, but not in ER- patients, indicating a role for USP11 in ER+ subtypes. However, the precise role of USP11 in controlling ER function remains undescribed. To interrogate USP11 function in ER+ breast cancer we generated a CRISPR USP11 knockout MCF7 breast cancer cell line. Our results showed for the first time that USP11 knockout significantly reduces proliferation, induces G2 cell cycle arrest and apoptosis, abrogates ER α transcriptional activity, significantly impairs cell migration and invasion, whilst also impairing MCF7 cancer stem-cell like properties and malignant transformation in vitro. In addition, we also observed significant dysregulation of epithelial-mesenchymal transition-related markers including E-cadherin, N-cadherin, Snail and Slug. Using RNA-seq of MCF7 cells +/- estradiol, +/- stable USP11 knockdown we identified dysregulated pathways in protein binding, cell adhesion molecule binding and cell cycle regulation following USP11 modulation. Of note, gene expression analysis indicated NCOA3 as the most differentially expressed coding gene. Further validation confirmed a significant reduction in NCOA3- encoded Steroid receptor coactivator- 3 (SRC-3) protein expression following USP11 modulation with immunocytochemical analysis also indicating co-localisation within the nucleus. Frequently upregulated in breast cancer and associated with poor outcome, SRC-3 promotes ER transcriptional activity and co-activates a wide range of additional pro-tumorigenic transcription factors. Thus, SRC-3 modulation offers an attractive therapeutic target in breast cancer. This finding may present a novel role for USP11 in controlling SRC-3 and therefore associated ER transcriptional activity. We then aimed to explore the therapeutic potential of USP11. Although rare in primary breast cancer,

activating mutations in the ER ligand-binding domain have recently been linked to recurrent, anti-endocrine resistant disease and metastasis. As such cancers remain dependent on ER-signalling for proliferation, but are resistant to ER targeted therapies, we identified USP11 as a potential novel therapeutic target. Using CRISPR knock-in ER mutant MCF7 cell lines expressing the four most common ER activating mutations, we demonstrated that USP11 knockdown continues to significantly reduce proliferation and abrogates mutant ER α transcriptional activity. We then explored amphipathic cell penetrating peptide RALA encapsulation as a delivery method for siRNA targeting USP11. Optimisation of nanoparticle delivery in the Y537S ER-mutant MCF7 breast cancer cell line achieved significant knockdown of USP11 and ER-related target genes including TFF1, PgR, GREB1 and PKIB in 2D with minimal associated cellular toxicity. To overcome the siRNA-related issues of rapid clearance upon systemic delivery, we then explored the use of a freeze-dried collagen-based scaffold model as an in vitro 3D RALA-encapsulated siRNA delivery system. Here we observed successful delivery of nanoparticle to MCF7 breast cancer cells, with a significant reduction in USP11 mRNA expression. Bio-compatible scaffold-facilitated delivery may therefore offer a more feasible translation of this siRNA-based therapeutic. Overall, this study highlights a novel role for USP11 in various oncogenic pathways. USP11 may therefore offer a novel therapeutic target to be exploited for the management of ER-positive breast cancer, including ER mutant breast cancer.

PO2-24-06

Cancer-Associated Fibroblasts Promote Tumor Stemness in Aggressive Breast Cancers via NDRG1

Presenting Author(s) and Co-Author(s):

E. Villodre. MD Anderson Cancer Center, United States

J. M Hogstrom. Beth Israel Deaconess Medical Center and Harvard Medical School, United States

X. Hu. MD Anderson cancer center, houston, Texas, United States

N. Kozlova. Beth Israel Deaconess Medical Center and Harvard Medical School, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Muranen. Beth Israel Deaconess Medical Center and Harvard Medical School, United States

B. Debeb. MD Anderson Cancer Center, United States

Background: Inflammatory breast cancer (IBC) and triple negative breast cancer (TNBC) have the lowest 5-year survival rates among breast cancers: 40% for IBC and 77% for TNBC. Effective treatments for these aggressive tumors are urgently needed. To develop better treatments, it is crucial to understand the underlying mechanisms driving their aggressive biology. Our recent research has identified N-myc downstream regulated gene 1 (NDRG1) as a crucial driver of tumor progression and metastasis in aggressive breast cancers. We have also found that NDRG1 expression in tumors is correlated with poorer outcomes in IBC patients. Additionally, we have observed that cancer-associated fibroblasts (CAFs), derived from breast cancer biopsies, stimulate NDRG1 expression and phosphorylation as well as tumor stemness. Based on these findings, we hypothesize that NDRG1 is a key regulator of tumor stemness and progression, and secreted stromal factors regulate tumor stemness through NDRG1. Methods: To assess tumor stemness, we conducted in vitro experiments by quantifying the CD44⁺/CD24⁻ subpopulation and performing mammosphere assays in NDRG1 control and depleted cells (SUM149, BCX010, MDA-IBC3). In vivo, we employed a limiting dilution transplantation assay, where NDRG1 control and knockdown SUM149 cells were transplanted into the mammary fat pad at different dilutions. We treated NDRG1 control and knockdown breast cancer cells with different patient-derived CAF-conditioned media (CAFs-CM, 50%, 24h) or control medium. The expression of NDRG1/pNDRG1 and CD44⁺/CD24⁻ cells was evaluated by immunoblotting and flow cytometry. qPCR array was performed to evaluate tumor stemness markers. Results: NDRG1 depletion significantly reduced the CD44⁺/CD24⁻ subpopulation ($p < 0.001$) and the efficiency of mammosphere formation ($p = 0.001$). In vivo limiting dilution experiments demonstrated a substantial reduction in the frequency of breast cancer stem cells in NDRG1 knockdown cells ($p = 1 \times 10^{-12}$). Treatment of IBC cells with CAF-CM derived from breast cancer patients stimulated the cancer stem cell subpopulation [CD44⁺/CD24⁻: Control medium (43.1 ± 0.1) vs CAF-CM (55.1 ± 0.7); $p = 0.004$] and increased NDRG1 and phospho-NDRG1 expression. However, the stimulation of NDRG1 knockdown cells with CAF-CM did not significantly alter the cancer stem cell population (0.2 ± 0.2 in Control medium versus 0.4 ± 0.3 in CAF-CM) and the expression of NDRG1/phospho-NDRG1. Additionally, qPCR array analysis revealed the upregulation of several cancer stem cell and self-renewal markers in CAF-CM stimulated cells compared to control-medium treated cells. Conclusions: Our data strongly support the role of NDRG1 as a critical regulator of tumor stemness. Moreover, we have discovered that conditioned media from patient-derived CAFs induces tumor stemness in

breast cancer cells, and this effect is dependent on the expression NDRG1.

PO2-24-07

Investigation into potential Estrogen Receptor (ER)-mediated regulation of Phosphoserine Aminotransferase (PSAT1)

Presenting Author(s) and Co-Author(s):

M. Sumlut. University of Louisville, United States

J. Wittliff. University of Louisville, United States

B. Clem. University of Louisville, United States

Breast cancer is one of the leading causes of death among women. Expression of different proteins, such as hormone receptors (HR), are used to classify different types of breast cancer (i.e., HR+BC or triple negative breast cancer (TNBC)). While activation of the estrogen receptor (ER) in HR+BC is known to regulate a vast number of downstream targets in promoting breast cancer, there may be additional ER-regulated processes that are still unknown. The serine synthetic pathway has been demonstrated to be crucial in the proliferation and survival of select subtypes of breast cancer and phosphoserine aminotransferase 1 (PSAT1) is a key regulatory step. Previous studies have demonstrated higher PSAT1 levels in cells lacking ER and we now show a negative correlation between ER α protein levels and PSAT1 transcripts in human patient samples. This indicates that ER may potentially regulate PSAT1 expression. To initially investigate this potential relationship, either WT or constitutively active mutant ER α was expressed in TNBC cells (MDA-MB-231), which have high endogenous PSAT1 expression and no ER. Immunoblot was used to verify ER α levels and to assess effects on PSAT1. We observed a qualitative trend in decreasing PSAT1 levels with re-expression of ER α in the TNBC cells. While the variabilities in these results preclude any conclusion of a ER α :PSAT1 regulatory axis, the lack of a quantifiable effect on PSAT1 levels is postulated to be due to the transient nature of ER α expression/suppression in these systems. A more profound effect would be expected under durable changes in ER α levels and is a focus on-going studies.

PO2-24-08

GD3 Synthase is a Master Regulator of Wild-Type p53–Mediated Apoptosis and Mutant p53–Mediated Tumorigenesis

Presenting Author(s) and Co-Author(s):

V. Anand. The University of Texas MD Anderson Cancer Center, United States

F. EL-DANA. UT MD ANDERSON CANCER CENTER, TX, HOUSTON, Texas, United States

J. BORGMAN. UT MD ANDERSON CANCER CENTER, TX, HOUSTON, Texas, United States

M. ANDREEFF. UT MD ANDERSON CANCER CENTER, TX, HOUSTON, Texas, United States

V. Battula. The University of Texas MD Anderson Cancer Center, United States

The tumor suppressor protein p53 is essential for maintaining genomic stability and regulating cellular responses to stress. TP53 mutations are common in breast cancer (BC) and other malignancies. We previously showed that ganglioside GD2 identifies BC stem-like cells (BCSCs) and that GD3 synthase (GD3S/ST8SIA1) is upregulated in breast tumors with TP53 mutations. Here, we demonstrate the direct involvement of p53 in the transcriptional regulation of GD3S in the GD2 biosynthesis pathway. Our results uncover a novel role of GD3S in inhibiting p53-mediated apoptosis and promoting mutant p53–induced tumor initiation.

To investigate the p53-mediated regulation of GD3S expression, we used the TCGA and METABRIC datasets and examined GD3S mRNA expression in breast tumors with different p53 mutation status. GD3S expression was significantly upregulated in BC patients with hotspot (HS) p53 mutations compared to those with wild-type (WT) p53 or non-HS p53 mutations ($P < 0.0001$). Immuno-histochemical analysis of GD3S and p53 in FFPE primary tumor tissues from BC patients ($n=84$) with varying p53 expression status demonstrated that patients with HS p53 mutations had higher histological scores for GD3S than did patients with WT p53 ($P < 0.0001$) or non-HS p53 mutations ($P=0.009$). GD3S and p53 expression were significantly positively correlated in patients with HS p53 mutations ($r=0.735$; $P=0.006$) but not in patients with WT p53 ($r=-0.09$) or non-HS p53 mutations ($r=0.14$). Consistent with these patient data, BC cells harboring HS p53 mutations had significantly upregulated and positively correlated expressions of GD3S and p53 ($n=8$; $r=0.85$). Moreover, compared to those with WT p53, the cells with HS p53 mutations had substantially greater populations of GD2⁺ BCSCs ($P=0.02$) and GD3⁺ BCSCs ($P=0.01$). Subsequently, we investigated the regulatory role of p53 in the GD2 biosynthetic pathway by stabilizing WT p53 expression by nutlin-3a treatment in 4 BC cell lines and suppressing the expression of HS p53 mutants by p53 knockdown in their respective cell lines ($n=4$). In cell lines with WT p53, nutlin-3a significantly decreased GD3S expression and GD2 levels ($P < 0.05$ and $P < 0.0001$, respectively), suggesting that WT p53 inhibits GD3S expression. In cell lines with p53 mutations, p53 knockdown significantly inhibited GD3S expression. In both cells with WT p53 (MCF7 and ZR751) and cells with HS p53 mutations (Hs578T and BT549), the stable overexpression of GD3S effectively suppressed apoptosis even when WT p53 was stabilized or HS p53 mutant expression was depleted. Consistent with these results, in mice bearing MCF7 cell–derived xenografts, the overexpression of GD3S counteracted the effect of stabilized WT p53–mediated apoptosis and facilitated tumor growth ($P < 0.0001$).

The results of a promoter-luciferase reporter assay demonstrated that nutlin-3a reduced GD3S promoter activity in a dose-dependent manner in MCF7 and ZR751 cells ($P < 0.0001$), whereas doxycycline (1 μ M) significantly reduced GD3S promoter activity in Hs578T and BT549 cells

with inducible p53 knockdown ($P < 0.001$). CHIP-qPCR analysis confirmed specific enrichment of WT p53 at the 300-bp upstream regions and additional enrichment of HS p53 mutants at the downstream regions of the GD3S promoter, indicating that WT p53 and HS p53 mutations have distinct promoter regulation patterns.

In summary, our study reveals that GD3S has a previously unknown anti-apoptotic function in BC, in that it helps attenuate p53-mediated apoptosis while activating tumor-promoting pathways that operate independently of p53.

PO2-24-09

Prolonged Effects of Hypoxia in Luminal Breast Cancer Cells Promotes an Aggressive Phenotype

Presenting Author(s) and Co-Author(s):

A. Moriarty. University of Maryland School of Medicine, Baltimore, Maryland, United States

O. Iriando. CICBioGune, United States

D. Mecnas. University of California, United States

Y. Li. University of Southern California, United States

Y. Amzaleg. City of Hope Comprehensive Cancer Center, United States

R. Klotz. University of Maryland School of Medicine, United States

M. Yu. University of Maryland School of Medicine, United States

Aidan Moriarty

Mentor: Dr. Min Yu Hypoxic Memory in Breast Cancer Cells Metastasis is the main cause of tumor-related mortality in breast cancer patients. Improving our understanding of the metastatic cascade is imperative to improve patient outcomes. Prior research indicates cancer cells with increased metastatic potential have acquired adaptive properties induced by factors in the tumor microenvironment (TME), including hypoxia. However, previous hypoxia research has been primarily focused on signaling changes that occur when cancer cells are in the hypoxic TME and does not account for long-term changes that may occur once cancer cells re-enter normoxia, such as when they metastasize. Our research in patient-derived circulating tumor cell (CTCs) lines and breast cancer cell lines has indicated that certain transcriptional changes are maintained after cells leave hypoxia, and that these post-hypoxic CTCs maintain a higher metastatic potential compared to cells not exposed to hypoxia. Taking an un-biased approach to define changes in hypoxia-exposed breast cancer cells upon reoxygenation, we performed bulk RNA-Seq on luminal breast cancer cell lines in various oxygen conditions over time. We found that a subset of genes that were differentially expressed in hypoxic conditions were maintained as up- or down-regulated after cells were reoxygenated, indicating a “hypoxic memory”. Additionally, a subset of genes were differentially expressed in the post-hypoxic cells compared to normoxia controls, demonstrating novel and prolonged gene expression changes induced by hypoxia exposure. We performed functional assays and observed that this post-hypoxic state is associated with a more aggressive phenotype in vitro. Current research in our lab is on-going to understand the epigenetic changes that may be responsible for this hypoxic memory to further understand the consequences of hypoxic memory in CTC biology and metastasis. Finally, we have designed a dual-reporter hypoxia-tracing system to validate our findings in vivo. This research will improve our understanding of the prolonged influence of hypoxia on metastatic potential in breast cancer cells and has the potential to inform future therapeutic strategies.

PO2-24-10

Anti-Tumorigenic Immuno-Microenvironment by AB-329, a Potent and Selective AXL inhibitor, combined with paclitaxel in Triple-Negative Breast Cancer Preclinical Model

Presenting Author(s) and Co-Author(s):

D. Rampa. University of Hawaii Cancer Center, Honolulu, Hawaii, United States

J. Fuson. The University of Texas MD Anderson Cancer Center, United States

H. Liu. UT MD Anderson Cancer Center, United States

M. Pan. AnHeart Therapeutics, Inc., United States

N. Ueno. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

J. lee. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

Anti-Tumorigenic Immuno-Microenvironment by AB-329, a Potent and Selective AXL inhibitor, combined with paclitaxel in Triple-Negative Breast Cancer Preclinical Model Dileep Reddy Rampa^{1,3}, Jon A. Fuson¹, Huey Liu¹, Max Pan², Naoto T. Ueno^{1,3}, Jangsoon Lee^{1,3}¹ Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas. ² AnHeart Therapeutics, Inc., New York, New York. ³ Department of Cancer Biology, University of Hawai'i Cancer Center, Honolulu, Hawaii. **BACKGROUND** The Gas6/AXL signaling pathway plays a substantial role in cancer cell survival, proliferation, immunosuppression, and metastasis. Elevated AXL expression is associated with advanced cancer stages and decreased overall survival rates, underscoring its potential as a therapeutic target for metastatic cancers. We investigated this possibility by utilizing AB-329, a selective small molecule AXL kinase inhibitor, to treat triple-negative breast cancer (TNBC). TNBC, typified by the lack of ER, PR, and HER2 expression, frequently displays mesenchymal characteristics and carries a significant risk of metastasis and an immunosuppressive tumor microenvironment. **METHODS** We assessed AXL protein expression in 28 human and 11 mouse breast cancer cell lines using Western blotting. The Microarray database was utilized to examine AXL gene expression in 40 human breast cancer cells. The Sulforhodamine B proliferation and soft agar assays measured the antiproliferative effect of AB-329 in TNBC cell lines. The in vitro anti-metastatic impact of AB-329 was evaluated through migration and invasion assays. We appraised the anti-tumor effects of AB-329 in combination with paclitaxel using 4T1 and E0771-LMB mouse TNBC xenograft models. We used FACS and CIBERSORTx to perform immune cell type profiling in E0771-LMB xenograft tumor tissues. To understand AB-329's immunomodulatory effects in tumors, single-cell RNA sequencing was conducted in a humanized mouse model with SUM149 human TNBC xenografts. **RESULTS** Microarray data revealed higher AXL expression in TNBC cells compared to non-TNBC cells. Western blotting supported this, showing higher AXL protein expression, particularly in basal and mesenchymal subtypes of TNBC cells, compared to luminal breast cancer cells. AB-329 presented moderate antiproliferative effects as a monotherapy in the TNBC cell lines tested, with half-maximal inhibitory concentrations exceeding 5 μ M. Nevertheless, combining AB-329 with paclitaxel resulted in significant growth inhibition in all tested TNBC cell lines ($p < 0.05$). Importantly, AB-329 alone could inhibit TNBC migration and invasion at a concentration of 1 μ M ($p < 0.01$) and showed enhanced inhibition rates when paired with paclitaxel ($p < 0.05$). The combination of AB-329 and paclitaxel considerably reduced tumor growth in the 4T1 and E0771-LMB xenograft models compared to paclitaxel or AB-329. Total RNA sequencing and CIBERSORTx analysis indicated that the AB-329 and paclitaxel combination increased Natural Killer (NK) cells' infiltration into E0771-LMB mouse TNBC xenograft tumors compared to single agent-treated tumors. A nearly 2.5-fold increase in NKT cell infiltration was also detected with AB-329

treatment compared to Control in SUM149 human TNBC xenografts. CONCLUSIONS Our preclinical data suggest that AB-329, an AXL inhibitor, could synergize effectively with paclitaxel in TNBC treatment, notably inhibiting tumor cell proliferation and migration while enhancing NK cell infiltration. Intriguingly, we observed an increased infiltration of NKT cells into tumors following AB-329 treatment, which may promote an anti-tumorigenic immunomicroenvironment. These results underscore the necessity for further investigation into the role of AB-329 in modulating the tumor immunomicroenvironment through AXL pathway inhibition and accentuate the potential for combining AB-329 with immunotherapy.

PO2-24-11

Hedgehog signaling influences tumor immunogenicity by the modulation of T cell populations in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

C. Swain. University of Alabama at Birmingham, Birmingham, Alabama, United States

D. Hinshaw. University of Alabama at Birmingham, United States

H. Alsheikh. University of Alabama at Birmingham, United States

B. Metge. University of Alabama at Birmingham, United States

L. Shevde-Samant. University of Alabama at Birmingham, United States

Breast cancer is becoming more prevalent as it now makes up 30% of all new cancer cases yearly for U.S. women. Additionally, highly aggressive triple-negative breast cancer (TNBC) presents as immunologically “cold” tumors characterized by limited infiltration of anti-tumorigenic lymphocytes and the promotion of immunosuppressive cell populations. Therefore, it is essential to consider possible combinational therapies in treating primary tumors and in preventing metastases and recurrence. In the breast tumor microenvironment (TME), the presence and activity of regulatory T cells (Tregs) have been associated with poorer prognoses in breast cancer due to their ability to promote the progression of tumor growth and metastasis. Our group has extensively studied how the Hedgehog (Hh) signaling pathway can modulate the aggressiveness and the immune portfolio of the mammary TME, and we have recently reported the role of this pathway in regulating Treg activity and abundance. We have discovered that Hh inhibition can influence Treg-to-Th17 plasticity, promoting Tregs into a pro-inflammatory Th17-like phenotype (Tr17). As Tregs are highly influential to other immune populations of the TME, it is imperative to determine what phenotypic changes are induced in other T cell populations after systemic Hh inhibition in the mammary TME.

We hypothesize that systemic Hh inhibition reshapes the tumor-immune microenvironment to be tumor-eradicating by influencing key immune populations of the mammary TME. Therefore, we further investigated how CD4⁺ and CD8⁺ T cells are influenced by systemic Hh blockade in a mammary carcinoma mouse model using single-cell RNA-Sequencing (scRNA-Seq) and R programming for data analyses and visualization. We sought to assess transcriptomic changes in tumoral T cells and to interpret how these elicited changes may be influencing the immunogenicity of the primary tumor. In these investigations, we found that systemic Hh inhibition modified the abundance and activation profile of CD4⁺ and CD8⁺ T cell populations within the primary tumor.

As the infiltration and persistence of certain T cell subsets within the TME can influence tumor growth, dictate tumor recurrence, and contribute to immunotherapy responsiveness, it is essential to determine the mechanisms that modulates tumoral CD4⁺ and CD8⁺ T cells in the mammary TME. These studies will expand on the mechanism by which Hh signaling modulates mammary tumorigenesis systemically. This comprehensive work will also contribute to understanding the role of Hh signaling in modulating T cell subsets and inform future studies for innovative combinational therapeutic strategies to treat highly aggressive TNBC.

PO2-24-12

Tumor-specific circRNAs elicit anti-tumor immune response via encoding cryptic antigenic peptides

Presenting Author(s) and Co-Author(s):

D. Huang. Sun Yat Sen Memorial Hospital, United States

J. Chen. Sun Yat Sen Memorial Hospital, United States

S. Su. Sun Yat Sen Memorial Hospital, United States

E. Song. Breast Tumour Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Emerging data have shown that previously defined noncoding genomes might encode human leukocyte antigen (HLA) binding peptides as cryptic antigens to stimulate adaptive immunity. However, the significance and mechanisms of cryptic antigens in anti-tumor immunity remain unclear. Here, mass spectrometry for HLA class I (HLA-I) peptidome coupled with ribosome sequencing of human breast cancer samples identified HLA-I binding cryptic antigenic peptides, which were noncanonically translated by a tumor-specific circular RNA CEIP (circCEIP). Importantly, the cryptic peptides efficiently primed naive CD4⁺ and CD8⁺ T cells in an antigen-specific manner and elicited anti-tumor immunity. Clinically, the expression of circCEIP and its encoding peptides was associated with massive infiltration of antigen-specific CD8⁺ T cells and better survival of breast cancer and melanoma patients. Mechanistically, circCEIP-encoding peptides had strong binding affinity to both HLA-I and II molecules, respectively. In vivo, administration of vaccines devised by tumor-specific circRNA or its encoding peptides in breast cancer or melanoma-bearing mice dramatically enhanced the infiltration of tumor-antigen specific cytotoxic T cells, leading to effective tumor control. Overall, our findings revealed that noncanonical translation of circRNAs can drive efficient anti-tumor immunity, suggesting that vaccination exploiting tumor-specific circRNAs may serve as an appealing immunotherapeutic strategy against malignant tumors.

PO2-25-01

Tumor Derived Chitinase-3 like 1 Induces Neutrophil Extracellular Traps that Promote T cell Exclusion and Resistance to Immunotherapies in Breast Cancer

Presenting Author(s) and Co-Author(s):

T. Taifour. Goodman Cancer Institute (GCI) / McGill University, Montreal, Canada
S. Attalla. Department of Biochemistry & Goodman Cancer Institute, Faculty of Medicine and Health Sciences, McGill University, QC H3A 1A3, Canada, United States
D. Zuo. Goodman Cancer Institute (GCI) / McGill University, Quebec, Canada
Y. Gu. Goodman Cancer Institute (GCI) / McGill University, Quebec, Canada
V. Sanguin-Gendreau. Goodman Cancer Institute (GCI) / McGill University, United States
H. Dall-Proud. Department of Biochemistry & Goodman Cancer Institute, Faculty of Medicine and Health Sciences, McGill University, QC H3A 1A3, Canada, United States
E. Solymoss. Goodman Cancer Institute (GCI) / McGill University, Quebec, Canada
T. Bui. Goodman Cancer Institute (GCI) / McGill University, Quebec, Canada
H. Kuasne. McGill University, United States
V. Papavasiliou. Goodman Cancer Institute (GCI) / McGill University, Quebec, Canada
C. Lee. Brown University, Rhode Island, United States
S. Kamle. Brown University, Rhode Island, United States
P. Siegel. Goodman Cancer Institute (GCI) / McGill University, Quebec, Canada
J. Elias. Brown University, Rhode Island, United States
M. Park. McGill University, United States
W. Muller. Department of Biochemistry & Goodman Cancer Institute & Dept. Experimental Medicine, Faculty of Medicine and Health Sciences, McGill University, QCH3A 1A3, Canada, United States

Breast cancer remains the most prevalent cancer and a major cause of mortality affecting women worldwide. Chemotherapy along with radiation and surgery have long been the standard of care for breast cancer patients. However, devastating side effects, resistance to treatments and relapse are major concerns for patients and physicians. With the rise of immunotherapies as a treatment option for various cancers, there is a critical need to understand the mechanisms through which cancers evade the immune system. Targeting such mechanisms holds the key to improve patient response to immunotherapy, especially in breast cancer where efficacy rates remain low.

In a subset of poor outcome Triple Negative Breast Cancers, cytotoxic T cells are excluded from the tumor nest and restricted to the surrounding stroma, a phenomenon known as stromal restriction. Our data from genetically engineered mouse models and human tumors identified that the secreted cytokine Chitinase-3 like 1 (Chi3l1) promotes stromal restriction of T cells in several tumor types including breast, lung and colon. Chi3l1 ablation in pre-clinical models of breast cancer results in increased T cell infiltration into the tumor nest which delayed mammary tumorigenesis and improved response to immunotherapy. We further demonstrate that Chi3l1 promotes T cell exclusion through the direct induction and deposition of neutrophil extracellular traps (NETs) which form a barrier that restricts T cell entry. Neutrophil depletion or pharmacological disruption of NET formation abrogates Chi3l1-induced T cell exclusion and

histologically phenocopies Chi3l1 ablation.

Thus, our results indicate that Chi3l1 is a major immunosuppressive cytokine that promotes breast cancer progression by inducing NET formation and inhibiting T cell infiltration. Given the importance of T cell infiltration in immune elimination of nascent tumors, the future targeting of Chi3l1 should improve immunotherapy efficacy and outcomes in patients with tumors characterized by a T cell excluded microenvironment.

PO2-25-02

The microbial metabolite trimethylamine N-oxide promotes antitumor immunity in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

H. Wang. Fudan University Shanghai Cancer Center, United States

Immunotherapy has achieved limited success in patients with triple-negative breast cancer (TNBC), an aggressive disease with a poor prognosis. Commensal microbiota have been proven to colonize the mammary gland, but whether and how they modulate the tumor microenvironment remains elusive. We performed a multiomics analysis of a cohort of patients with TNBC (n = 360) and found genera under Clostridiales, and the related metabolite trimethylamine N-oxide (TMAO) was more abundant in tumors with an activated immune microenvironment. Patients with higher plasma TMAO achieved better responses to immunotherapy. Mechanistically, TMAO induced pyroptosis in tumor cells by activating the endoplasmic reticulum stress kinase PERK and thus enhanced CD8⁺ T cell-mediated antitumor immunity in TNBC in vivo. Collectively, our findings offer new insights into microbiota-metabolite-immune crosstalk and indicate that microbial metabolites, such as TMAO or its precursor choline, may represent a novel therapeutic strategy to promote the efficacy of immunotherapy in TNBC.

PO2-25-03

Deciphering the immune molecular signature associated with pembrolizumab efficacy in the neoadjuvant setting of Triple-Negative Breast Cancer patients: a single-centre experience

Presenting Author(s) and Co-Author(s):

E. Gasparini. Azienda USL-IRCCS di Reggio Emilia, United States

G. Manzotti. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

M. Ragazzi. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

B. Donati. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

F. Torricelli. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

E. Salviato. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

A. Bisagni. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

E. Zanetti. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

A. Bologna. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

S. Coiro. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

R. Vacondio. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

G. Ferrari. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

G. Bisagni. IRCCS AUSL Reggio Emilia, United States

C. Pinto. IRCCS AUSL Reggio Emilia, United States

A. Ciarrocchi. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

F. Reggiani. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

Triple-negative breast cancer (TNBC) accounts for 15-20% of all breast cancers and is characterized by a high rate of recurrence, despite the improvement of the therapeutic approaches in recent years. Neoadjuvant chemotherapy (NACT) is the standard treatment for early-stage TNBC. Achieving a pathological complete response (pCR) is considered an essential prognostic factor for long-term outcomes. However, the percentage of pCR patients after NACT is limited to 30-40%, thus requiring the implementation of novel therapeutic strategies.

Recently, by applying a morphology-guided spatial transcriptomic approach on Tru-Cut biopsies, we showed that intratumoral infiltrating lymphocytes (iTILs) and stromal Natural Killer (NK) cells are major determinants of chemotherapy efficacy in TNBC. These data highlight a complex three-dimensional organization of the tumor landscape and underline how spatiality and molecular activation of immune cells are essential to enhance the efficacy of neoadjuvant NACT in TNBC.

The fact that immune cells are important players in this setting is corroborated by the clinical success shown by the KEYNOTE-522 study. This trial paved the way for the use of immunotherapy in neoadjuvant settings, obtaining a significant improvement in the patient's overall response compared to standard NACT.

Still, the implementation of chemotherapy with immunotherapy in the TNBC neoadjuvant treatment implicates several compelling questions, including how to further increase the percentage of patients with a complete response, overcoming resistance mechanisms, and how to improve the personalization of treatment, evaluating which patients can benefit from a therapy de-scalation or another combined therapeutic strategy.

In this prospective cohort study, we decided to define the relevance of different immune populations in affecting pembrolizumab efficacy in the neoadjuvant treatment of TNBC patients. We treated 40 patients with an early-TNBC diagnosis with the KEYNOTE-522 regimen that consists of four cycles of an intravenous infusion of pembrolizumab plus paclitaxel and carboplatin, followed by four cycles of pembrolizumab plus epirubicin and cyclophosphamide. Only patients with evident side effects to immunotherapy administration were a priori excluded. Currently, 18 patients ended the neoadjuvant schedule and underwent surgical excision. Our data indicate that 15 patients displayed a pCR at the end of the therapy, whereas 3 patients displayed only partial response.

To further clarify the immune dynamics that lead to a complete response to pembrolizumab in these patients, we collected peripheral blood before and after neoadjuvant treatment to isolate peripheral blood mononucleated cells (PBMCs). We applied a single-cell transcriptome analysis to shape any variations in circulating immune cells occurring during neoadjuvant treatment and associated with patient response.

In addition, we collected residual tumors at surgery from partial responders and derived three-dimensional organoids that recapitulate the characteristics of the original patient tumor. These ex vivo organoid-based platforms are applied to clarify the molecular mechanisms driving neoadjuvant resistance. To this aim, we are performing co-cultures with autologous immune cells to identify novel combined therapeutic strategies to rescue pembrolizumab efficacy in these models.

Overall, our study is defining the immune-related molecular mechanisms driving pembrolizumab and chemotherapy response in the neoadjuvant treatment of TNBC patients. Our findings can improve our understanding of which immune populations are determinant players in anti-TNBC immune response and can be proposed as novel biomarkers of pembrolizumab efficacy during the neoadjuvant treatment.

PO2-25-04

Anti-TIGIT upregulate CD226 on CD8+T cell as a potential therapeutic manner in HER2 positive breast cancer

Presenting Author(s) and Co-Author(s):

L. Zhang. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

Q. Zhang. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

Z. Wang. Fudan University Shanghai Cancer Center, China (People's Republic)

Z. Shao. Fudan University Shanghai Cancer Center, China (People's Republic)

J. Xue. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

Y. Chi. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

B. Xiu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Purpose: HER2 positive breast cancer subtype shows high malignancy, aggressive invasion, frequent recurrence, and low efficacy to PD-1 inhibitor though enriches in immune microenvironment. TIGIT is an immune checkpoint which expresses on T/NK cells and participates in immune evasion of cancer cells. Here, we investigated the effect of anti-HER2 and anti-TIGIT combination regarding to HER2 breast cancer treatment and tumor microenvironment, further exploring mechanisms behind the combination utilization.

Methods: We re-analyzed the untreated human and mouse HER2 breast cancer scRNA-seq dataset to explore proportions of unique cell clusters in tumor immune microenvironment and communicated signals between immune cells and tumor cells. Mouse HER2 non-sensitive model and 27 non-pCR patients were utilized to investigate the variation of TIGIT and its ligand CD112/CD155 in HER2 non-sensitive population. Relevance between CD112/CD155 and prognosis was verified by 200 patients tissue microarray IHC. We validated the efficacy of combination of anti-TIGIT and anti-Neu and delineated scRNA-seq landscape via mouse model. Multilayer analysis including CellChat and AuCell were used to investigate difference of immune network between ctrl group, monotherapy and combination. In vitro and in vivo studies were used to verify the efficacy of anti-TIGIT and pivotal clusters.

Results: We found that CD8+T cells occupied major proportion in TILs in both human and mouse HER2 breast cancer tumor immune microenvironment. CD8+T cells showed TIGIT signal to malignant epithelial cells instead of PD-1 signal. Increased CD8+TIGIT+T cells were related to poor prognosis in 200-patients cohort. In HER2 non-sensitive mouse model,

significantly increased CD8+TIGIT+T cells were found in HER2 non-sensitive group. Multiplex IHF of 27 non-pCR patients also confirmed that CD8+TIGIT+T cells increased after treatment. CD112, ligand of TIGIT on malignant cells, demonstrated higher expression after anti-HER2 treatment in HER2 non-sensitive population and negatively correlated with prognosis. In scRNA-seq about control group, monotherapy and combination group, we defined malignant cells as sensitive subclone, Neu resistant subclone and others according to cell ratio variation in ctrl, monotherapy and combination group. CD112 upregulated in all subclones in monotherapy group. GSVA analysis indicated Neu resistant subclone had highest IFN- γ response among subclones. In Neu resistant subclone, combination group showed highest expression of MHC-I genes and upregulated IFN- γ response, suggested the restored antigen presenting ability of Neu resistant subclone. Higher CD226, MHC-I and IFN- γ signals between malignant epithelial cells and CD8+T cells was found in combination group via CellChat. AuCell manifested upregulated T cell activation and IFN- γ production pathways in combination group. Public dataset showed favorable results. Increased CD226 expression and promoted cytotoxicity on CD8+T cells can only be induced by anti-TIGIT therapy in vitro and in vivo. 200-patients cohort indicated the predictive values of CD8+CD226+T cells in HER2 breast cancer.

Conclusion: In conclusion, engaged immune checkpoint TIGIT shades malignant cells from CD8+T mediated immune surveillance in HER2 breast cancer. Disruption of TIGIT inhibit tumor growth in vivo by immune elimination of malignant cells. Besides, CD8+CD226+T cells induced by combined therapy can predict patient prognosis.

PO2-25-05

Spatial multiplexing of protein biomarkers for immune cell profiling of the tumor microenvironment with ChipCytometry

Presenting Author(s) and Co-Author(s):

B. Berigan. Canopy Biosciences, United States

Understanding the spatial distribution of key immune cell populations is critical in advancing our understanding of cancer and the development of novel therapeutics. Historically, the spatial analysis of the tumor microenvironment (TME) has been limited to relatively low-plex immunohistochemical (IHC) or immunofluorescent (IF) assays, which were inadequate for deep immune cell profiling of the TME. Here, we present the analysis of fresh-frozen human breast tissue using spatial multiplexing technology called ChipCytometry, which combines iterative immuno-fluorescent staining using open-source antibodies for quantitative measure of virtually unlimited protein biomarkers on the same sample and high dynamic range imaging to facilitate quantitative phenotyping with single-cell resolution. In addition to traditional pathology review of the high-plex dataset, subsequent image analysis can be done using open-source or commercial software for advanced spatial analyses, including cluster analysis, neighborhood analysis and advanced data visualization. The results show precise expression levels for each of the protein biomarkers in the assay for each individual cell within the sample while maintaining spatial information about each cell. Dozens of immune cell subtypes were identified and quantified based on protein expression profiles. Spatial analysis of the samples revealed quantifiable heterogeneity of immune cell infiltration within the tumor samples, demonstrating the utility of the ChipCytometry platform for in-depth immune profiling in clinical samples. The ChipCytometry platform enables simultaneous detection of multiple protein biomarkers on a single tissue section for deep immune cell profiling in the TME. Combined with the single-cell spatial information, such datasets provide an opportunity for the discovery of new complex multiplexed biomarker signatures to inform therapeutic development and personalized medicine.

PO2-25-06

A hybrid breast cancer/mesenchymal stem cell population increases distant metastasis and chemoresistance of metaplastic breast carcinomas

Presenting Author(s) and Co-Author(s):

A. Eido. University of Michigan, United States

M. Gonzalez. University of Michigan, United States

C. Kleer. University of Michigan Medical School, Ann Arbor, Michigan, United States

Background: Metaplastic breast carcinoma is a heterogenous, highly aggressive and chemoresistant subtype of triple negative breast cancer (TNBC) with histological evidence of deregulated differentiation towards non-glandular components including spindle, squamous, and sarcomatoid. The role of the tumor microenvironment in the metastatic behavior and chemotherapy response of metaplastic carcinomas needs investigation to improve patient outcomes. Our lab has generated a model of spindle metaplastic breast carcinomas based on mammary epithelial cell-specific CCN6 knockout (MMTV-Cre;Ccn6^{fl/fl} or CCN6KO). We have recently shown that a subset of TNBC cells engulf mesenchymal stem/stromal cells (MSC) generating a hybrid cell population with metastatic ability, which is detected in breast cancer tissue samples. In this study, we tested the hypothesis that hybrid cells may promote chemoresistant distant metastasis in spindle metaplastic breast carcinomas and that the tumor immune microenvironment may play a role in this function. Methods: Luc-GFP-CCN6KO cells were cultured with DsRED-MSCs for 7 days, yielding >90% of hybrid cells detected by flow cytometry. Hybrids or CCN6KO single cultures (1x10⁵) cells were injected intracardially in FVB/NJ syngeneic immune competent mice (n=20 mice per group). Four days after injection, each group was treated with Paclitaxel (PTX, 10 mg/kg twice a week, i.p.) or PBS control. The metastatic burden was evaluated by bioluminescence imaging twice a week. Mice were euthanized 23 days after heart injections, followed by necropsy and histopathological evaluation of the harvested organs. Results: All mice injected with single cultures of CCN6KO cells or hybrid cells formed distant metastasis. CCN6KO cells were highly invasive and spread to the lungs and lymph nodes in the chest. We noted that 5 of 20 (25%) mice injected with hybrid cells showed metastasis in the liver (n=3 mice), pancreas (n=1), and abdominal lymph nodes (n=1). PTX treatment significantly reduced metastatic burden in mice injected with CCN6KO single cultures compared to vehicle (p=0.035) but had no effect on the metastatic burden of hybrid cells. Histologically, while the metastasis from CCN6KO cells and hybrids showed similar pathological features, consisting of spindle cancer cells with high grade nuclei and >10 mitoses/10 high power fields, hybrid-derived tumors had abundant infiltration by immune cells, mainly neutrophils, compared to single culture tumors. Conclusion: Our data show that hybrid cancer cell/MSC derived from CCN6KO spindle metaplastic carcinomas have higher ability to disseminate to distant organs, especially in the abdomen, compared to cancer cells. Our data show that hybrid cell-derived metastases have increased immune cell infiltration. We provide evidence that hybrid cells enhance Paclitaxel resistance in a mouse model of metaplastic breast carcinoma. Ongoing studies are aimed at elucidating the role of hybrids in the immune microenvironment of metaplastic breast carcinoma and clinical significance.

PO2-25-07

PEGylated Functional Upstream Domain (PEG-FUD): an anti-cancer therapy for breast Cancer

Presenting Author(s) and Co-Author(s):

M. Gari. University of Wisconsin-Madison, Madison, Wisconsin, United States

Author(s): Metti K. Gari¹, Hye Jin Lee², David R. Inman¹, Brian M. Burkel¹, Glen S. Kwon², Suzanne M. Ponik¹

Background: Breast cancer (BC) is the most common cancer diagnosed in women. In breast cancers, the extracellular matrix (ECM) is known to play a key role in disease progression by mediating cell signaling processes that drive cancer cell proliferation, migration and invasion. Work by our group identified that aligned collagen fibers perpendicular to the tumor boundary are prognostic of poor patient prognosis. Further, through matrix targeted proteomics we determined that the ECM protein, Fibronectin (FN), organizes with aligned collagen fibers in BC tissues. FN is known as the master regulator of ECM assembly because FN deposition precedes and regulates the deposition of several other ECM proteins. Clinical evidence shows that high expression of FN levels in BC patients correlates with an increased mortality risk. Due to the abundant expression of FN in the tumor microenvironment, FN has been a useful biomarker for cancer imaging and therapy. Despite multiple efforts in developing therapies that target the ECM, currently there are no effective ECM treatments available due to toxicity and lack of specificity.

Methods: To target abnormal FN deposition, we used a FN binding peptide, Functional Upstream Domain (FUD), derived from the F1 adhesin from *Streptococcus pyogenes*. PEGylated-FUD (PEG-FUD) is a potent inhibitor of FN assembly which binds the 70 kDa N-terminal region of FN with high affinity. We hypothesize that PEG-FUD will localize to the tumor site and that targeted disruption of FN assembly with PEG-FUD will reduce ECM deposition, thus block tumor progression in-vivo. In this study, we used an in vivo imaging system to assess the biodistribution of 20-kDa PEG-FUD following subcutaneous injection of Cy5 labeled peptide in 4T1 mammary tumor bearing mice. Additionally, in a second therapeutic experiment, we treated 4T1 mammary tumor bearing mice with 20-kDa PEG-FUD every 48 hr for a total of 10 treatments and measured tumor volume as an indicator of primary tumor burden.

Results: As anticipated, we observed PEG-FUD's accumulation and localization in 4T1 tumors. Additionally, PEG-FUD treatment significantly reduced tumor growth compared to saline treatment. There were no observed changes in standard toxicity assessments such as body weight and spleen weight among treatment groups. After PEG-FUD's therapeutic treatment, we observed a significant reduction in the deposition of FN matrix and an increase in cleaved caspase-3, a known marker for apoptosis by western blotting providing a potential mechanism of action of PEG-FUD inducing changes in tumor growth.

Conclusions: PEG-FUD's localization in tumors suggests its utility as a solo cancer imaging agent while providing indications that PEG-FUD can be used to deliver other therapeutics to the tumor site as a conjugate in the future. In addition, therapeutic treatment of PEG-FUD inhibited tumor growth providing preliminary evidence for PEG-FUD's use as a tumor targeting anti-cancer agent.

PO2-25-08

Role of social isolation and support on all-cause and breast cancer specific mortality among women with breast cancer: The Western New York Exposures and Breast Cancer (WEB) Study

Presenting Author(s) and Co-Author(s):

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

J. Nie. University at Buffalo, United States

A. Patel. Roswell Park Comprehensive Cancer Center, United States

M. Trevisan. University at Buffalo, United States

K. Attwood. Roswell Park Comprehensive Cancer Center, United States

J. Freudenheim. Roswell Park Comprehensive Cancer Center, United States

Background: Studies of associations of social support with mortality among women diagnosed with breast cancer have been inconclusive. Further, there have been little study of related factors such as marital status, housing, and income, nor of differential impact by treatment received (chemotherapy, radiation, or hormonal therapy).

Methods: Women with incident, pathologically confirmed invasive breast cancer, stage I-IV, answered a social support questionnaire data (n=1015) in a population-based study, the Western New York Exposures and Breast Cancer (WEB) Study. Patients were queried regarding the number of their close friends, the number of people with whom they lived with, their income, education, and marital status. Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause and breast cancer-specific mortality were estimated with Cox proportional hazards models. Associations were also examined within strata of treatment type received.

Results: Median follow up time was 18.5 yrs, 449 died of which 279 deaths were from breast cancer. Out of 1015 patients, 98 patients reported 0-1 friends while 917 reported 2 or more friends. The crude association of social isolation, defined as reporting no or one close friend, was significantly associated with higher all-cause mortality with HR 1.57 (95% CI 1.19-2.07) (p=0.0014). Older age (62 yrs vs. 57 yrs), fewer years of education (12.5 yrs vs. 13.5 yrs), longer smoking history (17 pack years vs. 10.7 pack years), higher percentage of non-white population (15.3% vs. 7.52%), lower income (20.7% vs. 7.2%), living alone (45.9% vs. 21.9%), post-menopausal status (83.7% vs. 70.7%), lower receipt of chemotherapy (32.3% vs. 44.8%), higher receipt of hormone replacement therapy (43.9% vs. 37.0%), high blood pressure (53.6% vs. 33.8%), high blood cholesterol (45.8% vs. 34.1%), more likelihood of being divorced/separated, widowed, never married (20.8% v. 12.8%, 19.8% vs. 15.2%, 13.5% vs. 7.8%) were significantly associated with social isolation. After controlling for these variables, there was no association between social isolation and all-cause mortality, HR 1.14 (95% CI, 0.78-1.66). Being widowed (HR 1.53, 95% CI 1.19-1.95), divorced/separated (HR 1.5, 95% CI 1.14-1.99), having lower income (HR 3.58, 95% CI, 1.89-6.77) and lower education (HR 1.07, 95% CI 1.03-1.12) were associated with higher all-cause mortality. In multivariable analyses, only lower income was associated with higher all-cause mortality (HR 2.44, 95% CI 1.16-5.14). There was no association of social isolation, marital status, income, education, or housing with breast cancer specific mortality. There were also no significant associations of marital status, income, social support, or housing with mortality within strata of treatment received.

Conclusions: In this population-based study of women who had been diagnosed with breast

cancer, social support, measured as the number of friends the breast cancer patient could call on for assistance, was not associated with either all cause or breast cancer mortality. Higher income was associated with lower mortality. Our study focused on social networks; future studies should also analyze emotional domain of social support, that is, perceived social support: feeling encouraged, shared problem-solving etc., which have higher clinical relevance than structural support.

PO2-25-09

The hidden costs of beauty: An evaluation of breast cancer risk for Black women

Presenting Author(s) and Co-Author(s):

N. Sarkaria. Chapman University, United States

M. Ericson. University of Southern California, United States

A. Lopez. Chapman University, United States

D. Tete. Chapman University, Department of Health Sciences, Crean College of Health and Behavioral Sciences, California, United States

The Black identity, hair product use, and breast cancer scale (BHBS) was developed and previously validated to evaluate the relationship between identity, hair product use, and breast cancer risk for Black women. Black women are disproportionately affected by breast cancer compared to other racial/ethnic groups, with a mortality rate of 40% higher than all other groups. Endocrine Disrupting Chemicals (EDCs) are present in many hair care products and have been linked to several health issues including breast cancer. Due to these health inequities and the complexity of how cultural norms shape Black women's hair product usage, the purpose of this study was to assess the reliability of the BHBS for intervention planning and evaluate the hazard scores of hair products used by Black women. Methods: Participants were recruited using purposive convenience sampling techniques. The 11-item BHBS includes two subscales: five items measuring sociocultural perspectives about hair and identity (S1) and six items assessing perceived breast cancer risk related to hair product use (S2). To determine reliability, the BHBS was administered twice over a three-week period with sociodemographic factors obtained in the initial data collection phase. All statistical analyses, including descriptive statistics and test-retest reliability (Pearson correlations) were conducted using SPSS version 26. The Environmental Working Group's (EWG's) Skin Deep® database was used to determine hazard scores of hair products used by participants. Products are rated on a 10-point scale with low (0-2), moderate (3-6), and high hazard (7-10) scores. Results: Twenty-three (86.9% African, African American & Caribbean; 13% multiracial) female participants completed the study. Their age ranged from 18-63 years (30.78, SD= 15.40), 47.8% reported an income of less than \$25,000, and 34.8% completed some college education. Both subscales demonstrated highly significant and strong reliability (S1: $r=.82$, $p<.001$; S2: $r=.88$, $p<.001$). Participants primarily used conditioners (91.3% used wash out and 60.9% used leave-in), and professional hair dyes (34.8%). There was also a high frequency of non-use (91.3%) of do-it-yourself relaxers and hair dye kits. We evaluated 40 products across three categories including wash out conditioners, leave-in conditioners and other hair products (e.g., styling gels, shampoo, and hair oils), of which most had a moderate hazard rating of 5 denoting ingredients of health concerns (e.g., parabens, fragrance, and phenoxyethanol). Additionally, of the 22 company brands analyzed, only 10 (45%) are Black owned or founded. Conclusions: The BHBS is a valid and reliable instrument to assess sociocultural perspectives about hair, identity and perceived breast cancer risk. Black women use hair products including relaxers, hair dyes, and conditioners that contain EDCs that may be harmful to their health including risk for breast cancer. The BHBS will be used to evaluate psychosocial interventions that address the unique needs of Black women including exposure to EDCs from hair product use and breast cancer risk.

PO2-25-11

Incidence of Breast Cancer in Louisiana Compared to the United States

Presenting Author(s) and Co-Author(s):

A. Daily. Willis-Knighton Health System General Surgery, Shreveport, Louisiana, United States

J. Cupp. Willis-Knighton Health System, Shreveport, Louisiana, United States

K. Trosclair. Willis-Knighton Health System Graduate Medical Education, Shreveport, Louisiana, United States

Aside from skin cancer, breast cancer is the most common cancer in American women. More specifically, one in eight women will develop breast cancer during their lifetime. Breast cancer is classified into subtypes defined by immunohistochemistry (IHC) expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). ER+/PR+/HER2- tumors are the most common form of breast cancer and are typically associated with risk factors including older age, nulliparity, obesity following menopause, alcohol and tobacco use, sedentary lifestyle, and hormone therapy. ER-/PR-/HER2+ tumors comprise approximately 15-20% of breast cancers and are caused by overexpression of the HER2 gene. These tumors have similar risk factors to ER+/PR+/HER2- tumors, except for age. Women with HER2+ breast cancer are likely to be younger compared to ER+/PR+/HER2-. Tumors lacking hormone receptors are classified as ER-/PR-/HER2-, otherwise known as triple-negative breast cancer (TNBC). TNBC represents 10%-20% of breast cancers and carries a poorer prognosis, shorter survival, and unresponsiveness to hormone therapy compared to other forms of breast cancer. TNBC has been associated with African American race, socioeconomically deprived population, younger age at diagnosis (most frequently in women ages 40-50), more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer and BRCA1 mutations.

The primary aim of this study is to compare incidence of ER+/PR+/HER2-, ER-/PR-/HER2+, and ER-/PR-/HER2- (TNBC) in Louisiana to the national population. The Louisiana Tumor Registry (LTR) was utilized to obtain state and national level data. The LTR is a participant of the National Cancer Institute's Surveillance, Epidemiology and End Results Program, and the Centers for Disease Control and Prevention's National Program of Cancer Registries. Our study evaluated women in Louisiana diagnosed with ER+/PR+/HER2-, ER-/PR-/HER2+, and ER-/PR-/HER2- from 2010-2019. The populations were subdivided by age at time of diagnosis. Data was subdivided into ages 0-49, and >50. Rates were calculated per 100,00 and age-adjusted to the 2000 United States Standard Population (19 age groups - Census P25-1130). A p-value of < 0.05 indicates a significantly different rate in Louisiana comparative to the United States (SEER).

Our results are as follows. Unexpectedly, Louisiana has a significantly lower rate of ER+/PR+/HER2- cancer in women ages 0-49 and ages >50 compared to the United States. Based on epidemiological risk factors, Louisiana should have a much higher rate of ER+/PR+/HER2- comparative to the United States population. Louisiana has a significantly higher rate of ER-/PR-/HER2+ cancer in women ages >50 and ER-/PR-/HER2- (TNBC) in women ages 0-49 and ages >50 compared to the United States. These findings are discordant with traditional epidemiologic studies regarding breast cancer and require further investigation.

Breast Cancer Incidence Rates¹ by Age from 2010-2019 in Louisiana and the United States

<i>Breast Cancer Incidence Rates¹ by Age from 2010-2019 in Louisiana and the United States</i>						
	All Ages		Women ages 0-49		Women ages >50	
	United States	Louisiana	United States	Louisiana	United States	Louisiana
ER+/PR+/HER2-	45.8	43.4*	13.5	12.4*	130	124.5*
ER-/PR-/HER2+	2.7	3.1*	1.2	1.3	6.8	7.9*
ER-/PR-/HER2-	13.6	18.2*	6.2	8.4*	33.1	43.9*

¹Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard.

*The rate ratio indicates that the rate is significantly different than the rate for United States (SEER) ($p < 0.05$).

Table 1: Breast Cancer Incidence Rates in women ages 0-49 and ages >50 from 2010-2019 in Louisiana Compared to the United States.

PO2-25-12

Production of a bespoke muscle resistance exercise (MRE) programme for use in a future clinical trial, following a detailed patient engagement program (PEP) in patients with advanced breast cancer (ABC).

Presenting Author(s) and Co-Author(s):

A. Clarke. Kent Oncology Centre, West Kent, Maidstone, England, United Kingdom

J. Glendenning. Kent Oncology Centre, East Kent, Canterbury, England, United Kingdom

G. Davison. School of Sports and Exercise University of Kent, United States

C. Harper-Wynne. Maidstone Hospital, Kent, UK, United Kingdom

Background: MRE investigations in early breast cancer have been undertaken but there has been little evaluation in ABC. Cancer guidelines suggest the use of physical activity, including MRE, to improve fatigue (National Comprehensive Cancer Network, 2.2020; European Society of Medical Oncology 2020) but improvement in other outcomes in ABC is less clear. In clinical trials, adherence to exercise intervention has been a challenge and has hampered investigation of other outcomes and little data exists evaluating the possible reasons for this poor adherence and compliance. In preparation for an exercise component as part of lifestyle intervention trial in ABC, a PEP was undertaken to evaluate an on-line web-based exercise program. Results would support continued usage of the program or creation of a new program. Methods: A commercially available program was used containing a library of exercises created for multiple disease types. There was no voice over. Using an exercise science professional, 2 sets of muscular resistance exercise programmes were created (A &B), selecting exercises for upper and lower limb major muscle groups. Set A and B differed , with A involving younger leaner demonstrators and B older, less lean. Volunteers were asked to view the sets and complete a survey. The results of the survey, involving 21 volunteers of which 43% were over 60 years and presented previously, indicated that the following main modifications were needed to a program: use of demonstrators similar to patient's habitus and use of a voice-over to guide exercises. A short test video was produced incorporating these and other visual changes and viewed by a focus group of four volunteers. Results: The focus group concluded that the new visual and audio changes would allow them to more easily perform the exercises and increase the likelihood of compliance compared to the on-line program. The group advised involvement of a more diverse demonstrator group and further improvements to the voice-over. A professionally produced video has now been made with all the above changes. Conclusions: This PEP indicates that is necessary to review exercise programmes with patients and not assume they are all suitable for use in clinical trials. We believe a PEP of this kind with the resultant bespoke video is the first produced involving patients with ABC. This video will now be evaluated in a much larger diverse PPE which will help the development of a national UK clinical trial of exercise in ABC.

PO2-26-01

Prognostic Role of HER2 Expression in Patients with ER-positive/HER2-negative Breast Cancer. Results from a Population-Based Cancer Registry Study

Presenting Author(s) and Co-Author(s):

A. Musolino. University of Parma, United States

O. Serra. Medical Oncology and Breast Unit, University Hospital of Parma, Italy, United States

B. Pellegrino. Department of Medicine and Surgery, University of Parma, Italy; Emilia-Romagna Cancer Registry, Parma Unit, Medical Oncology and Breast Unit, University Hospital of Parma, Italy; Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), Italy

C. Tommasi. Department of Medicine and Surgery, University of Parma, Italy; Emilia-Romagna Cancer Registry, Parma Unit, Medical Oncology and Breast Unit, University Hospital of Parma, Italy; Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), Italy

D. Zanoni. Emilia-Romagna Cancer Registry, Parma Unit, Medical Oncology and Breast Unit, University Hospital of Parma, Italy; Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), Italy

F. Faccini. Emilia-Romagna Cancer Registry, Piacenza Unit, Public Health Department, AUSL Piacenza, Italy, Italy

M. Michiara. Emilia-Romagna Cancer Registry, Parma Unit, Medical Oncology and Breast Unit, University Hospital of Parma, Italy; Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), Parma, Italy., Italy

P. Sgargi. Emilia-Romagna Cancer Registry, Parma Unit, Medical Oncology and Breast Unit, University Hospital of Parma, Italy, Italy

G. Carrozzi. Emilia-Romagna Cancer Registry, Modena Unit, Public Health Department, Local Health Authority, Modena, Italy, Italy

S. Ferretti. Emilia-Romagna Cancer Registry, Ferrara Unit, Local Health Authority, Ferrara; University of Ferrara, Italy, Israel

V. Grossi. Emilia-Romagna Cancer Registry, Romagna Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Forlì, Italy, Italy

A. Ravaioli. Emilia-Romagna Cancer Registry, Romagna Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Forlì, Italy, United States

F. Zamagni. Emilia-Romagna Cancer Registry, Romagna Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Forlì, Italy, Italy

F. Falcini. Emilia-Romagna Cancer Registry, Romagna Unit, IRCCS - IRST, Meldola, Italy

Background: Estrogen Receptor (ER)-positive (+)/Human Epidermal Growth Factor Receptor 2 (HER2)-negative (-) breast cancers (BCs) express variable protein levels of HER2, which can influence prognosis. Materials and Methods: This cohort study was conducted using data on all consecutive patients (pts) diagnosed with BC between 2005 and 2017, which were systematically and prospectively collected by the Emilia-Romagna Cancer Registry (Provinces of Piacenza, Parma, Modena, and Ferrara), Italy. The study included 13527 pts with ER+/HER2- BC. Tumors were classified by HER2 IHC score (0 [n=7155], 1+ [n=5186], or 2+ with negative FISH [n=1186]). Comparisons of clinicopathologic characteristics and disease outcome were performed. Results: BCs with late-stage diagnosis, high histological grade, or high proliferative rate were more likely to be HER2 1+ or 2+/FISH- in comparison with earlier stage, low-grade, or low-proliferative tumors (lower bounds of 95% confidence intervals [CIs] for odds ratios [ORs] > 1). BCs with high expression of ER ($\geq 80\%$ [n=12383]) were more enriched

with HER2 1+ (OR 1.39; 95%CI, 1.2-1.6) or 2+/FISH- tumors (OR 1.26; 95%CI, 1.0-1.6) than ER-low/moderate (1-79% [n=1144]) ones. The 5-year overall survival (OS) for HER2 1+ BCs was lower than that for HER2 0 or 2+/FISH- tumors (P = 0.0018). This finding was confirmed also after stratification by ER status (low/moderate and high expression; P = 0.07 and 0.007, respectively). By multivariate logistic regression, the following variables were significantly associated with HER2 1+, or 2+/FISH- expression compared to HER2 0 tumors: age at diagnosis < 50, high histological grade, ER expression \geq 80% (lower bounds of 95% CIs for ORs > 1). Multivariate Cox's regression analysis showed that histological grades G2 and G3 were independently associated with poor survival vs. G1 tumors (HR 1.2; 95%CI, 1.1-1.3 and 1.3; 95%CI, 1.1-1.4, respectively). Furthermore, HER2 2+/FISH- status was significantly associated with better survival in comparison with HER2 0 tumors (HR 0.82; 95%CI, 0.7-0.9). This finding was confirmed also after stratification by ER status (ER 1-79% and \geq 80%). No significant difference in OS was observed between HER2 1+ and 0 BCs. Conclusions: The putative worse prognostic impact of HER2 expression in pts with ER-positive/HER2-negative BCs was not confirmed. The better outcome observed in pts with HER2 2+/FISH- BCs may be related to the known FISH-negative (HER2-non-amplified) status of this subgroup. These findings may help identify optimal patient inclusion criteria for clinical trials with novel anti-HER2 therapies in ER-positive/HER2-negative disease.

PO2-26-03

Patient decision making and preferences regarding neoadjuvant chemotherapy in Mexican women with early breast cancer

Presenting Author(s) and Co-Author(s):

Y. Chavarri-Guerra. Instituto Nacional de Ciencias Medicas y Nutricion "Salvador Zubiran", Distrito Federal, Mexico

H. Verduzco-Aguirre. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

R. Gonzalez-Salazar. Hospital General del Estado de Sonora, United States

I. de la Puente Tawil. Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, United States

P. Quiroz-Friedman. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, United States

A. Alfaro-Goldaracena. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, United States

S. Sanchez-Roman. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, United States

Z. Nieto-Garcia. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, United States

Background: Neoadjuvant therapy in breast cancer is considered standard treatment for the majority of patients with locally advanced breast cancer. Its use has been extended to early breast cancer aiming to downstage the extent of disease and surgery in the breast and/or axillary lymph nodes, to provide information regarding effectiveness of systemic therapy (which might guide adjuvant treatment recommendations), to provide prognostic information, as well as to extend time for appropriate genetic testing and planning breast reconstruction. However, little is known about patient decision making and preferences in this scenario. We aimed to describe patients' preferences regarding neoadjuvant chemotherapy (NAC) for early breast cancer, patient decision-making patterns, and satisfaction with their decisions.

Methods: Single arm prospective study at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán in Mexico City. We included patients aged ≥ 18 years with recent localized and operable breast cancer diagnosis. Electronic preferences and decision-making questionnaires were completed by each patient before NAC was started. A decision regret scale was completed within the first month after surgery was performed. Demographic and clinico-pathologic characteristics were extracted from the electronic medical records.

Results: From March 2020 to April 2023, 29 women were enrolled. Mean age was 49.2 (SD 16.2), 55.5% (n=16) were married or had a partner, 79.3% (n= 23) had at least one child, 58.6% (n=17) had high school or higher education, and 48.2% (n=14) were housewives. 75.8% of women answered that they were proposed to be treated with NAC because of the tumor size, 55.1% due to positive lymph nodes, 72.4% to obtain a conserving surgery and 72.4% to obtain prognostic information. In 75.8% of the cases the oncologist made the decision of NAC and in 96.5% the chemotherapy schedule was explained to patients and their families. 82.7% of women answered that it was important for them to have a breast conserving surgery, 93.1% were worried about adverse events, 79.3% thought that there were possibilities to disappear

the tumor with the chemotherapy and 31% thought that if the tumor disappear, they would not require surgery. After surgery was performed 96.1% answered that the decision of NAC was the right one, 7.6% would not make the same choice, and 23% felt that the decision to receive NAC caused them harm.

Conclusion: Our study suggests that the reason to make a treatment decision related to NAC for early breast cancer was discussed and explained to the majority of the patients. However, physicians' opinion was the most powerful to influence decision. A significant proportion of patients desire to have a conserving surgery and were worried about adverse events. Perspectives of patients' preferences regarding NAC should be considered in treatment decision making to improve their decision satisfaction.

PO2-26-04

Nature and Trends of Pharmaceutical Payments to the Board Certified Breast Cancer Specialists in Japan between 2016 and 2019

Presenting Author(s) and Co-Author(s):

A. Ozaki. Medical Governance Research Institute, Japan

K. Gonda. Jyoban Hospital of Tokiwa Foundation, United States

M. Wada. Utsunomiya Central Clinic/Department of Breast and Thyroid Surgery, Jyoban Hospital of Tokiwa Foundation, Japan

H. Saito. Medical Governance Research Institute, Japan

E. Yamashita. Medical Governance Research Institute, United States

T. Tanimoto. Medical Governance Research Institute, United States

Background The field of breast cancer care has experienced a rapid influx of new treatments, making it a potential focus for promotional activities by pharmaceutical companies. These financial relationships could turn into significant sources of conflict of interest within the healthcare sector, possibly leading to undue influence on breast cancer care. Despite the potential ramifications of these ties, there is a noticeable lack of understanding about the details of financial relationships between pharmaceutical companies and breast cancer specialists. The aim of this investigation was to understand the extent and distribution of financial relationships between pharmaceutical companies and breast cancer specialists, along with their trends over recent years in Japan. **Methods** Our study included all 1733 board-certified breast cancer specialists registered with the Japan Breast Cancer Society as of May 2021. We obtained data on the payments they received, along with the intended purpose of each payment, from 92 leading Japanese pharmaceutical companies between 2016 and 2019. This data was disclosed by the companies following the transparency guidelines set forth by the Japan Pharmaceutical Manufacturers Association. Firstly, we conducted a descriptive analysis of the extent and distribution of payments to specialists, including a calculation of the Gini index to illustrate the disparity of payments among these specialists. Secondly, we assessed the overall trends and individual-based payment patterns over a four-year period. Finally, we explored whether the introduction of new agents was associated with variations in payment values at the company level. **Results** In total, 64 companies made 11,774 payments, collectively amounting to 13,329,919 USD, with speaking fees comprising 81.4% of this total. Among the 1733 specialists, 1306 (75.4%) received at least one payment from these companies. The average payment per physician was 7,692 USD (with a standard deviation of 24,162), and the median payment was 2,044 USD (with an interquartile range from 798 to 5,207 USD). Among these specialists, 27 received payments of 100,000 USD or more. The Gini index was 0.99, indicating a significant disparity in payment distribution among the specialists. There was a rising trend in total payment values, from 2,883,954 USD in 2016, to 3,037,888 USD in 2017, 3,589,583 USD in 2018, and finally 3,820,041 USD in 2019. A notable increase in payment value occurred with Pfizer in 2018, following the launch of Palbociclib in December 2017. Similarly, Eli Lilly, which launched Abemaciclib in November 2018, also increased its payments to specialists from 2018 onward. **Conclusion:** The majority of board-certified specialists in Japan received payments from pharmaceutical companies between 2016 and 2019. However, these payments were concentrated among only a small fraction of the specialists. During the study period, the overall value of payments increased. This surge likely resulted from the launch of key drugs within the same class and with similar indications, specifically CDK4/6 inhibitors.

PO2-26-05

Disparities at the Convergence of Race and Ethnicity: Examining Trends and Outcomes in Young Women Diagnosed with Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Gopalakrishnan. mount sinai, United States

E. Gandhi. mount sinai, United States

m. fernandez. MS SINAI, United States

Purpose: In breast cancer, research has shown that race/ethnicity can be associated with disease predisposition, access to care, and outcomes. There are numerous studies that combine Hispanic and Haitian women of all races into a single group may overlook opportunities to identify important characteristics within this heterogeneous group that could more accurately predict outcomes and reveal opportunities to improve care. While these groups have been studied, there is limited data about the impact race and ethnicity has on young adult populations with breast cancer. In this study, we sought to compare tumor subtype, stage at diagnosis, time to surgery (TTS), and overall survival (OS) among Hispanic and Haitian patients to patients of non-Hispanic descent. Methods: Women 18 years of age or older who had been diagnosed with stage 0-IV breast cancer and who had undergone lumpectomy or mastectomy were identified in the National Cancer Database (2015-2021). Tumor subtype and stage at diagnosis were compared by race/ethnicity. Multivariable linear regression and Cox proportional hazards modeling were used to estimate associations between race/ethnicity and adjusted TTS and OS, respectively. Results: A total of 48,150 patients were included in this study. Age ranged from 18-40. (American Indian [AI]: 79 [0.2%]; Haitian: 15,011 [31.2%]; White: 20,109 [85.48%]; Hispanic: 13,030 [27%]. Hispanic women had higher rates of triple-negative disease (23.9%) than did Haitian women (11.5%) and white women (10.9%; $P < .001$). Hispanic women had higher rates of node-positive disease (26.2%) in comparison to Haitian women (17%) and Non-Haitian/Hispanic women (10% $P < .001$). Hispanic women had worse PFS when diagnosed at Stage II and III (37 and 39 months, respectively) than Haitian women (57 and 59 months, respectively) and Non-Haitian/Hispanic women (82 and 87 months). Hispanic women had worse OS when diagnosed at Stage II and III (45 and 49 months) than Black women (70 and 75 months) and non- women (95 and 99 months). Conclusion: Hispanic women had worse PFS versus non-Hispanic and Haitian women as well as present with high-risk characteristics and nodal disease at the time of presentation. This suggests that racial differences in tumor subtype and nodal stage among Hispanic women highlight the importance of developing additional studies which can investigate the disparity in patient outcomes with young Hispanic women in breast cancer research.

PO2-26-06

Prognostic factors pregnancy associated breast cancer: one year versus two years

Presenting Author(s) and Co-Author(s):

M. Izquierdo. Hospital Universitario Dexeus, United States

S. Baulies. Hospital Universitario Dexeus, United States

C. Ara. Hospital Universitario Dexeus, United States

M. Garcia. Hospital Universitario Dexeus, Spain

F. Fargas. Hospital Universitario Dexeus, Spain

R. Fabregas. Hospital Universitario Dexeus, Spain

F. Tresserra. Hospital Universitario Dexeus, Spain

P. Barri S. Hospital Universitario Dexeus, Spain

Aims: The trend of delayed delivery, the number of women with breast cancer during a pregnancy or in the years after pregnancy is expected to increase. Pregnancy breast cancer confers a worse prognosis. Study if the interval pregnancy breast cancer more one year to two years influences the prognostic factors like pregnancy breast cancer one year after.

Methods: Study 1186 patients with breast cancer and prognostic factors. Analyze delivery before breast cancer, and the interval of last childbirth, one year, more one year to two years and more two years, with prognostic factors (nodes, estrogen receptor, progesterone receptor, HER2 receptor and Ki 67).

Results: Breast cancer pregnancy one year after were in 37 patients, more one year to two years in 25 patients and more two years in 491 patients. Positive nodes one year after were in 21 patients, more one year to two year were in seven patients ($p < 0.05$), and more two years in 155 patients ($p=ns$). There are not differences ($p=ns$) in estrogen receptor, progesterone receptor and Ki67, one year versus more one year to two years and more to two years. HER2 and histologic grade there are not differences ($p=ns$) in one year after versus more one year to two years, but there are differences ($p < 0.05$) versus more two years.

Conclusion: Interval last childbirth breast cancer more than one year to two years influences prognostic factors for later breast cancer, and not have differences with prognostic factors than pregnancy one year after.

PO2-27-01

TFX06, a next-generation oral CERAN/SERD, shows favorable safety and PK profile, extracranial and intracranial efficacy in patients with ER+/HER2- breast cancer: Preliminary results from a phase 1/2 first-in-human trial

Presenting Author(s) and Co-Author(s):

Z. Fu. VyBio, United States

Z. Zhang. The Cancer Institute, The First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, United States

J. Song. VyBio, United States

Y. Chen. The Cancer Institute, The First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, United States

D. Fang. VyBio, United States

W. Sha. VyBio, United States

J. Zhang. Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

C. Ding. VyBio, United States

TFX06, a next-generation oral CERAN/SERD, shows favorable safety and PK profile, extracranial and intracranial efficacy in patients with ER⁺/HER2⁻ breast cancer: Preliminary results from a phase 1/2 first-in-human trial Zhaojian Fu¹, Zhiye Zhang², Jia Song¹, Yang Chen³, Douglas D. Fang¹, Wei Sha¹, Jian Zhang^{3*}, Charles Z. Ding^{1*} ¹Shenzhen Yangli Pharmaceutical Technology Co., Ltd., Haiwai Lianyi Building Rm 2701Y3, No. 12 Yingchun Road, Louhu District, Shenzhen, Guangdong Province, China. ²Henan Key Laboratory of Cancer Epigenetics, The Cancer Institute, The First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, Henan Province, China. ³Phase I Clinical Trial Center, Fudan University Shanghai Cancer Center, Shanghai, China. *Corresponding authors 3400 characters. Aims: TFX06 is an investigational oral complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD) (Wu J, et al., 2023 AACR annual meeting). A Phase 1/2, multicenter, open-label dose-escalation and dose-expansion study (CTR20230789) was initiated in China to evaluate TFX06 in previously heavily treated patients with ER+/HER2- locally advanced and/or metastatic breast cancer. The primary objectives were to assess safety and tolerability, recommended Phase 2 dose (RP2D), and pharmacokinetics (PK). Methods: A 3+3 dose-escalation design was implemented. TFX06 tablets were orally administered at 60 mg/100 mg daily for 28 days of treatment cycle until disease progression or intolerant to TFX06. As of the cut-off date (Sept. 15, 2023), the Phase 1 study enrolled five patients with Stage IV diseases with distant metastases. Three were treated with TFX06 at 60 mg, the starting dose and two at the next dose level of 100 mg. Median age of patients were 50 years (39-65) with a ECOG score of 0-1. Two out of five patients carried estrogen receptor 1 (ESR1) mutations (ctDNA). Prior anticancer treatments included one or two lines of endocrine therapies, including fulvestrant, and/or one or two lines of chemotherapies. Clinical responses by investigator according to RECIST v1.1 were performed every two cycles to explore preliminary efficacy. Results: Three patients in 60 mg and one in 100 mg dose cohorts completed dose-limiting toxicity (DLT) observation period. No DLT observed. All treatment related adverse events (TRAEs) were grade 1-2 in severity, including nausea, drowsiness, decreases in WBC and neutrophils, and anemia. Analyses of plasma concentrations of TFX06 in all three patients receiving 60 mg revealed a similar PK profile with

small variations in C_{max} . The average steady-state C_{max} and C_{min} of TFX06 were 101 ng/mL and 65 ng/mL, respectively, and the C_{max} of TFX06 was approximately 4-fold higher than that of fulvestrant administered intramuscularly at 500 mg in clinic (28 ng/mL). Two patients in the 60 mg cohort were evaluable for response assessment. One patient discontinued due to progressive disease (PD) after two cycles of treatment. This patient experienced a 17.1% decrease in target lesions in the lung; however, new metastases to bone observed. The other patient who carried ESR1 D538G mutation showed a decrease of 91% in ESR1 mutation burden 8 days after treatment, and a decrease of 34.2% in target lesions (partial response, PR), including a substantial shrinkage of 78.6% in the brain lesion (target lesion), as well as complete responses (CR) of non-target lesions in lung after 4 cycles of treatment. This patient remains on the study as of the cut-off date. Conclusions: Based on the preliminary results, oral administration of TFX06 at 60 or 100 mg once daily had favorable safety and PK profiles. TRAEs, such as gastrointestinal toxicities, bradycardia, and visual disturbances were not observed. Pleasingly, TFX06 demonstrated early extracranial and intracranial antitumor activity (PR) in a patient with a brain metastasis.

PO2-27-02

Re-sensitizing the Refractory Breast Cancer Bone Metastasis to Endocrine Therapies

Presenting Author(s) and Co-Author(s):

A. Das. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

C. Ernst. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

Approximately 90% of Breast Cancer (BrCa) related deaths are caused by metastasis and bone is the first and most frequent site of breast cancer metastatic expansion, which can lead to severe pain, immobility, fractures, and nerve damage, as well as the development of metastases in other organs, hence; a poor quality of life in patients. Currently, treatment options for these bone metastases (BoM) are limited because most patients with BoM shows reduced ER dependency which leads to resistance to standard endocrine or hormonal therapies for estrogen receptor-positive (ER⁺) BrCa. The long-term goal of the proposed research is to develop a strategy where metastatic cancer cells in bone can be dependent on ER signaling again thereby restoring their sensitivity to endocrine therapies. We observed a transient loss of ER expression in concert with enhanced activity of the transcriptional coactivators YAP/TAZ - the downstream effectors of the Hippo pathway (responsible for regulating cell proliferation and death) during bone colonization by BrCa cells. We hypothesize that the interaction between cancer cells and osteoblasts in the bone microenvironment leads to the activation of calcium signaling in cancer cells, resulting in the de-phosphorylation and nuclear localization of YAP/TAZ which subsequently suppresses the transcription of the estrogen receptor gene (ESR). Our research strategy is as presented below. First, we will employ a combination of 2D/3D co-culture models of BoM along with a mechanical loading system and determine the molecular mechanism driving the dynamical activation of YAP/TAZ in BrCa BoM. Using a unique ex vivo BM model called Bone In Culture Array (BICA) which replicates the in-vivo conditions, we will determine if verteporfin, a YAP/TAZ antagonist, can synergize and possibly enhance the effects of Fulvestrant, an ER antagonist in current use for certain types of BrCa in preventing BoM outgrowths and treating established BoM in mice. This research could ultimately lead to a favorable combination strategy to treat endocrine-resistant BoM in BrCa patients and prolong their survival.

PO2-27-03

Clinical Results of Subjects Remaining in the Phase 3 ARTEST Study Enobosarm Therapy in AR+ER+HER2- Metastatic Breast Cancer with 3 or Greater Prior Lines of Therapy

Presenting Author(s) and Co-Author(s):

K. Rinn. CCNW, Washington, United States

E. Krill Jackson. UMHC of Miami, United States

G. Barnette. Veru Inc., United States

D. Rodriguez. Veru Inc., United States

I. Shalev. Veru Inc., United States

M. Steiner. Veru Inc., United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

Background: Targeting the androgen receptor (AR) with an oral selective AR agonist, enobosarm, is a novel approach to overcome ER and CDK4/6 inhibitor resistance to suppress AR+ER+HER2- metastatic breast cancer (mBC). Preclinical studies in CDK4/6 inhibitor and estrogen blocking agent resistant PDX mBC models demonstrated that enobosarm alone suppressed tumor growth. In a small subgroup analysis of patients with ER+HER2- mBC who progressed on estrogen blocking agent and a CDK 4/6 inhibitor from the Phase 2 802 study, enobosarm treatment resulted in a best overall response rate of 30% (2 CRs and 1 PR) and a 6-month clinical benefit rate (CBR) of 50%. Methods: The clinical activity of enobosarm 9mg alone was evaluated compared to standard of care (SOC) in the Phase 3 ARTEST, open-label, randomized, multicenter study in AR+ER+HER2-mBC who have progressed on 2 or greater lines of prior therapies, including estrogen blocking agents and CDK4/6 inhibitors. The study was discontinued for administrative reasons not related to efficacy or safety. Results: At the time study was discontinued, 34 patients with confirmed AR positivity were randomized to either enobosarm (n=16) or SOC control (n=18). SOC control treatment group received an average of 2.6 (range 1-5) and enobosarm 9mg monotherapy an average of 2.9 (range 1-5) prior lines of treatment. On average, enobosarm or the SOC control was given in the 4th line treatment for AR+ER+HER2- metastatic breast cancer. In the evaluable population, two partial responses were observed in the enobosarm treatment arm versus no responses in the SOC control arm. In patients with ≤ 3 lines of prior endocrine therapy, the best objective response rate (ORR) was 18.8% for enobosarm and 0% for control. In patients with ≤ 3 lines of prior endocrine therapy with ≤ 1 prior treatment with CDK 4/6 inhibitor, best ORR was 33% in the enobosarm group versus no responses in the SOC control (Table 1). CBR on day 180 was 33.3% (4/12) in the enobosarm group vs 0% (0/11) in the control group. Enobosarm treatment was well tolerated without masculinizing adverse events and no increases in hematocrit changes. Conclusions: Activity of enobosarm in this heavily pretreated patient population is encouraging and supports further clinical investigation. The Phase 3 ENABLAR-2 study is underway to further evaluate enobosarm alone or in combination with abemaciclib for the second-line treatment of AR+ER+HER2- metastatic breast cancer in patients who have received a prior estrogen

blocking agent and a CDK 4/6 inhibitor. Clinical trial information: NCT04869943. Research Sponsor: Veru Inc.

Table 1. Responses in patients with enobosarm versus SOC treatment.

Efficacy (CR)	Enobosarm monotherapy	Estrogen blocking agent active control
Evaluable patients	2 PR / 16 (12.5%)	0 PR / 18 (0%)
Patients with ≥3 lines of prior endocrine therapy	2 PR / 16 (12.5%)	0 PR / 18 (0%)
Patients with ≥3 lines of prior endocrine therapy with ≥1 prior treatment with CDK 4/6 inhibitor	2 PR / 6 (33.3%)	0 PR / 18 (0%)

PO2-27-04

Unravelling the role of FGFR1 in innate immune sensing and endocrine resistance in breast cancer

Presenting Author(s) and Co-Author(s):

S. Dhakal. Oslo University Hospital, Oslo, Norway

T. Amundsen Lien. Oslo University Hospital, United States

J. Norum. Oslo University Hospital, United States

H. Bergholtz. Oslo University Hospital, United States

H. Midtun Flatekvål. Oslo University Hospital, United States

T. Sørli. Oslo University Hospital, United States

Fibroblast Growth Factor Receptor 1 (FGFR1) has emerged as a critical player in various cancer types, including breast cancer. FGFR1 alterations, including gene amplification, overexpression, and activating mutations, have been identified in subsets of breast cancers, contributing to aberrant signaling pathways that promote tumor growth, angiogenesis, and metastasis. Our current research endeavors are directed towards unravelling the intricate mechanistic underpinnings of FGFR1's dual impact on breast tumor progression, specifically its contribution to endocrine resistance and its regulatory role in innate immune sensing and subsequent induction of Type 1 interferons (IFNs). Our investigative efforts have previously established a direct association between FGFR1 and endocrine resistance in hormone receptor positive T47D breast cancer cells. Moreover, a remarkable and distinct inverse correlation linking FGFR1 expression to the Type 1 IFN response was observed. We noticed that in vitro stimulation of T47D cells with Type 1 interferons induces the expression of FGFR1 and ESR1, thereby suppressing the interferon-stimulated genes. Interestingly, we observed that the FGFR1-mediated suppression of the Type 1 interferon response is associated with intracellular nucleic acid sensors, specifically toll-like receptors TLR7 and TLR9. Furthermore, we found that the inhibition of FGFR kinase enhances the expression of IFN-alpha, IFN-beta, TLR7, and TLR9 in T47D cells when stimulated with the TLR7 agonist loxoribine. These results strongly suggest that FGFR1 functions as an innate checkpoint and may be exploited by tumor cells to dampen Type 1 interferon responses, thereby inhibiting antitumor immunity in hormone receptor-positive breast cancer.

PO2-27-05

Composite biomarkers for the prediction of progression-free survival with CDK4/6 inhibitors in metastatic HR+/HER2- breast cancer

Presenting Author(s) and Co-Author(s):

A. Witkiewicz. Roswell Park Comprehensive Cancer Center, United States

J. Wang. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

E. Knudsen. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

E. Levine. Roswell Park Comprehensive Cancer Center, United States

T. O'Connor. Moffitt Cancer Center, United States

CDK4/6 inhibitors are widely used in combination with endocrine therapy in the treatment of HR+/HER2- metastatic breast cancer. Generally the CDK4/6 inhibitors lead to a doubling of progression-free survival (PFS) over single agent endocrine therapy. In spite of a known mechanism of action, biomarkers to define the duration of response to CDK4/6 inhibitors with either aromatase inhibitors (AI) or fulvestrant (FUL) remain lacking. A cohort of over 300 patients receiving standard of care CDK4/6 inhibitor combination therapy for metastatic disease were consented for participation (NCT04526587). The duration of PFS in both AI and FUL treated sub-groups were comparable to that observed in randomized clinical trials. In this cohort progesterone receptor-status (HR 0.70, $p=0.0123$), visceral disease (HR 1.55, $p=0.0013$), prior endocrine therapy (HR 2.34, $p<0.001$), and type of endocrine therapy (HR 2.16, $p<0.001$) were associated with duration of PFS. To develop biomarkers, gene expression analyses was performed on 313 tumor samples representing over 200 individual patients. Focusing on the pre-treatment metastatic biopsy, established signatures associated with prognosis in HR+/HER2- breast cancer were employed to determine association with response to combination therapy in the metastatic setting. Proliferation-associated signatures were associated with shorter PFS. For example, an established RB loss signature was associated with PFS in both AI (HR 1.9, $p=0.009$) and FUL (HR 2.8, $p=0.007$) treated patients. Clinically employed signatures (e.g. OncotypeDx and MammaPrint) harbored variable associations with outcomes. Random Survival Forest feature selection was applied to individual and combined prognostic signatures. This approach resulted in a potent classifier for progression-free survival (HR 10, $p<1E-20$). To enable applicability to different manifestations of disease, significant clinical pathological variables were incorporated into the model so that there was equivalent performance in AI and FUL treated patients for prediction of PFS. This predictive algorithm was also strongly associated with overall survival (HR 4.6, $p=2.7E-8$). Ongoing studies are evaluating the algorithms prospectively in NCT04526587.

PO2-27-06

ANXA9 facilitates the exocrine secretion of S100A4 and promotes pleural metastasis in breast cancer.

Presenting Author(s) and Co-Author(s):

X. Zhou. School of Medicine, Tongji University, United States

D. Li. School of Medicine, Tongji University, United States

L. Fang. School of Medicine, Tongji University, United States

J. Zhao. School of Medicine, Tongji University, United States

Metastasis to distant organs stands as the primary contributor to mortality in cases of breast cancer. While localized breast cancer boasts a 5-year survival rate of roughly 99%, this figure drastically declines to approximately 26% for patients afflicted with distant metastasis. Regrettably, the current therapeutic landscape lacks efficacious and targeted interventions for the treatment of metastatic breast cancer. Our investigation has revealed a significant upregulation of S100A4 in metastatic breast cancer tissues, with notably high expression observed in the malignant pleural effusion of patients in advanced stages of the disease. Upon acceptance of the effective treatment, the expression of S100A4 in malignant pleural effusion decreased, along with a decrease in several cytokines, including IL-6, IL-8, CCL2, and CCL5. The breast cancer cellular models demonstrated that ANXA9 has the ability to regulate the excretion of S100A4 from cells into the surrounding medium. Similarly, the mice model of pleural metastasis indicated that the downregulation of ANXA9 (sh-ANXA9) resulted in decreased levels of S100A4 and cytokines IL-6, IL-8, CCL2, and CCL5 in the mice's hydrothorax. Additionally, our findings suggest that ANXA9 regulates the excretion of S100A4 through phosphorylation of ANXA9. The cellular membrane harbored phosphorylated ANXA9, which exhibited two phosphorylation sites. Upon mutation of these sites, the level of ANXA9 phosphorylation decreased, leading to a reduction in the exocrine release of ANXA9 from cells into the medium. Our research further revealed the significant involvement of ANXA9 in facilitating the progression of breast cancer, thereby suggesting that therapeutic interventions targeting ANXA9 could prove efficacious in treating metastatic breast cancer. This work was supported by Shanghai Sailing Program to Dengfeng Li (No. 20YF1437800), grant from the National Natural Science Foundation of China to Dengfeng li (No. 82103454) and grant from the National Natural Science Foundation of China to Lin Fang (No. 82073204).

PO2-27-07

The Role of HCMV Infection in Facilitating Brain Metastasis through the Creation of a Suppressive Tumor Microenvironment in Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

W. Dong. Houston Methodist Research Institute, United States

X. Wang. Houston Methodist Hospital, United States

K. Han. Houston Methodist Hospital, United States

A. Puri. Our Lady of Lourdes, United States

A. Irfan. Houston Methodist Research Institute, United States

W. Qian. Houston Methodist Research Institute, United States

L. Guzman. Houston Methodist, United States

R. Rosato. Houston Methodist, United States

J. Sheng. Houston Methodist Research Institute, United States

H. Zhao. Houston Methodist, United States

J. Chang. Houston Methodist Hospital, United States

S. Wong. Houston Methodist, United States

Human Cytomegalovirus (HCMV) infection has emerged as a noteworthy factor in breast cancer patients, particularly those experiencing brain metastasis. Despite being prevalent and often asymptomatic, HCMV's contribution to tumor progression remains enigmatic. Notably, a high proportion of breast cancer patients with brain metastasis exhibit HCMV positivity in both primary tumors and metastatic lesions. This study aims to elucidate the influence of HCMV infection on brain metastasis by investigating its impact on the tumor microenvironment. Our findings reveal a distinctive immune suppressive tumor microenvironment in HCMV-positive breast cancer patients. This environment is characterized by impaired NK cell function and an elevated accumulation of TH2 cells. To comprehend the role of HCMV in promoting brain metastasis, we have developed a murine breast tumor model using MCMV, enabling us to mirror the clinical trajectory of tumor progression and metastasis. The integration of a GFP reporter gene into the MCMV genome facilitates the tracking of infected cancer cells. Within this model, we observe a significant increase in brain metastasis coupled with reduced survival rates. Single-cell sequencing analysis uncovers diminished NK cell presence and activation, along with heightened TH2 cell accumulation within the tumor microenvironment—results that parallel the clinical observations in breast cancer patients. GSEA analysis underscores the secretion of inhibitory cytokines by MCMV-infected cancer cells, contrasting with their non-infected counterparts. Collectively, our study reveals that CMV infection contributes to brain metastasis in breast cancer by generating inhibitory cytokines. This hampers the recruitment and proliferation of immune cells within the tumor microenvironment and concurrently impairs the cytotoxic capabilities of NK cells. These insights shed light on the intricate interplay between viral infection and tumor progression, offering potential avenues for therapeutic exploration.

PO2-27-08

Discovery of glucocorticoid receptor-induced EMT and integrin gene expression and increased cell motility in invasive lobular breast cancer

Presenting Author(s) and Co-Author(s):

B. Porter. ut southwestern medical center, dallas, Texas, United States

C. Frerich. ut southwestern medical center, United States

M. Laine. the university of chicago, United States

S. Sahoo. ut southwestern medical center, United States

G. Greene. University of Chicago, Chicago, Illinois, United States

J. Lee. ut southwestern medical center, United States

L. Bennett. University of Texas Southwestern Medical Center, Dallas, Texas, United States

S. Conzen. University of Texas Southwestern Medical Center, United States

Estrogen receptor (ER)-positive, invasive lobular carcinoma (ILC) is the second most common histological subtype of breast cancer. Although the five-year stage-matched survival is improved compared to infiltrating ductal carcinoma (IDC), ILC late metastatic recurrences (>5 years) are more frequent. Understanding the molecular mechanisms of lobular breast cancer's significantly dormant yet ultimately metastatic phenotype is important to improve clinical outcomes. Our laboratory had previously shown that GR activation in ER+ IDC was associated with decreased cell proliferation, but little is known about GR activity in ER+ ILC. By examining gene expression following GR activation in metastases-derived ER+/GR+ human ILC cell lines, we recently uncovered that GR-activation increases EMT and integrin pathways. Here we show for the first time that in addition to activation of these gene expression pathways, GR activation increases ILC cellular migration in microchannels coated with collagen and fibronectin, consistent with a potential for GR activation to increase ILC metastases. We examined GR expression and activation in SUM44 GR+/GR-, and BCK4 GR+/GR- and MM134 GR+ cell lines and will present data comparing gene GR-mediated expression in the presence of cortisol and clinically relevant GR modulation. Ongoing investigations also include in vivo MIND modeling with GR modulation.

PO2-27-09

Clinical impact of routine MRI screening for brain metastases in patients with HER2 positive or triple negative metastatic breast cancer

Presenting Author(s) and Co-Author(s):

G. Kim. Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, United States

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

M. Kim. Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, United States

S. Kim. Hematology and Oncology, Internal Medicine Department, CHA Bundang Medical Center, United States

H. Park. Division of Medical Oncology, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea., United States

J. Jang. Department of Neurosurgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

Y. Kim. Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

S. Lee. Department of Radiology and Research Institute of Radiological Science and Center for Clinical Imaging Data Science, Yonsei University College of Medicine, Seoul, Republic Korea, United States

Title: Clinical impact of routine MRI screening for brain metastases in patients with HER2 positive or triple negative metastatic breast cancer
Background: Routine screening for brain metastases (BMs) is currently not recommended in patients with metastatic breast cancer (BC). There is a growing consensus on the need for the screening of BMs in HER2 positive and triple negative breast cancer (TNBC) because 40% of patients experience BMs throughout the disease course and systemic treatment options with intracranial efficacy are now available. However, there is a lack of prospective study data on this matter. We conducted a prospective cohort study to evaluate the role of brain MRI screening for the patient with metastatic BC.
Methods: Patients who newly diagnosed metastatic HER2+ or TNBC were eligible. Screening brain MRI was planned at diagnosis and failure from first line and second line of systemic therapy. All patients underwent complete physical examination and comprehensive neurologic assessment at baseline and thereafter. Patients who diagnosed symptomatic BMs were dropped from the study and subsequent treatment including local therapies and survival data were collected. Primary endpoint was the percentage of patients diagnosed with asymptomatic BMs. Results: A total of 147 patients were enrolled between Sep 2018 and Aug 2023 at Yonsei Cancer Center. The median age was 51 years (range, 29-80) and most patients (92.5%, n=136) had good performance status (ECOG 0-1). The tumor subtypes were as follows: TNBC, 51.0%; HER2 (ER-, HER2+), 29.3%; luminal-HER2 (ER+, HER2+), 19.7%. The cumulative incidence of asymptomatic BMs was 20.4% for overall patients; 24.0% for TNBC (18/75), 14.0% for HER2 (6/43), and 20.7% for luminal HER2 (6/29). Symptomatic detection of BMs during study period was 14.7% for TNBC, 18.6% for HER2, and 6.9% for luminal-HER2. Initial local treatment was stereotactic radiosurgery in 30 patients (58.8%), whole-brain radiation therapy in 14 patients (27.5%), surgical resection in 2 patients (3.9%) and 6 patients (11.8%) did not receive any treatment for BMs. After a median follow-up of 20.1 months, the median overall survival following a diagnosis of BMs was 23.7 vs 7.3 months (hazard ratio 0.41; 95% CI, 0.17 to 0.95; P = .04) in patients with asymptomatic and symptomatic BMs, respectively.

Conclusions: We identified approximately 20% of patients with HER2+ or TNBC as asymptomatic BMs. Emerging systemic therapies showed promising intracranial response would warrant the detection of asymptomatic BMs through routine MRI screening.

Incidence of brain metastases by subtypes

	TNBC	ER-/HER2+	ER+/HER2+
	N=75	N=43	N=29
Initial Brain Metastases	8 (10.7)	5 (11.6)	1 (3.4)
Asymptomatic Brain Metastases	18 (24.0)	6 (14.0)	6 (20.7)
Symptomatic Brain Metastases	11 (14.7)	8 (18.6)	2 (6.9)
All Brain Metastases	29 (38.7)	14 (32.6)	8 (27.6)

PO2-27-11

Antitumor efficacy and safety of sacibertinib (Hemay022) in combination with endocrine therapy in patients with ER+ and HER2+ metastatic breast cancer: A phase Ib study

Presenting Author(s) and Co-Author(s):

H. Li. Department of Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, Beijing, China (People's Republic)

Q. Zhang. Department of Breast Oncology, Harbin Medical University Cancer Hospital, Harbin, China, United States

R. Zhang. Department of Breast Oncology, Peking University Cancer Hospital & Institute, United States

Y. Liu. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital and Institute, 100142, China, United States

C. Liu. Tianjin Hemay Pharmaceutical CO, United States

X. Hu. Tianjin Hemay Pharmaceutical CO. China, United States

PURPOSE Sacibertinib (Hemay022) is a novel irreversible tyrosine kinase inhibitor (TKI) blocking epidermal growth factor receptor and human epidermal growth factor receptor 2 (HER2). This study aimed to explore the safety and efficacy of sacibertinib plus endocrine therapy in patients with estrogen receptor-positive (ER+) and HER2-positive (HER2+) >metastatic breast cancer (MBC). **PATIENTS AND METHODS** Using a phase 1b 3+3 dose escalation and expansion study design, patients with ER+/ HER2+ MBC were treated with sacibertinib (200mg-500mg daily) plus endocrine therapy including exemestane, letrozole, fulvestrant . The safety, pharmacokinetic (PK) and clinical efficacy, including objective response rate (ORR), clinical benefit rate (CBR), disease control rate (DCR) and progression-free survival (PFS) were assessed. (Clinical Trials.gov identifier: NCT03308201). **RESULTS** A total of 55 ER+/ HER2+ MBC patients pretreated with chemotherapy and anti-HER2 therapy were enrolled in the study between March, 2018 and July, 2021. Fifty-five patients were included in safety analysis and 51 patients were assessed for efficacy analysis. Sacibertinib plus endocrine therapy was well-tolerated without dose-limiting toxicities. The overall median PFS was 9.0 months [95% confidence interval (95% CI), 5.5 ~ 11.0]. The ORR, CBR, and DCR were better in the 400 mg and 500mg dose cohorts than in the 200 mg and 300 mg cohorts. The DCR of the 500 mg combined with the exemestane cohort was better than that of cohorts of other doses. In the 400 mg sacibertinib plus exemestane cohort (N = 18), ORR was 38.9% (7/18) , DCR was 72.2%(13/18), CBR was 66.7%(12/18), and median PFS was 8.9 months (95%CI, 2.7 ~ 16.4) ; In the 500 mg sacibertinib plus exemestane cohort (N = 12), ORR was 25.0% (3/12), DCR was 100%(12/12), CBR was 50.0%(6/12), and median PFS was 9.0 months (95%CI, 2.1~NA. Treatment-emergent AEs (TEAEs) were mostly within grades 1–2. The most frequent grade 3 TEAE was diarrhea (9.1%). One (1.8%) had grade 4 abnormal liver function. **CONCLUSIONS** Sacibertinib plus endocrine therapy had a favorable safety profile and antitumor activity in patients with ER+/ HER2+ MBC, 400 -500mg sacibertinib daily showed more efficacy, supporting further assessment in randomized studies.

Summary of efficacy data(EAS)

	Sacibertinib (200mg/d) +exemestane N=3	Sacibertinib (300mg/d) +exemestane N=7	Sacibertinib (400mg/d) N=31			Sacibertinib (500mg/d) +exemestane N=12	Total N=51
			+exemestane N=18	+letrozole N=6	+fulvestrant N=5		
Best overall response, n (%)							
Complete (CR)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)
Partial response (PR)	0 (0)	1 (14.3)	7 (38.9)	3 (50.0)	1 (20.0)	3 (25.0)	15 (29.4)
Stable disease (SD)	2 (66.7)	3 (42.9)	6(33.3)	2 (33.3)	4(80.0)	9(75.0)	26 (51.0)
Progressive disease (PD)	1 (33.3)	2(28.6)	5(27.8)	1 (16.7)	0 (0)	0 (0)	9 (17.6)
Disease control rate(DCR)	2(66.7)	5(71.4)	13(72.2)	5(83.3)	5(100.0)	12(100.0)	42(82.4)
Overall response rate (ORR)	0 (0)	2(28.6)	7(38.9)	3 (50.0)	1(20.0)	3(25.0)	16(31.4)
Clinical benefit rate (CBR)	1 (33.3)	3(42.9)	12(66.7)	5 (83.3)	4(80.0)	6(50.0)	31 (60.8)
Median PFS (months)	3.6(1.8-NA)	5.4(1.7-9.5)	8.9(2.7-16.4)	12.7(1.7-NA)	13.3(5.7-NA)	9.0(2.1-NA)	9.0(5.5-11.0)

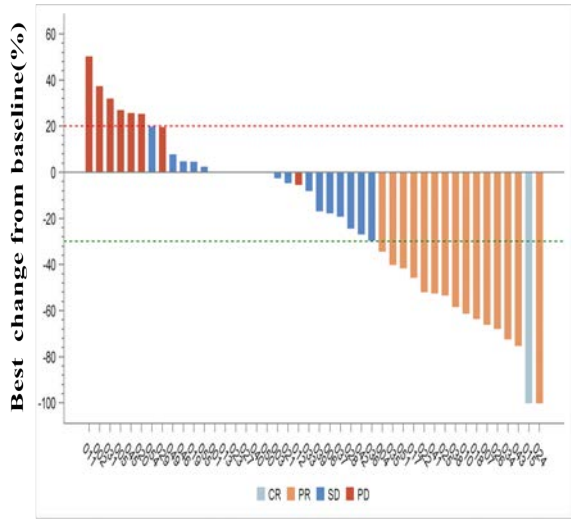
NOTE. NA, not available (because cannot be calculated)

Treatment-Emergent Adverse Events Occurring in ≥ 10% of Patients in the Safety Population

	Sacibertinib (200mg/d) +exemestane N=3		Sacibertinib (300mg/d) +exemestane N=8		Sacibertinib (400mg/d) N=31						Sacibertinib (500mg/d) +exemestane N=12		Total N=55								
					+exemestane N=19	-letrozole N=6	-fulvestrant N=6														
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4						
Diarrhea	1(33.3)	1(33.3)	0(0)	6(75.0)	2(25.0)	0(0)	12(63.2)	0(0)	0(0)	4(66.7)	1(16.7)	0(0)	5(83.3)	0(0)	0(0)	11(84.6)	1(7.7)	0(0)	29(70.9)	5(9.1)	0(0)
Nausea	0(0)	0(0)	0(0)	3(37.5)	0(0)	0(0)	3(37.5)	1(15.0)	0(0)	0(0)	0(0)	0(0)	3(33.3)	0(0)	0(0)	1(7.7)	0(0)	0(0)	9(51.4)	1(11.8)	0(0)
Vomiting	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	3(37.5)	1(15.0)	0(0)	0(0)	0(0)	0(0)	3(33.3)	0(0)	0(0)	2(15.4)	0(0)	0(0)	6(18.9)	1(11.8)	0(0)
Leucopenia	3(100.0)	0(0)	0(0)	3(37.5)	0(0)	0(0)	5(26.3)	0(0)	0(0)	3(50.0)	0(0)	0(0)	3(33.3)	0(0)	0(0)	4(30.8)	0(0)	0(0)	24(36.4)	0(0)	0(0)
Neutropenia	1(33.3)	0(0)	0(0)	2(25.0)	0(0)	0(0)	3(15.8)	0(0)	0(0)	2(33.3)	0(0)	0(0)	3(33.3)	0(0)	0(0)	3(23.1)	0(0)	0(0)	12(22.0)	0(0)	0(0)
ALT increase	0(0)	0(0)	0(0)	4(80.0)	0(0)	0(0)	4(21.1)	2(33.3)	0(0)	1(16.7)	0(0)	0(0)	0(0)	0(0)	0(0)	2(15.4)	0(0)	0(0)	11(22.0)	2(23.6)	0(0)
AST increase	0(0)	0(0)	0(0)	4(80.0)	0(0)	0(0)	4(21.1)	1(15.0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(15.4)	0(0)	0(0)	10(18.2)	1(11.8)	0(0)
Blood bilirubin increased	0(0)	0(0)	0(0)	3(37.5)	0(0)	0(0)	4(21.1)	0(0)	0(0)	1(16.7)	0(0)	0(0)	1(11.7)	0(0)	0(0)	2(15.4)	0(0)	0(0)	10(18.2)	0(0)	0(0)
Urinary tract infection	0(0)	0(0)	0(0)	3(37.5)	0(0)	0(0)	3(15.8)	0(0)	0(0)	1(16.7)	0(0)	0(0)	0(0)	0(0)	0(0)	2(15.4)	0(0)	0(0)	8(14.5)	0(0)	0(0)
Hypertriglyceridemia	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	3(15.8)	0(0)	0(0)	1(16.7)	0(0)	0(0)	0(0)	0(0)	0(0)	2(15.4)	0(0)	0(0)	8(14.5)	0(0)	0(0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase;

Waterfall plot of best change rate in target-lesion size from baseline



Patients

PO2-27-12

Genomic determinants of benefit to nivolumab (NIVO) plus low dose ipilimumab (IPI) among patients (pts) with hypermutated HER2-negative metastatic breast cancer (MBC): results of NIMBUS trial

Presenting Author(s) and Co-Author(s):

R. Barroso-Sousa. Dana Oncology, United States
T. Chinsky. Dana-Farber Cancer Institute, Boston, MA, USA, United States
T. Li. Dana-Farber Cancer Institute, United States
S. Reddy. UT Southwestern Medical Center, Dallas, Texas, United States
L. Emens. UPMC, United States
B. Overmoyer. Dana-Farber Cancer Institute, Boston, MA, USA, United States
S. AIDubayan. Dana-Farber Cancer Institute, Boston, MA, USA, United States
H. Chu. Dana-Farber Cancer Institute, Boston, MA, USA, United States
P. Lange. Dana-Farber Cancer Institute, Boston, MA, USA, United States
J. Kasparian. Dana-Farber Cancer Institute, Boston, MA, USA, United States
A. Basta. Dana-Farber Cancer Institute, Boston, MA, USA, United States
M. DiLullo. Dana-Farber Cancer Center, United States
V. Attaya. Dana-Farber Cancer Institute, United States
M. Hughes. Dana Farber Cancer Institute, United States
N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States
N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
E. Mittendorf. Dana Farber Cancer Institute, Boston, Massachusetts, United States
S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Genomic determinants of benefit to immune checkpoint inhibitors (ICI) among pts with MBC and high tumor mutational burden (TMB-H) are largely unknown. NIMBUS was an open-label, single-arm, multicenter, phase 2 study assessing the efficacy of NIVO 3 mg/kg intravenously every 14 days plus IPI 1 mg/kg IV every 6 weeks in pts with TMB-H HER2-negative MBC. The objective of this current study was to evaluate genomic profiling of pts included in NIMBUS and its association with benefit to ICI. Methods: In NIMBUS, eligible pts were required to have measurable HER2-negative MBC, TMB ≥ 9 Mut/Mb assessed by a cancer-gene panel evaluating > 300 genes and performed in a CLIA-certified laboratory, and 0-3 prior lines of chemotherapy in the advanced setting. The primary objective was overall response rate (ORR) according to RECIST 1.1. Secondary objectives include progression-free survival (PFS), and overall survival (OS). We performed genomic analyses on the pre-treatment tissue, and on baseline and on treatment plasma from pts run on the Foundation Medicine Inc (Boston, MA) FoundationOne®CDx (F1CDx®) and FoundationOne®Liquid CDx (F1LCDx®) panel, respectively. Results: A total of 30 pts (21 with estrogen receptor (ER)-positive and 9 with triple-negative breast cancer) were included in this study. After a median follow-up of 30.6 months, 6 pts (20%) achieved partial response (PR) for a confirmed ORR of 20% (95% CI: 7.7-38.6%). Exploratory analyses did not reveal differences in ORR based on ER status, PD-L1

status, or stromal TIL. The median PFS was 1.4 months (95% CI: 1.3 – 4.6), and the median OS was 16.9 months (95% CI: 7.1-not reached). Pts who achieved PR had a 3-year OS of 75% versus 25% in non-responders. A total of 29 pts (6 responders and 23 non-responders) had at least one pre-treatment genomic panel performed: 16 had both, 5 had pretreatment F1CDx only and 8 had F1LCDx panel only. Blood TMB (bTMB) was highly correlated with tissue TMB by F1CDx ($r = 0.95$). Using data from the most recent genomic panel available, (24 for baseline blood, and 5 for pretreatment tissue), the most frequently mutated genes ($> 30\%$) in this population were: TP53 (66%); PIK3CA (45%), ESR1 (35%), CDH1 (35%), ROS1 (31%). ESR1 and PTEN mutations were associated with absence of PR while PALB2 was associated with objective response. We observed a significant correlation between ESR1 mutations and a decrease in OS among pts with ER+ disease. Among the entire 29 pts, a negative correlation between PTEN with PFS and OS, and positive correlation between PALB2 with PFS was observed (Table). Among the 24 pts with baseline F1LCDx panel evaluable, the median TMB was 7.6 Mut/Mb ([interquartile range 0.0–113.8). Median TMB was 8.9 Mut/Mb and 41.7 Mut/mB among pts without and with PR, respectively. Baseline TMB > 20 mut/Mb was found in all pts with PR and in one of those without response. Paired serial blood samples demonstrated that among responding pts, TMB was significantly reduced from baseline to end of treatment (EOT) compared to those with no clinical benefit [$n=16$, $p=0.0015$]. Lastly, the tumor fraction (TF) estimates from 7 paired baseline to EOT samples demonstrated that all responders had a decrease or no change in TF compared to an increase in non-responders [$n=7$, $p=0.017$]. Conclusion: In the NIMBUS trial, all pts with PR to NIVO plus low dose IPI had a TMB > 20 Mut/Mb and had a decrease in TMB during treatment. ESR1 and PTEN mutations were associated with lack of benefit, while PALB2 mutation was associated with increased benefit. If validated, these results could help tailor the use of ICI among pts with TMB-H MBC.

Association between genomic alterations in ESR1, PTEN and PALB2 and benefit to nivolumab and low dose ipilimumab among patients with HER2-negative MBC and TMB-H

	Objective response		P value	mPFS	HR (PFS)	mOS	HR (OS)
	NO	YES					
ESR1							
Mut (n = 7)	7 (100%)	0 (0%)	0.049	1.35 (95% CI 1.35 – NA)	1.93 (95% CI 0.63 – 5.95)	1.9 (95% CI 1.68 – NA)	2.92 (95% CI 0.93 – 9.17)
WT (n = 12)	9 (75%)	3 (25%)		1.41 (95% CI 1.38 – NA)	p = 0.251	18.63 (95% CI 8.18 – NA)	p = 0.043
PTEN							
Mut (n = 6)	6 (100%)	0 (0%)	0.161	1.36 (95% CI 1.35 – NA)	2.87 (95% CI 0.85 – 9.63)	4.29 (95% CI 3.29 – NA)	2.9 (95% CI 0.96 – 8.77)
WT (n = 23)	17 (77%)	6 (23%)		1.48 (95% CI 1.41 – 9.49)	p = 0.089	19.35 (95% CI 7.75 – NA)	p = 0.059
PALB2							
Mut (n = 7)	4 (57%)	3 (43%)	0.096	9.43 (95% CI 4.63 – NA)	0.29 (95% CI 0.08 – 1)	NA (95% CI 7.1 – NA)	0.49 (95% CI 0.14 – 1.72)
WT (n = 22)	19 (86%)	3 (14%)		1.41 (95% CI 1.35 – 2.63)	p = 0.051	8.18 (95% CI 3.65 – NA)	p = 0.266

HR: hazard ratio; MBC: metastatic breast cancer; mOS: median overall survival (months); mPFS: median progression-free survival (months); TMB-H: tumor mutational burden above > 9 mutations/megabase.

PO2-28-01**Deleting caveolin-1 in epithelial cells increases doxorubicin sensitivity in advance stage of breast cancer**

Presenting Author(s) and Co-Author(s):

A. Pandit. Louisiana State University, United States

D. Singh. Indiana University, United States

R. Pathak. Louisiana State University, United States

S. Thota. Louisiana State University, United States

J. Francis. Louisiana State University, United States

Caveolin-1 (Cav-1) is a lipid raft protein with a dual role, serving as a tumor suppressor and a promoter. Studies have unveiled Cav-1's significance in breast cancer progression, impacting various aspects, including cell proliferation, apoptosis, autophagy, invasion, migration, and metastasis. Previously, our research demonstrated that the knockout (KO) of Cav-1 from epithelial cells reduced lung metastasis originating from primary tumors. In this study, we sought to investigate whether Cav-1 KO in epithelial cells increases sensitivity to doxorubicin (Dox) using both in vitro and in vivo studies. In our in vitro study, we observed reduced cell numbers in doxorubicin-treated Cav-1 KO cells compared to Dox-treated 4T1 cells (wild type). Flow cytometry-based cell cycle assay showed a significant increase in G2M phase arrest in Dox-treated Cav-1 KO cells compared with wild-type, confirming reduced cell growth and proliferation. To validate the increased sensitivity to Dox in vivo, we used a syngeneic tumor model using Cav-1 KO and 4T1 wild-type cells injected into the mammary fat of female Balb/c mice intraperitoneally. Subsequently, after one week of tumor cell injection, both groups received Dox at a dose of 8 mg/kg body weight/week for 3 weeks (a cumulative dose of 24 mg/kg body weight). Primary tumor sizes exhibited a significant reduction in Dox-treated mice, and this was further reduced in Cav-1 KO mice compared to the wild type. To quantify lung metastasis, we explanted the mice's lungs and plated dissociated single cells in complete RPMI media supplemented with 6-thioguanine (6-GT). The number of 6-TG-resistant 4T1 metastatic cells was significantly lower in the lungs' suspension of Cav-1 KO mice treated with Dox compared to wild-type Dox-treated mice. Our findings confirm that knockout of Cav-1 increased the sensitivity of Dox treatment and inhibited breast cancer lung metastasis in Balb/c mice. Our ongoing analysis of the molecular pathways seeks to elucidate the underlying mechanism.

PO2-28-02

ROR1 regulates CREB3L1 via a novel signaling pathway in triple negative breast cancer.

Presenting Author(s) and Co-Author(s):

V. Reed. Saint Joseph's University, United States

E. Lalu. St. Joseph's University, United States

B. Peethambaran. Saint Joseph's University, United States

Triple negative breast cancer (TNBC) is the most aggressive subtype of breast cancer; it is highly metastatic and incredibly difficult to treat due to its lack of the hormone receptors (estrogen, progesterone, and human epidermal growth factor receptor 2) that are used as therapeutic targets to treat breast cancer patients. TNBC patients are left with limited treatment options besides potent chemotherapy drugs that often leave them with undesirable side effects. My work intends to reveal a novel oncogenic signaling pathway that could be used to specifically target and eliminate TNBC in patients. Our lab is focused on a surface receptor that is found to be highly expressed only in cancerous tissue and during fetal development, Receptor tyrosine kinase-like orphan receptor 1 (ROR1). TNBC patients with high ROR1 expression are found to have poor prognosis and decreased overall survival rate compared to patients with low expression. ROR1 is thought to be a good drug target because it activates various oncogenic pathways such as PI3K/AKT and STAT3 in order to increase TNBC metastasis and chemoresistance. Previous single cell RNA sequencing data showed that TNBC tumors with high ROR1 expression also had reduced expression of cAMP responsive element binding protein 3 like 1 (CREB3L1). Often TNBC patients are found to have low CREB3L1 expression, a transcription factor is thought to play a tumor suppressive role in TNBC by increasing the expression of genes associated with the unfolded protein response (UPR) when ER stress occurs. CREB3L1 silencing in TNBC is due to hypermethylation of its promoter region by DNA methyltransferases (DNMTs). We hypothesize that ROR1 regulates CREB3L1 by influencing DNMT activity. This project aims to reveal the tumor suppressors that are downregulated in TNBC by ROR1 activation.

PO2-28-03

E-Cigarette Aerosol Exposure: Unraveling the Nexus of Autophagy, Cancer Stem Cells, and EMT in Breast Cancer Metastasis

Presenting Author(s) and Co-Author(s):

S. Thota. Louisiana State University, United States

R. Begum. Louisiana State University, United States

N. Chintalaramulu. Louisiana State University, United States

B. Sapkota. Louisiana State University, United States

A. Pandit. Louisiana State University, United States

Electronic cigarettes (E-cigs) have emerged as a significant public health concern due to their increasing popularity. These products have been associated with various harmful effects on human health. In the United States, breast cancer is the most diagnosed cancer among women, and its recurrence and metastasis are primary contributors to morbidity and mortality. Two critical factors in cancer progression are Epithelial-mesenchymal transition (EMT) and Cancer stem-like cells (CSCs), both of which play pivotal roles in metastasis. As a result, targeting the signaling pathways involved in these processes has become a promising avenue for cancer therapy. Autophagy, a cellular process, has dual roles in cancer development depending on the cancer type and stage. Given these considerations, our hypothesis centers on disrupting the EMT-mediated metastatic cascade in breast cancer by targeting autophagy in Cancer Stem Cells (CSCs). To investigate this hypothesis, we conducted experiments using mouse breast epithelial cells (HC11) and Triple-negative mouse breast cancer cells (4T1) exposed to E-cig aerosol at the air-liquid interphase (ALI) for 1 hr followed by a 24 hr recovery period. Our findings indicate that exposure to E-cig aerosols led to a decrease in epithelial markers (E-Cadherin and β -catenin) and an increase in mesenchymal markers (N-Cadherin and Vimentin) in HC11 cells. This suggests that normal cells may acquire characteristics associated with solitary migration. Furthermore, we observed significant changes in the levels of autophagy-related proteins (LC3B, Beclin-1, ATG12, and ATG16) and upregulation of stem cell markers (OCT4, SOX2, NANOG, KLF4, and c-MYC) in response to E-cig aerosol exposure, both in HC11 and 4T1 cells. Additionally, these alterations extended to changes in the expression of genes associated with the Transforming Growth Factor-beta (TGF- β) signaling pathway, known to play a potential role in promoting EMT. Our results provide a deeper understanding of the interplay between EMT, CSCs, and the autophagy process in the context of ALI exposure in normal and cancer cells. This underscores the need for further research into the shared molecular mechanisms of these three processes to identify common therapeutic targets that can simultaneously affect them.

PO2-28-04

Pregnancy-associated relapse of triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

V. Abbagoni. St Vincents Medical center, United States

Introduction: Pregnancy Triple-negative breast cancer(TNMC) is the absence of ER PR and HER2 receptor expression. It constitutes about 15-20% of all breast cancers and is known to be the aggressive form with a high relapse rate (1). Interestingly, it usually affects women aged < 40 and has a low survival rate in African-American females. This case is a typical presentation of a 38-year-old young woman with PMH of T2NO right triple-negative breast cancer diagnosed in 2017 s/p right mastectomy with sentinel LN biopsy, received immunotherapy and chemotherapy, has been cancer-free for two years, and developed metastatic cancer during her pregnancy. In this case, we understand the diagnostic and therapeutic challenges of TNBC during pregnancy. **Case:** A 38-year-old African American woman, G0, T2NO triple negative invasive ductal carcinoma, underwent a right breast mastectomy and sentinel LN biopsy. She received treatment with (Anti-PD-L1 Antibody) concomitant with weekly paclitaxel and Doxorubicin/Cyclophosphamide (AC) chemotherapy. However, she had a residual 4cm tumor for which she was treated with adjuvant therapy with capecitabine for six months. A repeat Mammogram in 2019 showed no evidence of malignancy. In 2021, the patient was G2P2L1, admitted to the hospital after having a seizure. CT reported cystic/necrotic left parietal lesion mass effect with 8mm right-sided midline shift with metastasis to lungs and abdominal wall. She underwent L parietal craniectomy with resection of the tumor. At 32 weeks of gestation , chemotherapy with carboplatin and paclitaxel was given after her C-section and Gamma knife radiosurgery for metastatic lesions. She developed super refractory seizures, was induced into a coma with therapeutically anesthetic agents, and passed eventually. **Discussion:** Little literature exists on pregnancy-associated relapse of triple-negative breast cancer and its deterioration. Our patient was in remission for two years and was diagnosed with metastatic cancer during her second pregnancy. John et al., (2018) discussed an interesting association between breastfeeding, parity, and occurrence of TNBC, that there is a two-fold increased risk of developing TNBC with high parity(3 full-term pregnancies) and short-term breastfeeding (< 12 months) (2). Studies have also shown that cancers during or postpartum pregnancy are aggressive with more tumor burden and metastasize to the lungs, liver, and brain, which is consistent with our patient. (3) **Conclusion:** Pregnancy-associated breast cancer is diagnostically and therapeutically challenging during or in the postpartum period and with a high propensity of the triple-negative type. It requires a multidisciplinary team approach, awareness in the African American population, clinical suspicion of breast mass during pregnancy warrants imaging, and prolonged breastfeeding postpartum. Diagnosis is usually delayed due to pregnancy, and more research is needed on the diagnostic modalities during pregnancy for early treatment initiation. **References**

1. Almansour NM. Triple-Negative Breast Cancer: A Brief Review About Epidemiology, Risk Factors, Signaling Pathways, Treatment and Role of Artificial Intelligence. *Front Mol Biosci.* 2022 Jan 25;9:836417. doi: 10.3389/fmolb.2022.836417. PMID: 35145999; PMCID: PMC8824427.
2. John EM, Hines LM, Phipps AI, et al. Reproductive history, breast-feeding and risk of triple-negative breast cancer: The Breast Cancer Etiology in Minorities (BEM) study. *International Journal of Cancer.* 2018;142(11):2273. doi:10.1002/ijc.31258

3. Amant F, Deckers S, Van Calsteren K, Loibl S, Halaska M, Brepoels L, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. *Eur J Cancer* (2010) 46(18):3158–68. 10.1016/j.ejca.2010.09.010

PO2-28-06

An on-line deep learning decision support tool, iBRISK, aimed at improving breast cancer risk estimation and reducing unnecessary biopsies for BI-RADS 4 patients.

Presenting Author(s) and Co-Author(s):

C. Ezeana. Houston Methodist Hospital Neal Cancer Center, United States
X. Yu. Houston Methodist Hospital Neal Cancer Center, United States
Z. Wan. Houston Methodist Hospital Neal Cancer Center, United States
T. He. Houston Methodist Hospital Neal Cancer Center, United States
T. Patel. MD Anderson Cancer Center, United States
V. Kaklamani. UT Health San Antonio, San Antonio, Texas, United States
M. Elmi. The START Center, United States
E. Brigmon. University of Texas San Antonio MD Anderson Mays Cancer Center, United States
P. Otto. UT health San Antonio, United States
K. Kist. Mays Cancer Center, United States
L. Wang. Houston Methodist Hospital Neal Cancer Center, United States
J. Ensor. Houston Methodist Hospital Neal Cancer Center, United States
H. Speck. University of the Incarnate Word San Antonio, United States
Y. Shih. University of Texas MD Anderson Cancer Center, United States
B. Kim. University of Texas MD Anderson Cancer Center, United States
I. Pan. University of Texas MD Anderson Cancer Center, United States
D. Spak. University of Texas MD Anderson Cancer Center, United States
W. Yang. University of Texas MD Anderson Cancer Center, Houston, Texas, United States
J. Chang. Houston Methodist Hospital, United States
S. Wong. Houston Methodist, United States

Probability of malignancy (POM) for Breast Imaging Reporting and Data System (BI-RADS) category 4 designated breast lesions ranges from 2% – 95% and contributes to a high unnecessary biopsy rate. This is as most clinicians often stick to the biopsy option to rule in or out breast cancer early; withholding biopsy could be risky, and biopsies of BI-RADS 4 lesions serve as a quality metric and performance standard. At 21.1%, biopsy-proven positive predictive value (PPV3) rates for BI-RADS 4 have not improved for decades, translating to high false-positive rates of mammography. Unnecessary biopsies are a big issue in the management of BI-RADS 4 lesions with negative implications including increased medical costs, healthcare wastes, unnecessary psychological burdens to the patients, and potential complications and risks. Objectives 1. Optimize the precision breast cancer risk assessment tool, iBRISK, that utilizes artificial intelligence (AI) technologies, including natural language processing (NLP), image processing, and deep learning, with clinical risk factors and imaging features. 2. Develop a user-friendly web interface for iBRISK to facilitate clinicians or insurers in estimating cancer risk and making informed biopsy decisions for BI-RADS 4 lesions. Methods Our intelligent-augmented breast cancer risk calculator (iBRISK) model was trained on multimodal data collected from 10,778 patients, including demographic factors, historical and clinical characteristics, mammographic features, and pathologic signatures. We validated iBRISK using 4,200 patients from multiple leading hospitals, including Houston Methodist Neal

Cancer Center, the University of Texas MD Anderson Cancer Center, and the University of Texas Health San Antonio MD Anderson Mays Cancer Center. The iBRISK was connected to a backend server which is linked to a frontend web user interface using technologies like Hypertext Preprocessor (PHP) for the backend application running on an APACHE HTTP server and React-JavaScript for the front-end web application that communicates with the backend using Representational State Transfer Application Programming Interface (RESTful API) and JavaScript Object Notation (JSON) format. The communication was secured using Secure Sockets Layer (SSL) encryption. Results The iBRISK model demonstrated high sensitivity in malignancy prediction and achieved an accuracy of 89.5%, area under the receiver operating characteristic curve of 0.93 (95% CI: 0.92-0.95), sensitivity of 100%, and specificity of 81%. Only 0.16% of lesions determined to have low POM by the model were malignant. Our multi-center study shows that iBRISK achieves at least 50% reduction in unnecessary biopsies of BI-RADS 4 cases. Data elements for the required 20 features are entered into the interface using a variety of imputation methods including direct text, dropdown menus and radio button selections. The user-friendly web interface provides risk scores (0 – 1), risk levels (low, medium, and high), and associated biopsy recommendations. Conclusion The user-friendly iBRISK web interface is proposed as an adjunct to the BI-RADS system, enhancing the precision of BI-RADS 4 lesion cancer risk stratification. It is expected to reduce unnecessary biopsies, lower health costs, and enhance the quality of health care. This approach aims to tackle a critical issue in breast cancer diagnosis by leveraging advanced AI technologies and big data and providing clinicians with a tool to make more informed and precise biopsy decisions for BI-RADS 4 lesions.

PO2-28-07

Artificial Intelligence-based Computer-aided Diagnosis for Mammography: Predicting Occult Invasive Cancer in Women with Biopsy-proven Ductal Carcinoma in Situ

Presenting Author(s) and Co-Author(s):

S. Lee. Seoul National University Hospital, Seoul, Seoul-t'ukpyolsi, Republic of Korea

H. Kim. Seoul National University Hospital, Seoul-t'ukpyolsi, Republic of Korea

S. Ha. Seoul National University Hospital, Seoul-t'ukpyolsi, Republic of Korea

S. Kim. Seoul National University Hospital, Seoul-t'ukpyolsi, Republic of Korea

J. Chang. Department of Radiology, Seoul National University College of Medicine, United States

N. Cho. Seoul National University Hospital, Seoul-t'ukpyolsi, Republic of Korea

W. Moon. Seoul National University Hospital, Seoul-t'ukpyolsi, Republic of Korea

Background: Ductal carcinoma in situ (DCIS) is a noninvasive breast cancer confined within the basement membrane. Due to the increase in breast cancer screening, DCIS is increasingly being diagnosed on biopsy. Active surveillance is a novel and evolving treatment strategy for DCIS to reduce overtreatment. Currently ongoing clinical trials of active surveillance include only mammographic findings in their eligibility criteria, however mammography has limited ability to detect occult invasive cancer. The objective of this study was to investigate whether an artificial intelligence-based computer-aided diagnosis (AI-CAD) application for mammography can improve the prediction of occult invasive cancer in women with percutaneous needle biopsy-proven DCIS. Methods: A retrospective search of our database identified consecutive women with percutaneous needle biopsy-proven DCIS who underwent surgery at Seoul National University Hospital (Seoul, Korea) between June 2019 and May 2021. Two board-certified breast radiologists reviewed preoperative mammographic findings of the primary tumor in consensus according to the Breast Imaging Reporting and Data System. Using a commercially available AI-CAD (Lunit INSIGHT for Mammography, Lunit Inc.), quantitative abnormality scores of 0 to 100% of the ipsilateral breast were obtained. Data were collected on age at diagnosis, symptoms, biopsy methods, DCIS grade on biopsy, and presence or absence of invasive cancer and axillary lymph node metastases on surgical pathology. Multivariable logistic regression models were used to evaluate factors associated with prediction of occult invasive cancer. Results: Of 692 biopsy-proven DCIS in 692 women (mean age, 53 years \pm 11 [standard deviation]), 298 (43%) presented as calcifications only, 160 (23%) as mass or asymmetry, and 111 (16%) as masses with calcifications. The other 123 (18%) cancers were not demonstrable on mammography. Surgical pathology revealed occult invasive cancer in 278 (40%) women and 18 (3%) had axillary metastasis. Women with occult invasive cancer showed higher abnormality scores on AI-CAD than women with pure DCIS (mean, 70% vs. 51%; $P < .001$), and women with axillary metastasis had higher abnormality scores on AI-CAD than women without axillary metastasis (mean, 88% vs. 58%; $P = .002$). High (>75%) abnormality score on AI-CAD (Odds ratio [OR], 1.8 [95% CI: 1.3, 2.6]; $P < .001$), age of 55 years or higher (OR, 1.6 [95% CI: 1.2, 2.3]; $P = .005$), present symptoms in the ipsilateral breast (OR, 2.7 [95% CI: 1.9, 4.0]; $P < .001$), biopsy performed with a 14-gauge automated gun (OR, 2.5 [95% CI: 1.7, 3.6]; $P < .001$), and high-grade DCIS at biopsy (OR, 2.5 [95% CI: 1.7, 3.5]; $P < .001$) were independent predictors of occult invasive cancer with a C-index of 0.75 (95% CI: 0.72, 0.78). Conclusion: The quantitative score of preoperative mammography obtained from a commercially available AI-CAD was able to predict occult invasive cancer in an easy and simple manner. AI-CAD applications for preoperative mammography may be useful in

predicting occult invasive cancer in women with biopsy-proven DCIS, especially in those without preoperative breast MRI.

PO2-28-08

A spatial transcriptomic study of a triple-negative breast cancer (TNBC) patient-derived xenograft (PDX) model of residual disease refractory to conventional chemotherapy

Presenting Author(s) and Co-Author(s):

B. Strobe. Baylor College of Medicine, United States

K. Pendleton. Baylor College of Medicine, United States

W. Bowie. Baylor College of Medicine, United States

G. Echeverria. Baylor College of Medicine, United States

Q. Zhu. Baylor College of Medicine, United States

TNBC is one of the most aggressive subtypes of breast cancer. Combating chemotherapy resistance is critical to improving quality of care and reducing fatality among TNBC patients. In order to understand the mechanisms of chemoresistance in TNBC tumors, it has been proposed that the spatial interactions between cell types in the tumor microenvironment (TME) could offer insights into the differential response to therapy among tumors, and metastatic potential of certain tumors over others. Thus, this study utilizes spatially resolved transcriptomic (SRT) technology to profile the spatial interactions in the TNBC TME. With the goal of better understanding chemoresistance in TNBC and providing a proof-of-concept for new technology, we have launched a longitudinal SRT study of a TNBC PDX of residual disease before, during, and after adriamycin and cyclophosphamide (AC) treatment (Tx). SRT by 10X Genomics Visium was performed on vehicle, AC-treated residual tumor (21 days post-Tx), and AC-treated regrown tumor (50 days post-Tx when tumors regrew to starting tumor volume). This study is divided into two parts: 1) development of a computational pipeline; 2) spatial colocalization analysis of residual and regrown tumors to understand chemoresistance. PART 1: Due to the lack of specialized tools for processing and sorting xenograft reads from SRT data, we developed the Xenomake pipeline, which combines a xenograft sorting algorithm (Xengsort) and spatial barcode demultiplexing pipeline to assign reads into the host and graft organisms for each spatial spot. RESULTS: Xenomake permits clustering the spatial spots into stroma-rich (enriched for mouse mRNAs), and epithelial-rich (enriched for human mRNAs) regions. We show that Xenomake can find differential cytokine production in the stroma and epithelium. Since PDX data separate the tumor into stroma and epithelium by organism, the pipeline enables fine-tuned downstream analysis such as stromal-stromal and stromal-epithelial interactions. Xenomake is thus generally applicable for SRT involving PDX samples. PART 2: Previously we detailed patterns of tumor regression into a residual tumor state, followed by uncontrolled regrowth in the absence of treatment in multiple PDX models of TNBC. Although using PDX models necessitates immune-compromised mice, several types of stromal populations are present and analyzable in these models. Thus, using organism-assigned reads processed by Xenomake, we computationally inferred the localization pattern of stromal cell types in Visium spots including cancer associated fibroblasts (CAF), macrophages (MP), endothelial cells (ENDO), monocytes, and perivascular-like cells. We compared the spatial localization profiles (SLP) of stromal cell types across samples. With human reads, we computed the spatial pathway activity map (SPAM) for the ~30 HALLMARK pathways across samples. We correlated the patterns of SPAM with stroma cell-type SLP to survey the stroma-epithelial interactions across samples. RESULTS: Stroma cells are generally distributed in the tumor periphery in vehicle and AC50, while in AC21 there is a notable increase in stroma abundance and stroma infiltration within tumor mass. SLP of MP (Cd68+ and Csf1r+) is correlated with ENDO (Pecam1+), and with CAF (Acta2+ and Pdgrfb+). Additionally, all 3 cell types are correlated with Vim and Cd44 expression. Although all samples show enrichment of

MP, ENDO, and CAF, they interact differently with pathway activities of adjacent epithelial cells. In vehicle and AC50, the 3 cell types are colocalized with OXPHOS, MYC targets, E2F pathway, while in AC21, a switch to colocalization with EMT is observed. Furthermore, hypoxia response and glycolysis display anti-correlation with stroma cell types, meaning that these pathway activities are further away from stroma and occupy distinct territories. The results suggest stroma-tumor metabolic crosstalk and ways of targeting residual disease.

PO2-28-09

Long-term Breast Cancer Risk Prediction in Black Women: External Validation of a Mammography-driven AI Model

Presenting Author(s) and Co-Author(s):

J. Hernandez Lopez. Washington University School of Medicine, United States

Z. Sun. Washington University McKelvey school of engineering, United States

S. Shoushtari. Washington University McKelvey School of Engineering, United States

U. Kamilov. Washington University McKelvey School of Engineering, United States

D. Bennett. Washington University School of Medicine, Saint Lois, Missouri, United States

A. Gastounioti. Washington University in St. Louis, United States

Despite the demonstrated potential of artificial intelligence (AI) in breast cancer risk assessment for personalizing screening recommendations, further validation is required regarding AI model bias and generalizability. We performed external validation in Black women of a mammography-driven AI breast cancer risk model (Mirai) originally developed on screening cohorts primarily consisting of White women. In this institutional review board-approved, Health Insurance Portability and Protection Act (HIPAA)-compliant study under a waiver of consent, we retrospectively analyzed a case-cohort sample nested within the core academic breast cancer screening practice of BJC Healthcare, the hospital partner of Washington University in St. Louis. For the purposes of this validation study, relying on 2D digital mammography (DM) images, we focused on Black women presenting for annual DM screening (Selenia or Selenia Dimensions; Hologic) between 2008 and 2018. Eligible breast cancer cases were derived from all women with a breast cancer diagnosis (with associated biopsy-confirmed tumor pathology via institutional cancer registry) after negative (BI-RADS 1 or 2) DM screening 1 to 5 years prior to cancer diagnosis. We also identified a random sample of controls, defined as women who had negative (BI-RADS 1 or 2) DM screening, with 1 to 5 years of screening follow-up without a cancer diagnosis. Risk scores for all DM exams were calculated via the Mirai model. Performance was evaluated using concordance-index (C) analyses and associated 95% confidence intervals (CIs) for the entire cohort, as well as for study subgroups of invasive versus in-situ cancer and cancer molecular subtypes. We analyzed 1368 DM screening exams, including 672 DM exams from 391 women diagnosed with breast cancer (mean age, 58 years; standard deviation, 10 years) and 696 DM exams from 406 controls (mean age, 55 years; standard deviation, 10 years). The overall C-index was 0.62 [95% CIs 0.60–0.64] for all Black women, which was lower compared to previously reported validation results for Mirai in studies of similar design on predominantly White and racially diverse screening cohorts (C-index = 0.67-0.78). There was no evidence of a significant difference between invasive and in-situ cancer (C-index = 0.64 [95% CIs 0.61–0.66] vs. 0.64 [95% CIs 0.61–0.67]). Compared to other cancer molecular subtypes, performance was significantly higher among triple-negative (C-index = 0.67 [95% CIs 0.62–0.71]) and estrogen receptor (ER) negative cancer (C-index = 0.66 [95% CIs 0.61–0.70]). A previously developed mammography-driven AI model showed overall good performance in long-term breast cancer risk assessment in a dataset of Black women only, particularly for triple-negative and ER- cancer types. However, performance was lower compared to previously reported validation results from similar studies on predominantly White and racially diverse screening cohorts. Our results suggest that further refinements are needed towards more accurate breast cancer risk assessment in Black women.

Long-term breast cancer risk prediction performance (C-indices) of Mirai in the full cohort of Black women and in study subgroups.

Table 1. Long-term breast cancer risk prediction performance (C-indices) of Mirai in the full cohort of Black women and in study subgroups.

Study Group	Size (# cases, # controls)	C-index (95% CIs)
All cancer cases & controls	(689, 679)	0.62 (0.60 - 0.64)
Invasive cancer cases & All controls	(449, 679)	0.64 (0.61 - 0.66)
In-situ cancer cases & All controls	(240, 679)	0.64 (0.61 - 0.67)
Triple-negative cancer cases & All controls	(106, 679)	0.67 (0.62 - 0.71)
Non-Triple-negative cancer cases & All controls	(355, 679)	0.64 (0.61 - 0.67)
ER+ cancer cases & All controls	(517, 679)	0.63 (0.61 - 0.65)
ER- cancer cases & All controls	(136, 679)	0.66 (0.61 - 0.70)

Confidence intervals estimated using bootstrapping.

PO2-28-10

Analysis of whole breast ultrasound image sequence reading time with a new FDA approved automated whole breast ultrasound tomography system for supplemental screening in women with dense breasts

Presenting Author(s) and Co-Author(s):

M. Yamashita. Keck School of Medicine, University of Southern California, South Pasadena, California, United States

T. Mahoney. Avania Clinical, Marlborough, Massachusetts, United States

P. Walker. Avania Clinical, United States

L. Hovanessian Larsen. Keck Medicine of University of Southern California, California, United States

Purpose: Ultrasound technology as a supplement to mammography for screening women with dense breasts increases cancer detection. However, automated whole breast ultrasound technologies have been shown to substantially increase radiologist reading time. We conducted a reading validation program to assess how quickly and accurately radiologists could interpret images from a new automated whole breast ultrasound prior to launching a prospective case collection registry. Methods: The study analyzed 500 reading times of bilateral screening breast ultrasounds obtained from SoftVue Automated Whole Breast Ultrasound (SV) (Delphinus Medical) in women with dense breasts. For this proctored reading validation program, 20 bilateral screening ultrasound cases were selected. The cases included a mix of normal, cysts, benign masses, cancers, and implants. 25 MSQA-trained radiologists with varying experience from 9 institutions across the United States each read the 20 cases. The same hanging protocol was used, beginning with sequences of Wafer and Sound Speed to identify an area of interest, Reflection to determine if the area persists, and then Stiffness Fusion for further confirmation and characterization. The primary outcome was reading time per bilateral ultrasound. Reading times were compared using linear mixed effects models for findings in neither, one, or both breasts and for subgroups of cancer and benign findings. Mean reading time was 3.3 ± 1.76 minutes ($n=498$, median 2.9min) per case. Cases that were negative in both breasts tended to have faster read times (2.7min, $sd=1.32$) compared to those with findings in one breast (3.2min, $sd=1.57$) or findings in both breasts (3.8min, $sd=2.14$). Mean read times for cases with clinical findings were within a minute of the mean time for normal cases across all case types. Conclusion Breast image sequences of Wafer, Sound Speed, Reflection, and Stiffness Fusion from SV ultrasound tomography facilitate bilateral ultrasound mean reading times of less than 4 minutes per case. Clinical Significance: SV, used as an adjunct to mammography in screening women with dense breasts, offers the benefits of increased cancer detection with supplemental ultrasound with little increase in radiologist reading time.

Table 1: Analysis of Bilateral SV Read Time Across Types of Case Clinical Findings

Figure for Yamashita et al. "Analysis of whole breast ultrasound image sequence reading time with a new FDA approved automated whole breast ultrasound tomography system for supplemental screening in women with dense breasts"

Table 1: Analysis of Bilateral SV Read Time Across Types of Case Clinical Findings

	All Reading Times N=498 [1]	Cancer	FA/Benign Mass	Cyst	Implant with FA	Normal	P-value [2]
Bilateral SV Reading Time (Minutes)							
Mean ± SD (N)	3.3 ± 1.76 (498)	3.5 ± 1.85 (278)	3.6 ± 2.25 (75)	3.1 ± 1.57 (54)	3.7 ± 1.58 (25)	2.7 ± 1.32 (105)	<0.001
Median (Q1, Q3)	2.8 (2.1, 4.2)	3.0 (2.1, 4.4)	3.0 (2.1, 4.3)	3.8 (2.2, 3.7)	3.4 (3.0, 4.2)	2.3 (1.8, 3.3)	

[1] The sample size for this analysis denotes all reading times across all radiologists and all cases. Each of the 28 cases were read by each of the 21 radiologists, however there are two instances where read time is missing, yielding 56-498 read times.

[2] P-value is derived from the type 3 effects for case clinical findings type generated from a linear mixed effects model including clinical finding type as the single fixed effect and a random intercept for radiologist, where the outcome is read time.

PO2-28-11

How to improve margins in breast cancer surgery: a

Presenting Author(s) and Co-Author(s):

M. Baù. Asl città di Torino, turin, Italy

V. Marra. AOU Città della Salute e della Scienza, Department of Gynaecology, University of Turin, Turin, Italy, United States

A. Surace. Ospedale Ferrero di Verduno, United States

D. Tota. AOU Città della Salute e della Scienza, Department of Radiology University of Turin, Turin, Italy, United States

M. Mano. AOU Città della Salute e della Scienza di Torino, Italy

A. Mondino. Asl città di Torino, Turin, Italy

A. Bottero. ASL Città di Torino, Italy

E. Robba. Asl Città di Torino, United States

Objective: Intraoperative specimen mammography (ISM) is a diffuse technique that allows surgeons to check specimens immediately after lumpectomy, instead of intraoperative frozen sections, definitely abandoned. In Italy and Europe, because it is regarded as too expensive and time-consuming examination. Although the specimen is slightly compressed, the radiological image can be distorted by tissue overlap, and this may affect the evaluation of tumor borders, resulting in extension of the lumpectomy. As ISM may be less precise due to inadequate compression, a vacuum effect was applied to the specimen to increase the precision of margin detection. **Study design:** This study was conducted at St. Anna Hospital Breast Unit, Turin, Italy. Women who underwent lumpectomy for cancer were eligible for inclusion. BCS resection was performed with a free margin, and the surgical specimen was imaged immediately by SSM and evaluated by an expert radiologist and surgeon. Inclusion criteria were: breast cancer detected by a screening test, and treatment with surgical lumpectomy. Both standard ISM (sISM) and vacuum ISM (vISM) were performed. A dedicated breast surgeon at the study institution performed both surgery and radiological scans, and their interpretation. A dedicated radiologist reviewed all of the images. ISM was performed by a digital specimen mammography system (Faxitron, Bioptics Inc., Tucson, AZ, USA) in the operating room. Specimen registration and ISM analysis took 3 min. sISM (two orthogonal projections) was performed. Specimens were sealed in plastic bags in the vacuum apparatus (TissueSAFE Milestone Medical, Sorisole, Italy); this process took a few seconds. 152 specimens obtained after lumpectomy from 1 April 2021 to 31 April 2022 were scanned. sISM (two orthogonal projections) was performed. Next, the specimen was placed in a vacuum bag, and vISM was performed. Additional tissue was removed if the surgeon considered that excision was inadequate. Finally, the specimen was sent for definitive histopathological analysis, which is the gold standard for the assessment of surgical margins. Intraoperative histological margin assessment was not performed. The sISM and vISM images and final histopathology reports were compared. A first experience on a limited number of patients to demonstrate feasibility of the technique, is reported in table 1 and 2. **Results:** For sISM, specificity was 43,85% [95 % confidence interval (CI) 35.96-51.73], sensitivity was 40.91% (95 % CI 33.09-48.73), positive predictive value (PPV) 10.98% (95 % CI 6.01-15.95) and negative predictive value (NPV) 81.43% (95 % CI 75.25-87.61). For vISM, specificity 92,31% (95 % CI 88,07-96.54), sensitivity 72.73% (95 % CI 65.65-79.81), PPV 61.54% (95 % CI 53.80-69.27) and NPV 95.24% (95 % CI 91.85-98.62). **Conclusion:** ISM is a valid, safe and quicker alternative to intraoperative histopathological study, but has been

reported to be limited due to less compression than standard SSM. Consequently, ISM may result in a high percentage of false-positive results, meaning unnecessary wider resections that lead to increased operative times and worse aesthetic results. A vacuum effect was performed on the specimen to increase the precision of margin detection. vISM images seem to be easier to interpret than sISM images (Figs. 1–3) as they are characterized by a vacuum-created radiolucent rim that better defines the tumor margins. These data suggest that the vacuum technique is feasible, cost-saving and yields results that are similar to those from frozen sections but without the limitations, such as prolonged operating time, high variability in sensitivity due to pathologists abilities, risk of compromising the histology, and unreliability for small lumps and ductal carcinoma in situ. Keywords: Breast cancer; Intraoperative mammography; Lumpectomy; Specimen mammography; Vacuum intraoperative mammography.

Table 1. Clinical Data

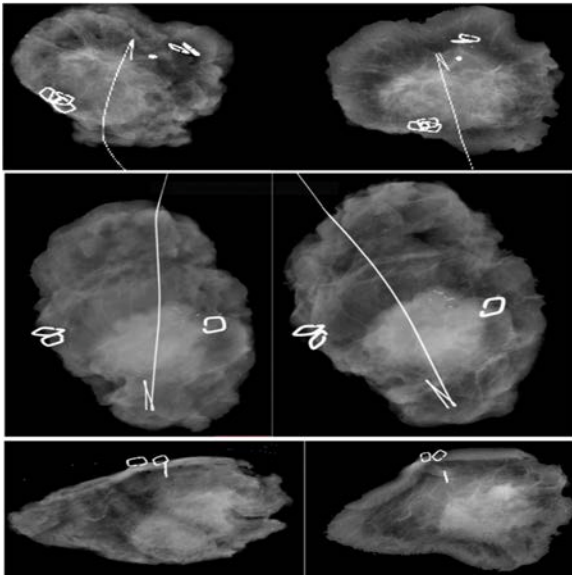
IC, invasive cancer; DCIS ductal carcinoma in situ; ADH, atypical ductal hyperplasia; ILC, invasive lobular cancer; B3, lesions of uncertain malignant potential; IMPC, invasive micropapillary carcinoma; NST, no special type; sISM, standard intraoperative specimen mammography; vISM, vacuum intraoperative specimen mammography.

^a Margin: 0, involved; 1, free

Table 2.

	Histological type			statistics	95% confidence interval	p-value
	free	involved	total			
sISM Margin				sensitivity 9/22 40.91%	33.09-48.73	0.667
free	73	9	82	specificity 57/130 43.85%	35.96-51.73	0.467
involved	57	13	70	PPV 9/82 10.98%	6.01-15.95	0.2
total	130	22	152	NPV 57/152 81.43%	75.25-87.61	0.875
vISM Margin				sensitivity 16/22 72.73%	65.65-79.81	0.667
free	10	16	26	specificity 120/130 92.31%	88.07-96.54	1
involved	120	6	126	PPV 16/26 61.54%	53.80-69.27	1
total	130	22	152	NPV 120/152 95.24%	91.85-98.62	0.938

Figure 1 - 2 - 3



Standard intraoperative specimen mammography (left) and vacuum intraoperative specimen mammography (right).

PO2-28-12

Rapid diagnosis of breast biopsies with open-top light-sheet microscopy

Presenting Author(s) and Co-Author(s):

B. Olin. Alpenglow Biosciences, Seattle, Washington, United States

R. Alvarez. University of Washington, United States

C. Childers. University of Washington, United States

S. Dintzis. University of Washington, United States

S. Javid. Fred Hutchinson Cancer Center, United States

N. Reder. Alpenglow Biosciences, Seattle, Washington, United States

H. Rahbar. University of Washington, United States

Introduction: Breast cancer is typically diagnosed through a diagnostic work-up that involves specialized breast imaging, image-guided biopsy, and pathological assessment. Pathology results require 2 to 7 business days before a diagnosis is rendered, creating anxiety in women presenting with a breast abnormality. Decreasing pathology evaluation lead-time has the potential to reduce anxiety, streamline patient care, and reduce healthcare costs. In this pilot study, we evaluated the potential of open-top light-sheet microscopy to deliver a preliminary breast pathology diagnosis within 30 minutes of biopsy. **Methods:** Fresh 14-gauge breast biopsies (N=40) in normal saline were received directly from the breast imaging clinic and immediately stained using the nuclear marker SYBR Gold (Invitrogen) and pan-protein marker Atto 655 NHS Ester (Sigma) prepared in dimethyl sulfoxide, washed, and cleared for imaging at a refractive index of 1.46 using 2,2'-Thiodiethanol (Sigma). The full process requires approximately 14 minutes for staining and clearing. After staining, we placed the biopsy in an in-house-built specimen holder and imaged a 100 micron cross section along the full length of the biopsy using our custom open-top light-sheet microscope. Images were subsequently converted computationally to a standard H&E color format using Fiji and Aivia (Leica) software and were ready for evaluation by a pathologist the same day they were collected. Images were assessed by two pathologists with subspecialization in breast pathology for a two-category diagnosis: benign or atypical. After imaging, the biopsy was frozen, a frozen section was cut, and an H&E-stained slide was produced. **Results:** Using the protocol above, we demonstrated the ability to stain, clear, image, and visualize needle core biopsies within 30 minutes of receiving the tissue sample. Processing and converting the data to an H&E color palette required additional time, surpassing the 30-minute turnaround time goal. The images contained readily identifiable stroma, epithelial cells, immune cells, and duct structures to a depth of 100 microns. 29/40 biopsies yielded interpretable results. 11/40 had insufficient staining, clearing, or imaging quality for diagnosis. The number of non-diagnostic images improved in the second half of the study (5%) compared to the first half of the study (50%) with sample prep and imaging optimization. Agreement between the two breast pathologists on classifying the biopsies as benign vs. atypical was 89.7%. **Discussion:** We describe a novel method to obtain a microscopic image of breast core biopsy specimens to facilitate preliminary diagnosis within 30 minutes of receipt of tissue. The quality of the images produced by the method shows promise for preliminary diagnosis, especially after protocol optimization for the second half of the study. Additional optimization is needed in data processing to meet the 30-minute turnaround time requirement. This optimization can be achieved by parallelization of the data processing on a cluster or cloud, which is currently under investigation by our team.

PO2-29-01

POSITIVE PREDICTIVE VALUE FOR THE MALIGNANCY OF MAMMOGRAPHIC ABNORMALITIES IN A ONE-STOP CLINIC MODEL FOR BREAST CANCER IN COLOMBIA

Presenting Author(s) and Co-Author(s):

K. Corredor. Ayudas diagnósticas SURA, United States

S. Gil. Ayudas Diagnósticas SURA, Antioquia, Colombia

C. Agudelo. Ayudas Diagnósticas SURA, United States

C. Piedrahita. Ayudas Diagnósticas SURA, United States

M. Naranjo. Ayudas Diagnósticas SURA, United States

Breast cancer (BC) is the most prevalent malignancy among women in Colombia, with the greatest incidence rate among malignancies. According to available data through the year 2020, the Colombian female population has officially documented 52,025 cases of breast cancer. This variety of cancer has emerged as the leading cause of cancer-related mortality among Colombian women. Currently, it is essential to emphasize the significance of the BI-RADS (Breast Imaging Reporting and Data System) classification as a means of categorizing patients' risk levels based on criteria for subsequent breast pathology evaluation and diagnosis. We aimed to assess the positive predictive value of BIRADS IV and V in predicting the risk of breast cancer in the Colombian population. From September 2018 to December 2022, consecutive patients referred for breast mammography and suspected of having breast cancer underwent triple assessment of breast tumor and were included in this retrospective study. 27,937 patients were included with breast imaging report and BIRADS classification system 4 and 5. Patients with a previously diagnosed case of breast cancer and a BIRADS score of 1, 2 or 3 were excluded. The positive predictive value of categories 4 and 5 was determined using histopathologic results of ultrasound- or stereotactically-guided biopsies as the gold standard. 46% of 21,442 patients had BACAF biopsies, 39% TRUCUT, and 15% stereotactic. Category 4A was found in 12,865 patients (60%) with a 7% positivity rate, 4B in 8,362 (25%) with 20%, and 4C and 5 in 3,216 (15%) with 75%. BIRADS 4 and 5 had a 20% positive predictive value, with 4,371 positive participants (31% under 49 and 69% over 50). Categories 4 - 5 were found to be beneficial for predicting the likelihood of malignancy, with categories 4C and 5 yielding the highest rates of positive results. Comparable to previous research, the PPV for malignancy in the present investigation was comparable.

PO2-29-02

Towards Precision Medicine in Breast Imaging: A Novel Open Mammography Database with Tailor-Made 3D Image Retrieval for Artificial Intelligence and Teaching

Presenting Author(s) and Co-Author(s):

N. Cordeiro. Federal University of São Paulo, United States

G. Facina. Universidade Federal de São Paulo, United States

A. Nazário. Universidade Federal de São Paulo, United States

V. Sanvido. Universidade Federal de São Paulo/ Hospital do Coração (Hcor), United States

J. Araujo Neto. Universidade Federal de São Paulo, São Paulo, Sao Paulo, Brazil

M. Silva. Universidade Federal de São Paulo - Unifesp, United States

S. Elias. Federal University of São Paulo, São Paulo, Sao Paulo, Brazil

Objectives: According to the World Health Organization (WHO), breast cancer is the most frequent malignant neoplasia and leading cause of cancer death among women worldwide. Low- and middle-income countries hold the worst survival rates mainly owing to a lack of access to appropriate diagnosis and treatment related resources. For proper early diagnosis, it is established that besides the physical structure itself (e.g., mammography units), there's a need for adequate interpretation of imaging and that might be a particularly major problem in low-income societies once there is a tendency of greater education setbacks. Mammography datasets can improve this resource-driven gap by enabling the development of artificial intelligence technologies (AI) which can make breast cancer diagnosis more accurate in a cost-effective and scalable way. We aim to create a new database of high quality digital mammography images suitable for AI development and education. Methods: Our mammography database was developed by means of retrospective selection of 100 exams performed by Hospital São Paulo - Federal University of São Paulo ranging from 2019 to 2023. The project is assumed to be safe, versatile, and usable, and required an extensive search for the appropriate tool. Ambra Health, an American company, has developed cloud-based software for medical image management and stood out as a viable alternative. Their platform meets international data security criteria, they also made the intended careful customization possible, in addition to the possibility of associating image and text attachments. The categories were created in accordance with the BI-RADS® descriptors, a wide range of clinical scenarios and additional materials available, and they served as the basis for the advanced search feature, which intuitively filters exams that meet the selected criteria simultaneously. The platform was integrated with an automatic anonymization system upon upload, ensuring data privacy. After submission, the exams are retained in a restricted area for anonymization verification, categorization, and attachment management, before being released to the end-user. So as to broaden geographic coverage, the descriptors were entered in American English, respecting the origin of the BI-RADS® lexicon, as for the website structure, automatic translation to the accessing browser standard language was selected. Results: Our website is active and available at <http://mamografia.unifesp.br>, with access granted upon a simple registration process. 941 mammography images from 100 anonymized cases, 62% of which include 3D images, can be filtered based on the combination of 113 clinical and imaging variables, as well as attachment availability. The language is adaptable to the user's native language, and categorized searches can be accessed directly from the browser or downloaded as customized datasets. Additionally, features such as saved searches or starred exams are also available. Conclusion: We have developed an online and free mammography database that is completely innovative by integrating various resources into a single platform. We provide

high-resolution and 3D digital images that can be searched using an advanced search system. Moreover, we offer supplementary clinical information in various attachment formats, favoring a rich clinical correlation. In this way, we have achieved the ambivalence of our goal, which was to promote education and research. *"images speak louder than words"

Database: <https://mamografia.unifesp.br>

Tutorials: <https://www.youtube.com/@Mamografiaunifesp>

e-mail: acesso@mamografia.unifesp.br

password: acesso@mamografia12 (valid until dec/23)

PO2-29-03

Factors Affecting the Mammography Sensitivity and the Quality of the Breast Cancer Screening Program in the State of São Paulo, Brazil

Presenting Author(s) and Co-Author(s):

A. Câmara. Fundação Oncocentro de São Paulo, São Paulo, Sao Paulo, Brazil

L. Cury. Fundação Oncocentro de São Paulo, São Paulo, Sao Paulo, Brazil

V. Filho. Fundação Oncocentro de São Paulo, Sao Paulo, Brazil

Background: Previous researches found that false-positive mammogram results during breast cancer screening are related to age, family history of breast cancer, body mass index, and breast density. In Brazil, there is limited data available on possible factors that may influence the sensitivity of mammography and, consequently, the overall quality of the breast cancer screening program. **Aims:** This study aims to conduct a sensitivity analysis comparing the results of screening mammograms with diagnosis of breast cancer, taking into account factors that could impact this sensitivity. **Methods:** All mammogram and biopsy results in the state of São Paulo in 2013 were obtained from the Brazilian Breast Cancer Information System (SISMAMA) database. We obtained information on age (< 50, 50-59, 60-69, or 70+ years), type of lesion (solid, cyst, or calcifications), lesion size (< 10mm, 11-20mm, 21-50mm, or >50mm), lesion boundaries (defined or undefined), lesion characteristics (regular or irregular), and breast density (fatty/predominant fatty or dense/predominant dense). In addition, we evaluated the hormonal therapy usage (yes or no), radiotherapy treatment (yes or no), ethnicity (caucasian, asian, or black), education (illiterate, completed elementary school, completed high school, or completed higher education), skin type (retracted, thickened, or normal), and type of mammogram (simple or computerized). Our analysis focused on mammograms classified as BI-RADS 4, BI-RADS 5, and those with inconclusive results, which subsequently led to a biopsy for diagnosis. We conduct statistical analysis using SPSS v.29 software. To assess the agreement between mammograms and biopsy results (sensitivity), we calculated the proportion of true positive results. We compared the sensitivity across different strata of variables using the Chi-Square test and the V-Cramer measure. **Results:** A total of 6,064 women with BI-RADS 4, BI-RADS 5, or inconclusive mammogram results underwent biopsy procedures for breast cancer diagnosis. Among these cases, 3,414 (56.3%) were false positives, 1,765 (29.1%) were true positives, and 885 (14.6%) were inconclusive results. The sensitivity of mammographic screening was not significantly associated with ethnicity, education, type of mammogram, skin type, or previous radiotherapy. However, a higher proportion of false positive results was linked to high breast density (71.2%), irregular lesions with defined boundaries (87.5%), particularly calcifications (68.7%) smaller than 10 mm (67.5 %). True positive results, on the other hand, were associated with solid (87.1%) and irregular lesions with undefined boundaries (82.1 %), often larger than 50 mm (57.2%) in fatty breasts (82.7%). A notable proportion of inconclusive results was associated with the presence of dense/predominant dense breasts (88.4%) and irregular lesions with undefined boundaries (87%), particularly solid lesions (89.8%) ranging from 21 to 50 mm in size (60.8%). False positive and inconclusive results were more prevalent among women under 50 years old (79.8%) and those using hormonal therapy (54.8%) compared to true positives. This study has certain limitations, including the availability of data related to lesion density and morphology, as well as body mass index in the SISMAMA database, all of which can potentially impact mammography sensitivity. Furthermore, a notable limitation was a substantial number of missing values for ethnicity and education in the SISMAMA dataset. **Conclusion:** We identified associations between false-positive and inconclusive results on screening mammograms and factors such as age, breast density, lesion

size, lesion types, and hormonal therapy. These results provide valuable information about potential factors that may affect the accuracy of mammography interpretations. Therefore, they must be taken into consideration when planning a breast cancer screening program.

PO2-29-04

An AI-based safeguard process to reduce aggressive missed cancers in dense breasts at screening mammography

Presenting Author(s) and Co-Author(s):

B. Haslam. DeepHealth, Inc., United States

J. Kim. DeepHealth, Inc., United States

A. Soresen. RadNet, Inc., United States

Background: Dense breast tissue makes cancerous lesions difficult to identify on mammograms, resulting in many cancers missed at screening in patients with dense breasts. These missed cancers are then only diagnosed once they have grown to the point they can be more easily distinguished from the surrounding dense tissue. Dense breast tissue is more common in younger women, for whom early detection and diagnosis could lead to fewer years of life lost. This challenge motivated the FDA's decision this year to require breast density to be included in patient reports, but notification does not solve the problem that these cancers are still often missed. Missing aggressive, fast growing cancers is particularly worrisome given they are more likely to progress to a stage where they are difficult to treat by the time they are detected in the future. Methods: A prospective study was conducted at one group practice of 6 radiologists over the course of 12 months to test a safeguard process to detect missed cancers so they could be treated more readily. AI software (Saige, DeepHealth, Inc.) was used to flag the most suspicious screening mammography exams that had not been recalled for work-up by an initial interpreting radiologist. An expert breast imager performed a safeguard review of each exam flagged. If the expert decided a recall was warranted, she would consult with the initial interpreting radiologist to decide if the patient should be recalled for further (diagnostic) imaging. Data was collected for each breast cancer diagnosed during this period. Patient data included breast density, age, and race. Cancer follow up data included pathology classification, hormone status, grade, staging, and Ki67 score. Aggressive cancers were identified as those with high grade (Grade 3), high Ki67 ($\geq 20\%$) or clinical stage of IIA or greater. A comparison was performed between cancers detected by the original interpreting radiologist and those detected through the safeguard process. Results: During the study period, 40,532 mammograms were obtained and 2,296 were flagged for safeguard review. The safeguard review led to 130 additional patient recalls and 41 additional cancer diagnoses. In women with dense breast tissue, 103 cancers were detected by routine interpretation and an additional 18 cancers (17.5%) detected through the safeguard process. In women without dense breast tissue, 116 cancers were detected by routine interpretation and 23 additional cancers were detected through the safeguard process. The cancers detected through the safeguard process included a larger percent of aggressive cancers (34.1% vs 30.6%, $p=0.66$) and more than double the percent of triple-negative cancers (9.8% vs 4.1%, $p=0.13$), though these differences were not statistically significant. The cancers detected through the safeguard process were from patients with similar demographics (age and race) to those whose cancers were detected by the interpreting radiologist. Conclusion: The AI-driven safeguard process results in a significant increase in breast cancers that would have been missed in patients with dense breast tissue. Many of the additional cancers were aggressive with almost 10% being triple-negative cancers. Without the safeguard process those aggressive cancers would not likely have been diagnosed until the next screening cycle in 1-2 years when treatment would likely have been less effective and outcomes poorer.

PS07-01

Exemestane and breast cancer prevention: how low can we go? Drug and biomarker tissue levels in a randomized presurgical trial on exemestane alternative dosing regimen.

Presenting Author(s) and Co-Author(s):

- D. Serrano. IEO, European Institute of Oncology IRCCS, Milano, Italy
H. Johansson. IEO, European Institute of Oncology IRCCS, Italy
B. Bertelsen. Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Norway
G. Mellgren. Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Norway
P. Thomas. MD Anderson Cancer Center, Texas, United States
K. Crew. Columbia University Irving Medical Center, United States
N. Kumar. Moffitt Cancer Center, University of South Florida, United States
D. Macis. IEO, European Institute of Oncology IRCCS, Italy
V. Aristarco. IEO, European Institute of Oncology IRCCS, Italy
A. Guerrieri Gonzaga. IEO - European Institute of Oncology IRCCS, Milan, Italy
S. Gandini. IEO, European Institute of Oncology IRCCS, Italy
M. D'Amico. Ospedali Galliera, Genoa, Italy
T. Buttiron Webber. E.O. Ospedali Galliera, Genoa, Italy
I. Briata. E.O. Ospedali Galliera, Genoa, Genoa, Italy
S. Spinaci. Ospedale Villa Scassi ASL3, Genoa, Italy
V. Galimberti. European Institute of Oncology, Milan, Italy
G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy
L. Vornik. University of Texas, MD Anderson Cancer Center, United States
E. Villar-Sanchez. University of Texas, MD Anderson Cancer Center, United States
P. Brown. MD Anderson Cancer Center, Department of Clinical Cancer Prevention, United States
B. Heckman-Stoddard. Division of Cancer Prevention, NCI Bethesda, United States
E. Szabo. Division of Cancer Prevention, NCI Bethesda, United States
B. Bonanni. 4. Division of Cancer Prevention and Genetics, European Institute of Oncology, IRCCS, Milan, Italy
A. De Censi. E.O. Ospedali Galliera, Genova, Italy, Liguria, Italy

Exemestane is an effective drug to reduce breast cancer risk reaching an overall 65% reduction in breast cancer in the placebo-controlled phase III MAP.3 trial. To improve its acceptability in primary prevention programs, we are seeking the minimal effective dose. In a 3-arm presurgical trial of 4-6 weeks before breast surgery in 180 postmenopausal women with ER-positive breast cancer, we investigated the activity of alternative exemestane schedules: 25 mg per day (QD), 25 mg three times/week (TIW) or 25 mg per week (QW) and showed that in adherent participants TIW was not inferior to QD in reducing circulating estradiol (Serrano et al JAMA Oncol. doi:10.1001/jamaoncol.2023.0089). Moreover, Ki67 reduction was seen in all arms with

no significant difference among arms. Here, we analyzed the concentration of sex steroids, exemestane, and its main metabolite in the cancer and adjacent non-cancerous breast tissue. Tissues samples were homogenized before liquid-liquid extraction. After reconstitution, samples were analyzed by coupling liquid chromatography with tandem mass spectrometry (Sciex QTRAP 6500, Nexera system, Shimadzu). We obtained breast cancer tissue from 93 and non-cancerous breast tissue from 117 participants to measure exemestane, 17-OH-exemestane, and sex steroids. Exemestane and 17-OH-exemestane concentrations were detectable only in the QD arm, while in TIW and QW arms levels were below the Lower Limit of Detection (< LLD). Median exemestane level was 3807 fmol/g and 17485 fmol/g and median 17-OH-exemestane level was 338 fmol/g and 1343 fmol/g in cancer and non-cancerous tissue, respectively. Interestingly, drug and its metabolite accumulated 4-5-fold in non-cancerous tissue compared to cancer tissue in the QD arm. Despite the between-arm drug concentration difference, estradiol was almost completely suppressed in all arms in the non-cancerous tissue, attaining level < LLD in QD and TIW arms, and barely detectable in QW arm. The median in the QW arm was < LLD (< LLD, interquartile range < LLD, 25.5 fmol/g) showing no differences in QD vs TIW and QD vs QW ($p = 0.364$ and $p = 0.693$ respectively). While a dose-response trend was observed in cancer tissue, estradiol level was < LLD (< LLD, 52.2 fmol/g) on QD, 17.1 (< LLD, 125.3) on TIW, and 128 (< LLD, 224.8) on QW ($p=0.046$ QD vs TIW arms). Estrone showed a clear dose response trend among arms, whereas no differences were observed for testosterone and androstenedione for both cancer and non-cancerous tissue in all arms. The Ki-67 change was analyzed in the previous paper; here we report the data for those patients who had drug and hormones tissue concentration measured, where Ki-67 decreased in all arms: median Ki67 change from baseline was QD -8 (-10, -3), TIW -6 (-11, -2), QW -4 (-8, -1). Conclusions: Exemestane 25 mg three times a week maintains comparable activity to the standard dose on tissue estradiol suppression and Ki67 decrease. Considering the estradiol suppression in non-cancerous tissue of the lowest exemestane dose, QW might even be considered for breast cancer risk reduction in primary prevention. Further analyses are ongoing to investigate the correlation with other biomarkers including the role of polymorphic UGT2B17 genotype that could identify candidates to lower exemestane dosage.

PS07-02

Benign breast disease and microcalcifications in percutaneous biopsies and breast cancer risk

Presenting Author(s) and Co-Author(s):

S. Schrup. Mayo Clinic, Rochester, Minnesota, United States

R. Vierkant. MAYO CLINIC, United States

S. Winham. Mayo Clinic, United States

C. Vachon. Mayo Clinic, Rochester, Minnesota, United States

D. Radisky. Mayo Clinic, United States

J. Carter. University of Alberta, Edmonton, Alberta, Canada

L. Pacheco-Spann. Mayo Clinic, United States

M. Jensen. Mayo Clinic, United States

A. Degnim. Mayo Clinic, United States

M. Sherman. Mayo Clinic, United States

Objectives: Mammographic microcalcifications (calcs) are a sentinel marker of in-situ and invasive breast cancer (BC) but most calcs reflect benign breast disease (BBD). BBD comprises a diverse set of lesions, variably associated with increased BC risk. While calc frequency data for the modern era are limited, historically, calcs were reported in 11% of BBD biopsies. Some studies suggest that calcs in BBD impact BC risks; however, the frequency and BC risks associated with calcs during the percutaneous biopsy era have not been clearly established. Accordingly, we assessed the association of calcs with specific BBD lesions and BC risk in a large contemporaneous BBD cohort including detailed pathology review. **Methods:** A cohort of 4,819 patients with percutaneously diagnosed BBD from 2002-2013 at Mayo Clinic, were identified. The cohort was followed from 6 months after biopsy until censoring, BC diagnosis, or December 2021. Mean follow-up was 11.3 (SD=5.1) years for BBD patients who remained cancer-free in follow-up compared with 7.4 (SD=4.3) years for cases. Histology of all biopsies were reviewed microscopically to record pathologic findings. A natural language processing algorithm (NLPA) was developed and utilized to identify the presence of calcs based on pathology reports. NLPA results were compared to 300 matched biopsy reports, taken as ground truth. We performed age-adjusted Cox proportional hazards regression to assess hazard ratios (HRs) with 95% confidence intervals (CIs) for specific BBD lesions, stratified by the presence (calc+) or absence of calcs (calcs-), with estimation of an interaction term to test for differences in risks by calc strata. Standardized incidence ratios (SIRs) estimated risks for calc+ and calc- BBD lesions versus matched strata for Iowa SEER population-based BC incidence rates. **Results:** The NLPA achieved sensitivity=0.993 and specificity=0.986. Overall, 42.8% of BBD biopsies were calc+, including 49.1% of biopsies preceding BC and 42.4% of biopsies not preceding BC (Chi-square p=0.02). Overall, risks of BC among women with BBD calc+ biopsies did not differ significantly from those of women with calc- BBD: HR=1.13 (95% CI: 0.90,1.41), p=0.290. SIRs were also similar for the two groups; women with BBD calc+ biopsies had an SIR =2.00 (95% CI: 1.72, 2.33) and BBD calc- biopsies yielded an SIR= 1.91 (95% CI: 1.64,2.22) (Table 1). HRs were similar for specific calc+ and calc- BBD lesions, with progressively higher risks for non-proliferative disease (NP), proliferative disease without atypia (PDWA) and atypical hyperplasia (AH) (p_{interaction}=0.55). Interaction terms were not significant for any specific lesion, apart from a marginally significant result for dilated ducts, wherein risks were marginally higher for calc- lesions (p_{interaction}

=0.048), perhaps representing a chance finding. SIRs for calc+ versus calc- BBD lesions were also similar. Overall, 77.3% of AH was calc+; for AH calc+, SIR=3.76 (95%CI: 2.74-5.17) and for AH calc-, SIR=4.41 (95%CI: 2.56-7.59). Conclusion: In this recent, larger percutaneous BBD cohort, calcs were present in 42.8% of all specimens, representing a marked increase compared with historical BBD data, particularly those dominated by surgical biopsy for diagnosis and preceding implementation of full-field digital mammography. In this study, calcs in percutaneously diagnosed BBD were not associated with increased BC risk.

Table 1: Comparison of standard incidence ratio of subsequent breast cancer with and without microcalcifications in benign breast disease by histologic impression (NP = non-proliferative disease, PDWA = proliferative disease without atypia, and AH = atypical hyperplasia).

Histologic Impression	Calcs	BC cases, N (%)	Non-cases, N (%)	Expected No. events (1)	SIR (95% CI) (1)
All BBD	No	172	2584	90.1	1.91 (1.64,2.22)
	Yes	166	1897	83.1	2.00 (1.72,2.33)
NP	No	68 (39.5%)	1539 (59.6%)	48.0	1.42 (1.12,1.80)
	Yes	50 (30.1%)	791 (41.7%)	34.9	1.43 (1.09,1.89)
PDWA	No	91 (52.9%)	978 (37.8%)	39.1	2.33 (1.89,2.86)
	Yes	78 (47.0%)	878 (46.3%)	38.1	2.05 (1.64,2.56)
AH	No	13 (7.6%)	67 (2.6%)	3.0	4.41 (2.56,7.59)
	Yes	38 (22.9%)	228 (12.0%)	10.1	3.76 (2.74,5.17)

(1) compared to Iowa SEER population

PS07-03

Randomized trials of oestrogen-alone and breast cancer incidence: a meta-analysis

Presenting Author(s) and Co-Author(s):

R. Chlebowski. The Lundquist Institute, United States

A. Aragaki. Fred Hutchinson Cancer Research Center, United States

K. Pan. Kaiser Permanente Southern California, Downey, California, United States

J. Mortimer. City of Hope, Duarte, California, United States

K. Johnson. University of Tennessee Health Science Center, United States

J. Wactawski-Wende. University of Buffalo, United States

M. LeBoff. Harvard Medical School, United States

S. Lavasani. City of Hope Cancer Center, United States

D. Lane. Renaissance School of Medicine at Stony Brook University, United States

R. Nelson. CITY OF HOPE, United States

J. Manson. Harvard Medical School, United States

Background Findings from cohort studies compared with those from the Women's Health initiative (WHI) randomized, placebo-controlled clinical trial regarding estrogen-alone and breast cancer risk are discordant. The WHI randomized trial enrolled 10,729 postmenopausal women with prior hysterectomy, mean age 64 years (33.2% 50-59), no prior breast cancer and a non-suspicious baseline mammogram. After 7.2 years intervention and 16.2 years cumulative follow-up, conjugated equine estrogen (CEE)-alone (vs placebo) significantly reduced breast cancer incidence by 22% ($P = 0.005$) and significantly reduced breast cancer mortality by 40% ($P = 0.04$) (Chlebowski JAMA 2020). In contrast, cohort studies had opposite findings, estrogen-alone use was associated with significantly higher breast cancer incidence and significantly higher breast cancer mortality. Therefore, we identified all available estrogen-alone randomized clinical trials where breast cancer findings were reported to conduct a meta-analysis examining the totality of the randomized clinical trial evidence regarding estrogen-alone influence on breast cancer incidence. Methods We conducted PubMed and Google Scholar searches on randomized trials and: estrogen, hormone therapy, and breast cancer, and searches from a prior meta-analyses and reviews. In the current meta-analysis, for trials with published relative risks (RR) and 95% confidence intervals (CI), each log-RR was multiplied by weight = $1/V$, where V = variance of the log-RR, and V was derived from the corresponding 95% CI. For smaller trials with only breast cancer numbers, a different method was used, the corresponding log-RR = $(O - E)/weight$, where O is the observed case number in the oestrogen-alone group and E the corresponding expected case number, $E = nP$. Findings Ten randomized trials, incorporating WHI findings, and findings from nine smaller trials included 14,272 randomized participants and 591 incident breast cancers. Of 9 smaller trials, 6 required negative baseline screening mammograms; mean entry age: 50 to 56 years in 5 trials and 62 to 71 years in 4 trials. In the nine smaller trials, 1.2% (24 of 2029) vs 2.2% (33 of 1514) randomized to estrogen-alone vs placebo (open label, one trial) were diagnosed with breast cancer, respectively (RR 0.65 95% CI 0.38-1.11, $P = 0.12$). For 5 trials evaluating estradiol formulations, RR = 0.63 95% CI 0.34-1.16, $P = 0.15$. In the WHI trial, 4.5% (238 of 5310) vs 5.5% (296 of 5429) randomized to estrogen-alone were diagnosed with breast cancer, respectively (RR 0.78 95% CI 0.65-0.93, $P = 0.005$). Combining smaller trials and WHI results, 3.6% (262 of 7339) vs 4.7% (329 of 6943) randomized to estrogen-alone vs placebo were diagnosed with breast cancer, respectively (overall RR 0.77 95% CI 0.65-0.91, $P = 0.002$).

Results from a sensitivity analysis for the smaller trials using exact conditional logistic regression were essentially unchanged (RR 0.64 95% CI 0.35-1.13). Interpretation The totality of randomized clinical trial evidence supports a conclusion that estrogen-alone use, among postmenopausal women with prior hysterectomy, significantly reduces breast cancer incidence. This consistent pattern seen in these randomized trials suggests the WHI CEE-alone findings are not “stand alone” outcomes or due to chance.

PS07-04

Improved uptake and adherence to prevention medication with use of baby tamoxifen in patients at high risk for breast cancer

Presenting Author(s) and Co-Author(s):

L. Cornell. Mayo Clinic Florida, Jacksonville, Florida, United States

S. Pruthi. Mayo Clinic, Rochester, Minnesota, United States

K. Ghosh. Mayo Clinic, Rochester, Minnesota, United States

k. Christine. Mayo Clinic, United States

P. Advani. Mayo Clinic, United States

Background: Women at increased risk for breast cancer (BC) may benefit from taking prevention medication (PM) with tamoxifen (tam). Historical uptake to PMs for women who qualify has been low. Recent studies have shown baby tam (5mg/day) to have similar efficacy to standard dosing (20mg/day) with lower risk for adverse events (AEs) in women with DCIS or high risk intraepithelial lesions. Herein, we aimed to evaluate uptake, adherence, and tolerability of baby tam in women at increased risk for BC and those with DCIS. Methods: Women seen at the Mayo Clinic Breast Center in Minnesota or Florida who qualified for PM due to DCIS, high risk intraepithelial lesions (IELs) including LCIS and/or AH, or with increased risk based on validated BRCAT or IBIS model calculation (BCRAT 5 year risk $\geq 3\%$ or IBIS 10 year risk $\geq 8\%$) were offered participation. All women received consultation with a breast specialist for discussion of PM rationale, benefits, side effects, and risks. Patients received baseline survey to assess understanding of their risk and role for PM and then 1 year follow-up survey to assess adherence and tolerability. Results: 41 patients consented for participation and 31 of those completed follow-up at 1 year. Median age of enrollment was 49 years. After initial consultation, 90% (n=37) reported good or complete understanding of BC risk. Of the 31 patients included in 1 year follow-up, 5 patients had DCIS, 13 had high-risk IELs, and 13 qualified based on BCRAT/IBIS calculation. Seventy-four percent (n= 23) of patients reported they took baby tam after consultation. No differences in age (p=0.89), education (p=0.13), or menopause status (p=0.11) between those who did and did not take medication were seen. Those who initiated baby tam were more likely to have DCIS or high risk IEL compared to those who did not (p< 0.001). Seventy-eight percent (n=18) of those who initiated baby tam were still taking medication at 1 year follow-up. Of patients who discontinued baby tam, all cited side effects as primary reason for discontinuation, with hot flashes (n=2), night sweats (n=2), and fatigue (n=2) being most common. Patients who continued medication had higher estimated BC risk compared to those who discontinued baby tam (IBIS 10 yr risk 12.7% vs 7.6%, p = 0.027). Patients with DCIS or high risk IEL were more likely to continue medication at 1 year compared to those patients who qualified for PM based on calculated BCRAT/IBIS score (p=0.05). Only 1 patient with DCIS and 1 patient with high-risk IEL discontinued baby tam at 1 year. Conclusions: Uptake to baby tam after informed discussion in patients who qualify is high, especially in those patients with high risk IELs or DCIS. Adherence and tolerability at 1 year follow-up is improved compared with traditional dosing of tam. Qualifying criteria for patients who did and did not take baby tamoxifen after informed consultation with breast specialist

	Qualifying Criteria			Total
	Calculated BCRAT/IBIS Score (n=13)	High risk intraepithelial lesion (AH/LCIS) (n=13)	DCIS (n=5)	
# that did not initiate baby tam	8	0	0	8
# that initiated baby tam	5 (38%)	13 (100%)	5 (100%)	23
Of those initiated, # patients still taking baby tam at 1 year	2 (40%)	12 (92.3%)	4 (80%)	18 (78.2%)

PS07-06

A novel citrullinated-ENO1 peptide-based vaccine for triple-negative breast cancer prevention

Presenting Author(s) and Co-Author(s):

R. Leon Letelier. MD Anderson Cancer Center, Houston, Texas, United States

H. Katayama. MD Anderson Cancer Center, Texas, United States

Y. Chen. MD Anderson Cancer Center, Texas, United States

Y. Cai. MD Anderson Cancer Center, Texas, United States

F. Hsiao. MD Anderson Cancer Center, Texas, United States

B. Arun. UT MD Anderson Cancer Center, Houston, Texas, United States

S. Hanash. University of MD Anderson Cancer Center, United States

Purpose: To evaluate the merits of a novel citrullinated-enolase 1 (ENO1) peptide-based vaccine for inducing an effective response against triple negative breast cancer (TNBC). **Background:** Targets for cancer vaccines have included mutated proteins and peptides, as well as proteins that are overexpressed in cancer but otherwise ubiquitous in their structure. However, protein modifications other than mutation may also induce an immune response. Several lines of evidence have demonstrated a role for the posttranslational modification (PTM) citrullination as inducing immunogenicity. Dysregulated protein citrullination by peptidyl arginine deiminases (PADI) has been associated with autoimmune diseases and is currently being explored for its relevance to cancer. Previously, our group established PADI2, which catalyzes the PTM from arginine to citrulline, to be highly expressed in TNBC compared to normal mammary and other tissues. We observed that PADI2-associated protein citrullination promotes antigenicity. Importantly, we demonstrated that protein citrullination, non-occurring in DNA and RNA-based vaccines, is highly cancer specific. On the basis of these findings, we developed a novel vaccine based on cancer-selective citrullinated-enolase 1 peptides (cit-ENO1) that were identified from mass spectrometry surfaceome and immunopeptidome data from breast cancer cells. We assessed the extent to which a citENO1 peptide based vaccine elicits a potent host response and attenuates tumor development in a syngeneic mouse model of TNBC. **Design:** To confirm that the cit-ENO1 peptide vaccine elicited an immune response, we immunized female B6129SF1/J mice with 10nmol cit-ENO1 peptides or 10nmol of corresponding unmodified peptides as the antigen, plus the TLR3 agonist poly I:C as an adjuvant (10mg), subcutaneously once a week, for three weeks. Saline or the adjuvant alone were used as controls. One week post the last round of immunization, draining lymph nodes (LNs) and immunized skin were harvested, and T cell phenotypes evaluated using flow-cytometry. To assess anti-cancer efficacy, female B6129SF1/J mice were immunized with cit-ENO1 peptides or unmodified peptides with poly I:C as an adjuvant followed by orthotopic implantation with murine BRCA1^{co/co}; MMTV-Cre; p53^{+/-} TNBC cells (1.5×10^6) and tumor growth as well as overall survival were assessed. **Results:** We observed that the cit-ENO1 peptide vaccination induced a statistically significantly greater percentage of activated CD8+ PD-1+ effector T cells as well as CD8+ CD44+ CD62L- effector memory T cells in the LNs compared with either the control groups or the unmodified ENO1 peptide. CD8+ PD-1+ T-cells were also found to be significantly elevated in immunized skin of cit-ENO1 vaccinated mice. Both cit-ENO1 and unmodified ENO1 vaccine increased CD4+ PD-1+ T cells from the LNs and immunized skin. Remarkably, the cit-ENO1 vaccine but not the unmodified-ENO1 vaccine significantly delayed tumor growth and markedly improved overall survival compared to respective controls (Logrank test for trend 2-sided $p < 0.05$). **Conclusion:** We have developed a

novel vaccine based on cancer-selective cit-ENO1 peptides that stimulates a potent anti-cancer immune response and significantly delays tumor initiation and progression in a preclinical, immune competent mouse model of TNBC. Importantly, the anti-cancer effects were not observed with corresponding unmodified ENO1 peptides.

PS07-07

The RXR agonist, IRX4204, delays the formation of Brca1 mutant mammary tumors via modulation of the anti-tumor immune response

Presenting Author(s) and Co-Author(s):

C. Moyer. University of Texas MD Anderson Cancer Center, Missouri City, Texas, United States

D. Coleman. University of Texas MD Anderson Cancer Center, United States

J. Hill. University of Texas MD Anderson Cancer Center, United States

L. Vornik. University of Texas, MD Anderson Cancer Center, United States

M. Savage. University of Texas MD Anderson Cancer Center, United States

M. Sanders. Io Therapeutics, Inc, United States

S. Shizuko. National Institutes of Health/National Cancer Institute, United States

A. Mohammed. National Institutes of Health/National Cancer Institute, United States

P. Brown. MD Anderson Cancer Center, Department of Clinical Cancer Prevention, United States

A. Mazumdar. MD Anderson Cancer Center, Department of Clinical Cancer Prevention, United States

Background: Women with germline BRCA1 mutations are at an increased risk for developing breast cancer in their lifetime, often at a young age with more aggressive tumors. At present, prophylactic bilateral mastectomy is the most effective strategy for reducing breast cancer risk. However, this invasive procedure is irreversible and associated with potential complications. We and others have found that PARP inhibitors can delay Brca1-mutant tumor formation in mice and could be beneficial for the prevention of breast cancer. However, currently available PARP inhibitors are associated with modest toxicities that may not be acceptable to women without cancer. Thus, there remains an urgent need for the development of safe and effective therapies for the prevention of breast cancer. Here, we present data demonstrating the activity of IRX4204, a minimally toxic and highly specific agonist of the nuclear retinoid X receptor (RXR), to delay the formation of mammary tumors in a Brca1-deficient mouse model. This inhibitory effect on tumor growth is due, in part, to the role of IRX4204 in stimulating the anti-tumor immune response. Methods: We used the established MMTV-Cre, conditional Brca1 gene knockout, p53 heterozygous loss mouse model (BRCA1^{co/co}; MMTV-Cre^{+/+}; p53^{+/-}) and selected for mutant female pups using PCR genotyping. At 16 weeks of age, all mice were separated into 4 treatment groups (n=10 per group): (1) sesame oil control; (2) the novel RXR agonist, IRX-4204 (10mg/kg); (3) high-dose IRX4204 (20 mg/kg); and (4) the RXR agonist, 9-cis-UAB-30 (5 mg/kg). All treatments were given by oral gavage five days per week, and mice were observed daily for tumor formation and toxicity. At the study endpoint, tumors and normal mammary glands were collected for additional analyses. Immunohistochemical staining was used to quantify CD8a, Ki-67 and cleaved caspase 3 expression in Brca1-deficient tumors. Oil Red O staining was used to measure changes in lipid accumulation in Brca1-deficient cell lines treated with IRX4204. qPCR was used to quantify the changes in gene expression of lipid metabolism-associated genes upon treatment with IRX4204 in vitro. Results: Vehicle-treated Brca1-deficient mice had a median time-to-tumor formation (TTF) of 211 days, with 100% developing tumors by 330 days. Mice treated with UAB 5 mg/kg had an improved median TTF of 261 days, whereas mice treated with IRX4204 10mg/kg or 20mg/kg had a median TTF of 347 and 304 days, respectively (p< 0.01). In addition, 60% of mice treated with IRX4204 10

mg/kg remained tumor-free at 330 days. IRX4204-treated tumors showed an increased infiltration of CD8-positive T-cells over vehicle-treated tumors ($p < 0.05$). Treatment of Brca1-deficient cell lines with IRX4204 in vitro resulted in a significant increase in lipid accumulation accompanied by a 2-fold increase of Srebf1 expression (a key transcription factor that regulates lipid homeostasis) within 24 hours of treatment ($p < 0.05$). Conclusion: These data demonstrate a novel use of the RXR agonist, IRX4204, to delay the formation of Brca1-deficient mammary tumors. We have found that IRX4204 treatment modulates the tumor immune response through increased infiltration of cytotoxic CD8-positive T-cells in Brca1-deficient mammary tumors in vivo. We have also determined that IRX4204 modulates lipid metabolism in breast cancer cell lines in vitro. It is known that lipid-derived antigens can stimulate T-cell activity. Our findings suggest that RXR agonists may alter lipid antigen production to activate an anti-tumor response. Additional immune and lipidomic studies are on-going. This work was supported by NCI-PREVENT grant (to PB and AM HHSN26100008) and CFP Foundation (Odyssey Fellowship to CM).

PS07-08

Bazedoxifene plus conjugated estrogen reduces mammary proliferation markers and improves adipocyte size, gut microbiome, and metabolic health: Findings from a preclinical model of obesity and breast cancer risk.

Presenting Author(s) and Co-Author(s):

K. Cook. Wake Forest University School of Medicine, United States

R. Jenschke. Texas A&M University, United States

K. Corleto. Texas A&M University, United States

C. Fabian. University of Kansas Cancer Center, Kansas City, Kansas, United States

S. Hursting. University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

B. Kimler. University of Kansas Medical Center, Kansas City, Kansas, United States

D. Landrock. Texas A&M University, United States

E. Giles. University of Michigan, Ann Arbor, Michigan, United States

Background: Many women at high risk for breast cancer will not take tamoxifen or aromatase inhibitors for cancer prevention due to concern of side effects including hot flashes. Further, tamoxifen has detrimental metabolic effects in some overweight/obese women. Duavee®, a tissue-selective complex of bazedoxifene + conjugated estrogen, is FDA-approved for relief of hot-flashes and prevention of osteoporosis. Preclinical studies suggest favorable metabolic effects and potential for breast cancer risk reduction. In a single arm clinical trial, BZA+CE reduced Ki-67 and mammographic density (PMID: 31420361), and this combination is currently being assessed further in a Phase IIB trial of postmenopausal high risk women with vasomotor symptoms. Here, we examined the modifying effects of obesity on response to BZA+CE in a rodent model of obesity and breast cancer risk. **Methods:** Rats received carcinogen at 7-weeks of age to induce mammary tumors and were fed a high-fat diet (46% kcal fat) to promote obesity. Lean and obese rat were selected based on adiposity at 16 weeks. Separate cohorts of lean and obese ovary-intact or ovariectomized (OVX) rats were randomized to a daily dose of BZA+CE or placebo control for 8 weeks. We assessed tumor development throughout the study and end of study RNA from mammary glands was analysed by gene expression microarray (Affymetrix). We also analyzed body weight/composition, markers of metabolic health (circulating glucose, insulin, adiponectin), as well as changes in the gut microbiome (metagenomic sequencing on DNA isolated from baseline and end-of-study fecal samples) in response to BZA+CE. **Results:** BZA+CE improved metabolic health in both ovary intact and OVX rats, including reduced body weight and % body fat, particularly in the visceral regions. These effects were greater in obese rats compared to lean. BZA+CE reduced the number of large adipocytes and increased small (insulin sensitive) adipocytes in the mammary adipose, indicating beneficial changes in local tumor microenvironment. We found no evidence that Duavee® promoted tumor development or growth in ovary-intact or OVX'd rats. Gene set enrichment analysis (GSEA) of microarray data showed enrichment of cell proliferation pathways in MG from obese rats and these same pathways were downregulated with BZA+CE, consistent with anti-cancer effects. Analysis of the microbiome found that BZA+CE increased proportional abundance of *Odoribacter laneus* in the gut, regardless of lean/obese or intact/OVX status. Previous studies have demonstrated that this bacterium improves glucose control and reduces inflammatory cytokines when administered to obese mice, suggesting a possible mechanistic link in this study. **Conclusions:** Unlike traditional SERMs that can have negative metabolic effects, BZA+CE improved whole body and mammary gland metabolic health and

reduced expression of cell proliferation pathways, particularly in obese rats. Preliminary data suggest that changes in the gut microbiome could contribute, at least in part, to these effects. Together this supports BZA+CE (Duavee) as an agent with potential beneficial effects on breast cancer risk reduction and improvements in metabolic health in women with obesity. Further analyses will guide assessment of outcomes in an ongoing parallel clinical study in postmenopausal women at high risk for breast cancer.

PS07-09

Prenatal BRCA1 epimutations is a major cause of triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

P. Lonning. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Hordaland, Norway

H. Eikesdal. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Hordaland, Norway

E. Ognedal. haukeland University Hospital, Norway

B. Gilje. Stavanger University Hospital, Norway

S. Lundgren. cancer Clinic, St Olav University Hospital, Trondheim, Norway

E. Blix. Department of Oncology, University Hospital of North Norway, Tromso, Norway

H. Espelid. Department of Surgery, Haugesund Hospital, Haugesund, Norway

J. Geisler. University of Oslo, Norway, Lorenskog, Norway

S. Geisler. Akershus University Hospital, United States

E. Janssen. Stavanger University Hospital, United States

S. Yndestad. Department of Clinical Science, University of Bergen, Bergen, Hordaland, Norway

L. Minsaas. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Norway

B. Leirvaag. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Norway

R. Lillestol. University of Bergen, Norway

S. Knappskog. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Norway

O. Nikolaienko. University of Bergen, Norway

Background: Low level normal cell BRCA1 epimutations have been associated with an increased risk of triple-negative breast cancer (TNBC). However, the fraction of TNBCs that may have BRCA1 epimutations as their underlying cause is unknown. Neither are the time of occurrence and the potential inheritance pattern of BRCA1 epimutations established. **Methods:** To address these questions, we analyzed BRCA1 methylation status in breast cancer tissue and matched white blood cells (WBC) from 411 patients with primary breast cancer, including 66 TNBCs. Samples were analyzed by a highly sensitive next-generation sequencing (NGS) assay on an Illumina MiSeq sequencer, allowing allele-resolved methylation assessment. Further, to assess the time of origin and the characteristics of normal cell BRCA1 methylation, we analyzed umbilical cord samples from 1260 newborn girls and 200 newborn boys. To assess potential Mendelian heritage, we analyzed BRCA1 methylation status in WBCs from 575 mothers and 531 fathers of newborn girls with (n = 102) and without (n = 473) WBC BRCA1 methylation. **Results:** We found concordant tumor and mosaic WBC BRCA1 epimutations in 10 out of 66 patients with TNBC and in four out of six patients with estrogen receptor (ER)-low expression (< 10%) of tumors (combined 14 out of 72; 19.4%, CI: 11.1-30.5). These exceeded the number of tumors harboring germline (n = 5) or somatic (n = 4) BRCA1 mutations. Notably, BRCA1 methylation and BRCA1 mutations were mutually exclusive. Contrasting the findings in TNBC and ER-low expression tumors, we found WBC and tumor BRCA1 methylation concordance in only three out of 221 patients with ER >10+% tumors and zero out of 116

patients with HER2 positive tumors. Intraindividually, BRCA1 epimutations affected the same allele in normal and tumor cells. Assessing BRCA1 methylation in umbilical cord WBCs from newborn girls, we found mosaic, predominantly monoallelic BRCA1 epimutations, with qualitative features similar to those in adults, in 113/1260 (9.0%) of individuals. We found no correlation between WBC BRCA1 methylation in newborns and methylation status in their mothers, fathers, or any parent. Notably, WBC BRCA1 methylation occurred at a significantly lower frequency in newborn boys (9 / 200; 4.5%) as compared to newborn girls ($p = 0.038$). Similarly, WBC BRCA1 methylation was found less common among fathers (16 / 531; 3.0%), as compared to mothers (46 / 575; 8.0%; $p = 0.0003$). Conclusions: Our findings suggest prenatal BRCA1 epimutations might be the underlying cause of around 20% of TNBC and low-ER expressing breast cancers. Such constitutional mosaic BRCA1 methylation likely arise through gender-related mechanisms in utero, independent of Mendelian inheritance.

PS07-01

Exemestane and breast cancer prevention: how low can we go? Drug and biomarker tissue levels in a randomized presurgical trial on exemestane alternative dosing regimen.

Presenting Author(s) and Co-Author(s):

- D. Serrano. IEO, European Institute of Oncology IRCCS, Milano, Italy
H. Johansson. IEO, European Institute of Oncology IRCCS, Italy
B. Bertelsen. Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Norway
G. Mellgren. Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Norway
P. Thomas. MD Anderson Cancer Center, Texas, United States
K. Crew. Columbia University Irving Medical Center, United States
N. Kumar. Moffitt Cancer Center, University of South Florida, United States
D. Macis. IEO, European Institute of Oncology IRCCS, Italy
V. Aristarco. IEO, European Institute of Oncology IRCCS, Italy
A. Guerrieri Gonzaga. IEO - European Institute of Oncology IRCCS, Milan, Italy
S. Gandini. IEO, European Institute of Oncology IRCCS, Italy
M. D'Amico. Ospedali Galliera, Genoa, Italy
T. Buttiron Webber. E.O. Ospedali Galliera, Genoa, Italy
I. Briata. E.O. Ospedali Galliera, Genoa, Genoa, Italy
S. Spinaci. Ospedale Villa Scassi ASL3, Genoa, Italy
V. Galimberti. European Institute of Oncology, Milan, Italy
G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy
L. Vornik. University of Texas, MD Anderson Cancer Center, United States
E. Villar-Sanchez. University of Texas, MD Anderson Cancer Center, United States
P. Brown. MD Anderson Cancer Center, Department of Clinical Cancer Prevention, United States
B. Heckman-Stoddard. Division of Cancer Prevention, NCI Bethesda, United States
E. Szabo. Division of Cancer Prevention, NCI Bethesda, United States
B. Bonanni. 4. Division of Cancer Prevention and Genetics, European Institute of Oncology, IRCCS, Milan, Italy
A. De Censi. E.O. Ospedali Galliera, Genova, Italy, Liguria, Italy

Exemestane is an effective drug to reduce breast cancer risk reaching an overall 65% reduction in breast cancer in the placebo-controlled phase III MAP.3 trial. To improve its acceptability in primary prevention programs, we are seeking the minimal effective dose. In a 3-arm presurgical trial of 4-6 weeks before breast surgery in 180 postmenopausal women with ER-positive breast cancer, we investigated the activity of alternative exemestane schedules: 25 mg per day (QD), 25 mg three times/week (TIW) or 25 mg per week (QW) and showed that in adherent participants TIW was not inferior to QD in reducing circulating estradiol (Serrano et al JAMA Oncol. doi:10.1001/jamaoncol.2023.0089). Moreover, Ki67 reduction was seen in all arms with

no significant difference among arms. Here, we analyzed the concentration of sex steroids, exemestane, and its main metabolite in the cancer and adjacent non-cancerous breast tissue.

Tissues samples were homogenized before liquid-liquid extraction. After reconstitution, samples were analyzed by coupling liquid chromatography with tandem mass spectrometry (Sciex QTRAP 6500, Nexera system, Shimadzu).

We obtained breast cancer tissue from 93 and non-cancerous breast tissue from 117 participants to measure exemestane, 17-OH-exemestane, and sex steroids. Exemestane and 17-OH-exemestane concentrations were detectable only in the QD arm, while in TIW and QW arms levels were below the Lower Limit of Detection (< LLD). Median exemestane level was 3807 fmol/g and 17485 fmol/g and median 17-OH-exemestane level was 338 fmol/g and 1343 fmol/g in cancer and non-cancerous tissue, respectively. Interestingly, drug and its metabolite accumulated 4-5-fold in non-cancerous tissue compared to cancer tissue in the QD arm. Despite the between-arm drug concentration difference, estradiol was almost completely suppressed in all arms in the non-cancerous tissue, attaining level < LLD in QD and TIW arms, and barely detectable in QW arm. The median in the QW arm was < LLD (< LLD, interquartile range < LLD, 25.5 fmol/g) showing no differences in QD vs TIW and QD vs QW ($p = 0.364$ and $p = 0.693$ respectively). While a dose-response trend was observed in cancer tissue, estradiol level was < LLD (< LLD, 52.2 fmol/g) on QD, 17.1 (< LLD, 125.3) on TIW, and 128 (< LLD, 224.8) on QW ($p=0.046$ QD vs TIW arms). Estrone showed a clear dose response trend among arms, whereas no differences were observed for testosterone and androstenedione for both cancer and non-cancerous tissue in all arms. The Ki-67 change was analyzed in the previous paper; here we report the data for those patients who had drug and hormones tissue concentration measured, where Ki-67 decreased in all arms: median Ki67 change from baseline was QD -8 (-10, -3), TIW -6 (-11, -2), QW -4 (-8, -1).

Conclusions:

Exemestane 25 mg three times a week maintains comparable activity to the standard dose on tissue estradiol suppression and Ki67 decrease. Considering the estradiol suppression in non-cancerous tissue of the lowest exemestane dose, QW might even be considered for breast cancer risk reduction in primary prevention. Further analyses are ongoing to investigate the correlation with other biomarkers including the role of polymorphic UGT2B17 genotype that could identify candidates to lower exemestane dosage.

Disclosure(s):

Davide Serrano, MD: No financial relationships to disclose

Poster Spotlight Session 7: Prevention

Presenting Author(s) and Co-Author(s):

N. Iyengar. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Disclosure(s):

Neil M. Iyengar, MD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated), Becton Dickinson (Terminated), Gilead Science (Terminated), Novartis (Terminated), Pfizer, Inc. (Terminated), Puma Biotechnology, Inc (Terminated), Seattle Genetics/Seagen (Terminated), TerSera (Terminated); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Novartis (Ongoing), SynDevRx, Inc (Ongoing)

PS07-02

Benign breast disease and microcalcifications in percutaneous biopsies and breast cancer risk

Presenting Author(s) and Co-Author(s):

S. Schrup. Mayo Clinic, Rochester, Minnesota, United States

R. Vierkant. MAYO CLINIC, United States

S. Winham. Mayo Clinic, United States

C. Vachon. Mayo Clinic, Rochester, Minnesota, United States

D. Radisky. Mayo Clinic, United States

J. Carter. University of Alberta, Edmonton, Alberta, Canada

L. Pacheco-Spann. Mayo Clinic, United States

M. Jensen. Mayo Clinic, United States

A. Degnim. Mayo Clinic, United States

M. Sherman. Mayo Clinic, United States

Objectives:

Mammographic microcalcifications (calcs) are a sentinel marker of in-situ and invasive breast cancer (BC) but most calcs reflect benign breast disease (BBD). BBD comprises a diverse set of lesions, variably associated with increased BC risk. While calc frequency data for the modern era are limited, historically, calcs were reported in 11% of BBD biopsies. Some studies suggest that calcs in BBD impact BC risks; however, the frequency and BC risks associated with calcs during the percutaneous biopsy era have not been clearly established. Accordingly, we assessed the association of calcs with specific BBD lesions and BC risk in a large contemporaneous BBD cohort including detailed pathology review.

Methods:

A cohort of 4,819 patients with percutaneously diagnosed BBD from 2002-2013 at Mayo Clinic, were identified. The cohort was followed from 6 months after biopsy until censoring, BC diagnosis, or December 2021. Mean follow-up was 11.3 (SD=5.1) years for BBD patients who remained cancer-free in follow-up compared with 7.4 (SD=4.3) years for cases. Histology of all biopsies were reviewed microscopically to record pathologic findings. A natural language processing algorithm (NLPA) was developed and utilized to identify the presence of calcs based on pathology reports. NLPA results were compared to 300 matched biopsy reports, taken as ground truth. We performed age-adjusted Cox proportional hazards regression to assess hazard ratios (HRs) with 95% confidence intervals (CIs) for specific BBD lesions, stratified by the presence (calc+) or absence of calcs (calcs-), with estimation of an interaction term to test for differences in risks by calc strata. Standardized incidence ratios (SIRs) estimated risks for calc+ and calc- BBD lesions versus matched strata for Iowa SEER population-based BC incidence rates.

Results:

The NLPA achieved sensitivity=0.993 and specificity=0.986. Overall, 42.8% of BBD biopsies were calc+, including 49.1% of biopsies preceding BC and 42.4% of biopsies not preceding BC (Chi-square $p=0.02$). Overall, risks of BC among women with BBD calc+ biopsies did not differ significantly from those of women with calc- BBD: HR=1.13 (95% CI: 0.90,1.41), $p=0.290$. SIRs were also similar for the two groups; women with BBD calc+ biopsies had an SIR =2.00 (95%

CI: 1.72, 2.33) and BBD calc- biopsies yielded an SIR= 1.91 (95% CI: 1.64,2.22) (Table 1). HRs were similar for specific calc+ and calc- BBD lesions, with progressively higher risks for non-proliferative disease (NP), proliferative disease without atypia (PDWA) and atypical hyperplasia (AH) ($p_{\text{interaction}}=0.55$). Interaction terms were not significant for any specific lesion, apart from a marginally significant result for dilated ducts, wherein risks were marginally higher for calc- lesions ($p_{\text{Interaction}} =0.048$), perhaps representing a chance finding. SIRs for calc+ versus calc- BBD lesions were also similar. Overall, 77.3% of AH was calc+; for AH calc+, SIR=3.76 (95%CI: 2.74-5.17) and for AH calc-, SIR=4.41 (95%CI: 2.56-7.59).

Conclusion:

In this recent, larger percutaneous BBD cohort, calcs were present in 42.8% of all specimens, representing a marked increase compared with historical BBD data, particularly those dominated by surgical biopsy for diagnosis and preceding implementation of full-field digital mammography. In this study, calcs in percutaneously diagnosed BBD were not associated with increased BC risk.

Table 1: Comparison of standard incidence ratio of subsequent breast cancer with and without microcalcifications in benign breast disease by histologic impression (NP = non-proliferative disease, PDWA = proliferative disease without atypia, and AH = atypical hyperplasia).

Histologic Impression	Calcs	BC cases, N (%)	Non-cases, N (%)	Expected No. events (1)	SIR (95% CI) (1)
All BBD	No	172	2584	90.1	1.91 (1.64,2.22)
	Yes	166	1897	83.1	2.00 (1.72,2.33)
NP	No	68 (39.5%)	1539 (59.6%)	48.0	1.42 (1.12,1.80)
	Yes	50 (30.1%)	791 (41.7%)	34.9	1.43 (1.09,1.89)
PDWA	No	91 (52.9%)	978 (37.8%)	39.1	2.33 (1.89,2.86)
	Yes	78 (47.0%)	878 (46.3%)	38.1	2.05 (1.64,2.56)
AH	No	13 (7.6%)	67 (2.6%)	3.0	4.41 (2.56,7.59)
	Yes	38 (22.9%)	228 (12.0%)	10.1	3.76 (2.74,5.17)

(1) compared to Iowa SEER population

Disclosure(s):

Sarah E. Schrup, B.S.: No financial relationships to disclose
Celine M. Vachon, PhD: No financial relationships to disclose

PS07-03

Randomized trials of oestrogen-alone and breast cancer incidence: a meta-analysis

Presenting Author(s) and Co-Author(s):

R. Chlebowski. The Lundquist Institute, United States

A. Aragaki. Fred Hutchinson Cancer Research Center, United States

K. Pan. Kaiser Permanente Southern California, Downey, California, United States

J. Mortimer. City of Hope, Duarte, California, United States

K. Johnson. University of Tennessee Health Science Center, United States

J. Wactawski-Wende. University of Buffalo, United States

M. LeBoff. Harvard Medical School, United States

S. Lavasani. City of Hope Cancer Center, United States

D. Lane. Renaissance School of Medicine at Stony Brook University, United States

R. Nelson. CITY OF HOPE, United States

J. Manson. Harvard Medical School, United States

Background

Findings from cohort studies compared with those from the Women's Health initiative (WHI) randomized, placebo-controlled clinical trial regarding estrogen-alone and breast cancer risk are discordant. The WHI randomized trial enrolled 10,729 postmenopausal women with prior hysterectomy, mean age 64 years (33.2% 50-59), no prior breast cancer and a non-suspicious baseline mammogram. After 7.2 years intervention and 16.2 years cumulative follow-up, conjugated equine estrogen (CEE)-alone (vs placebo) significantly reduced breast cancer incidence by 22% ($P = 0.005$) and significantly reduced breast cancer mortality by 40% ($P = 0.04$) (Chlebowski JAMA 2020). In contrast, cohort studies had opposite findings, estrogen-alone use was associated with significantly higher breast cancer incidence and significantly higher breast cancer mortality. Therefore, we identified all available estrogen-alone randomized clinical trials where breast cancer findings were reported to conduct a meta-analysis examining the totality of the randomized clinical trial evidence regarding estrogen-alone influence on breast cancer incidence.

Methods

We conducted PubMed and Google Scholar searches on randomized trials and: estrogen, hormone therapy, and breast cancer, and searches from a prior meta-analyses and reviews. In the current meta-analysis, for trials with published relative risks (RR) and 95% confidence intervals (CI), each log-RR was multiplied by weight = $1/V$, where V = variance of the log-RR, and V was derived from the corresponding 95% CI. For smaller trials with only breast cancer numbers, a different method was used, the corresponding log-RR = $(O - E)/\text{weight}$, where O is the observed case number in the oestrogen-alone group and E the corresponding expected case number, $E = nP$.

Findings

Ten randomized trials, incorporating WHI findings, and findings from nine smaller trials included 14,272 randomized participants and 591 incident breast cancers. Of 9 smaller trials, 6 required negative baseline screening mammograms; mean entry age: 50 to 56 years in 5 trials and 62 to 71 years in 4 trials. In the nine smaller trials, 1.2% (24 of 2029) vs 2.2% (33 of 1514) randomized to estrogen-alone vs placebo (open label, one trial) were diagnosed with breast

cancer, respectively (RR 0.65 95% CI 0.38-1.11, P = 0.12). For 5 trials evaluating estradiol formulations, RR = 0.63 95% CI 0.34-1.16, P = 0.15. In the WHI trial, 4.5% (238 of 5310) vs 5.5% (296 of 5429) randomized to estrogen-alone were diagnosed with breast cancer, respectively (RR 0.78 95% CI 0.65-0.93, P = 0.005). Combining smaller trials and WHI results, 3.6% (262 of 7339) vs 4.7% (329 of 6943) randomized to estrogen-alone vs placebo were diagnosed with breast cancer, respectively (overall RR 0.77 95% CI 0.65-0.91, P = 0.002). Results from a sensitivity analysis for the smaller trials using exact conditional logistic regression were essentially unchanged (RR 0.64 95% CI 0.35-1.13).

Interpretation

The totality of randomized clinical trial evidence supports a conclusion that estrogen-alone use, among postmenopausal women with prior hysterectomy, significantly reduces breast cancer incidence. This consistent pattern seen in these randomized trials suggests the WHI CEE-alone findings are not “stand alone” outcomes or due to chance.

Disclosure(s):

Joanne Mortimer, MD, FACP, FASCO: Consulting Fees (e.g., advisory boards): GE Healthcare (Ongoing)

PS07-04

Improved uptake and adherence to prevention medication with use of baby tamoxifen in patients at high risk for breast cancer

Presenting Author(s) and Co-Author(s):

L. Cornell. Mayo Clinic Florida, Jacksonville, Florida, United States

S. Pruthi. Mayo Clinic, Rochester, Minnesota, United States

K. Ghosh. Mayo Clinic, Rochester, Minnesota, United States

k. Christine. Mayo Clinic, United States

P. Advani. Mayo Clinic, United States

Background:

Women at increased risk for breast cancer (BC) may benefit from taking prevention medication (PM) with tamoxifen (tam). Historical uptake to PMs for women who qualify has been low. Recent studies have shown baby tam (5mg/day) to have similar efficacy to standard dosing (20mg/day) with lower risk for adverse events (AEs) in women with DCIS or high risk intraepithelial lesions. Herein, we aimed to evaluate uptake, adherence, and tolerability of baby tam in women at increased risk for BC and those with DCIS.

Methods:

Women seen at the Mayo Clinic Breast Center in Minnesota or Florida who qualified for PM due to DCIS, high risk intraepithelial lesions (IELs) including LCIS and/or AH, or with increased risk based on validated BCRAT or IBIS model calculation (BCRAT 5 year risk \geq 3% or IBIS 10 year risk \geq 8%) were offered participation. All women received consultation with a breast specialist for discussion of PM rationale, benefits, side effects, and risks. Patients received baseline survey to assess understanding of their risk and role for PM and then 1 year follow-up survey to assess adherence and tolerability.

Results:

41 patients consented for participation and 31 of those completed follow-up at 1 year. Median age of enrollment was 49 years. After initial consultation, 90% (n=37) reported good or complete understanding of BC risk. Of the 31 patients included in 1 year follow-up, 5 patients had DCIS, 13 had high-risk IELs, and 13 qualified based on BCRAT/IBIS calculation. Seventy-four percent (n= 23) of patients reported they took baby tam after consultation. No differences in age (p=0.89), education (p=0.13), or menopause status (p=0.11) between those who did and did not take medication were seen. Those who initiated baby tam were more likely to have DCIS or high risk IEL compared to those who did not (p < 0.001). Seventy-eight percent (n=18) of those who initiated baby tam were still taking medication at 1 year follow-up. Of patients who discontinued baby tam, all cited side effects as primary reason for discontinuation, with hot flashes (n=2), night sweats (n=2), and fatigue (n=2) being most common. Patients who continued medication had higher estimated BC risk compared to those who discontinued baby tam (IBIS 10 yr risk 12.7% vs 7.6%, p = 0.027). Patients with DCIS or high risk IEL were more likely to continue medication at 1 year compared to those patients who qualified for PM based on calculated BCRAT/IBIS score (p=0.05). Only 1 patient with DCIS and 1 patient with high-risk IEL discontinued baby tam at 1 year.

Conclusions:

Uptake to baby tam after informed discussion in patients who qualify is high, especially in those patients with high risk IELs or DCIS. Adherence and tolerability at 1 year follow-up is improved

compared with traditional dosing of tam.

Qualifying criteria for patients who did and did not take baby tamoxifen after informed consultation with breast specialist

	Qualifying Criteria			Total
	Calculated BCRAT/IBIS Score (n=13)	High risk intraepithelial lesion (AH/LCIS) (n=13)	DCIS (n=5)	
# that did not initiate baby tam	8	0	0	8
# that initiated baby tam	5 (38%)	13 (100%)	5 (100%)	23
Of those initiated, # patients still taking baby tam at 1 year	2 (40%)	12 (92.3%)	4 (80%)	18 (78.2%)

Disclosure(s):

Lauren Cornell, MD: No financial relationships to disclose

PS07-06

A novel citrullinated-ENO1 peptide-based vaccine for triple-negative breast cancer prevention

Presenting Author(s) and Co-Author(s):

R. Leon Letelier. MD Anderson Cancer Center, Houston, Texas, United States

H. Katayama. MD Anderson Cancer Center, Texas, United States

Y. Chen. MD Anderson Cancer Center, Texas, United States

Y. Cai. MD Anderson Cancer Center, Texas, United States

F. Hsiao. MD Anderson Cancer Center, Texas, United States

B. Arun. UT MD Anderson Cancer Center, Houston, Texas, United States

S. Hanash. University of MD Anderson Cancer Center, United States

Purpose:

To evaluate the merits of a novel citrullinated-enolase 1 (ENO1) peptide-based vaccine for inducing an effective response against triple negative breast cancer (TNBC). Background: Targets for cancer vaccines have included mutated proteins and peptides, as well as proteins that are overexpressed in cancer but otherwise ubiquitous in their structure. However, protein modifications other than mutation may also induce an immune response. Several lines of evidence have demonstrated a role for the posttranslational modification (PTM) citrullination as inducing immunogenicity. Dysregulated protein citrullination by peptidyl arginine deiminases (PADI) has been associated with autoimmune diseases and is currently being explored for its relevance to cancer. Previously, our group established PADI2, which catalyzes the PTM from arginine to citrulline, to be highly expressed in TNBC compared to normal mammary and other tissues. We observed that PADI2-associated protein citrullination promotes antigenicity. Importantly, we demonstrated that protein citrullination, non-occurring in DNA and RNA-based vaccines, is highly cancer specific. On the basis of these findings, we developed a novel vaccine based on cancer-selective citrullinated-enolase 1 peptides (cit-ENO1) that were identified from mass spectrometry surfaceome and immunopeptidome data from breast cancer cells. We assessed the extent to which a citENO1 peptide based vaccine elicits a potent host response and attenuates tumor development in a syngeneic mouse model of TNBC. Design: To confirm that the cit-ENO1 peptide vaccine elicited an immune response, we immunized female B6129SF1/J mice with 10nmol cit-ENO1 peptides or 10nmol of corresponding unmodified peptides as the antigen, plus the TLR3 agonist poly I:C as an adjuvant (10mg), subcutaneously once a week, for three weeks. Saline or the adjuvant alone were used as controls. One week post the last round of immunization, draining lymph nodes (LNs) and immunized skin were harvested, and T cell phenotypes evaluated using flow-cytometry. To assess anti-cancer efficacy, female B6129SF1/J mice were immunized with cit-ENO1 peptides or unmodified peptides with poly I:C as an adjuvant followed by orthotopic implantation with murine BRCA1^{co/co}; MMTV-Cre; p53^{+/-} TNBC cells (1.5 x 10⁶) and tumor growth as well as overall survival were assessed. Results:

We observed that the cit-ENO1 peptide vaccination induced a statistically significantly greater percentage of activated CD8+ PD-1+ effector T cells as well as CD8+ CD44+ CD62L- effector memory T cells in the LNs compared with either the control groups or the unmodified ENO1 peptide. CD8+ PD-1+ T-cells were also found to be significantly elevated in immunized skin of cit-ENO1 vaccinated mice. Both cit-ENO1 and unmodified ENO1 vaccine increased CD4+ PD-1+ T cells from the LNs and immunized skin. Remarkably, the cit-ENO1 vaccine but not the unmodified-ENO1 vaccine significantly delayed tumor growth and markedly improved overall

survival compared to respective controls (Logrank test for trend 2-sided $p < 0.05$). Conclusion: We have developed a novel vaccine based on cancer-selective cit-ENO1 peptides that stimulates a potent anti-cancer immune response and significantly delays tumor initiation and progression in a preclinical, immune competent mouse model of TNBC. Importantly, the anti-cancer effects were not observed with corresponding unmodified ENO1 peptides.

Disclosure(s):

Ricardo A. Leon Letelier, PhD: No financial relationships to disclose

Banu K. Arun, MD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca, (Ongoing)

PS07-07

The RXR agonist, IRX4204, delays the formation of Brca1 mutant mammary tumors via modulation of the anti-tumor immune response

Presenting Author(s) and Co-Author(s):

C. Moyer. University of Texas MD Anderson Cancer Center, Missouri City, Texas, United States

D. Coleman. University of Texas MD Anderson Cancer Center, United States

J. Hill. University of Texas MD Anderson Cancer Center, United States

L. Vornik. University of Texas, MD Anderson Cancer Center, United States

M. Savage. University of Texas MD Anderson Cancer Center, United States

M. Sanders. Io Therapeutics, Inc, United States

S. Shizuko. National Institutes of Health/National Cancer Institute, United States

A. Mohammed. National Institutes of Health/National Cancer Institute, United States

P. Brown. MD Anderson Cancer Center, Department of Clinical Cancer Prevention, United States

A. Mazumdar. MD Anderson Cancer Center, Department of Clinical Cancer Prevention, United States

Background:

Women with germline BRCA1 mutations are at an increased risk for developing breast cancer in their lifetime, often at a young age with more aggressive tumors. At present, prophylactic bilateral mastectomy is the most effective strategy for reducing breast cancer risk. However, this invasive procedure is irreversible and associated with potential complications. We and others have found that PARP inhibitors can delay Brca1-mutant tumor formation in mice and could be beneficial for the prevention of breast cancer. However, currently available PARP inhibitors are associated with modest toxicities that may not be acceptable to women without cancer. Thus, there remains an urgent need for the development of safe and effective therapies for the prevention of breast cancer. Here, we present data demonstrating the activity of IRX4204, a minimally toxic and highly specific agonist of the nuclear retinoid X receptor (RXR), to delay the formation of mammary tumors in a Brca1-deficient mouse model. This inhibitory effect on tumor growth is due, in part, to the role of IRX4204 in stimulating the anti-tumor immune response.

Methods:

We used the established MMTV-Cre, conditional Brca1 gene knockout, p53 heterozygous loss mouse model (BRCA1^{co/co}; MMTV-Cre^{+/+}; p53^{+/-}) and selected for mutant female pups using PCR genotyping. At 16 weeks of age, all mice were separated into 4 treatment groups (n=10 per group): (1) sesame oil control; (2) the novel RXR agonist, IRX-4204 (10mg/kg); (3) high-dose IRX4204 (20 mg/kg); and (4) the RXR agonist, 9-cis-UAB-30 (5 mg/kg). All treatments were given by oral gavage five days per week, and mice were observed daily for tumor formation and toxicity. At the study endpoint, tumors and normal mammary glands were collected for additional analyses. Immunohistochemical staining was used to quantify CD8a, Ki-67 and cleaved caspase 3 expression in Brca1-deficient tumors. Oil Red O staining was used to measure changes in lipid accumulation in Brca1-deficient cell lines treated with IRX4204. qPCR was used to quantify the changes in gene expression of lipid metabolism-associated genes upon treatment with IRX4204 in vitro.

Results:

Vehicle-treated Brca1-deficient mice had a median time-to-tumor formation (TTF) of 211 days, with 100% developing tumors by 330 days. Mice treated with UAB 5 mg/kg had an improved median TTF of 261 days, whereas mice treated with IRX4204 10mg/kg or 20mg/kg had a median TTF of 347 and 304 days, respectively ($p < 0.01$). In addition, 60% of mice treated with IRX4204 10 mg/kg remained tumor-free at 330 days. IRX4204-treated tumors showed an increased infiltration of CD8-positive T-cells over vehicle-treated tumors ($p < 0.05$). Treatment of Brca1-deficient cell lines with IRX4204 in vitro resulted in a significant increase in lipid accumulation accompanied by a 2-fold increase of Srebf1 expression (a key transcription factor that regulates lipid homeostasis) within 24 hours of treatment ($p < 0.05$).

Conclusion:

These data demonstrate a novel use of the RXR agonist, IRX4204, to delay the formation of Brca1-deficient mammary tumors. We have found that IRX4204 treatment modulates the tumor immune response through increased infiltration of cytotoxic CD8-positive T-cells in Brca1-deficient mammary tumors in vivo. We have also determined that IRX4204 modulates lipid metabolism in breast cancer cell lines in vitro. It is known that lipid-derived antigens can stimulate T-cell activity. Our findings suggest that RXR agonists may alter lipid antigen production to activate an anti-tumor response. Additional immune and lipidomic studies are ongoing. This work was supported by NCI-PREVENT grant (to PB and AM HHSN26100008) and CFP Foundation (Odyssey Fellowship to CM).

Disclosure(s):

Cassandra Moyer, PhD: No financial relationships to disclose

PS07-08

Bazedoxifene plus conjugated estrogen reduces mammary proliferation markers and improves adipocyte size, gut microbiome, and metabolic health: Findings from a preclinical model of obesity and breast cancer risk.

Presenting Author(s) and Co-Author(s):

K. Cook. Wake Forest University School of Medicine, United States

R. Jenschke. Texas A&M University, United States

K. Corleto. Texas A&M University, United States

C. Fabian. University of Kansas Cancer Center, Kansas City, Kansas, United States

S. Hursting. University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

B. Kimler. University of Kansas Medical Center, Kansas City, Kansas, United States

D. Landrock. Texas A&M University, United States

E. Giles. University of Michigan, Ann Arbor, Michigan, United States

Background:

Many women at high risk for breast cancer will not take tamoxifen or aromatase inhibitors for cancer prevention due to concern of side effects including hot flashes. Further, tamoxifen has detrimental metabolic effects in some overweight/obese women. Duavee®, a tissue-selective complex of bazedoxifene + conjugated estrogen, is FDA-approved for relief of hot-flashes and prevention of osteoporosis. Preclinical studies suggest favorable metabolic effects and potential for breast cancer risk reduction. In a single arm clinical trial, BZA+CE reduced Ki-67 and mammographic density (PMID: 31420361), and this combination is currently being assessed further in a Phase IIB trial of postmenopausal high risk women with vasomotor symptoms. Here, we examined the modifying effects of obesity on response to BZA+CE in a rodent model of obesity and breast cancer risk.

Methods:

Rats received carcinogen at 7-weeks of age to induce mammary tumors and were fed a high-fat diet (46% kcal fat) to promote obesity. Lean and obese rat were selected based on adiposity at 16 weeks. Separate cohorts of lean and obese ovary-intact or ovariectomized (OVX) rats were randomized to a daily dose of BZA+CE or placebo control for 8 weeks. We assessed tumor development throughout the study and end of study RNA from mammary glands was analysed by gene expression microarray (Affymetrix). We also analyzed body weight/composition, markers of metabolic health (circulating glucose, insulin, adiponectin), as well as changes in the gut microbiome (metagenomic sequencing on DNA isolated from baseline and end-of-study fecal samples) in response to BZA+CE.

Results:

BZA+CE improved metabolic health in both ovary intact and OVX rats, including reduced body weight and % body fat, particularly in the visceral regions. These effects were greater in obese rats compared to lean. BZA+CE reduced the number of large adipocytes and increased small (insulin sensitive) adipocytes in the mammary adipose, indicating beneficial changes in local tumor microenvironment. We found no evidence that Duavee® promoted tumor development or growth in ovary-intact or OVX'd rats. Gene set enrichment analysis (GSEA) of microarray data showed enrichment of cell proliferation pathways in MG from obese rats and these same pathways were downregulated with BZA+CE, consistent with anti-cancer effects. Analysis of

the microbiome found that BZA+CE increased proportional abundance of *Odoribacter laneus* in the gut, regardless of lean/obese or intact/OVX status. Previous studies have demonstrated that this bacterium improves glucose control and reduces inflammatory cytokines when administered to obese mice, suggesting a possible mechanistic link in this study.

Conclusions:

Unlike traditional SERMs that can have negative metabolic effects, BZA+CE improved whole body and mammary gland metabolic health and reduced expression of cell proliferation pathways, particularly in obese rats. Preliminary data suggest that changes in the gut microbiome could contribute, at least in part, to these effects. Together this supports BZA+CE (Duavee) as an agent with potential beneficial effects on breast cancer risk reduction and improvements in metabolic health in women with obesity. Further analyses will guide assessment of outcomes in an ongoing parallel clinical study in postmenopausal women at high risk for breast cancer.

Disclosure(s):

Carol J. Fabian, MD: No financial relationships to disclose

Stephen D. Hursting, MPH, PhD: No financial relationships to disclose

Erin D. Giles, PhD: No financial relationships to disclose

PS07-09

Prenatal BRCA1 epimutations is a major cause of triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

P. Lonning. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Hordaland, Norway

H. Eikesdal. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Hordaland, Norway

E. Ognedal. haukeland University Hospital, Norway

B. Gilje. Stavanger University Hospital, Norway

S. Lundgren. cancer Clinic, St Olav University Hospital, Trondheim, Norway

E. Blix. Department of Oncology, University Hospital of North Norway, Tromsø, Norway

H. Espelid. Department of Surgery, Haugesund Hospital, Haugesund, Norway

J. Geisler. University of Oslo, Norway, Lorenskog, Norway

S. Geisler. Akershus University Hospital, United States

E. Janssen. Stavanger University Hospital, United States

S. Yndestad. Department of Clinical Science, University of Bergen, Bergen, Hordaland, Norway

L. Minsaas. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Norway

B. Leirvaag. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Norway

R. Lillestøl. University of Bergen, Norway

S. Knappskog. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Norway

O. Nikolaienko. University of Bergen, Norway

Background:

Low level normal cell BRCA1 epimutations have been associated with an increased risk of triple-negative breast cancer (TNBC). However, the fraction of TNBCs that may have BRCA1 epimutations as their underlying cause is unknown. Neither are the time of occurrence and the potential inheritance pattern of BRCA1 epimutations established.

Methods:

To address these questions, we analyzed BRCA1 methylation status in breast cancer tissue and matched white blood cells (WBC) from 411 patients with primary breast cancer, including 66 TNBCs. Samples were analyzed by a highly sensitive next-generation sequencing (NGS) assay on an Illumina MiSeq sequencer, allowing allele-resolved methylation assessment. Further, to assess the time of origin and the characteristics of normal cell BRCA1 methylation, we analyzed umbilical cord samples from 1260 newborn girls and 200 newborn boys. To assess potential Mendelian heritage, we analyzed BRCA1 methylation status in WBCs from 575 mothers and 531 fathers of newborn girls with (n = 102) and without (n = 473) WBC BRCA1 methylation.

Results:

We found concordant tumor and mosaic WBC BRCA1 epimutations in 10 out of 66 patients

with TNBC and in four out of six patients with estrogen receptor (ER)-low expression (< 10%) of tumors (combined 14 out of 72; 19.4%, CI: 11.1-30.5). These exceeded the number of tumors harboring germline (n = 5) or somatic (n = 4) BRCA1 mutations. Notably, BRCA1 methylation and BRCA1 mutations were mutually exclusive. Contrasting the findings in TNBC and ER-low expression tumors, we found WBC and tumor BRCA1 methylation concordance in only three out of 221 patients with ER >10+% tumors and zero out of 116 patients with HER2 positive tumors. Intraindividually, BRCA1 epimutations affected the same allele in normal and tumor cells. Assessing BRCA1 methylation in umbilical cord WBCs from newborn girls, we found mosaic, predominantly monoallelic BRCA1 epimutations, with qualitative features similar to those in adults, in 113/1260 (9.0%) of individuals. We found no correlation between WBC BRCA1 methylation in newborns and methylation status in their mothers, fathers, or any parent. Notably, WBC BRCA1 methylation occurred at a significantly lower frequency in newborn boys (9 / 200; 4.5%) as compared to newborn girls (p = 0.038). Similarly, WBC BRCA1 methylation was found less common among fathers (16 / 531; 3.0%), as compared to mothers (46 / 575; 8.0%; p = 0.0003).

Conclusions:

Our findings suggest prenatal BRCA1 epimutations might be the underlying cause of around 20% of TNBC and low-ER expressing breast cancers. Such constitutional mosaic BRCA1 methylation likely arise through gender-related mechanisms in utero, independent of Mendelian inheritance.

Disclosure(s):

Per Lonning, MD, PhD: Consulting Fees (e.g., advisory boards): Laboratorios Farmaceuticos Rovi (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Dagnes Medicine (Terminated); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Cytavation ASA (Ongoing)

PS08-01

Antibody-Drug Conjugates (ADCs) in Breast Cancer: Real World Analysis of Outcomes

Presenting Author(s) and Co-Author(s):

A. Singareeka Raghavendra. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Z. Wang. University of Texas MD Anderson Cancer Center, United States

R. Bassett. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Methods: We estimated the distribution of progression-free survival (PFS), overall survival (OS), and time to treatment failure (TTF) using the Kaplan-Meier method. Differences in survival curves between groups categorized by initial ADC treatment and subsequent ADC treatments were assessed using the log-rank test. Cox proportional hazards regression models were employed to evaluate the association between each survival outcome and various measures of interest, such as age, gender, race, number of prior lines of treatment, hormone receptor status, and HER2 status. **Results:** The analysis included a total of 469 breast cancer patients, with the distribution of clinical characteristics summarized in Table 1. The median age at the start of ADC treatment was 50 years (range: 20-85). Among the patients, 263 patients (56%) received SC as their initial ADC treatment, while 44% received T-DXd. Additionally, 29 patients received both ADCs during metastatic treatment. The median follow-up time for all patients was 7.9 months (range: 0.1- 39.1). Out of the total patient population, 29% died, while 71% were still alive at the last follow-up. The median OS for all patients was 21.6 months. Median OS of patients receiving SC or T-DXd as their initial ADC treatment, was 14 and 37.1 months, respectively. Patients who received both SC and T-DXd had a median OS of 26.1 months. The median PFS for all patients was 6.0 months. Patients initially treated with SC had a median PFS of 4.7 months, whereas those treated with T-DXd had a median PFS of 9.0 months. In patients who received both, median of PFS was 4.9 months for T-DXd after SC, and 5.0 months for SC after T-DXd. The median TTF for all patients was 6.1 months. Patients initially treated with SC had a median TTF of 4.7 months, while those treated with T-DXd had a median TTF of 9.0 months. In patients who received T-DXd after SC, TTF was 4.9 months and SC after T-DXd was 5.0 months. Clinician-judged responses were seen in 180 (74%) of patients with SC only, 80 (41%) with T-DXd only, 9 (100%) with SC as 2nd ADC and 20 (100%) with T-DXd as 2nd ADC. Furthermore, the analysis explored the association of OS, PFS, and TTF with various measures of interest, including age, gender, race, number of prior lines of treatment, type of treatment, hormone receptor status, HER2 status, Ki67, and best response to ADC. Some notable associations were observed, such as ER-positive status being associated with marginally longer OS compared to ER-negative status (median 24.7 vs. 16.4 months; $p=0.06$), and HER2-positive status being associated with longer PFS compared to HER2-negative status (median 14.2 vs. 5.4 months; $p< 0.001$). However, these associations should be interpreted cautiously as they were obtained from univariate analysis. **Conclusions:** Overall, these results highlight the significant differences in survival outcomes between different ADC treatments in breast cancer patients, likely due to differing patient characteristics.

Distribution of clinical characteristics across ADCs

Variables	Level	T-DXd (N=206)	Sacituzumab (N=263)
No. of prior lines of treatment, n (%)	0	16 (8)	38 (14)
	1	38 (18)	81 (31)
	2	35 (17)	70 (27)
	>= 3	117 (57)	74 (28)
ER status, n (%)	0-9	61 (30)	178 (68)
	10-100	145 (70)	85 (32)
PR status, n (%)	0-9	100 (49)	207 (79)
	10-100	106 (51)	54 (21)
HER2 status, n (%)	0	20 (10)	111 (42)
	Low	26 (13)	50 (19)
	Pos	77 (38)	100 (38)
	HER2 FISH Neg (no IHC)	85 (18)	2 (1)

PS08-02

Efficacy of Sacituzumab-Govitecan (SG) post Trastuzumab-deruxtecan (T-DXd) and vice versa for HER2low advanced or metastatic breast cancer (MBC): a French multicentre retrospective study.

Presenting Author(s) and Co-Author(s):

F. Poumeaud. Department of medical oncology, Oncopole Claudius Régaud IUCT-O, Toulouse, Midi-Pyrenees, France

M. Morisseau. Oncopole Claudius Régaud, Midi-Pyrenees, France

L. Cabel. Institut Curie, France

A. Gonçalves. Institut Paoli-Calmettes, France

C. Rivier. Department of medical oncology, Centre Léon Bérard, Lyon, Rhone-Alpes, France

O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France

E. Volant. Department of medical oncology, Institut de cancérologie de l'Ouest, Nantes, Pays de la Loire, France

J. FRENEL. ICO, United States

S. Ladoire. Centre Georges François Leclerc, France

W. Jacot. Institut du Cancer de Montpellier, Université de Montpellier, INSERM U1194, Paris, Montpellier, Languedoc-Roussillon, France

M. Jamelot. Institut Universitaire de Cancérologie, Sorbonne Université, Département d'oncologie médicale, Site de l'hôpital Tenon, Paris, Ile-de-France, France

H. Fokatichoue. Institut Universitaire de Cancérologie, Sorbonne Université, Département d'oncologie médicale, Site de l'hôpital de la Pitié-Salpêtrière, Paris, Ile-de-France, France

L. Teixeira. APHP Hôpital Saint Louis, France

F. Bidard. Institut Curie, Paris, France

D. Loirat. Institut Curie, Medical Oncology Department and D3i, Paris, France

C. Levy. Centre François Baclesse, Caen, Basse-Normandie, France

B. Cabarrou. 2Biostatistics Unit, Oncopole Claudius Régaud IUCT-O, Toulouse, Midi-Pyrenees, France

A. Deleuze. Department of medical oncology, Centre Eugène Marquis, Rennes, Bretagne, France

e. Deluche. Centre Hospitalier Universitaire de Limoges, Limoges, Limousin, France

T. Grellety. Centre hospitalier de la Côte Basque, Bayonne, France

F. Fiteni. Department of medical oncology, Centre Hospitalier Universitaire de Nîmes, Nîmes, Languedoc-Roussillon, France

H. Bischoff. Department of medical oncology, Institut de Cancérologie de Strasbourg Europe, Strasbourg, Alsace, France

R. Vion. Département d'Oncologie Médicale, Centre Henri Becquerel, Rouen, France

S. Becourt. Centre Oscar Lambret, Lille, Nord-Pas-de-Calais, France

T. Reverdy. Centre Hospitalier Universitaire de Lyon, Lyon, Rhone-Alpes, France

A. de Nonneville. Institut Paoli-Calmettes, Aix Marseille Université, Centre de Recherche en Cancérologie de Marseille (CRCM), Inserm U1068, CNRS U7258, France

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

Background: Based on ASCENT, TROPICS-02 and DESTINY-Breast04 trials, SG and T-DXd recently became approved for HER2low MBC. Since the payloads of both SG and T-DXd belong to the same cytotoxic class (topoisomerase-1 inhibitor), cross-resistance is a potential concern. However, no data is available on the efficacy of one antibody drug conjugate (ADC) after another and the best therapeutic sequence has not been evaluated yet. Methods: We conducted a retrospective study in 19 French comprehensive cancer centres. All patients (pts) with HR+ or HR- and HER2low MBC treated with SG followed, immediately or not, by T-DXd (or vice versa) were included. HR expression was defined on the last available tumor sample. The study primary objective was to report the second ADC (ADC2) progression-free survival (PFS) in the whole population. Secondary objectives included first ADC (ADC1) progression-free interval (PFI) and overall survival (OS) in the whole population and subgroup analyses by HR status. Results: The individual data of 126 eligible women were obtained from 19 participating centres. Median age was 54.5 years (range: 30-80y). N=110 (87.3%) pts had invasive carcinoma of not special type, N=12 (9.5%) invasive lobular carcinoma and 4 (3.2%) other histological subtype. N=87 (69%) and 39 (31%) had HR+/HER2low and HR-/HER2low MBC, respectively. N=16 patients were germline mutation carriers (BRCA1 N=7; BRCA2 N=6; other genes on HBOC panel N=3). ADC1 was given as a median of third (range: 1-10) line of chemotherapy and ADC2 as fifth (range: 2-12) line. A large majority (N=94, 74.6%) of pts received SG as ADC1 (N=82 with HR- and N=12 with HR+ MBC) while N=32 (25.4%) received T-DXd as ADC1 (N=27 with HR+ and n=5 with HR- MBC). 53.2% (N=67) received ADC1 immediately followed by ADC2 while 46.8% (N=59) received ADC2 after 1 (N=40) or 2 (N=12) or ≥ 3 (N=6) other lines of chemotherapy. N=19 (15.07%) and N=26 (20.63%) had a meningeal and/or cerebral metastasis at the time of the initiation of ADC1 and ADC2 respectively. After a median follow-up of 3 months, ADC2 was discontinued in 63 pts of which 51 (82.3%) for progression disease and 4 (6.5%) for toxicity due to T-DXd. Importantly, 50% of pts (N=63) were still under ADC2 at the time of this first analysis. The observed median PFS for ADC2 and median PFI for ADC1 are presented in the Table below:

Population and sequential regimen	Median (mo) PFI ADC1	Median (mo) PFS ADC2
Whole population (N=126)		
SG → T-DXd (N=94)	4.5 (95%CI [3.4-5.1])	2.7 (95%CI [2.1-3.3])
T-DXd→SG (N=32)		
HR-/HER2low (N=82)		
having received SG as ADC1 then T-DXd as ADC2	4.8 (95%CI [3.8-5.1])	3.3 (95%CI [2.5-3.7])
HR+/HER2low (n=27)		
having received T-DXd as ADC1 then SG as ADC2	2.7 (95%CI [2.0-3.2])	2.0 (95%CI [1.6-NR])

Median OS was not reached independently of the sub-populations of pts. Conclusion: To the best of our knowledge, this is the largest cohort evaluating the efficacy of subsequent ADCs administration in HER2low MBC. In these heavily pre-treated pts, subsequent use of ADCs seem to be associated with shortened PFS in both HR+/HR- subgroups, independently of their administration order. Data will be updated and completed for the meeting. Moreover, the number of eligible pts will be increased.

Table 1: median TPP and PFS2 in whole population and HR subgroups

Population and sequential regimen	Median (mo) PFI ADC1	Median (mo) PFS ADC2
<u>Whole population (N=126)</u>		
SG → T-DXd (N=94)	4.5 (95%CI [3.4-5.1])	2.7 (95%CI [2.1-3.3])
T-DXd → SG (N=32)		
<u>HR-/HER2low (N=82)</u>		
having received SG as ADC1 then T-DXd as ADC2	4.8 (95%CI [3.8-5.1])	3.3 (95%CI [2.5-3.7])
<u>HR+/HER2low (n=27)</u>		
having received T-DXd as ADC1 then SG as ADC2	2.7 (95%CI [2.0-3.2])	2.0 (95%CI [1.6-NR])

PS08-03

Sequencing Antibody-Drug Conjugate after Antibody-Drug Conjugate in Metastatic Breast Cancer (A3 study): Multi-Institution Experience and Biomarker Analysis

Presenting Author(s) and Co-Author(s):

R. Abelman. Mass General Cancer Center/Dana-Farber Cancer Institute, Boston, Massachusetts, United States

L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

G. Fell. Dana-Farber Cancer Institute, United States

A. Davis. Washington University in St Louis School of Medicine, United States

W. Hensing. St. Luke's Cancer Institute, United States

P. Ryan. Massachusetts General Hospital, United States

N. Vidula. Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, United States

S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States

A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States

J. Shin. Cancer Center, Massachusetts General hospital, United States

E. Abraham. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

S. Isakoff. Cancer Center, Massachusetts General Hospital, United States

B. Moy. Massachusetts General Hospital, United States

L. Ellisen. Massachusetts General Hospital, Boston, Massachusetts, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background: Antibody-drug conjugates (ADCs) improve survival in patients with metastatic breast cancer (MBC) and offer the potential for targeted delivery of highly potent therapy. Many patients are now candidates for multiple ADCs, but optimal strategies for sequencing are unknown. We previously reported on a single institution experience of patients receiving multiple ADCs for MBC (Abelman, ASCO 2023). Here we report a multi-institution update with biomarker analysis. Methods: We included all patients treated at three academic medical institutions who received multiple ADCs for MBC. Patients were included if they had hormone receptor positive, HER2-negative (HR+/HER2-) breast cancer or triple-negative breast cancer (TNBC); patients with HER2+ metastatic breast cancer were excluded. Clinical information was determined by chart review. The metric of “cross-resistance” to the second ADC was defined as patients with progressive disease on first restaging assessment or progression within 60 days of treatment initiation. Every subsequent ADC beyond the first was compared against the prior ADC for presence of identical “antibody target” and “payload”. Comparisons across ADCs were performed using Fisher’s exact test. Significance was determined to be a type I error less than 0.05. A subset of patients had available whole exome tissue sequencing through commercially available sequencing platforms (BostonGene and Caris) performed around the time of receipt of ADC. All sequencing reports were examined for presence of pathogenic variants, variants of uncertain significance, and currently undefined variants and fusions as defined by each sequencing platform. Results: 68 patients were identified who received two or more ADCs for

metastatic HR+/HER2- breast cancer or TNBC from August 2014-June 2023. 30 patients (44.1%) had HR+/HER2- disease and 38 patients (55.9%) had TNBC; 50 patients (73.5%) had HER2-low disease. Median age at time of second ADC was 59.6 (range 29.9-88.6). Patients had received a median of 4 lines of treatment in the metastatic setting prior to initiation of the second ADC. At time of first restaging, cross-resistance was present in 38/64 evaluable cases (59.4%). When the antibody target of the latter ADC was the same as the prior, cross-resistance was present in 11/14 cases (78.5%) compared to 26/49 cases (53.1%) when the later ADC targeted a different tumor-associated antigen. Relatively similar patterns of cross-resistance were observed regardless of whether the later ADC contained an identical payload to prior (6/10 cases, 60%) versus a different payload (22/42, 52.4%). Sequencing information was available for 20 patients who received multiple ADCs with 15 unique reports performed at the time of resistance to ADC1, prior to initiation of ADC2, or after ADC2 if presence of cross-resistance. Variants in topoisomerase-I associated genes (TOP1, TOP2A, TOP3A, TOP3B) were identified in a subset of patients mediating cross-resistance to the second ADC with a topoisomerase-I inhibitor payload. Conclusions: In this multi-institution study, cross-resistance to the second ADC appears to be driven by the antibody target in some patients versus the payload in others, highlighting the heterogeneity of mechanisms related to ADC resistance. Tumor sequencing revealed candidate resistance mutations that may guide optimal sequencing for patients with MBC.

PS08-04

Multicenter retrospective cohort study of the sequential use of the antibody-drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2-low metastatic breast cancer (MBC)

Presenting Author(s) and Co-Author(s):

L. Huppert. University of California, San Francisco, Oakland, California, United States

R. Mahtani. Miami Cancer Institute, Plantation, Florida, United States

S. Fisch. University of California, San Francisco, United States

N. Dempsey. Miami Cancer Institute, Baptist Health of South Florida, United States

S. Premji. Department of Oncology, Mayo Clinic, Rochester, Minnesota, United States

A. Raimonde-Taylor. Rush, United States

S. Jacob. University of California, San Francisco, California, United States

L. Quintal. University of California, San Francisco, United States

J. Chien. University of California, San Francisco, San Francisco, California, United States

M. Melisko. University of California at San Francisco, San Francisco, California, United States

A. Sandoval-Leon. Miami Cancer Institute, Miami, Florida, United States

L. Carcas. Miami Cancer Institute, United States

M. Ahluwalia. Baptist Health, United States

N. Harpalani. Baptist Health, United States

J. Hoppenworth. Mayo Clinic, United States

D. Idossa. University of Minnesota, United States

R. Rao. Rush, United States

K. Giridhar. Mayo Clinic, Rochester, Minnesota, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

Introduction. T-DXd is FDA-approved for patients (pts) with hormone receptor positive (HR+) or HR- HER2-low (IHC 1+ or 2+, ISH-) MBC and SG is FDA-approved for pts with HR+/HER2- and triple negative MBC. However, several outstanding questions impact the use of these drugs in clinic, including: 1) what is the efficacy and safety of these agents in real-world populations with diverse pt characteristics not well represented in the pivotal phase III trials, and 2) what is the impact of sequential treatment with ADCs on the efficacy and safety of these agents. **Methods.** In this multicenter retrospective cohort study, we identified pts with HR+/HER2-low and HR-/HER2-low MBC who had received both T-DXd and SG monotherapy (in either order, with or without intervening therapies) treated at 5 academic centers between 2020-2023. Pts received treatment per standard of care or on a clinical trial with ADC monotherapy. We describe pt demographic and clinical characteristics, treatment history, key safety parameters, and response and survival data by HR+ status and ADC sequence order. **Results.** Sixty pts with MBC treated sequentially with T-DXd and SG were included in this analysis, including 45 pts with HR+/HER2-low MBC (75.0%) and 15 pts with HR-/HER2-low MBC (25.0%). Most pts were female (n=59; 98.3%), non-Hispanic (n=49, 81.7%), and white (n=43, 71.7%). Median age at start of ADC #1 was 56.6 years (range 23-82). Prior to treatment with ADC #1, most pts had visceral disease (n=45, 75.0%) and 16 (26.7%) had central nervous

system metastases. Among pts with HR+/HER2-low MBC, median time from MBC diagnosis to treatment with ADC #1 was 49.0 months, with 4 median lines of prior therapy in the metastatic setting (2 endocrine, 2 chemo). Approximately half of the HR+ pts received T-DXd prior to SG (n=22, 48.9%; median 3.0 prior lines of therapy for MBC, range 1-9) while the other half received SG prior to T-DXd (n=23, 51.1%; median 4.5 prior lines of therapy for MBC, range 1-10). 44% (n=20) received an intervening therapy between ADCs. For HR+ pts who received T-DXd prior to SG, response and survival data is as follows for T-DXd and SG respectively: Overall response rate (ORR) [54.5% and 21.1%], time to next treatment (TTNT) [4.3 mo and 1.6 mo], and real-world overall survival (rwOS) [19.8 mo and 4.9 mo]. For HR+ pts who received SG prior to T-DXd, response and survival data is as follows for SG and T-DXd respectively: ORR [78.3% and 42.9%], TTNT [8.6 mo and 2.8 mo], and rwOS [22.3 mo and 7.3 mo]. Among pts with HR-/HER2-low MBC, median time from MBC diagnosis to treatment with ADC #1 was 8.2 months with 2 median lines of prior therapy in the metastatic setting (2 chemotherapy); 66.7% (n=10) received prior immunotherapy. Most HR- pts received SG prior to T-DXd (n=14, 93.3%) and 40.0% (n=6) received an intervening therapy between ADCs. For HR- pts who received SG prior to T-DXd, response and survival data is as follows for SG and T-DXd respectively: ORR [64.3% and 38.5%], TTNT [6.2 mo and 2.7 mo], and rwOS [15.7 mo and 6.5 mo]. In terms of key safety parameters during treatment with T-DXd, 13.3% of pts (8/60) required a dose reduction. 16.7% (10/60) were diagnosed with interstitial lung disease (ILD)/pneumonitis of any grade including 3 pts with grade 3-4 ILD (5.0%) and 3 pts with grade 5 ILD (5.0%). During treatment with SG, 40.0% of pts (24/60) required a dose reduction. 83.3% (50/60) received growth factor support (24 pts primary prophylaxis; 26 pts secondary prophylaxis); 9 pts (15%) required treatment delay due to neutropenia. Conclusion. This study represents the largest multicenter series to date of pts treated with sequential ADCs for HR+/HER2-low or HR-/HER2-low. ORR was higher and TTNT was longer for ADC #1 than ADC #2 in all subgroups, regardless of HR+ status and ADC sequence order. An additional ~30 pts will be reported at time of final analysis. Future prospective studies are planned to further clarify the efficacy and safety of sequential ADC use and to identify biomarkers of response and resistance.

Key demographic, clinical and treatment characteristics in pts with HR+ and HR- HER2-low MBC treated sequentially with T-DXd and SG (in either order, with or without intervening therapies)

	HR+/HER2-low MBC (n=45)	HR-/HER2-low MBC (n=15)
Demographic data		
Median age at time of ADC #1, yrs (range)	56.4 (23.0-81.7)	56.9 (37.7-70.2)
Sex, n (%)		
Female	44 (97.8%)	15 (100.0%)
Male	1 (2.2%)	0 (0%)
Ethnicity, n (%)		
Non-Hispanic	36 (80.0%)	12 (80.0%)
Hispanic	9 (20.0%)	3 (20.0%)
Race, n (%)		
White	33 (73.3%)	9 (60.0%)
Black	3 (6.7%)	3 (20.0%)
Asian	5 (11.1%)	3 (20.0%)
Other/unknown	4 (8.9%)	0 (0%)
Histology, n (%)		
Ductal	34 (75.6%)	12 (80.0%)
Lobular	4 (8.9%)	1 (6.7%)
Mixed ductal/lobular	3 (6.7%)	1 (6.7%)
Other/unknown	4 (8.9%)	1 (6.7%)
De novo metastatic disease, n (%)	7 (15.6%)	3 (17.6%)
Sites of metastatic disease prior to ADC #1		
Bone	35 (77.8%)	10 (66.7%)
Liver	29 (64.4%)	8 (50.0%)
Lung	14 (31.1%)	9 (60.0%)
CNS	9 (20.0%)	4 (26.7%)
Prior and intervening treatment		
Median time from MBC diagnosis to ADC #1, months (range)	49.0 (1.2-140.6)	8.2 (0.5-56.4)
Median lines of therapy prior to ADC #1 by type of therapy		
Endocrine	2 (0-5)	0 (0)
Chemotherapy	2 (0-6)	2 (0-4)
Median total lines of therapy, number (range)	4 (0-10)	2 (0-5)
Median lines on ET for MBC, months (range)	30.0 (0-111.1)	n/a
Receipt of prior immunotherapy, n (%)	13 (28.9%)	10 (66.7%)
Receipt of intervening therapy between ADCs, n (%)	20 (44.4%)	6 (40.0%)
Median lines intervening therapy, number (range)	0 (0-1)	0 (0-6)
ADC use and efficacy data		
T-DXd → SG, n (%)	22 (48.9%)	1 (6.7%)
Median prior lines of therapy, range	4.5 (1-9)	3.0 (n/a)
ORR by investigator assessment ADC #1 (T-DXd), %	54.5% (12/22)	0% (0/1)
ORR by investigator assessment ADC #2 (SG), %	21.1% (4/19)*	0% (0/1)
TTNT ADC #1 (T-DXd), months (95% CI)	4.3 (2.7-6.3)	2.3 (n/a)
TTNT ADC #2 (SG), months (95% CI)	1.6 (0.9-2.9)	0.3 (n/a)
rwOS ADC #1 (T-DXd), months (95% CI)	19.8 (13.2-25.0)	5.1 (n/a)
rwOS ADC #2 (SG), months (95% CI)	4.9 (2.2-7.1)	0.1 (n/a)
SG → T-DXd, n (%)	23 (51.1%)	14 (93.3%)
Median prior lines of therapy, range	3.0 (1-10)	2.0 (1-5)
ORR by investigator assessment ADC #1 (SG), %	78.3% (18/23)	64.3% (9/14)
ORR by investigator assessment ADC #2 (T-DXd), %	42.9% (8/21)*	38.5% (5/13)*
TTNT ADC #1 (SG), months (95% CI)	8.6 (4.9-11.0)	6.2 (1.9-11.3)
TTNT ADC #2 (T-DXd), months (95% CI)	2.8 (1.5-3.1)	2.7 (1.4-4.8)
rwOS ADC #1 (SG), months (95% CI)	22.3 (18.0-27.1)	15.7 (10.3-21.6)
rwOS ADC #2 (T-DXd), months (95% CI)	7.3 (5.5-9.8)	6.5 (4.2-11.1)

Abbreviations: T-DXd (trastuzumab deruxtecan), SG (sacituzumab govitecan), MBC (metastatic breast cancer), ADC (antibody drug conjugate), HR (hormone receptor), HER2 (human

epidermal growth factor receptor 2), CNS (central nervous system), ET (endocrine therapy),
ORR (overall response rate), TTNT (time to next treatment), rwOS (real world overall survival),
CI (confidence interval) * Several pts on ADC #2 with ongoing treatment and first scan pending,
hence smaller denominator for response assessment

PS08-06

A Phase Ib/II Study to Assess the Safety and Efficacy of PM8002 (Anti-PD-L1 x VEGF-A Bispecific Antibody) in Combination with Nab-Paclitaxel for First Line Treatment of Locally Advanced or Metastatic Triple-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

J. Zhang. Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

Z. Tong. Tianjin Medical University Cancer Institute & Hospital, United States

Q. Zhang. Harbin Medical University Cancer Hospital, United States

Y. Wang. Shandong Cancer Hospital & Institute, Jinan, Shandong, China, Jinan, Shandong, China (People's Republic)

Q. Cheng. Department of Breast Surgery, The First Affiliated Hospital Of Chongqing Medical University, Chongqing, China

X. Chen. Department of Oncology, The Second People's Hospital of Yibin, Sichuan, China

Z. Li. Department of Breast Surgery, Nanchang People's Hospital, Jiangxi, China

Y. Yin. Department of Medical Oncology, Jiangsu Province Hospital, Nanjing, China (People's Republic)

Background: PD-L1 and VEGF play important roles in immune evasion and pro-tumor angiogenesis promoting cancer growth and metastasis. PM8002 is a bispecific antibody targeting PD-L1 and VEGF-A for treating cancer. Here, we present results from a Phase Ib/II study of PM8002 in combination with nab-paclitaxel in patients with locally-advanced or metastatic triple-negative breast cancer (TNBC). Methods: 42 patients with locally-advanced or metastatic TNBC (without prior systemic treatment) were enrolled in this Phase Ib/II study to test the safety and efficacy of PM8002 in combination with nab-paclitaxel. The first 6 patients were enrolled during Phase Ib with safety as the primary endpoint, and the remaining patients were enrolled during Phase II with objective response rate (ORR) as the primary endpoint. Each treatment cycle lasts 28 days. All patients received PM8002 at 20 mg/kg (Q2W) and nab-paclitaxel at 100 mg/m² on the 1st, 8th, and 15th days of each cycle until unacceptable toxicity or disease progression were observed. Tumor responses were evaluated every 8 weeks according to RECIST 1.1. Safety was evaluated according to CTCAE 5.0. Nab-paclitaxel dose was reduced according to toxicity, while PM8002 dose was kept consistent according to body weight. PD-L1 expression in tumors was tested, and subgroup analysis of ORR data stratified by PD-L1 expression was also included. Results: As of June 30, 2023, 42 patients were treated and evaluated at least once for treatment efficacy. The median duration of drug exposure was 4.6 months (min, max: 2.0, 7.6). The best overall ORR was 76.2% (32/42), including 1 complete response (CR) and 31 partial responses (PRs) with 29 objective responses occurring at the patient's first evaluation. The confirmed ORR was 57.2% (24/42) and the overall disease control rate (DCR) was 95.2% (40/42). The median time to response (TTR) was 1.9 months (95% CI: 1.8~2.0) and the median best percentage change from baseline for target lesions was -47.2% (Q1, Q3: -56.9%, -33.5%). Among 13 patients with PD-L1 combined positive scores (CPS) < 1, the best ORR and DCR were 69.2% (9/13) and 100.0% (13/13), respectively. Among 25 patients with PD-L1 CPS ≥ 1, the best ORR and DCR were 80.0% (20/25) and 96.0%

(24/25), respectively. Among 9 patients with PD-L1 CPS \geq 10, the best ORR and DCR were both 100.0% (9/9). At the cut-off date of data analysis, 38 patients were still on treatment with a median progression-free survival (mPFS) of 7.4 months (95% CI: 7.4~NA); 38 patients were censored due to no disease progression or death. The incidence of treatment-related adverse events (TRAEs) was 95.2%, of which 26.2% were Grade 3 or 4; no Grade 5 TRAEs were observed. The incidence of drug-related TRAEs related to PM8002 was 92.9%, of which 23.8% were Grade 3 or 4. The incidence of drug-related TRAEs related to nab-paclitaxel was 95.2%, of which 26.2% were Grade 3 or 4. 1 patient (2.4%) reduced nab-paclitaxel dose due to diarrhea. 1 patient (2.4%) discontinued PM8002 and nab-paclitaxel treatment due to diarrhea. The most common TRAEs related to PM8002 and nab-paclitaxel included neutropenia (69.0%), leukocytopenia (59.5%), anemia (52.4%) and proteinuria (26.2%). The incidence of immune-related adverse events (irAEs) was 11.9%, which included hyperthyroidism, hypothyroidism, and rash. No \geq Grade 3 irAEs were observed. AEs related to targeting VEGF were also analyzed, including hypertension 19.0% (4.8% at Grade 1, 11.9% at Grade 2, and 2.4% at Grade 3) and proteinuria 26.2% (9.5% at Grade 1, and 16.7% at Grade 2). Conclusions: Rapid, deep, and durable tumor responses were observed for the combination of PM8002 and nab-paclitaxel in patients with first line TNBC. PM8002 did not enhance toxicity that is typically observed for nab-paclitaxel. This Phase II study is still ongoing with plans for entering late-stage clinical development for solid tumors.

PS08-07

BL-B01D1, a first-in-class EGFRxHER3 bispecific antibody-drug conjugate, in patients with Locally Advanced or Metastatic Breast Cancer and other Solid Tumor: Results from a phase 1 study.

Presenting Author(s) and Co-Author(s):

J. Zhang. Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Y. Du. Fudan University Shanghai Cancer Center, China (People's Republic)

W. Zou. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., United States

M. Ding. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., China (People's Republic)

H. Yang. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., China (People's Republic)

S. Xiao. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., China (People's Republic)

H. Wang. SystImmune Inc., United States

H. Zhu. SystImmune Inc., United States

M. Olivo. SystImmune Inc, Port Jefferson, New York, United States

Y. Zhu. SystImmune Inc., United States

Background: BL-B01D1 is a first-in-class novel antibody drug conjugate (ADC) consisting of an EGFRxHER3 bispecific antibody bounded to a novel TOP-I inhibitor payload via a cleavable linker. We now present safety/efficacy data from a phase I study of BL-B01D1 in breast cancer. **Methods:** This study included patients (pts) with locally advanced or metastatic breast cancer (BC) and other solid tumors. BL-B01D1 was administered intravenously at doses of 2.5mg/kg Day 1 & Day 8 every 3 weeks (D1D8Q3W) or 5.0mg/kg Day 1 every 3 weeks (D1Q3W) during dose escalation (D-ESC, i3+3) based on the information obtained during the first-in-human study in solid tumors. A subset of pts will be enrolled in the dose-expansion (D-EXP) phase. **Results:** As of June 26, 2023, 42 pts were enrolled and received at least one dose (D-ESC, n=8; D-EXP, n=34) of BL-B01D1. Only one DLT of febrile neutropenia was observed at 5.0mg/kg D1 Q3W, maximum tolerated dose (MTD) has not been reached. D-EXP was conducted at 2.5mg/kg D1D8 Q3W. Forty-one pts with BC and 1 pt with non-small cell lung cancer (NSCLC) were enrolled in this study. The most common TRAEs (>10%, all grade / ≥ G3) were leukopenia (67%/24%), neutropenia (55%/33%), anemia (55%/26%), thrombocytopenia (60%/24%), nausea (38%/0%), vomiting (38%/0%), stomatitis (31%/2%), asthenia (29%/0%), hypokalemia (21%/5%), aspartate aminotransferase increased (19%/0), alanine aminotransferase increased (19%/0%), decreased appetite (19%/0%), hypertriglyceridemia (19%/0%), hyperglycemia (19%/0%), hyperglycemia (17%/0%), weight decreased (14%/0%), diarrhea (12%/0%), epistaxis (12%/0%), hypercholesterolemia (12%/0%). No ILD was observed. Twenty-four pts. were evaluable for efficacy (at least 1 tumor assessment). Updated information will be provided during the meeting. **Conclusions:** BL-B01D1 demonstrated encouraging efficacy in metastatic/locally advanced breast cancer that have failed standard of care, especially in pts with TNBC. The safety profile showed adequate safety and tolerability. Clinical trial information: NCT05470348.
Efficacy in Patients with Breast Cancer

	TNBC (n=11)	HR+ HER2 Low/Zero (n=9)	HER2 positive (n=8)
Median Prior treatment line (range)	2(1-6)	4(3-13)	5(2-6)
Best Response, n ¹			
PR	5	3	2
SD	6	5	5
PD	0	1	1
CRR, % (95% CI)	45.5% (16.8-78.6)	33.3% (7.5-70.1)	25.0% (3.2-65.1)
DCR, % (95% CI)	100%	88.9% (51.8-99.7)	87.5% (47.4-99.7)

1 Including pts whose PRs were not yet confirmed but still under treatment.

PS08-08

Updated efficacy and safety of SKB264 (MK-2870) for previously treated metastatic triple negative breast cancer (mTNBC) in Phase 2 study

Presenting Author(s) and Co-Author(s):

Y. Yin. Department of Medical Oncology, Jiangsu Province Hospital, Nanjing, China (People's Republic)

X. Wu. Hubei Cancer Hospital, China

Q. Ouyang. Department of Medical Oncology, Hunan Cancer Hospital, United States

M. Yan. Henan Cancer Hospital, Henan, China

L. Song. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

Y. Liu. The first Hospital of China Medical University, United States

Z. Tong. Tianjin Medical University Cancer Institute & Hospital, United States

C. Geng. The Fourth Hospital of Hebei Medical University, United States

Y. Wang. Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, United States

G. Yu. Weifang People's Hospital, United States

X. Wang. Xuzhou Central Hospital, United States

Y. Cheng. Jilin Cancer Hospital, 1066 Jinhua Road, China (People's Republic)

W. Zhao. Chinese PLA General Hospital, United States

X. Jin. Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., United States

Y. Diao. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

G. Liu. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

M. Yang. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

Y. Yang. Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., United States

Y. Yang. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

L. Lu. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

J. Ge. Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., United States

J. Li. Shanghai East Hospital, United States

Q. Li. Shanghai East Hospital, United States

Background: Patients (pts) with mTNBC have limited treatment options and poor prognosis. The estimated median overall survival (OS) of pts with mTNBC is 12 to 18 months (mo) after diagnosis. SKB264, an antibody drug conjugate (ADC) composed of an anti-TROP2 antibody coupled to a cytotoxic belotecan-derivative via a novel linker with an average Drug to Antibody Ratio (DAR) of 7.4, has shown promising anti-tumor activity and tolerable safety profile in pts with mTNBC (Yin, Y. et al. SABCS 2022). Here, we report the updated data from a Phase 2 expansion cohort for pts with mTNBC (NCT04152499). Methods: Pts with previously treated mTNBC were enrolled to receive SKB264 at 4 mg/kg Q2W or 5 mg/kg Q2W in a non-randomized manner until disease progression or unacceptable toxicity. Tumor assessment was performed every 8 weeks per RECIST v1.1 assessed by investigator. The primary objective was to assess objective response rate (ORR). Secondary objectives included DoR, PFS, and OS. The TROP2 expression was scored using the semi-quantitative H-score method, and a

preliminary cutoff was set as 200. TROP2 expression and its association with anti-tumor activity were retrospectively analyzed. Results: At data cut-off date (May 05, 2023), 59 pts were enrolled (23 in 4 mg/kg, 36 in 5 mg/kg), and 88% (52 pts) had received ≥ 3 prior lines of therapy for metastatic disease. The median follow-up was 22.8 months (mo; 95% CI, 21.3-25.2). The ORR was 42.4% (25/59, 22 confirmed and 3 unconfirmed) and disease control rate (DCR) was 76.3% (45/59). The median duration of response (DoR) was 11.5 mo (range, 3.7 to 22.1+). Median PFS (mPFS) was 5.7 mo (95% CI: 3.8, 9.1). Median OS (mOS) was 16.8 mo (95% CI: 12.7, NE), while 12-mo and 24-mo OS rates were 65.0% and 39.5%, respectively. In the subset of pts with high TROP2 expression (H-score >200 , N=32), ORR was 53.1% (including 3 complete response), mDoR was 11.1 mo (range, 3.7 to 22.1+), mPFS was 5.8 mo (95% CI: 3.7, 13.3), mOS was not reached (95% CI: 9.7, NE), while 12-mo and 24-mo OS rates were 65.3% and 57.3%, respectively. Treatment-related adverse events (TRAEs) of \geq Grade 3 severity were reported in 57.6% (34/59) of pts. The most common \geq Grade 3 TRAEs ($\geq 10\%$) were neutrophil count decreased (25.4%), white blood cell count decreased (23.7%), anemia (22.0%) and platelet count decreased (16.9%). TRAEs leading to dose reduction and dose delay occurred in 13.6% (8/59) and 47.5% (28/59) of pts, respectively. Three pts discontinued treatment due to TRAEs (platelet count decreased, dry eye, anaphylactic shock). No cases of interstitial lung disease (ILD), neuropathy or grade ≥ 3 diarrhea were observed. Serious TRAEs were reported in 28.8% (17/59) of pts; no deaths associated with TRAEs were observed. Conclusions: The updated data continues to demonstrate that pts with heavily pretreated mTNBC could achieve durable response and a trend of long-term OS benefit from SKB264 treatment, along with a manageable safety profile. Higher response rate was seen in mTNBC pts with high TROP2 expression. A Phase 3 study of SKB264 vs. investigator's choice of chemotherapy in 3L+ mTNBC (NCT05347134) and a Phase 2 study evaluating SKB264 as monotherapy or combination with anti-PD-L1 antibody in first-line setting (NCT05445908) are ongoing in China.

PS08-09

Impact of HER2 expression dynamics on the real-world activity of trastuzumab deruxtecan for metastatic breast cancer (RELIEVE)

Presenting Author(s) and Co-Author(s):

P. Tarantino. Breast Oncology Program, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

M. Hughes. Dana Farber Cancer Institute, United States

R. Kusmick. Dana-Farber Cancer Institute, United States

L. Alder. Duke Cancer Center, United States

A. Pereslete. Herbert Wertheim College of Medicine/Dana-Farber Cancer Institute, Miami, Florida, United States

L. Noteware. Duke Cancer Center, United States

H. Moore. Duke Cancer Institute, Durham, North Carolina, United States

A. Van Swearingen. Duke Cancer Center, United States

T. Li. Dana-Farber Cancer Institute, United States

H. Gupta. Broad Institute of Harvard and MIT, United States

K. Smith. Dana-Farber Cancer Institute, United States

S. Morganti. Dana-Farber Cancer Institute; Harvard Medical School; Broad Institute of MIT and Harvard, United States

J. Files. Dana-Farber Cancer Institute, United States

K. Sendrick. Dana-Farber Cancer Institute, United States

S. Buck. Dana-Farber Cancer Institute, United States

D. Dillon. Brigham and Women's Hospital, Breast Oncology Program, Susan F. Smith Center for Women's Cancers, Dana-Farber Brigham Cancer Center; Harvard Medical School, United States

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Y. Li. Medical Oncology, Dana-Farber Cancer Institute, United States

A. Cherniack. Medical Oncology, Dana-Farber Cancer Institute; Broad Institute, United States

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

N. Chan. Yale School of Medicine, New Haven, Connecticut, United States

D. Rimm. Yale University, New Haven, Connecticut, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

C. Anders. Duke Cancer Institute, Durham, North Carolina, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: trastuzumab deruxtecan (T-DXd) is a standard treatment for patients (pts) with HER2-positive (HER2+) and HER2-low metastatic breast cancer (MBC). HER2-low expression has been shown to be a highly unstable biomarker, and no data exists on the activity of T-DXd

among pts with changes in HER2 status over time. Furthermore, limited data exists on the performance of regimens administered after progression on T-DXd. Methods: We analyzed data for pts with MBC receiving T-DXd at Dana-Farber Cancer Institute between 7/2017 - 2/2023 and at Duke Cancer Center between 3/2020 - 4/2022. The disease was categorized HER2+ if IHC 3+ or ISH-amplified at any time point; HER2-negative cases were categorized as HER2-low (IHC 2+/ISH- or IHC 1+) or HER2-0 (IHC 0) based on the last biopsy before T-DXd; the HER2 status for the primary tumor and at first metastatic diagnosis were also collected. We determined time to next treatment (TTNT), overall survival (OS), toxicities with T-DXd, TTNT based on dynamic HER2 status and TTNT with post-T-DXd regimens. Genomic data was available for 58 pts using an in-house NGS assay on archival tumor samples. Results: A total of 191 pts were included in the analysis (126 HER2+, 44 HER2-low, 21 HER2-0). Median age at metastatic diagnosis was 50.9 (range 21 - 78), 26% had de-novo MBC and 38% had history of brain metastases before T-DXd. The proportion of hormone receptor (HR)-positive tumors based on the last biopsy prior to T-DXd was 53% in HER2+, 68% in HER2-low and 57% in HER2-0; pts within each cohort had received a median of 2 prior lines of chemotherapy before T-DXd (range 0 - 9). With a median follow-up of 10.4 months, median TTNT was 10.4 months for HER2+, 7.6 months for HER2-low and 3.7 months for HER2-0 MBC ($p < 0.001$). Switch in HER2 status between primary tumor and pre-T-DXd biopsy significantly impacted outcomes, with the shortest TTNT observed in pts switching from HER2-low to HER2-0 (TTNT 3.0 months) compared with 5.6 months if switching from HER2-0 to HER2-low, and 9.4 months if having stable HER2-low status ($p = 0.006$). Conversely, HER2 status switch within the metastatic setting did not impact outcomes (Table 1). No difference in TTNT was seen regardless of HR status (negative vs positive, 7.4 vs 10.2 months, $p = 0.25$) or number of prior chemotherapies (≤ 2 vs > 2 , 10.1 vs 8.8 months, $p = 0.50$). Median OS is shown in Table 1. At last follow-up, 55 pts remain on T-DXd (28.8%), 108 progressed (56.5%), 28 stopped due to toxicity (14.7%). A total of 22 pts (11.5%) developed interstitial lung disease (ILD, 6.2% grade [G]1, 3.1% G2, 1.6% G3, 0.5% G4, no G5). ILD occurred after a median of 8 months from T-DXd initiation and resolved in 63.6% of the cases, with a median time to resolution of 4 months (2 months for grade 1 events). 5 pts (2.6%) developed cardiotoxicity. T-DXd was dose reduced in 61 pts (31.9%), most often for fatigue (14.7%), nausea/vomiting (9.9%) or hematological toxicity (6.3%). Among 105 pts receiving post-T-DXd treatments, TTNT was 4 months for HER2+, 3.1 months for HER2-low and 4.3 months for HER2-0 MBC ($p = 0.62$). Pts with HER2-negative tumors and ERBB2 hemizygous deletions (6/58, 10.3 %) had a TTNT with T-DXd of 4.1 months, vs 7.6 months without ERBB2 deletions ($p = 0.41$). Additional biomarker data will be presented at the meeting. Conclusions: T-DXd showed promising real-world activity in pretreated pts with MBC, with the longest TTNT observed among pts with HER2+ disease or with stable HER2-low disease over time. Real world TTNT is relatively short post-T-DXd and further studies evaluating resistance mechanisms and optimal treatments in this setting are needed.

Table 1 – TTNT and OS among patients with metastatic breast cancer receiving T-DXd and post-T-DXd regimens according to HER2 status

Outcomes according to HER2 status assessed before T-DXd initiation				
	HER2-positive (n=126)	HER2-low (n=44)	HER2-0 (n=21)	p-value
TTNT (months)	10.4 (8.9 – 13.2)	7.6 (5.3 – 10.2)	3.7 (2.5 – 5.8)	p<0.001
OS (months)	23.1 (18.6 – 27.2)	14.2 (9.4 – 25.5)	9.5 (3.7 – 28.2)	p=0.003
TTNT of post-T-DXd treatment (months)	4.0 (2.7 – 4.6)	3.1 (1.7 – 5.6)	4.3 (2.6 – 5.6)	p=0.62
TTNT according to HER2 switch between primary tumor and pre-T-DXd biopsy				
	Switch from HER2-low to HER2-0 (n=10)	Switch from HER2-0 to HER2-low (n=21)	Stable HER2-low (n=21)	
TTNT (months)	3.0 (1.7 – 5.6)	5.6 (4.4 – 15.8)	9.4 (4.4 – 13.5)	p=0.006
TTNT according to HER2 switch between first metastatic diagnosis and pre-T-DXd biopsy				
	Switch from HER2-low to HER2-0 (n=5)	Switch from HER2-0 to HER2-low (n=19)	Stable HER2-low (n=25)	
TTNT (months)	8.5 (1.8 – 10.1)	5.4 (3.8 – 19.6)	8.6 (5.6 – 13.5)	p=0.4119

The activity of T-DXd significantly differed according to the HER2 status of the disease, with the longest TTNT observed among patients with HER2+ disease (at any timepoint in time) and among patients with stable HER2-low disease over time. Regimens administered immediately after T-DXd achieved a similar performance irrespective of the HER2 status of the disease, with a TTNT ranging between 3.1 and 4.3 months.

PS08-01

Antibody-Drug Conjugates (ADCs) in Breast Cancer: Real World Analysis of Outcomes

Presenting Author(s) and Co-Author(s):

A. Singareeka Raghavendra. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Z. Wang. University of Texas MD Anderson Cancer Center, United States

R. Bassett. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Methods:

We estimated the distribution of progression-free survival (PFS), overall survival (OS), and time to treatment failure (TTF) using the Kaplan-Meier method. Differences in survival curves between groups categorized by initial ADC treatment and subsequent ADC treatments were assessed using the log-rank test. Cox proportional hazards regression models were employed to evaluate the association between each survival outcome and various measures of interest, such as age, gender, race, number of prior lines of treatment, hormone receptor status, and HER2 status.

Results:

The analysis included a total of 469 breast cancer patients, with the distribution of clinical characteristics summarized in Table 1. The median age at the start of ADC treatment was 50 years (range: 20-85). Among the patients, 263 patients (56%) received SC as their initial ADC treatment, while 44% received T-DXd. Additionally, 29 patients received both ADCs during metastatic treatment. The median follow-up time for all patients was 7.9 months (range: 0.1-39.1). Out of the total patient population, 29% died, while 71% were still alive at the last follow-up. The median OS for all patients was 21.6 months. Median OS of patients receiving SC or T-DXd as their initial ADC treatment, was 14 and 37.1 months, respectively. Patients who received both SC and T-DXd had a median OS of 26.1 months.

The median PFS for all patients was 6.0 months. Patients initially treated with SC had a median PFS of 4.7 months, whereas those treated with T-DXd had a median PFS of 9.0 months. In patients who received both, median of PFS was 4.9 months for T-DXd after SC, and 5.0 months for SC after T-DXd.

The median TTF for all patients was 6.1 months. Patients initially treated with SC had a median TTF of 4.7 months, while those treated with T-DXd had a median TTF of 9.0 months. In patients who received T-DXd after SC, TTF was 4.9 months and SC after T-DXd was 5.0 months. Clinician-judged responses were seen in 180 (74%) of patients with SC only, 80 (41%) with T-DXd only, 9 (100%) with SC as 2nd ADC and 20 (100%) with T-DXd as 2nd ADC. Furthermore, the analysis explored the association of OS, PFS, and TTF with various measures of interest, including age, gender, race, number of prior lines of treatment, type of treatment, hormone receptor status, HER2 status, Ki67, and best response to ADC. Some notable associations were observed, such as ER-positive status being associated with marginally longer OS compared to ER-negative status (median 24.7 vs. 16.4 months; $p=0.06$), and HER2-positive status being associated with longer PFS compared to HER2-negative status (median 14.2 vs. 5.4 months; $p < 0.001$). However, these associations should be interpreted cautiously as they

were obtained from univariate analysis.

Conclusions:

Overall, these results highlight the significant differences in survival outcomes between different ADC treatments in breast cancer patients, likely due to differing patient characteristics.

Distribution of clinical characteristics across ADCs

Variables	Level	T-DXd (N=206)	Sacituzumab (N=263)
No. of prior lines of treatment, n (%)	0	16 (8)	38 (14)
	1	38 (18)	81 (31)
	2	35 (17)	70 (27)
	>= 3	117 (57)	74 (28)
ER status, n (%)	0-9	61 (30)	178 (68)
	10-100	145 (70)	85 (32)
PR status, n (%)	0-9	100 (49)	207 (79)
	10-100	106 (51)	54 (21)
HER2 status, n (%)	0	20 (10)	111 (42)
	Low	26 (13)	50 (19)
	Pos	77 (38)	100 (38)
	HER2 FISH Neg (no IHC)	85 (18)	2 (1)

Disclosure(s):

Akshara Singareeka Raghavendra, MD, MS: No financial relationships to disclose

Poster Spotlight Session 8: Antibody Drug Conjugates: Where are We Headed?

Presenting Author(s) and Co-Author(s):

S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

Disclosure(s):

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

PS08-02

Efficacy of Sacituzumab-Govitecan (SG) post Trastuzumab-deruxtecan (T-DXd) and vice versa for HER2low advanced or metastatic breast cancer (MBC): a French multicentre retrospective study.

Presenting Author(s) and Co-Author(s):

F. Poumeaud. Department of medical oncology, Oncopole Claudius Régaud IUCT-O, Toulouse, Midi-Pyrenees, France

M. Morisseau. Oncopole Claudius Régaud, Midi-Pyrenees, France

L. Cabel. Institut Curie, France

A. Gonçalves. Institut Paoli-Calmettes, France

C. Rivier. Department of medical oncology, Centre Léon Bérard, Lyon, Rhone-Alpes, France

O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France

E. Volant. Department of medical oncology, Institut de cancérologie de l'Ouest, Nantes, Pays de la Loire, France

J. FRENEL. ICO, United States

S. Ladoire. Centre Georges François Leclerc, France

W. Jacot. Institut du Cancer de Montpellier, Université de Montpellier, INSERM U1194, Paris, Montpellier, Languedoc-Roussillon, France

M. Jamelot. Institut Universitaire de Cancérologie, Sorbonne Université, Département d'oncologie médicale, Site de l'hôpital Tenon, Paris, Ile-de-France, France

H. Fokatichoue. Institut Universitaire de Cancérologie, Sorbonne Université, Département d'oncologie médicale, Site de l'hôpital de la Pitié-Salpêtrière, Paris, Ile-de-France, France

L. Teixeira. APHP Hôpital Saint Louis, France

F. Bidard. Institut Curie, Paris, France

D. Loirat. Institut Curie, Medical Oncology Department and D3i, Paris, France

C. Levy. Centre François Baclesse, Caen, Basse-Normandie, France

B. Cabarrou. 2Biostatistics Unit, Oncopole Claudius Régaud IUCT-O, Toulouse, Midi-Pyrenees, France

A. Deleuze. Department of medical oncology, Centre Eugène Marquis, Rennes, Bretagne, France

e. Deluche. Centre Hospitalier Universitaire de Limoges, Limoges, Limousin, France

T. Grellety. Centre hospitalier de la Côte Basque, Bayonne, France

F. Fiteni. Department of medical oncology, Centre Hospitalier Universitaire de Nîmes, Nîmes, Languedoc-Roussillon, France

H. Bischoff. Department of medical oncology, Institut de Cancérologie de Strasbourg Europe, Strasbourg, Alsace, France

R. Vion. Département d'Oncologie Médicale, Centre Henri Becquerel, Rouen, France

S. Becourt. Centre Oscar Lambret, Lille, Nord-Pas-de-Calais, France

T. Reverdy. Centre Hospitalier Universitaire de Lyon, Lyon, Rhone-Alpes, France

A. de Nonneville. Institut Paoli-Calmettes, Aix Marseille Université, Centre de Recherche en Cancérologie de Marseille (CRCM), Inserm U1068, CNRS U7258, France

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

Background:

Based on ASCENT, TROPICS-02 and DESTINY-Breast04 trials, SG and T-DXd recently became approved for HER2low MBC. Since the payloads of both SG and T-DXd belong to the same cytotoxic class (topoisomerase-1 inhibitor), cross-resistance is a potential concern. However, no data is available on the efficacy of one antibody drug conjugate (ADC) after another and the best therapeutic sequence has not been evaluated yet.

Methods:

We conducted a retrospective study in 19 French comprehensive cancer centres. All patients (pts) with HR+ or HR- and HER2low MBC treated with SG followed, immediately or not, by T-DXd (or vice versa) were included. HR expression was defined on the last available tumor sample. The study primary objective was to report the second ADC (ADC2) progression-free survival (PFS) in the whole population. Secondary objectives included first ADC (ADC1) progression-free interval (PFI) and overall survival (OS) in the whole population and subgroup analyses by HR status.

Results:

The individual data of 126 eligible women were obtained from 19 participating centres. Median age was 54.5 years (range: 30-80y). N=110 (87.3%) pts had invasive carcinoma of not special type, N=12 (9.5%) invasive lobular carcinoma and 4 (3.2%) other histological subtype. N=87 (69%) and 39 (31%) had HR+/HER2low and HR-/HER2low MBC, respectively. N=16 patients were germline mutation carriers (BRCA1 N=7; BRCA2 N=6; other genes on HBOC panel N=3). ADC1 was given as a median of third (range: 1-10) line of chemotherapy and ADC2 as fifth (range: 2-12) line. A large majority (N=94, 74.6%) of pts received SG as ADC1 (N=82 with HR- and N=12 with HR+ MBC) while N=32 (25.4%) received T-DXd as ADC1 (N=27 with HR+ and n=5 with HR- MBC). 53.2% (N=67) received ADC1 immediately followed by ADC2 while 46.8% (N=59) received ADC2 after 1 (N=40) or 2 (N=12) or ≥ 3 (N=6) other lines of chemotherapy. N=19 (15.07%) and N=26 (20.63%) had a meningeal and/or cerebral metastasis at the time of the initiation of ADC1 and ADC2 respectively. After a median follow-up of 3 months, ADC2 was discontinued in 63 pts of which 51 (82.3%) for progression disease and 4 (6.5%) for toxicity due to T-DXd. Importantly, 50% of pts (N=63) were still under ADC2 at the time of this first analysis. The observed median PFS for ADC2 and median PFI for ADC1 are presented in the Table below:

Population and sequential regimen	Median (mo) PFI ADC1	Median (mo) PFS ADC2
Whole population (N=126)		
SG → T-DXd (N=94)	4.5 (95%CI [3.4-5.1])	2.7 (95%CI [2.1-3.3])
T-DXd→SG (N=32)		
HR-/HER2low (N=82)		
having received SG as ADC1 then T-DXd as ADC2	4.8 (95%CI [3.8-5.1])	3.3 (95%CI [2.5-3.7])
HR+/HER2low (n=27)	2.7 (95%CI [2.0-3.2])	2.0 (95%CI [1.6-NR])

having received T-DXd as ADC1 then SG as ADC2		
--	--	--

Median OS was not reached independently of the sub-populations of pts.

Conclusion:

To the best of our knowledge, this is the largest cohort evaluating the efficacy of subsequent ADCs administration in HER2low MBC. In these heavily pre-treated pts, subsequent use of ADCs seem to be associated with shortened PFS in both HR+/HR- subgroups, independently of their administration order. Data will be updated and completed for the meeting. Moreover, the number of eligible pts will be increased.

Table 1: median TPP and PFS2 in whole population and HR subgroups

Population and sequential regimen	Median (mo) PFI ADC1	Median (mo) PFS ADC2
<u>Whole population (N=126)</u>		
SG → T-DXd (N=94)	4.5 (95%CI [3.4-5.1])	2.7 (95%CI [2.1-3.3])
T-DXd → SG (N=32)		
<u>HR-/HER2low (N=82)</u>		
having received SG as ADC1 then T-DXd as ADC2	4.8 (95%CI [3.8-5.1])	3.3 (95%CI [2.5-3.7])
<u>HR+/HER2low (n=27)</u>		
having received T-DXd as ADC1 then SG as ADC2	2.7 (95%CI [2.0-3.2])	2.0 (95%CI [1.6-NR])

Disclosure(s):

François Poumeaud, MD: No financial relationships to disclose

PS08-03

Sequencing Antibody-Drug Conjugate after Antibody-Drug Conjugate in Metastatic Breast Cancer (A3 study): Multi-Institution Experience and Biomarker Analysis

Presenting Author(s) and Co-Author(s):

R. Abelman. Mass General Cancer Center/Dana-Farber Cancer Institute, Boston, Massachusetts, United States

L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

G. Fell. Dana-Farber Cancer Institute, United States

A. Davis. Washington University in St Louis School of Medicine, United States

W. Hensing. St. Luke's Cancer Institute, United States

P. Ryan. Massachusetts General Hospital, United States

N. Vidula. Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, United States

S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States

A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States

J. Shin. Cancer Center, Massachusetts General hospital, United States

E. Abraham. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

S. Isakoff. Cancer Center, Massachusetts General Hospital, United States

B. Moy. Massachusetts General Hospital, United States

L. Ellisen. Massachusetts General Hospital, Boston, Massachusetts, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background:

Antibody-drug conjugates (ADCs) improve survival in patients with metastatic breast cancer (MBC) and offer the potential for targeted delivery of highly potent therapy. Many patients are now candidates for multiple ADCs, but optimal strategies for sequencing are unknown. We previously reported on a single institution experience of patients receiving multiple ADCs for MBC (Abelman, ASCO 2023). Here we report a multi-institution update with biomarker analysis.

Methods:

We included all patients treated at three academic medical institutions who received multiple ADCs for MBC. Patients were included if they had hormone receptor positive, HER2-negative (HR+/HER2-) breast cancer or triple-negative breast cancer (TNBC); patients with HER2+ metastatic breast cancer were excluded. Clinical information was determined by chart review. The metric of "cross-resistance" to the second ADC was defined as patients with progressive disease on first restaging assessment or progression within 60 days of treatment initiation. Every subsequent ADC beyond the first was compared against the prior ADC for presence of identical "antibody target" and "payload". Comparisons across ADCs were performed using Fisher's exact test. Significance was determined to be a type I error less than 0.05. A subset of patients had available whole exome tissue sequencing through commercially available

sequencing platforms (BostonGene and Caris) performed around the time of receipt of ADC. All sequencing reports were examined for presence of pathogenic variants, variants of uncertain significance, and currently undefined variants and fusions as defined by each sequencing platform.

Results:

68 patients were identified who received two or more ADCs for metastatic HR+/HER2- breast cancer or TNBC from August 2014-June 2023. 30 patients (44.1%) had HR+/HER2- disease and 38 patients (55.9%) had TNBC; 50 patients (73.5%) had HER2-low disease. Median age at time of second ADC was 59.6 (range 29.9-88.6). Patients had received a median of 4 lines of treatment in the metastatic setting prior to initiation of the second ADC. At time of first restaging, cross-resistance was present in 38/64 evaluable cases (59.4%). When the antibody target of the latter ADC was the same as the prior, cross-resistance was present in 11/14 cases (78.5%) compared to 26/49 cases (53.1%) when the later ADC targeted a different tumor-associated antigen. Relatively similar patterns of cross-resistance were observed regardless of whether the later ADC contained an identical payload to prior (6/10 cases, 60%) versus a different payload (22/42, 52.4%). Sequencing information was available for 20 patients who received multiple ADCs with 15 unique reports performed at the time of resistance to ADC1, prior to initiation of ADC2, or after ADC2 if presence of cross-resistance. Variants in topoisomerase-I associated genes (TOP1, TOP2A, TOP3A, TOP3B) were identified in a subset of patients mediating cross-resistance to the second ADC with a topoisomerase-I inhibitor payload.

Conclusions:

In this multi-institution study, cross-resistance to the second ADC appears to be driven by the antibody target in some patients versus the payload in others, highlighting the heterogeneity of mechanisms related to ADC resistance. Tumor sequencing revealed candidate resistance mutations that may guide optimal sequencing for patients with MBC.

Disclosure(s):

Rachel Occhiogrosso Abelman, MD: No financial relationships to disclose

Neelima Vidula, MD: Advisory Committee/Board Member: Aadi Biopharma (Terminated, December 5, 2023), Gilead (Terminated, December 5, 2023), Stemline Therapeutics (Terminated, December 5, 2023), TerSera (Terminated, December 5, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Daehwa (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer, Inc. (Ongoing)

Aditya Bardia, MD, MPH: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Menarini/Stemline (Ongoing)

PS08-04

Multicenter retrospective cohort study of the sequential use of the antibody-drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2-low metastatic breast cancer (MBC)

Presenting Author(s) and Co-Author(s):

L. Huppert. University of California, San Francisco, Oakland, California, United States
R. Mahtani. Miami Cancer Institute, Plantation, Florida, United States
S. Fisch. University of California, San Francisco, United States
N. Dempsey. Miami Cancer Institute, Baptist Health of South Florida, United States
S. Premji. Department of Oncology, Mayo Clinic, Rochester, Minnesota, United States
A. Raimonde-Taylor. Rush, United States
S. Jacob. University of California, San Francisco, California, United States
L. Quintal. University of California, San Francisco, United States
J. Chien. University of California, San Francisco, San Francisco, California, United States
M. Melisko. University of California at San Francisco, San Francisco, California, United States
A. Sandoval-Leon. Miami Cancer Institute, Miami, Florida, United States
L. Carcas. Miami Cancer Institute, United States
M. Ahluwalia. Baptist Health, United States
N. Harpalani. Baptist Health, United States
J. Hoppenworth. Mayo Clinic, United States
D. Idossa. University of Minnesota, United States
R. Rao. Rush, United States
K. Giridhar. Mayo Clinic, Rochester, Minnesota, United States
H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

Introduction.

T-DXd is FDA-approved for patients (pts) with hormone receptor positive (HR+) or HR- HER2-low (IHC 1+ or 2+, ISH-) MBC and SG is FDA-approved for pts with HR+/HER2- and triple negative MBC. However, several outstanding questions impact the use of these drugs in clinic, including: 1) what is the efficacy and safety of these agents in real-world populations with diverse pt characteristics not well represented in the pivotal phase III trials, and 2) what is the impact of sequential treatment with ADCs on the efficacy and safety of these agents.

Methods.

In this multicenter retrospective cohort study, we identified pts with HR+/HER2-low and HR-/HER2-low MBC who had received both T-DXd and SG monotherapy (in either order, with or without intervening therapies) treated at 5 academic centers between 2020-2023. Pts received treatment per standard of care or on a clinical trial with ADC monotherapy. We describe pt demographic and clinical characteristics, treatment history, key safety parameters, and response and survival data by HR+ status and ADC sequence order.

Results.

Sixty pts with MBC treated sequentially with T-DXd and SG were included in this analysis, including 45 pts with HR+/HER2-low MBC (75.0%) and 15 pts with HR-/HER2-low MBC (25.0%). Most pts were female (n=59; 98.3%), non-Hispanic (n=49, 81.7%), and white (n=43, 71.7%). Median age at start of ADC #1 was 56.6 years (range 23-82). Prior to treatment with ADC #1, most pts had visceral disease (n=45, 75.0%) and 16 (26.7%) had central nervous system metastases.

Among pts with HR+/HER2-low MBC, median time from MBC diagnosis to treatment with ADC #1 was 49.0 months, with 4 median lines of prior therapy in the metastatic setting (2 endocrine, 2 chemo). Approximately half of the HR+ pts received T-DXd prior to SG (n=22, 48.9%; median 3.0 prior lines of therapy for MBC, range 1-9) while the other half received SG prior to T-DXd (n=23, 51.1%; median 4.5 prior lines of therapy for MBC, range 1-10). 44% (n=20) received an intervening therapy between ADCs. For HR+ pts who received T-DXd prior to SG, response and survival data is as follows for T-DXd and SG respectively: Overall response rate (ORR) [54.5% and 21.1%], time to next treatment (TTNT) [4.3 mo and 1.6 mo], and real-world overall survival (rwOS) [19.8 mo and 4.9 mo]. For HR+ pts who received SG prior to T-DXd, response and survival data is as follows for SG and T-DXd respectively: ORR [78.3% and 42.9%], TTNT [8.6 mo and 2.8 mo], and rwOS [22.3 mo and 7.3 mo].

Among pts with HR-/HER2-low MBC, median time from MBC diagnosis to treatment with ADC #1 was 8.2 months with 2 median lines of prior therapy in the metastatic setting (2 chemotherapy); 66.7% (n=10) received prior immunotherapy. Most HR- pts received SG prior to T-DXd (n=14, 93.3%) and 40.0% (n=6) received an intervening therapy between ADCs. For HR- pts who received SG prior to T-DXd, response and survival data is as follows for SG and T-DXd respectively: ORR [64.3% and 38.5%], TTNT [6.2 mo and 2.7 mo], and rwOS [15.7 mo and 6.5 mo].

In terms of key safety parameters during treatment with T-DXd, 13.3% of pts (8/60) required a dose reduction. 16.7% (10/60) were diagnosed with interstitial lung disease (ILD)/pneumonitis of any grade including 3 pts with grade 3-4 ILD (5.0%) and 3 pts with grade 5 ILD (5.0%). During treatment with SG, 40.0% of pts (24/60) required a dose reduction. 83.3% (50/60) received growth factor support (24 pts primary prophylaxis; 26 pts secondary prophylaxis); 9 pts (15%) required treatment delay due to neutropenia.

Conclusion.

This study represents the largest multicenter series to date of pts treated with sequential ADCs for HR+/HER2-low or HR-/HER2-low. ORR was higher and TTNT was longer for ADC #1 than ADC #2 in all subgroups, regardless of HR+ status and ADC sequence order. An additional ~30 pts will be reported at time of final analysis. Future prospective studies are planned to further clarify the efficacy and safety of sequential ADC use and to identify biomarkers of response and resistance.

Key demographic, clinical and treatment characteristics in pts with HR+ and HR- HER2-low MBC treated sequentially with T-DXd and SG (in either order, with or without intervening therapies)

	HR+HER2-low MBC (n=48)	HR-HER2-low MBC (n=19)
Demographic data		
Median age at time of ADC #1, yrs (range)	56.4 (23.0-81.7)	56.9 (37.7-70.2)
Sex, n (%)		
Female	44 (97.8%)	15 (100.0%)
Male	1 (2.2%)	0 (0%)
Ethnicity, n (%)		
Non-Hispanic	36 (80.0%)	12 (80.0%)
Hispanic	9 (20.0%)	3 (20.0%)
Race, n (%)		
White	33 (73.3%)	9 (60.0%)
Black	3 (6.7%)	3 (20.0%)
Asian	5 (11.1%)	3 (20.0%)
Other/unknown	4 (8.9%)	0 (0%)
Histology, n (%)		
Ductal	34 (75.6%)	12 (80.0%)
Lobular	4 (8.9%)	1 (6.7%)
Mixed ductal/lobular	3 (6.7%)	1 (6.7%)
Other/unknown	4 (8.9%)	1 (6.7%)
De novo metastatic disease, n (%)	7 (15.6%)	3 (17.6%)
Sites of metastatic disease prior to ADC #1		
Bone	35 (77.8%)	10 (66.7%)
Liver	29 (64.4%)	6 (40.0%)
Lung	14 (31.1%)	9 (60.0%)
CNS	0 (20.0%)	4 (26.7%)
Prior and intervening treatment		
Median time from MBC diagnosis to ADC #1, months (range)	49.0 (1.2-140.6)	8.2 (0.5-56.4)
Median lines of therapy prior to ADC #1 by type of therapy		
Median lines ET, number (range)	2 (0-5)	0 (0)
Median lines chemotherapy, number (range)	2 (0-6)	2 (0-4)
Median total lines of therapy, number (range)	4 (0-10)	2 (0-5)
Median time on ET for MBC, months (range)	30.0 (0-111.1)	n/a
Receipt of prior immunotherapy, n (%)	13 (28.9%)	10 (66.7%)
Receipt of intervening therapy between ADCs, n (%)	20 (44.4%)	6 (40.0%)
Median lines intervening therapy, number (range)	0 (0-1)	0 (0-6)
ADC use and efficacy data		
T-DXd → SG, n (%)	22 (48.9%)	1 (6.7%)
Median prior lines of therapy, range	4.5 (1-9)	3.0 (n/a)
ORR by investigator assessment ADC #1 (T-DXd), %	54.5% (12/22)	0% (0/1)
ORR by investigator assessment ADC #2 (SG), %	21.1% (4/19)*	0% (0/1)
TTNT ADC #1 (T-DXd), months (95% CI)	4.3 (2.7-6.3)	2.3 (n/a)
TTNT ADC #2 (SG), months (95% CI)	1.6 (0.9-2.9)	0.3 (n/a)
rwOS ADC #1 (T-DXd), months (95% CI)	19.8 (13.2-26.0)	5.1 (n/a)
rwOS ADC #2 (SG), months (95% CI)	4.9 (2.2-7.1)	0.1 (n/a)
SG → T-DXd, n (%)	23 (91.1%)	14 (93.3%)
Median prior lines of therapy, range	3.0 (1-10)	2.0 (1-5)
ORR by investigator assessment ADC #1 (SG), %	78.3% (18/23)	64.3% (9/14)
ORR by investigator assessment ADC #2 (T-DXd), %	42.9% (9/21)*	38.5% (5/13)*
TTNT ADC #1 (SG), months (95% CI)	8.6 (4.9-11.0)	6.2 (1.9-11.3)
TTNT ADC #2 (T-DXd), months (95% CI)	2.8 (1.5-3.1)	2.7 (1.4-6.8)
rwOS ADC #1 (SG), months (95% CI)	22.3 (18.9-27.1)	16.7 (10.3-21.6)
rwOS ADC #2 (T-DXd), months (95% CI)	7.3 (5.5-9.8)	6.5 (4.2-11.1)

Abbreviations: T-DXd (trastuzumab deruxtecan), SG (sacituzumab govitecan), MBC (metastatic breast cancer), ADC (antibody drug conjugate), HR (hormone receptor), HER2 (human epidermal growth factor receptor 2), CNS (central nervous system), ET (endocrine therapy), ORR (overall response rate), TTNT (time to next treatment), rwOS (real world overall survival), CI (confidence interval)

* Several pts on ADC #2 with ongoing treatment and first scan pending, hence smaller denominator for response assessment

Disclosure(s):

Laura Huppert, MD: Consulting Fees (e.g., advisory boards): AstraZenica (Ongoing)
Reshma L. Mahtani, DO: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing)
Saya Jacob, MD: No financial relationships to disclose
Jo Chien, MD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Amgen Inc. (Ongoing), Merck & Co., Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), SeaGen (Ongoing)
Ana Sandoval-Leon, MD: Advisory Committee/Board Member: Merck & Co., Inc. (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated), Gilead (Terminated), Guardant Health Inc. (Terminated), Menarini/Stemline (Terminated), Oncocyte, Inc (Terminated), Sanofi Aventis (Terminated), Sermonix Pharmaceuticals Inc. (Terminated)
Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

PS08-06

A Phase Ib/II Study to Assess the Safety and Efficacy of PM8002 (Anti-PD-L1 x VEGF-A Bispecific Antibody) in Combination with Nab-Paclitaxel for First Line Treatment of Locally Advanced or Metastatic Triple-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Zhang. Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Z. Tong. Tianjin Medical University Cancer Institute & Hospital, United States

Q. Zhang. Harbin Medical University Cancer Hospital, United States

Y. Wang. Shandong Cancer Hospital & Institute, Jinan, Shandong, China, Jinan, Shandong, China (People's Republic)

Q. Cheng. Department of Breast Surgery, The First Affiliated Hospital Of Chongqing Medical University, Chongqing, China

X. Chen. Department of Oncology, The Second People's Hospital of Yibin, Sichuan, China

Z. Li. Department of Breast Surgery, Nanchang People's Hospital, Jiangxi, China

Y. Yin. Department of Medical Oncology, Jiangsu Province Hospital, Nanjing, China (People's Republic)

Background:

PD-L1 and VEGF play important roles in immune evasion and pro-tumor angiogenesis promoting cancer growth and metastasis. PM8002 is a bispecific antibody targeting PD-L1 and VEGF-A for treating cancer. Here, we present results from a Phase Ib/II study of PM8002 in combination with nab-paclitaxel in patients with locally-advanced or metastatic triple-negative breast cancer (TNBC).

Methods:

42 patients with locally-advanced or metastatic TNBC (without prior systemic treatment) were enrolled in this Phase Ib/II study to test the safety and efficacy of PM8002 in combination with nab-paclitaxel. The first 6 patients were enrolled during Phase Ib with safety as the primary endpoint, and the remaining patients were enrolled during Phase II with objective response rate (ORR) as the primary endpoint. Each treatment cycle lasts 28 days. All patients received PM8002 at 20 mg/kg (Q2W) and nab-paclitaxel at 100 mg/m² on the 1st, 8th, and 15th days of each cycle until unacceptable toxicity or disease progression were observed. Tumor responses were evaluated every 8 weeks according to RECIST 1.1. Safety was evaluated according to CTCAE 5.0. Nab-paclitaxel dose was reduced according to toxicity, while PM8002 dose was kept consistent according to body weight. PD-L1 expression in tumors was tested, and subgroup analysis of ORR data stratified by PD-L1 expression was also included.

Results:

As of June 30, 2023, 42 patients were treated and evaluated at least once for treatment efficacy. The median duration of drug exposure was 4.6 months (min, max: 2.0, 7.6). The best overall ORR was 76.2% (32/42), including 1 complete response (CR) and 31 partial responses

(PRs) with 29 objective responses occurring at the patient's first evaluation. The confirmed ORR was 57.2% (24/42) and the overall disease control rate (DCR) was 95.2% (40/42). The median time to response (TTR) was 1.9 months (95% CI:1.8~2.0) and the median best percentage change from baseline for target lesions was -47.2% (Q1, Q3: -56.9%, -33.5%). Among 13 patients with PD-L1 combined positive scores (CPS) < 1, the best ORR and DCR were 69.2% (9/13) and 100.0% (13/13), respectively. Among 25 patients with PD-L1 CPS ≥1, the best ORR and DCR were 80.0% (20/25) and 96.0% (24/25), respectively. Among 9 patients with PD-L1 CPS ≥10, the best ORR and DCR were both 100.0% (9/9). At the cut-off date of data analysis, 38 patients were still on treatment with a median progression-free survival (mPFS) of 7.4 months (95% CI: 7.4~NA); 38 patients were censored due to no disease progression or death. The incidence of treatment-related adverse events (TRAEs) was 95.2%, of which 26.2% were Grade 3 or 4; no Grade 5 TRAEs were observed. The incidence of drug-related TRAEs related to PM8002 was 92.9%, of which 23.8% were Grade 3 or 4. The incidence of drug-related TRAEs related to nab-paclitaxel was 95.2%, of which 26.2% were Grade 3 or 4. 1 patient (2.4%) reduced nab-paclitaxel dose due to diarrhea. 1 patient (2.4%) discontinued PM8002 and nab-paclitaxel treatment due to diarrhea. The most common TRAEs related to PM8002 and nab-paclitaxel included neutropenia (69.0%), leukocytopenia (59.5%), anemia (52.4%) and proteinuria (26.2%). The incidence of immune-related adverse events (irAEs) was 11.9%, which included hyperthyroidism, hypothyroidism, and rash. No ≥ Grade 3 irAEs were observed. AEs related to targeting VEGF were also analyzed, including hypertension 19.0% (4.8% at Grade 1, 11.9% at Grade 2, and 2.4% at Grade 3) and proteinuria 26.2% (9.5% at Grade 1, and 16.7% at Grade 2).

Conclusions:

Rapid, deep, and durable tumor responses were observed for the combination of PM8002 and nab-paclitaxel in patients with first line TNBC. PM8002 did not enhance toxicity that is typically observed for nab-paclitaxel. This Phase II study is still ongoing with plans for entering late-stage clinical development for solid tumors.

Disclosure(s):

Jian Zhang, MD: No financial relationships to disclose

Jiong Wu: Consulting Fees (e.g., advisory boards): AtraZeneca (Terminated, October 10, 2022), Novartis (Terminated, October 10, 2022); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): F. Hoffman La Roche Ltd (Terminated, February 5, 2023)

PS08-07

BL-B01D1, a first-in-class EGFRxHER3 bispecific antibody-drug conjugate, in patients with Locally Advanced or Metastatic Breast Cancer and other Solid Tumor: Results from a phase 1 study.

Presenting Author(s) and Co-Author(s):

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

J. Zhang. Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

Y. Du. Fudan University Shanghai Cancer Center, China (People's Republic)

W. Zou. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., United States

M. Ding. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., China (People's Republic)

H. Yang. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., China (People's Republic)

S. Xiao. Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., China (People's Republic)

H. Wang. SystImmune Inc., United States

H. Zhu. SystImmune Inc., United States

M. Olivo. SystImmune Inc, Port Jefferson, New York, United States

Y. Zhu. SystImmune Inc., United States

Background:

BL-B01D1 is a first-in-class novel antibody drug conjugate (ADC) consisting of an EGFRxHER3 bispecific antibody bounded to a novel TOP-I inhibitor payload via a cleavable linker. We now present safety/efficacy data from a phase I study of BL-B01D1 in breast cancer.

Methods:

This study included patients (pts) with locally advanced or metastatic breast cancer (BC) and other solid tumors. BL-B01D1 was administered intravenously at doses of 2.5mg/kg Day 1 & Day 8 every 3 weeks (D1D8Q3W) or 5.0mg/kg Day 1 every 3 weeks (D1Q3W) during dose escalation (D-ESC, i3+3) based on the information obtained during the first-in-human study in solid tumors. A subset of pts will be enrolled in the dose-expansion (D-EXP) phase.

Results:

As of June 26, 2023, 42 pts were enrolled and received at least one dose (D-ESC, n=8; D-EXP, n=34) of BL-B01D1. Only one DLT of febrile neutropenia was observed at 5.0mg/kg D1 Q3W, maximum tolerated dose (MTD) has not been reached. D-EXP was conducted at 2.5mg/kg D1D8 Q3W. Forty-one pts with BC and 1 pt with non-small cell lung cancer (NSCLC) were enrolled in this study. The most common TRAEs (>10%, all grade / ≥ G3) were leukopenia (67%/24%), neutropenia (55%/33%), anemia (55%/26%), thrombocytopenia (60%/24%), nausea (38%/0%), vomiting (38%/0%), stomatitis (31%/2%), asthenia (29%/0%), hypokalemia (21%/5%), aspartate aminotransferase increased (19%/0), alanine aminotransferase increased (19%/0%), decreased appetite (19%/0%), hypertriglyceridemia (19%/0%), hyperglycemia (19%/0%), hyperglycemia (17%/0%), weight decreased (14%/0%), diarrhea (12%/0%), epistaxis (12%/0%), hypercholesterolemia (12%/0%). No ILD was observed. Twenty-four pts. were evaluable for efficacy (at least 1 tumor assessment). Updated information will be provided during the meeting.

Conclusions:

BL-B01D1 demonstrated encouraging efficacy in metastatic/locally advanced breast cancer that have failed standard of care, especially in pts with TNBC. The safety profile showed adequate safety and tolerability.

Clinical trial information: NCT05470348.

Efficacy in Patients with Breast Cancer

	TNBC (n=11)	HR+ HER2 Low/Zero (n=9)	HER2 positive (n=8)
Median Prior treatment line (range)	2(1-6)	4(2-13)	5(2-6)
Best Response, n ¹			
PR	5	3	2
SD	6	5	5
PD	0	1	1
ORR, % (95% CI)	45.5% (16.8-79.6)	33.3% (7.5-70.1)	25.0% (3.2-65.1)
DCR, % (95% CI)	100%	66.7% (31.8-99.7)	62.5% (47.4-99.7)

1 Including pts whose PRs were not yet confirmed but still under treatment.

Disclosure(s):

Jiong Wu: Consulting Fees (e.g., advisory boards): AstraZeneca (Terminated, October 10, 2022), Novartis (Terminated, October 10, 2022); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): F. Hoffman La Roche Ltd (Terminated, February 5, 2023)

Jian Zhang, MD: No financial relationships to disclose

PS08-08

Updated efficacy and safety of SKB264 (MK-2870) for previously treated metastatic triple negative breast cancer (mTNBC) in Phase 2 study

Presenting Author(s) and Co-Author(s):

Y. Yin. Department of Medical Oncology, Jiangsu Province Hospital, Nanjing, China (People's Republic)

X. Wu. Hubei Cancer Hospital, China

Q. Ouyang. Department of Medical Oncology, Hunan Cancer Hospital, United States

M. Yan. Henan Cancer Hospital, Henan, China

L. Song. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

Y. Liu. The first Hospital of China Medical University, United States

Z. Tong. Tianjin Medical University Cancer Institute & Hospital, United States

C. Geng. The Fourth Hospital of Hebei Medical University, United States

Y. Wang. Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, United States

G. Yu. Weifang People's Hospital, United States

X. Wang. Xuzhou Central Hospital, United States

Y. Cheng. Jilin Cancer Hospital, 1066 Jinhua Road, China (People's Republic)

W. Zhao. Chinese PLA General Hospital, United States

X. Jin. Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., United States

Y. Diao. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

G. Liu. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

M. Yang. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

Y. Yang. Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., United States

Y. Yang. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

L. Lu. Sichuan Kelun-Biotech Biopharmaceutical Co., United States

J. Ge. Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., United States

J. Li. Shanghai East Hospital, United States

Q. Li. Shanghai East Hospital, United States

Background:

Patients (pts) with mTNBC have limited treatment options and poor prognosis. The estimated median overall survival (OS) of pts with mTNBC is 12 to 18 months (mo) after diagnosis. SKB264, an antibody drug conjugate (ADC) composed of an anti-TROP2 antibody coupled to a cytotoxic belotecan-derivative via a novel linker with an average Drug to Antibody Ratio (DAR) of 7.4, has shown promising anti-tumor activity and tolerable safety profile in pts with mTNBC (Yin, Y. et al. SABCs 2022). Here, we report the updated data from a Phase 2 expansion cohort for pts with mTNBC (NCT04152499).

Methods:

Pts with previously treated mTNBC were enrolled to receive SKB264 at 4 mg/kg Q2W or 5 mg/kg Q2W in a non-randomized manner until disease progression or unacceptable toxicity.

Tumor assessment was performed every 8 weeks per RECIST v1.1 assessed by investigator. The primary objective was to assess objective response rate (ORR). Secondary objectives included DoR, PFS, and OS. The TROP2 expression was scored using the semi-quantitative H-score method, and a preliminary cutoff was set as 200. TROP2 expression and its association with anti-tumor activity were retrospectively analyzed.

Results:

At data cut-off date (May 05, 2023), 59 pts were enrolled (23 in 4 mg/kg, 36 in 5 mg/kg), and 88% (52 pts) had received ≥ 3 prior lines of therapy for metastatic disease. The median follow-up was 22.8 months (mo; 95% CI, 21.3-25.2). The ORR was 42.4% (25/59, 22 confirmed and 3 unconfirmed) and disease control rate (DCR) was 76.3% (45/59). The median duration of response (DoR) was 11.5 mo (range, 3.7 to 22.1+). Median PFS (mPFS) was 5.7 mo (95% CI: 3.8, 9.1). Median OS (mOS) was 16.8 mo (95% CI: 12.7, NE), while 12-mo and 24-mo OS rates were 65.0% and 39.5%, respectively. In the subset of pts with high TROP2 expression (H-score >200 , N=32), ORR was 53.1% (including 3 complete response), mDoR was 11.1 mo (range, 3.7 to 22.1+), mPFS was 5.8 mo (95% CI: 3.7, 13.3), mOS was not reached (95% CI: 9.7, NE), while 12-mo and 24-mo OS rates were 65.3% and 57.3%, respectively. Treatment-related adverse events (TRAEs) of \geq Grade 3 severity were reported in 57.6% (34/59) of pts. The most common \geq Grade 3 TRAEs ($\geq 10\%$) were neutrophil count decreased (25.4%), white blood cell count decreased (23.7%), anemia (22.0%) and platelet count decreased (16.9%). TRAEs leading to dose reduction and dose delay occurred in 13.6% (8/59) and 47.5% (28/59) of pts, respectively. Three pts discontinued treatment due to TRAEs (platelet count decreased, dry eye, anaphylactic shock). No cases of interstitial lung disease (ILD), neuropathy or grade ≥ 3 diarrhea were observed. Serious TRAEs were reported in 28.8% (17/59) of pts; no deaths associated with TRAEs were observed.

Conclusions:

The updated data continues to demonstrate that pts with heavily pretreated mTNBC could achieve durable response and a trend of long-term OS benefit from SKB264 treatment, along with a manageable safety profile. Higher response rate was seen in mTNBC pts with high TROP2 expression. A Phase 3 study of SKB264 vs. investigator's choice of chemotherapy in 3L+ mTNBC (NCT05347134) and a Phase 2 study evaluating SKB264 as monotherapy or combination with anti-PD-L1 antibody in first-line setting (NCT05445908) are ongoing in China.

PS08-09

Impact of HER2 expression dynamics on the real-world activity of trastuzumab deruxtecan for metastatic breast cancer (RELIEVE)

Presenting Author(s) and Co-Author(s):

P. Tarantino. Breast Oncology Program, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

M. Hughes. Dana Farber Cancer Institute, United States

R. Kusmick. Dana-Farber Cancer Institute, United States

L. Alder. Duke Cancer Center, United States

A. Pereslete. Herbert Wertheim College of Medicine/Dana-Farber Cancer Institute, Miami, Florida, United States

L. Noteware. Duke Cancer Center, United States

H. Moore. Duke Cancer Institute, Durham, North Carolina, United States

A. Van Swearingen. Duke Cancer Center, United States

T. Li. Dana-Farber Cancer Institute, United States

H. Gupta. Broad Institute of Harvard and MIT, United States

K. Smith. Dana-Farber Cancer Institute, United States

S. Morganti. Dana-Farber Cancer Institute; Harvard Medical School; Broad Institute of MIT and Harvard, United States

J. Files. Dana-Farber Cancer Institute, United States

K. Sendrick. Dana-Farber Cancer Institute, United States

S. Buck. Dana-Farber Cancer Institute, United States

D. Dillon. Brigham and Women's Hospital, Breast Oncology Program, Susan F. Smith Center for Women's Cancers, Dana-Farber Brigham Cancer Center; Harvard Medical School, United States

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Y. Li. Medical Oncology, Dana-Farber Cancer Institute, United States

A. Cherniack. Medical Oncology, Dana-Farber Cancer Institute; Broad Institute, United States

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

N. Chan. Yale School of Medicine, New Haven, Connecticut, United States

D. Rimm. Yale University, New Haven, Connecticut, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

C. Anders. Duke Cancer Institute, Durham, North Carolina, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

Background:

trastuzumab deruxtecan (T-DXd) is a standard treatment for patients (pts) with HER2-positive (HER2+) and HER2-low metastatic breast cancer (MBC). HER2-low expression has

been shown to be a highly unstable biomarker, and no data exists on the activity of T-DXd among pts with changes in HER2 status over time. Furthermore, limited data exists on the performance of regimens administered after progression on T-DXd.

Methods:

We analyzed data for pts with MBC receiving T-DXd at Dana-Farber Cancer Institute between 7/2017 - 2/2023 and at Duke Cancer Center between 3/2020 - 4/2022. The disease was categorized HER2+ if IHC 3+ or ISH-amplified at any time point; HER2-negative cases were categorized as HER2-low (IHC 2+/ISH- or IHC 1+) or HER2-0 (IHC 0) based on the last biopsy before T-DXd; the HER2 status for the primary tumor and at first metastatic diagnosis were also collected. We determined time to next treatment (TTNT), overall survival (OS), toxicities with T-DXd, TTNT based on dynamic HER2 status and TTNT with post-T-DXd regimens. Genomic data was available for 58 pts using an in-house NGS assay on archival tumor samples.

Results:

A total of 191 pts were included in the analysis (126 HER2+, 44 HER2-low, 21 HER2-0). Median age at metastatic diagnosis was 50.9 (range 21 - 78), 26% had de-novo MBC and 38% had history of brain metastases before T-DXd. The proportion of hormone receptor (HR)-positive tumors based on the last biopsy prior to T-DXd was 53% in HER2+, 68% in HER2-low and 57% in HER2-0; pts within each cohort had received a median of 2 prior lines of chemotherapy before T-DXd (range 0 - 9). With a median follow-up of 10.4 months, median TTNT was 10.4 months for HER2+, 7.6 months for HER2-low and 3.7 months for HER2-0 MBC ($p < 0.001$). Switch in HER2 status between primary tumor and pre-T-DXd biopsy significantly impacted outcomes, with the shortest TTNT observed in pts switching from HER2-low to HER2-0 (TTNT 3.0 months) compared with 5.6 months if switching from HER2-0 to HER2-low, and 9.4 months if having stable HER2-low status ($p=0.006$). Conversely, HER2 status switch within the metastatic setting did not impact outcomes (Table 1). No difference in TTNT was seen regardless of HR status (negative vs positive, 7.4 vs 10.2 months, $p=0.25$) or number of prior chemotherapies (≤ 2 vs >2 , 10.1 vs 8.8 months, $p=0.50$). Median OS is shown in Table 1. At last follow-up, 55 pts remain on T-DXd (28.8%), 108 progressed (56.5%), 28 stopped due to toxicity (14.7%). A total of 22 pts (11.5%) developed interstitial lung disease (ILD, 6.2% grade [G]1, 3.1% G2, 1.6% G3, 0.5% G4, no G5). ILD occurred after a median of 8 months from T-DXd initiation and resolved in 63.6% of the cases, with a median time to resolution of 4 months (2 months for grade 1 events). 5 pts (2.6%) developed cardiotoxicity. T-DXd was dose reduced in 61 pts (31.9%), most often for fatigue (14.7%), nausea/vomiting (9.9%) or hematological toxicity (6.3%). Among 105 pts receiving post-T-DXd treatments, TTNT was 4 months for HER2+, 3.1 months for HER2-low and 4.3 months for HER2-0 MBC ($p=0.62$). Pts with HER2-negative tumors and ERBB2 hemizygous deletions (6/58, 10.3 %) had a TTNT with T-DXd of 4.1 months, vs 7.6 months without ERBB2 deletions ($p=0.41$). Additional biomarker data will be presented at the meeting.

Conclusions:

T-DXd showed promising real-world activity in pretreated pts with MBC, with the longest TTNT observed among pts with HER2+ disease or with stable HER2-low disease over time. Real world TTNT is relatively short post-T-DXd and further studies evaluating resistance mechanisms and optimal treatments in this setting are needed.

Table 1 – TTNT and OS among patients with metastatic breast cancer receiving T-DXd and post-T-DXd regimens according to HER2 status

Outcomes according to HER2 status assessed before T-DXd initiation				
	HER2-positive (n=126)	HER2-low (n=44)	HER2-0 (n=21)	p-value
TTNT (months)	10.4 (8.9–13.2)	7.6 (5.3–10.2)	3.7 (2.5–5.8)	p<0.001
OS (months)	23.1 (18.6–27.2)	14.2 (9.4–25.5)	9.5 (3.7–28.2)	p=0.003
TTNT of post-T-DXd treatment (months)	4.0 (2.7–4.6)	3.1 (1.7–5.6)	4.3 (2.6–5.6)	p=0.62
TTNT according to HER2 switch between primary tumor and pre-T-DXd biopsy				
	Switch from HER2-low to HER2-0 (n=10)	Switch from HER2-0 to HER2-low (n=21)	Stable HER2-low (n=21)	
TTNT (months)	3.0 (1.7–5.6)	5.6 (4.4–15.8)	9.4 (4.4–13.5)	p=0.006
TTNT according to HER2 switch between first metastatic diagnosis and pre-T-DXd biopsy				
	Switch from HER2-low to HER2-0 (n=5)	Switch from HER2-0 to HER2-low (n=19)	Stable HER2-low (n=25)	
TTNT (months)	8.5 (1.8–10.1)	5.4 (3.8–19.6)	8.6 (5.6–13.5)	p=0.4119

The activity of T-DXd significantly differed according to the HER2 status of the disease, with the longest TTNT observed among patients with HER2+ disease (at any timepoint in time) and among patients with stable HER2-low disease over time. Regimens administered immediately after T-DXd achieved a similar performance irrespective of the HER2 status of the disease, with a TTNT ranging between 3.1 and 4.3 months.

Disclosure(s):

Paolo Tarantino, MD: Advisory Committee/Board Member: AstraZeneca PLC (Terminated, October 24, 2023), Daiichi-Sankyo (Terminated, October 24, 2023), Loxo@Lilly | Eli Lilly and Company (Terminated, October 24, 2023); Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Terminated, October 24, 2023), Daiichi-Sankyo (Terminated, October 24, 2023), F. Hoffman La Roche Ltd (Terminated, October 24, 2023), Genentech (Terminated, October 24, 2023), Gilead Science (Terminated, October 24, 2023), Loxo@Lilly | Eli Lilly and Company (Terminated, October 24, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing)

Alyssa M. Pereslete, BA: No financial relationships to disclose

Aleix Prat, MD PhD: Advisory Committee/Board Member: Reveal Genomics, S.L. (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca/MedImmune (Inst) (Ongoing), Daiichi-Sankyo (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Novartis Pharma GmbH (Ongoing), Reveal Genomics, S.L. (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Reveal Genomics, S.L. (Ongoing)

Giuseppe Curigliano, Prof, MD, PhD: Advisory Committee/Board Member: Menarini Silicon Biosystems (Terminated); Consulting Fees (e.g., advisory boards): Astra Zeneca, Roche, Novartis, Biocad, R-Pharm, Eisai, Eli Lilly, Pfizer, MSD, BMS (Terminated), Gilead (Terminated), PFS Genomics/Exact Sciences (Terminated)

Sarah L. Sammons, MD: Advisory Committee/Board Member: : Roche, Astra Zeneca, Pfizer, GSK, Novartis (Ongoing), Loxo@Lilly (Ongoing); Consulting Fees (e.g., advisory boards): : Roche, Astra Zeneca, Pfizer, GSK, Novartis (Ongoing), Loxo@Lilly (Ongoing), Novartis AG (Ongoing); Industry Grant Support (Principal Investigators must provide information on research

funding from ineligible companies, even if received/managed by the institution): Loxo@Lilly (Ongoing), SeaGen (Ongoing)

Carey K. Anders, MD: Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing), Athenex (Ongoing), Elucida Oncology (Ongoing), Genentech-Roche (Ongoing), Immunomedics Inc (Ongoing), IPSEN (Ongoing), Novartis (Ongoing), Seattle Genetics/Seagen (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Caris Life Sciences, Inc. (Ongoing), Elucida Oncology (Ongoing), G1 Therapeutics (Ongoing), Genentech-Roche (Ongoing), GSK/Tesaro (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck Foundation (Ongoing), Nektar (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics/Seagen (Ongoing), Zion Pharmaceuticals (Ongoing); Royalty: Jones and Bartlett (Ongoing), UpToDate (Ongoing)

Nancy U. Lin, MD: Consulting Fees (e.g., advisory boards): Affinia Therapeutics (Ongoing), Aleta Biopharma (Ongoing), AstraZeneca (Ongoing), Blueprint Medicine (Ongoing), Daiichi-Sankyo (Ongoing), Genentech / Roche (Ongoing), Janssen (Ongoing), Menarini/Stemline (Ongoing), Olema Pharmaceuticals (Ongoing), Prelude Therapeutics (Ongoing), Reverie Labs (Ongoing), SeaGen (Ongoing), Voyager Therapeutics (Ongoing); Independent Contractor: Artera (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Genentech / Roche (Ongoing), Menarini/Stemline (Ongoing), Merck (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing), SeaGen (Ongoing), Zion Pharmaceuticals (Ongoing)

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

PS09-01

Individual patient data meta-analysis of clinical and translational biomarkers for prediction of pathological complete response (pCR) after de-escalated therapy in HER2+ breast cancer in four trials of the West German Study Group

Presenting Author(s) and Co-Author(s):

M. Graeser. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; Department of Gynecology, University Medical Center Hamburg, Moenchengladbach, Nordrhein-Westfalen, Germany

O. Gluz. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; University Clinics Cologne, Moenchengladbach, Nordrhein-Westfalen, Germany

C. zu Eulenburg. West German Study Group, Moenchengladbach, Germany; Department of Medical Biometry and Epidemiology, University Medical Center Hamburg, Hamburg, Germany

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

R. von Schumann. Ev. Bethesda Hospital, Breast Center Niederrhein, Moenchengladbach, Germany

M. Christgen. Medizinische Hochschule Hannover, Hannover, Niedersachsen, Germany

R. Wuerstlein. Breast Center, Dept. OB&GYN and CCC Munich, LMU University Hospital, Munich, Germany

E. Pelz. Institute for Pathology, Viersen, Germany

H. Kreipe. Medical School Hannover, Institute of Pathology, Hannover, Germany; Institute of Neuropathology, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

M. Thill. Agaplesion Markus Krankenhaus, 60431 Frankfurt a.M., Hessen, Germany

M. Braun. Rotkreuzklinikum München, Germany

J. Potenberg. Ev. Waldkrankenhaus Berlin, Berlin, Germany

C. Schumacher. St. Elisabeth Hospital, Cologne, Germany

J. Tio. University Hospital Münster, Gynaecology, Münster, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

M. Just. Onkologische Schwerpunktpraxis Bielefeld, Bielefeld, Germany

C. Schem. Mammazentrum am Krankenhaus Jerusalem, Hamburg, Germany

K. Lütke-Heckenkamp. Zentrum für Onkologie und Hämatologie MVZ II, Franziskus-Hospital Harderberg, Georgsmarienhütte, Germany

E. Grischke. Universitäts-Frauenklinik Tübingen, Eberhard Karls University, Tübingen, Germany

F. Hilpert. Breast Center Hamburg at Hospital Jerusalem, Hamburg, Germany

A. Kentsch. Diakovere Henriettenstift, Dept. for Gynecology, Hamburg, Germany

R. Kates. West German Study Group, Moenchengladbach, Germany

U. Nitz. West German Study Group and Breast Center Niederrhein, United States

N. Harbeck. University of Munich, Munich, Bayern, Germany

Background

Introduction of anti-HER2 therapies substantially improved outcomes for HER2-positive early breast cancer (HER2+ eBC). However, a considerable proportion of patients (pts) may still be overtreated with systemic chemotherapy (CTx) combinations. Establishing safe de-escalation strategies to avoid toxicities requires precise patient selection. Therefore, we set out to determine predictors for efficacy and survival in the unique setting of four de-escalation trials investigating short (12-week) neoadjuvant treatments (NAT) in HER2+ eBC. We investigated the prognostic ability of clinical and translational biomarkers for pCR to identify pts with the best prognosis after de-escalated systemic CTx-free NAT.

Methods

756 pts who received de-escalated NAT were analyzed: trastuzumab + pertuzumab (T + P, n=92) and T + P + paclitaxel (pac, n=42) in ADAPT-HR-/HER2+ (NCT01817452); trastuzumab emtansine (T-DM1, n=118), T-DM1 + endocrine therapy (ET, n=125), and T + ET (n=129) in ADAPT-HR+/HER2+ (NCT01779206), T + P + pac (n=107) and T + P + ET (n=100) in TP-II (NCT03272477); and T + P + pembrolizumab (n=43) in Keyriched-1 (NCT03988036) in HER2-enriched (HER2-E) subtype by PAM50. The primary endpoint of each trial was pCR (ypT0/is ypN0). Survival was a secondary endpoint in all trials but Keyriched-1; survival data for TP-II are pending.

Baseline gene expression was analyzed by BC360 assay; intrinsic molecular subtypes were determined using the PAM50 predictor. Stromal tumor infiltrating lymphocytes (sTILs) were evaluated at baseline and at week 3 of NAT. sTILs were categorized using a 30% threshold and the low cellularity category (< 500 invasive tumor cells) at week 3.

Prognostic markers for pCR were identified with univariate and multivariable logistic regression models with backstep algorithm excluding variables with $p \geq 0.1$; considered variables included age, sTILs (baseline, 3-weeks), cT, cN, grade, hormone receptor and HER2 status, intrinsic subtype, and standardized ERBB2 and ESR1 gene expression. These analyses were performed separately for NAT involving systemic CTx (i.e. containing pac, n=149) and systemic CTx-free NAT (n=607).

Results

Overall pCR rate was 39.1% (CTx: 66.4%; CTx-free: 32.5%). Multivariable analysis identified predictors of pCR after CTx-free NAT: low cellularity at week 3 (vs < 30% sTILs: OR 3.21, 95%CI 1.85-5.57), ERBB2 (OR 1.90, 95%CI 1.41-2.55), HER2 3+ (vs 1+/2+ and ISH+: OR 8.01, 95%CI 1.65-38.99), LumA/LumB/Basal subtype (vs HER2-E: OR 0.57, 95%CI 0.34-0.97), cT2 (vs 1: OR 0.54, 95%CI 0.33-0.89), and cN1-3 (vs 0, OR 0.46, 95%CI 0.27-0.78). In CTx-containing NAT, only ERBB2 (OR 2.08, 95%CI 1.28-3.40) and additionally ESR1 (OR 0.38, 95%CI 0.23-0.61) were prognostic for pCR.

Updated analysis including expanded gene expression data from ADAPT-HR+/HER2+ and a prognostic score for pCR after CTx-free NAT developed using machine learning methods will be presented at the meeting.

Conclusions

This pooled analysis demonstrated a 66% pCR rate after a short (12-week) de-escalated NAT in HER2+ eBC. In one-third of patients (with mainly stage I cancer, higher HER2 expression by immunohistochemistry and gene expression analysis, and low cellularity at 3 weeks), pCR can be achieved without systemic CTx. Identified biomarkers could pave the way for developing new patient selection strategies to spare CTx-associated acute and late toxicities in a clinically meaningful number of patients.

PS09-02

Event-free Survival by Residual Cancer Burden (RCB) and Intratumor HER2 Heterogeneity after Neoadjuvant T-DM1 and Pertuzumab for Early-stage HER2-positive Breast Cancer

Presenting Author(s) and Co-Author(s):

O. Metzger. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Kim. Dana Farber Cancer Institute, United States

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy

D. Yardley. Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, United States

A. Prat. Hospital Clinic Barcelona, Spain

V. Abramson. Vanderbilt University Medical Center, United States

L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

A. Waks. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

E. Wrabel. Dana-Farber Institute, United States

M. DeMeo. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

P. Dell'Orto. IEO, United States

L. Russo. Istituto Europeo di Oncologia, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

F. Michor. Department of Data Science, Dana-Farber Cancer Institute; Department of Biomedical Informatics, Harvard Medical School; Center for Cancer Evolution, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

K. Polyak. Dana Farber Cancer Institute, Harvard Medical School, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

I. Krop. Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, United States

Background: Intratumor HER2 heterogeneity (ITH-HER2) predicates resistance to targeted anti-HER2-based therapy, and understanding its impact on response to HER2-directed therapies is particularly important with regimens that rely solely on targeted anti-HER2 therapies without chemotherapy. Methods: To determine the effect of ITH-HER2 on response to therapy, we conducted a single-arm phase II study in which patients (pts) with centrally confirmed HER2+ early-stage breast cancer received six cycles of preoperative T-DM1 plus pertuzumab. Baseline image-guided biopsies allowed central pathology evaluation of ITH HER2, defined as an area with HER2 amplification in >5% but < 50% of tumor cells or a HER2-negative area by FISH. The study met its primary endpoint by demonstrating inferior pathologic complete response (pCR) measured by Residual Cancer Burden (RCB) in the subset of ITH-HER2 pts.

Single-cell ERBB2 FISH analysis identified the fraction of ERBB2 nonamplified cells as a factor associated with therapeutic resistance (Metzger et al. Cancer Discovery 2021). Secondary endpoints included event-free survival (EFS), invasive disease-free survival (iDFS), and breast cancer-specific survival (BCSS) by ITH-HER2 status and RCB scores. Results: 163 pts were enrolled and received treatment in the study from Jan 2015 to Jan 2018. Central pathology evaluation of HER2 heterogeneity was successful in 96% (157/163) of cases, with 16 classified as ITH-HER2. RCB-0 or -I rate in the ITH-HER2 vs. not was (25% v. 67%, OR = 5.6, p = 0.002). Median follow-up, including all treated pts (n =163), was 65.4 months (IQR, 60.3-76.6). The 5yr EFS, iDFS, and BCSS were 91% [86.5% - 95.6%], 89.4% [84.5% - 94.5%], and 96% [92.9% - 99.2%], respectively. ITH-HER2 was associated with numerically inferior outcomes for EFS, iDFS, and BCSS (Table 1). The subset of pts with non-ITH-HER2 at baseline (n= 141) and RCB-0 or -I (n = 95/141, 67%) had a 5-yr iDFS of 94.2% [89.3% - 99.3%]. A sensitivity analysis describing survival outcomes by chemotherapy use in the adjuvant setting will be presented at the meeting, along with translational research results evaluating the association of HER2DX assay with pCR and survival outcomes. Conclusions: The inferior pCR rates among cases classified as ITH-HER2 translated into numerically inferior outcomes for both EFS and iDFS. The number of events is small; therefore, our results are exploratory. Selecting pts whose tumors lack ITH-HER2 can increase the chances of achieving RCB 0/I with neoadjuvant TDM1 + pertuzumab. Neoadjuvant TDM1 + pertuzumab, followed by adjuvant HER2-directed therapy without classic chemotherapy agents, could represent an optimal regimen for non-ITH-HER2 pts experiencing RCB 0/I at the time of surgery and deserves further study.

	EFS	iDFS	BCSS
Overall (n=157)	91.3% [86.9% - 95.9%]	90.5% [85.8% - 95.4%]	96.5% [93.6% - 99.6%]
Total number of events	17	17	5
ITH-HER2	81.3% [64.2% - 100%]	81.3% [64.2% - 100%]	100%
Non-ITH- HER2	92.5% [88.2% - 97.1%]	91.6% [86.9% - 96.5%]	96.2% [92.9% - 99.5%]

Table 1. 5-year survival estimates by ITH-HER2

PS09-03

Neoadjuvant zanidatamab for stage I node negative HER2 positive breast cancer

Presenting Author(s) and Co-Author(s):

V. Valero. Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Bellaire, Texas, United States

J. Mouabbi. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

H. Alonzo. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

P. Pohlmann. MD ANDERSON CANCER CENTER, United States

A. Iheme. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Hassan. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

R. Murthy. MD ANDERSON CANCER CENTER, Houston, Texas, United States

X. Huang. MD ANDERSON CANCER CENTER, United States

W. Qiao. UT MD Anderson Cancer Center, United States

M. Patel. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

G. Rauch. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

C. Checka. MD ANDERSON CANCER CENTER, United States

W. Symmans. UT MD Anderson Cancer Center, United States

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

F. Meric-Bernstam. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background: The addition of trastuzumab+/-pertuzumab to chemotherapy has changed the natural history of earlyHER2+ breast cancer. However, trials with targeted therapy alone are needed to avoid acute and chronic toxicities of chemotherapy. Zanidatamab is a novel, humanized, bispecific, immunoglobulin G isotype 1-like, monoclonal antibody directed against the juxtamembrane extracellular and dimerization domains (ECD2, ECD4) of HER2. The biparatopic nature of zanidatamab results in HER2 clustering that modulates signaling and leads to immune activation. Zanidatamab has demonstrated antitumor activity in heavily pre-treated HER2 overexpressing metastatic breast cancer with an acceptable safety profile. We hypothesized that zanidatamab would be a safe and effective regimen for women with node negative stage I HER2+ BC. Methods: Patients with 1-3 cm, clinically node negative HER2+ BC were enrolled in a single-institution investigator-initiated clinical trial. Patients had HER2+ breast cancer: HER2 3+ by IHC or IHC 2+ and ISH +. Patients received six to ten doses of zanidatamab, 20 mg/kg IV every 2 weeks prior to surgery. Patients with ER+ tumors also received neoadjuvant endocrine therapy. Post-menopausal patients received letrozole 2.5 mg daily, and pre-menopausal patients received tamoxifen 20 mg daily or GNRH and letrozole 2.5 mg. The primary objective was to evaluate efficacy as determined by pathologic complete response (pCR). Secondary objectives included pathologic response by residual cancer burden

(RCB), radiological response, and safety profile of zanidatamab. Results: Twenty patients with HER2+ breast cancer were enrolled. Median age was 62 years old (range 30-73). Fifteen patients had HER2 3+, and 5 HER2 2+/ISH+ tumors with a median size of 1.95 cm (range 1-3 cm) and 10 patients had tumors >2 cm. Seven patients were pre-menopausal. Six received tamoxifen and 8 letrozole. Eleven patients completed 6 cycles and 9 patients will receive 10 cycles of zanidatamab. Eleven patients already had surgery the remainder patients will have surgery by Oct 30, 2023. Four (36%) had pCR, 3 RCB1 (28%) and 4 RCB2 (36%). Treatment was tolerated well. There were no grade 3 or 4 toxicities. One patient had minor infusion related reaction and grade 2 acne, and 2 grade 2 diarrhea. Conclusions: Neoadjuvant zanidatamab demonstrates significant preliminary efficacy, (pCR/RCB-1 64%) with a good safety profile in patients with stage I node negative HER2+ BC. An update of efficacy and safety of all patients will be presented at the time of meeting

PS09-04

The benefit of adjuvant pertuzumab and trastuzumab according to estrogen receptor and HER2 expression: sub-analysis of the APHINITY trial

Presenting Author(s) and Co-Author(s):

E. de Azambuja. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Brussels Hoofdstedelijk Gewest, Belgium

E. Agostinetto. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Bruxelles, Brussels Hoofdstedelijk Gewest, Belgium

F. Samy. Frontier Science Scotland, Kincaig, Kingussie, United Kingdom

S. Di Cosimo. Biomarker Unit, Department of Applied Research and Technological Development, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

P. Aftimos. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium

N. Pondé. Department of Medical Oncology, A.C. Camargo Cancer Center, São Paulo, Brazil

D. Eiger. F. Hoffmann-La Roche Ltd, Basel, Switzerland

M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy

D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom

A. Kiermaier. F.Hoffmann-La Roche Ltd, Basel, Switzerland

A. Bailey. Frontier Science Scotland, Kincaig, Kingussie, United Kingdom

G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

M. Piccart. Institut Jules Bordet, Anderlecht, Brussels Hoofdstedelijk Gewest, Belgium

Background: Some studies suggest that response to HER2-targeting agents may differ according to estrogen receptor (ER) and HER2 expression levels. This study aimed to investigate the magnitude of benefit from the addition of pertuzumab to trastuzumab and chemotherapy according to ER and HER2 expression levels in the APHINITY trial. **Methods:** APHINITY (NCT01358877; BIG 4-11) was a randomized, double-blind, phase III study comparing the addition of pertuzumab or placebo to adjuvant trastuzumab and chemotherapy in an ITT population of 4804 patients with HER2-positive early breast cancer. The primary objective of this exploratory, unplanned analysis was to compare whether the addition of pertuzumab to trastuzumab had an impact in invasive disease-free survival (IDFS) within different subgroups defined by HER2 FISH amplification ratio and/or ER percentage of positivity on immunohistochemistry (IHC) (centrally assessed). Patients with a FISH ratio less than 2 were excluded from this analysis, leaving 4782 patients. IDFS was defined as the time from randomization until the date of the first occurrence of an IDFS event. HER2 FISH amplification ratio was categorized as low ($2 \leq$ FISH ratio < 5) vs. high (FISH ratio ≥ 5). ER expression on IHC was categorized as negative ($< 1\%$) vs. positive ($\geq 1\%$). A subgroup analysis using Cox proportional hazards regression models was used to model IDFS, assessing four categories formed by cross classifying the FISH ratio and ER groups. The model was adjusted for randomized arm, adjuvant chemotherapy regimen received, and a combined variable of nodal status and protocol version. **Results:** The 4782 patients had a median age of 51 years old (IQR 44-59), with a median follow up time of 73.6 months (IQR 63.0-75.2). Most patients received an anthracycline-based chemotherapy (n=3712, 77.6%). ER expression was positive in 3047 patients (63.7%). HER2 FISH amplification ratio was high in 2479 patients (51.8%). All FISH

ratio/ER subgroups seem to derive IDFS benefit from the addition of pertuzumab (HR < 1) (Table 1). The HER2 FISH ratio-low/ER positive subgroup had the largest reduction in risk of an IDFS event, 30% for the pertuzumab arm (HR=0.70, 95% CI 0.51-0.95) versus placebo. Smaller differences in IDFS events were observed between the treatment arms in the other subgroups. The subgroup of tumors with HER2 FISH ratio-high/ER-negative expression showed the numerically smallest benefit in IDFS events with the addition of pertuzumab (HR 0.85, 95% CI 0.59-1.25), see Table 1. Conclusions: In this APHINITY sub-analysis, patients treated with pertuzumab/trastuzumab derive similar benefit regardless of ER and HER2 expression levels. More research is needed to find predictive biomarkers to escalate or de-escalate treatments.

Table 1.

Subgroup	Number of patients PIZ + Trz + chemo vs PBo + Trz + chemo	Number of events PIZ + Trz + chemo vs PBo + Trz + chemo	Percentage of IDFS at 6 years from randomisation (95% CI) PIZ + Trz + chemo vs PBo + Trz + chemo	Adjusted HR (95% CI)
FISH high/ER+	746 vs 696	64 vs 75	91.0 (88.8-93.1) vs. 89.3 (86.9-91.7)	0.79 (0.54 - 1.10)
FISH high/ER-	515 vs 520	53 vs 58	90.2 (87.6-92.8) vs. 88.4 (85.5-91.2)	0.85 (0.57 - 1.25)
FISH low/ER+	777 vs 826	67 vs 102	91.2 (89.1-93.2) vs. 87.4 (85.0-89.7)	0.70 (0.51 - 0.95)
FISH low/ER-	355 vs 347	39 vs 50	88.6 (85.2-92.0) vs. 84.8 (80.9-88.7)	0.74 (0.47 - 1.13)

Abbreviations: FISH: fluorescence in situ hybridization, ER: estrogen receptor; IDFS: invasive disease-free survival; CI: confidence interval; HR: hazard ratio

PS09-06

Tumor infiltrating lymphocytes as a predictor of pathologic complete response to neoadjuvant therapy in HER2 positive breast cancer

Presenting Author(s) and Co-Author(s):

A. Monroy Chargoy. Hospital Regional de Alta Especialidad de Ixtapaluca, Ciudad de Mexico, Mexico City, Mexico

H. Verduzco-Aguirre. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

J. Monroy Chargoy. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, United States

J. Espinosa-Fernandez. INSTITUTO NACIONAL DE CANCEROLOGIA, United States

J. Martinez Ojeda. Universidad de Sonora, United States

P. Cabrera-Galeana. Instituto Nacional de Cancerologia, CDMX, Distrito Federal, Mexico

Background The presence of tumor infiltrating lymphocytes (TILs) has shown positive prognostic relevance for certain subtypes of breast cancer, although its value as a predictive biomarker is still uncertain. The purpose of this study was to study the association between TILs expression with the pathologic complete response (pCR) following neoadjuvant therapy in Mexican patients with HER2+ breast cancer. **Methods** Retrospective cohort of patients with stage I-III HER2+ breast cancer who received neoadjuvant therapy between 2017 and 2020 at Instituto Nacional de Cancerología (INCan). We collected demographic and clinico-pathological characteristics. Stage was assigned using AJCC 7th criteria; hormone receptor (HR) and HER2 status were determined according to ASCO-CAP guidelines. Quantification of TILs was made by microscopy and stained with hematoxylin-eosin. TIL levels were defined as low (1-10%) intermediate (11-40%) and high (>40%). Complete pathologic response was defined as the absence of invasive disease in breast and axilla (ypT0/is N0). pCR rates were compared using X2 and Fisher's exact tests according to demographic and clinicopathologic characteristics. Univariate logistic regression analysis was performed to estimate the probability of pCR according to relevant characteristics. Those parameters with $p \leq 0.10$ on univariate analysis were included in a multivariate logistic regression model. A $p < 0.05$ was considered as statistically significant. **Results** We included 164 patients (mean age 51.0 years, SD 11.4). 86 patients (54.1%) were postmenopausal, 75 patients (47.2%) had T3-T4 tumors, 129 patients (81.1%) had positive lymph nodes, 133 patients (83.6%) presented Ki67 $\geq 30\%$, 59 patients (37.1%) had negative hormone receptors, 136 patients (85.5%) were treated with anthracyclines and 20 patients (12.6%) received dual anti-HER2 therapy with trastuzumab/pertuzumab. TIL expression was low in 84 patients (52.8%), intermediate in 47 (29.6%), and high in 28 patients (17.6%). The pathologic complete response (pCR) rate in the overall population was 50.9%. pCR rates according to the demographic and clinico-pathological features are listed in Table 1. In patients with intermediate-high TILs, pCR rates were 73.1% with trastuzumab, and 75.0% with dual HER2 blockade ($p=0.91$). Among patients with low TILs, pCR rates were 23.6% and 75.0%, respectively ($p < 0.001$). On univariate analysis, intermediate TILs (OR 3.59; 95% C.I 1.70-7.59; $p < 0.001$), high TILs (OR 29.00; 95% C.I 6.40-131.37; $p < 0.001$), Ki67 $\geq 30\%$ (OR 2.73, 95% C.I 1.11-6.73; $p=0.02$), and dual anti-HER2 therapy (OR 3.31; 95% C.I 1.14-9.63 $p= 0.021$) were associated with a higher probability of pCR. T3/T4 tumor size (OR 0.43; 95% C.I 0.22-0.81; $p = 0.009$) was associated with a lower probability of pCR. Positive lymph nodes, HR status, and use of anthracyclines were not significantly associated. On multivariate analysis, intermediate TILs (OR 3.28; 95% C.I 1.46-7.32 $p=.004$),

high TILs (OR 32.37; 95% C.I 6.84-153.04 $p < 0.001$), and dual anti-HER2 therapy (OR 6.58; 95% CI 2.01-21.47 $p = .002$) remained significantly associated with pCR. Conclusions Intermediate/high TIL expression was significantly associated with pCR. Our results suggest that TIL expression could help select patients with locally advanced HER2+ breast cancer for treatment intensification with dual HER2 blockade in resource-limited settings. However, these findings require confirmation in larger, prospective studies before implementation into routine practice.

TABLE 1. Pathologic complete response (pCR) rates according to demographic and clinical pathological features (n=164).

	pCR (n,%)	p
Age in years		
<65 years	70 (49.0%)	0.13
≥65 years	11 (68.8%)	
Menopausal status		
Premenopausal	33 (45.2%)	0.18
Postmenopausal	48 (55.8%)	
Tumor size		
T1-T2	51 (60.7%)	0.009
T3-T4	30 (40.0%)	
Lymph Nodes		
Negative	17 (56.7%)	0.48
Positive	64 (49.6%)	
TILs		
Low	26 (31.0%)	<0.001
Intermediate	29 (61.7%)	
High	26 (92.9%)	
Ki67		
< 30%	8 (30.8%)	0.02
≥ 30%	73 (54.9%)	
Grade		
1-2	37 (45.7%)	0.17
3	43 (56.6%)	
Hormone receptors (HR)		
HR negative	35 (59.3%)	0.10
HR positive	46 (46.0%)	
Use of anthracyclines		
No	12 (52.2%)	0.89
Yes	69 (50.7%)	
Dual anti-HER2 therapy		
No	66 (47.5%)	0.021
Yes	15 (75.0%)	

PS09-07

SPAG5 as a companion prognostic and predictive test for management of early stage HER2 positive breast cancer (BCs)

Presenting Author(s) and Co-Author(s):

T. ABDEL-Fatah. Nottingham University Hospital NHS Trust, Nottingham, England, United Kingdom

G. Ball. Intellomx Limited, United States

D. Yeo. Nottingham University Hospital NHS Trust, United States

G. Hickman. Nottingham Trent University, United States

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

I. Ellis. University of Nottingham, United Kingdom

S. Chan. Nottingham University Hospital NHS Trust, United States

Background: SPAG5 is a novel oncogene that is amplified in 40% of HER2+BC. Herein, we evaluated the prognostic and predictive significance of SPAG5 in HER2+ BC Methods: This retrospective cohort study included 2454 patients with HER2+BC derived from 6 cohorts in adjuvant (Adj) and neoadjuvant (NACT) settings. Adj cohorts: The association between SPAG5 and survivals were evaluated in 1354 HER2+ BC who received Adj therapy: 1) HER2+ Adj transcript cohort (n=448): 31% (137/448) did not receive Anthracycline (AC), Taxane (TX), Trastuzumab (TZ) or Pertuzuman (PZ) whereas 20% (89/448) had received AC alone and 35% (155/ 448) received TZ + AC +/- TX (Median follow- up (MFU): 60 months (m). 2) HER2+ Adj Molecular Taxonomy of BC International Consortium cohort (n=240): patients with ER- and lymph node (LN) + received Adj chemotherapy but none received TZ (MFU: 109 m). 3) HER2+ Adj Historical cohort (n=206): no TZ, AC or TX was received (MFU: 143 m). 4) HER2+/ER- cohort (n=101): AC alone was received; MFU: 62 m. 5) HER+ Adj TZ cohort (n=359): patients received TZ +TX+/-AC (MFU: 90 m). Neo-Adjuvant cohort: the associations of SPAG5 protein expression with pathological complete response (pCR) was evaluated in 1100 BCs (MFU: 67 m) including 200 local cases participated in ROSCO trial. In this cohort; 73% (803/1100) received AC+TX. AC alone was given to 187/1100 (17%) whereas 88/1100 (8%) received TX alone. Of HER2+ BC, 14% (54/399) received AC +/- TX and 63% received TZ + TX +/-AC and 23% (92/399) received TZ + PZ + TX +/- AC. Sections were IHC profiled for HER2, ER, PR, Ki67 and SPAG5 and stained for Fluorescent in situ hybridisation (FISH) using a novel triple colour probe (HER2/SPAG5/Ch17). ASCO guidelines recommendations were followed. Results: In univariate survival analysis, High SPAG5 (+) transcript was associated with shorter 5- year distant metastases free survival (5-y DRFS); $p < 0.0001$, compared to SPAG5 low (-) in HER2+ patients who did not receive TZ or AC whereas in those who received AC alone, SPAG5+ was associated with lower risk of 5-y DRFS than SPAG5- ($p < 0.001$). Multivariable Cox regression analysis showed that SPAG5+ transcript ; as well as LN status, was independently associated with poor prognosis (HR (95% CI): 4.9 (2.0-12.0), $p < 0.001$). The interaction term between SPAG5 and AC was significantly associated with lower risk of DR. Multivariable Cox regression analysis for 10-year relapse free survival (10y-RFS) in HER2+ patients who did not receive AC or TZ confirmed that SPAG5+ protein expression ; as well as LN status and tumour size, were independently associated with poor prognosis (HR (95% CI): 2.1 (1.3, 3.5), $p = 0.002$). SPAG5+ predicted response for NACT +/- HER2 targeting agents. For instance; None of HER2 IHC 2+ with SPAG5- expression/ (0/191) either with HER2 FISH- (0/121) or HER2 FISH+ (0/70) achieved pCR whereas 51% (48/95) of those of HER2

IHC 2+/SPAG5+ achieved pCR ($p < 0.0001$). Similarly patients with HER2+ IHC 3+ /SPAG5+ achieved higher pCR rate compared to those with SPAG5- expression [73% (107/146) vs., 10% (14/135); respectively]; $p < 0.0001$. Noteworthy, after receiving TZ+ PZ +Texans +/- AC, patients with SPAG5+ achieved higher pCR rate compared to those with SPAG5- expression [85% (50/59) vs., 0% (0/51); respectively, $p < 0.001$]. Similarly in HER2 + BC patients who received TZ + TX +/- AC, SPAG5+ expression was associated with higher pCR [67% (67/101)] compared to those with SPAG5- [10% (11/107)]; $p < 0.001$. In HER2+ who received AC alone, SPAG5+ cases achieved higher pCR compared to those with SPAG5- [56% (20/36) vs., 6% (3/47); $p < 0.001$; respectively]. Multivariable logistic regression analysis showed that SPAG5+ expression as well as ER, HER2 IHC, grade, clinical TNM and HER2 targeting agents were independent predictors for pCR (OR (95% CI: 13.74 (5.76-32.79); $p < 0.001$). Conclusions SPAG5 is an independent poor prognostic factor in HER2+ BC and could help in distinguishing those who would and would not benefit from NACT and HER2 targeting agents.

PS09-08

Genomic characterization of endocrine resistance in ER+HER2+ breast cancers in the POETIC Trial

Presenting Author(s) and Co-Author(s):

M. Cheang. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

X. Zhu. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

O. Sipos. The Institute of Cancer Research, Clinical Trials and Statistics Unit, London, United Kingdom.

A. Alataki. Breast Cancer Research, The Institute of Cancer Research, London, United States

M. Feldbauer. University of North Carolina, United States

E. López-Knowles. Breast Cancer Research, The Institute of Cancer Research, London, United States

H. Tovey. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

L. Kilburn. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

M. Bergamino Sirvén. Clinical Trial and Statistics Unit, The Institute of Cancer Research, London, United States

D. Patel. The Institute of Cancer Research, Clinical Trials and Statistics Unit, London, United Kingdom.

H. Xiao. Clinical Trial and Statistics Unit, The Institute of Cancer Research, London, United States

P. Maxwell. School of Medicine, Dentistry and Biomedical Sciences Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, United States

A. Skene. Royal Bournemouth and Christchurch NHS Foundation Trust, Bournemouth, United Kingdom

C. Holcombe. Liverpool University Hospital NHS Foundation Trust, United States

M. Salto-Tellez. The Institute of Cancer Research, London; Queen's University Belfast, Belfast, United Kingdom.

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

A. Dodson. UK NEQAS ICC & ISH, London, United Kingdom

I. Smith. The Royal Marsden NHS Foundation Trust, London, United States

J. Robertson. University of Nottingham, Nottingham, UK; University Hospitals of Derby and Burton, Derby, England, United Kingdom

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

G. Schuster. Breast Cancer Research, The Institute of Cancer Research, London, United States

R. Salgado. GZA-ZNA-Hospitals, Antwerp, Belgium; Peter Mac Callum Cancer Centre, Temse, Belgium

M. Dowsett. The Royal Marsden NHS Foundation Trust, London, UK; The Institute of Cancer Research, London, United Kingdom

K. Hoadley. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, United States

Background: Mechanisms of resistance to endocrine therapy are not well understood within ER+HER2+ breast cancer (BC). Our prior work suggested that intrinsic HER2-Enriched (HER2E) molecular subtype predicts early resistance to aromatase inhibitors (AI) (Bergamino eBioMedicine 2022) and high on-treatment (on-Txt) Ki67 levels predict poor survival (Smith Lancet Oncol 2020). Improved early detection of persistent proliferating tumor cells with endocrine resistance pathways could be targeted by pre-emptive personalized therapy and reduction in recurrence. In this study, we proposed to further identify additional alterations/features from genomic and spatial data to provide unprecedented new insight into intrinsic and adaptive resistant pathways in tumor cells that may assist to identify molecular targets for treatment. **Materials:** POETIC was a phase III trial of post-menopausal patients with ER/PR+ invasive BC (n = 4480) randomized 2:1 to 2 weeks of peri-operative AI (POAI) vs control, followed by standard-of-care treatment. Ki67 was assessed by IHC and intra-tumor heterogeneity was evaluated (5-15 regions) for all the POETIC POAI samples (N = 2487). ER+HER2+ samples were classified as good responders (GR) or poor responders (PR) based on a reduction in Ki67 between pre-treatment (pre-Txt) and 2-week on-Txt samples. Tumor-infiltrating lymphocytes were assessed; multiplex Immunofluorescence (mIF) was performed to measure immune cell densities in tumor and stroma compartments (CD3, CD20, CD68, FOXP3, and CD3 FOXP3 co-expression). Gene expression profiles by BC360™ (Nanostring) on all 210 pairs of POAI treated ER+/HER2+; whole exome sequencing (WES, 100X) were performed on pre-Txt tumor and blood samples from 13 GR, 17 PR, and 9 HER2E GR. We performed GeoMx Whole Transcriptome on 4 pairs (pre-Txt and on-Txt) of GR and GeoMx Proteins (77 including IO proteins) on 6 pairs of GRs and 6 pairs of PRs. **Results:** The most frequently mutated genes were TP53, PIK3CA, GATA3, and CHD4. Only TP53 was associated with PR (Fisher's exact p=0.01). TP53 mutated cases had higher expression of TP53 mutant-like gene expression signature compared to wild-type cases (Wilcoxon test p=0.001), mIF FOXP3 (Wilcoxon test p = 0.0005), and CD68 (Wilcoxon test p = 0.019) density score. However, within the HER2-E subset, we found that TP53 mutations were associated with GR (Fisher's exact p=0.02). We found spatial heterogeneity of Ki67 IHC levels across POAI samples. Examining IHC, while there was higher heterogeneity of Ki67 in the ER+HER2- samples (n = 2264) with 3% of pre-Txt and 9% on-Txt, 6% of ER+HER2+ samples (13/223, 6 LumA, 5 LumB, and 2 HER2E) showed heterogeneity of Ki67 exclusively on-Txt. Even in GR tumors with Ki67 < 10% on-Txt, we identified hotspots with retained proliferating Ki67+ cells after 2 weeks of POAI. The lobular tumors were GR and had characteristic CDH1 mutations. Importantly, cases with persistent areas of Ki67+ cells, regardless of Her2 status, were associated with late relapse. To further explore intratumoral heterogeneity, we performed spatial whole transcriptomics profiling on 95 regions from 4 pairs of GR samples (Ki67 > 10% at baseline and Ki67 < 10% on-Txt) and found low intratumoral heterogeneity in the pre-Txt samples that increased at 2 weeks on-Txt. In a larger set of samples including both GR and PR with the GeoMx protein method, we found increased intratumoral heterogeneity in the PR vs GR. **Conclusion:** While TP53 mutation was generally a predictor of poor response; in HER2-E it paradoxically was associated with a good early response to aromatase inhibitor which warrants further investigation. Ki67 levels in ER+HER2+ showed higher intratumoral heterogeneity in a subset of patients on treatment suggesting the potential of persistent, proliferating cells leading to later recurrence. Our spatial RNA and protein data further observe

the intratumoral heterogeneity that identifies pathways for use as potential spatial biomarkers.

PS09-09

Multomics profiling and molecular classification refine precision treatment strategies for HER2-positive breast cancer

Presenting Author(s) and Co-Author(s):

Y. Li. Fudan University Shanghai Cancer Center, China (People's Republic)
D. Ma. Fudan University Shanghai Cancer Center, China (People's Republic)
X. Wu. Fudan University Shanghai Cancer Center, China (People's Republic)
L. Dai. Fudan University Shanghai Cancer Center, China (People's Republic)
S. Zhao. Fudan University Shanghai Cancer Center, China (People's Republic)
Y. Xu. Fudan University Shanghai Cancer Center, China (People's Republic)
X. Jin. Fudan University Shanghai Cancer Center, China (People's Republic)
X. Yi. Fudan University Shanghai Cancer Center, China (People's Republic)
Y. Wang. Fudan University Shanghai Cancer Center, China (People's Republic)
C. Lin. Fudan University Shanghai Cancer Center, China (People's Republic)
Y. Zhou. Fudan University Shanghai Cancer Center, China (People's Republic)
T. Fu. Fudan University Shanghai Cancer Center, China (People's Republic)
W. Yang. Fudan University Shanghai Cancer Center, China (People's Republic)
M. Li. Fudan University Shanghai Cancer Center, China (People's Republic)
H. Lv. Fudan University Shanghai Cancer Center, China (People's Republic)
Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)
Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background: Anti-HER2 targeted therapy has achieved a series of breakthroughs. However, the current treatment strategy regarding HER2-positive breast cancer remains indiscriminate and lacks specificity, which limits the further improvement of overall treatment response and may lead to overtreatment and extra cost for some patients. Our study aims to reveal the molecular heterogeneity of HER2-positive breast cancer to guide a more precise treatment. **Patients and methods:** We selected HER2-positive breast cancer patients treated at Fudan University Shanghai Cancer Center between 2013 and 2014 and conducted genomic, transcriptomic, proteomic and metabolomic profiling. We then applied a non-negative matrix factorization algorithm on transcriptomic data to obtain an unsupervised classification. And we further studied the correlation between subtypes and corresponding treatment strategies in multiple cohorts of adjuvant and neoadjuvant therapy. For clinical accessibility, we developed convolutional neural network models through deep learning algorithm based on digital pathology to identify different subtypes. Additionally, we explored novel treatment strategies using the patient-derived organoids (PDOs) models. **Results:** We established a novel multomics cohort of 180 HER2- breast cancer patients and classified them into four clinically significant molecular subtypes: (1) A classical HER2-enriched (HER2-CLA, N=51) subtype characterized by strong ERBB2 signaling and remarkable sensitivity to anti-HER2-targeted therapy (pathologic complete response with dual-targeted therapy: 93%). (2) an immunomodulatory (HER2-IM, N=36) subtype characterized by an immune-activated

microenvironment and excellent prognosis with current treatment (no relapse in 97% of patients with a median follow-up of 86 months). Tumors of this subtype were therefore candidates for de-escalatory treatment. (3) A luminal-like (HER2-LUM, N=55) subtype distinguished by activated estrogen receptor signaling and (4) a basal/mesenchymal-like (HER2-BM, N=38) subtype enriched in activated receptor tyrosine kinase pathways. HER2-LUM and HER2- BM showed limited benefit from anti-HER2 therapy, and thus, add-on therapies might be needed. The overall area under the curve (AUC) of the convolutional neural network model based on digital pathology for identifying different subtypes is 0.77. In the exploration of novel treatment strategies, we found in the PDO model that the HER2-LUM subtype is more sensitive to a treatment regimen combining standard (chemotherapy and targeted therapy) with subsequent endocrine therapy and CDK4/6 inhibitors compared to other subtypes. Additionally, the HER2-BM subtype demonstrated greater sensitivity to treatment with a combination of EGFR inhibitors, PDGFR inhibitors or VEGFR inhibitors. Conclusion: We uncovered a high degree of molecular heterogeneity in HER2-positive breast cancer and illustrated its impact on treatment response. More precise treatment can be given according to the characteristics of different subtypes, which may achieve good efficacy and simultaneously reduce overtreatment and extra cost. The comprehensive profiling of HER2-positive breast cancers could also serve as an important resource for further exploration. Key Words: HER2-positive breast cancer cohort; molecular classification; targeted therapy; precision treatment; de-escalatory treatment.

PS09-01

Individual patient data meta-analysis of clinical and translational biomarkers for prediction of pathological complete response (pCR) after de-escalated therapy in HER2+ breast cancer in four trials of the West German Study Group

Presenting Author(s) and Co-Author(s):

M. Graeser. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; Department of Gynecology, University Medical Center Hamburg, Moenchengladbach, Nordrhein-Westfalen, Germany

O. Gluz. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; University Clinics Cologne, Moenchengladbach, Nordrhein-Westfalen, Germany

C. zu Eulenburg. West German Study Group, Moenchengladbach, Germany; Department of Medical Biometry and Epidemiology, University Medical Center Hamburg, Hamburg, Germany

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

R. von Schumann. Ev. Bethesda Hospital, Breast Center Niederrhein, Moenchengladbach, Germany

M. Christgen. Medizinische Hochschule Hannover, Hannover, Niedersachsen, Germany

R. Wuerstlein. Breast Center, Dept. OB&GYN and CCC Munich, LMU University Hospital, Munich, Germany

E. Pelz. Institute for Pathology, Viersen, Germany

H. Kreipe. Medical School Hannover, Institute of Pathology, Hannover, Germany; Institute of Neuropathology, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

M. Thill. Agaplesion Markus Krankenhaus Frankfurt, Frankfurt, Hessen, Germany

M. Braun. Rotkreuzklinikum München, Germany

J. Potenberg. Ev. Waldkrankenhaus Berlin, Berlin, Germany

C. Schumacher. St. Elisabeth Hospital, Cologne, Germany

J. Tio. University Hospital Münster, Gynaecology, Münster, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

M. Just. Onkologische Schwerpunktpraxis Bielefeld, Bielefeld, Germany

C. Schem. Mammazentrum am Krankenhaus Jerusalem, Hamburg, Germany

K. Lütke-Heckenkamp. Zentrum für Onkologie und Hämatologie MVZ II, Franziskus-Hospital Harderberg, Georgsmarienhütte, Germany

E. Grischke. Universitäts-Frauenklinik Tübingen, Eberhard Karls University, Tübingen, Germany

F. Hilpert. Breast Center Hamburg at Hospital Jerusalem, Hamburg, Germany

A. Kentsch. Diakovere Henriettenstift, Dept. for Gynecology, Hamburg, Germany

R. Kates. West German Study Group, Moenchengladbach, Germany

U. Nitz. West German Study Group and Breast Center Niederrhein, United States

N. Harbeck. University of Munich, Munich, Bayern, Germany

Background

Introduction of anti-HER2 therapies substantially improved outcomes for HER2-positive early breast cancer (HER2+ eBC). However, a considerable proportion of patients (pts) may still be overtreated with systemic chemotherapy (CTx) combinations. Establishing safe de-escalation strategies to avoid toxicities requires precise patient selection. Therefore, we set out to determine predictors for efficacy and survival in the unique setting of four de-escalation trials investigating short (12-week) neoadjuvant treatments (NAT) in HER2+ eBC. We investigated the prognostic ability of clinical and translational biomarkers for pCR to identify pts with the best prognosis after de-escalated systemic CTx-free NAT.

Methods

756 pts who received de-escalated NAT were analyzed: trastuzumab + pertuzumab (T + P, n=92) and T + P + paclitaxel (pac, n=42) in ADAPT-HR-/HER2+ (NCT01817452); trastuzumab emtansine (T-DM1, n=118), T-DM1 + endocrine therapy (ET, n=125), and T + ET (n=129) in ADAPT-HR+/HER2+ (NCT01779206), T + P + pac (n=107) and T + P + ET (n=100) in TP-II (NCT03272477); and T + P + pembrolizumab (n=43) in Keyriched-1 (NCT03988036) in HER2-enriched (HER2-E) subtype by PAM50. The primary endpoint of each trial was pCR (ypT0/is ypN0). Survival was a secondary endpoint in all trials but Keyriched-1; survival data for TP-II are pending.

Baseline gene expression was analyzed by BC360 assay; intrinsic molecular subtypes were determined using the PAM50 predictor. Stromal tumor infiltrating lymphocytes (sTILs) were evaluated at baseline and at week 3 of NAT. sTILs were categorized using a 30% threshold and the low cellularity category (< 500 invasive tumor cells) at week 3.

Prognostic markers for pCR were identified with univariate and multivariable logistic regression models with backstep algorithm excluding variables with $p \geq 0.1$; considered variables included age, sTILs (baseline, 3-weeks), cT, cN, grade, hormone receptor and HER2 status, intrinsic subtype, and standardized ERBB2 and ESR1 gene expression. These analyses were performed separately for NAT involving systemic CTx (i.e. containing pac, n=149) and systemic CTx-free NAT (n=607).

Results

Overall pCR rate was 39.1% (CTx: 66.4%; CTx-free: 32.5%). Multivariable analysis identified predictors of pCR after CTx-free NAT: low cellularity at week 3 (vs < 30% sTILs: OR 3.21, 95%CI 1.85-5.57), ERBB2 (OR 1.90, 95%CI 1.41-2.55), HER2 3+ (vs 1+/2+ and ISH+: OR 8.01, 95%CI 1.65-38.99), LumA/LumB/Basal subtype (vs HER2-E: OR 0.57, 95%CI 0.34-0.97), cT2 (vs 1: OR 0.54, 95%CI 0.33-0.89), and cN1-3 (vs 0, OR 0.46, 95%CI 0.27-0.78). In CTx-containing NAT, only ERBB2 (OR 2.08, 95%CI 1.28-3.40) and additionally ESR1 (OR 0.38, 95%CI 0.23-0.61) were prognostic for pCR.

Updated analysis including expanded gene expression data from ADAPT-HR+/HER2+ and a prognostic score for pCR after CTx-free NAT developed using machine learning methods will be presented at the meeting.

Conclusions

This pooled analysis demonstrated a 66% pCR rate after a short (12-week) de-escalated NAT in HER2+ eBC. In one-third of patients (with mainly stage I cancer, higher HER2 expression by immunohistochemistry and gene expression analysis, and low cellularity at 3 weeks), pCR can be achieved without systemic CTx. Identified biomarkers could pave the way for developing new patient selection strategies to spare CTx-associated acute and late toxicities in a clinically meaningful number of patients.

Disclosure(s):

Monika Graeser, PD Dr. med.: Consulting Fees (e.g., advisory boards): AstraZeneca (Terminated); Travel support: Daiichi Sankyo (Terminated, November 1, 2023)

Oleg Gluz, MD: Consulting Fees (e.g., advisory boards): Roche, Novartis, Lilly, MSD, Gilead, ExactScience, Agendia, Seagen, DaichiSankyo, Pfizer, Astra Zeneca (Ongoing)

Peter Schmid, MD, PhD: Consulting Fees (e.g., advisory boards): Eli Lilly & Company (Ongoing), Gilead Science (Ongoing)

Nadia Harbeck, MD, PhD: Advisory Committee/Board Member: Roche (Ongoing); Consulting Fees (e.g., advisory boards): Gilead (Ongoing), Sandoz (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Amgen (Ongoing), Astra Zeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Roche (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): West German Study Group (WSG) (Ongoing)

Poster Spotlight Session 9: Exploiting Tumor Biology in HER2-positive Breast Cancer to Escalate or De-escalate Neoadjuvant Therapy

Presenting Author(s) and Co-Author(s):

W. Sikov. Women & Infants Hospital of Rhode Island and Warren Alpert Medical School of Brown University , Providence, Rhode Island, United States

Disclosure(s):

William M. Sikov, MD, FACP, FNCBC: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Daiichi-Sankyo (Terminated, October 31, 2023), Eli Lilly, (Terminated, October 31, 2023), SeaGen (Terminated, October 31, 2023)

PS09-02

Event-free Survival by Residual Cancer Burden (RCB) and Intratumor HER2 Heterogeneity after Neoadjuvant T-DM1 and Pertuzumab for Early-stage HER2-positive Breast Cancer

Presenting Author(s) and Co-Author(s):

- O. Metzger. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
S. Kim. Dana Farber Cancer Institute, United States
N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy
D. Yardley. Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, United States
A. Prat. Hospital Clinic Barcelona, Spain
V. Abramson. Vanderbilt University Medical Center, United States
L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States
A. Waks. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
E. Wrabel. Dana-Farber Institute, United States
M. DeMeo. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States
P. Dell'Orto. IEO, United States
L. Russo. Istituto Europeo di Oncologia, United States
T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States
F. Michor. Department of Data Science, Dana-Farber Cancer Institute; Department of Biomedical Informatics, Harvard Medical School; Center for Cancer Evolution, Dana-Farber Cancer Institute, Boston, Massachusetts, United States
E. Winer. Yale Cancer Center, New Haven, Connecticut, United States
K. Polyak. Dana Farber Cancer Institute, Harvard Medical School, United States
S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States
I. Krop. Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, United States

Background:

Intratumor HER2 heterogeneity (ITH-HER2) predicates resistance to targeted anti-HER2-based therapy, and understanding its impact on response to HER2-directed therapies is particularly important with regimens that rely solely on targeted anti-HER2 therapies without chemotherapy.

Methods:

To determine the effect of ITH-HER2 on response to therapy, we conducted a single-arm phase II study in which patients (pts) with centrally confirmed HER2+ early-stage breast cancer received six cycles of preoperative T-DM1 plus pertuzumab. Baseline image-guided biopsies

allowed central pathology evaluation of ITH HER2, defined as an area with HER2 amplification in >5% but < 50% of tumor cells or a HER2-negative area by FISH. The study met its primary endpoint by demonstrating inferior pathologic complete response (pCR) measured by Residual Cancer Burden (RCB) in the subset of ITH-HER2 pts. Single-cell ERBB2 FISH analysis identified the fraction of ERBB2 nonamplified cells as a factor associated with therapeutic resistance (Metzger et al. Cancer Discovery 2021). Secondary endpoints included event-free survival (EFS), invasive disease-free survival (iDFS), and breast cancer-specific survival (BCSS) by ITH-HER2 status and RCB scores.

Results:

163 pts were enrolled and received treatment in the study from Jan 2015 to Jan 2018. Central pathology evaluation of HER2 heterogeneity was successful in 96% (157/163) of cases, with 16 classified as ITH-HER2. RCB-0 or -I rate in the ITH-HER2 vs. not was (25% v. 67%, OR = 5.6, p = 0.002). Median follow-up, including all treated pts (n = 163), was 65.4 months (IQR, 60.3-76.6). The 5yr EFS, iDFS, and BCSS were 91% [86.5% - 95.6%], 89.4% [84.5% - 94.5%], and 96% [92.9% - 99.2%], respectively. ITH-HER2 was associated with numerically inferior outcomes for EFS, iDFS, and BCSS (Table 1).

The subset of pts with non-ITH-HER2 at baseline (n= 141) and RCB-0 or -I (n = 95/141, 67%) had a 5-yr iDFS of 94.2% [89.3% - 99.3%]. A sensitivity analysis describing survival outcomes by chemotherapy use in the adjuvant setting will be presented at the meeting, along with translational research results evaluating the association of HER2DX assay with pCR and survival outcomes.

Conclusions:

The inferior pCR rates among cases classified as ITH-HER2 translated into numerically inferior outcomes for both EFS and iDFS. The number of events is small; therefore, our results are exploratory. Selecting pts whose tumors lack ITH-HER2 can increase the chances of achieving RCB 0/I with neoadjuvant TDM1 + pertuzumab. Neoadjuvant TDM1 + pertuzumab, followed by adjuvant HER2-directed therapy without classic chemotherapy agents, could represent an optimal regimen for non-ITH-HER2 pts experiencing RCB 0/I at the time of surgery and deserves further study.

	EFS	iDFS	BCSS
Overall (n=157)	91.3% [86.9% - 95.9%]	90.5% [85.8% - 95.4%]	96.5% [93.6% - 99.6%]
Total number of events	17	17	5
ITH-HER2	81.3% [64.2% - 100%]	81.3% [64.2% - 100%]	100%
Non-ITH- HER2	92.5% [88.2% - 97.1%]	91.6% [86.9% - 96.5%]	96.2% [92.9% - 99.5%]

Table 1. 5-year survival estimates by ITH-HER2

Disclosure(s):

Otto Metzger, MD: Consulting Fees (e.g., advisory boards): Alliance for Clinical Trials in Oncology (Terminated, September 19, 2023), Astra Zeneca (Terminated, September 19, 2023), Merck & Co., Inc. (Terminated, September 19, 2023); Independent Contractor: Alliance for Clinical Trials in Oncology (Ongoing), Grupo Oncoclinicas (Ongoing)

Adrienne G. Waks, MD: Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Genentech (Ongoing), Gilead (Ongoing), MacroGenics (Ongoing), Merck (Ongoing)

Aditya Bardia, MD, MPH: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Menarini/Stemline (Ongoing)

Tari A. King, MD: Consulting Fees (e.g., advisory boards): Exact Sciences (Genomic Health) (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Exact Sciences (Genomic Health) (Ongoing)

Eric Winer, MD: No financial relationships to disclose

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

PS09-03

Neoadjuvant zanidatamab for stage I node negative HER2 positive breast cancer

Presenting Author(s) and Co-Author(s):

V. Valero. Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Bellaire, Texas, United States

J. Mouabbi. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

H. Alonzo. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

P. Pohlmann. MD ANDERSON CANCER CENTER, United States

A. Iheme. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Hassan. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

R. Murthy. MD ANDERSON CANCER CENTER, Houston, Texas, United States

X. Huang. MD ANDERSON CANCER CENTER, United States

W. Qiao. UT MD Anderson Cancer Center, United States

M. Patel. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

G. Rauch. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

C. Checka. MD ANDERSON CANCER CENTER, United States

W. Symmans. UT MD Anderson Cancer Center, United States

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

F. Meric-Bernstam. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background:

The addition of trastuzumab+/-pertuzumab to chemotherapy has changed the natural history of earlyHER2+ breast cancer. However, trials with targeted therapy alone are needed to avoid acute and chronic toxicities of chemotherapy. Zanidatamab is a novel, humanized, bispecific, immunoglobulin G isotype 1-like, monoclonal antibody directed against the juxtamembrane extracellular and dimerization domains (ECD2, ECD4) of HER2. The biparatopic nature of zanidatamab results in HER2 clustering that modulates signaling and leads to immune activation. Zanidatamab has demonstrated antitumor activity in heavily pre-treated HER2 overexpressing metastatic breast cancer with an acceptable safety profile. We hypothesized that zanidatamab would be a safe and effective regimen for women with node negative stage I HER2+ BC.

Methods:

Patients with 1-3 cm, clinically node negative HER2+ BC were enrolled in a single-institution investigator-initiated clinical trial. Patients had HER2+ breast cancer: HER2 3+ by IHC or IHC 2+ and ISH +. Patients received six to ten doses of zanidatamab, 20 mg/kg IV every 2 weeks prior to surgery. Patients with ER+ tumors also received neoadjuvant endocrine therapy. Post-

menopausal patients received letrozole 2.5 mg daily, and pre-menopausal patients received tamoxifen 20 mg daily or GNRH and letrozole 2.5 mg. The primary objective was to evaluate efficacy as determined by pathologic complete response (pCR). Secondary objectives included pathologic response by residual cancer burden (RCB), radiological response, and safety profile of zanidatamab.

Results:

Twenty patients with HER2+ breast cancer were enrolled. Median age was 62 years old (range 30-73). Fifteen patients had HER2 3+, and 5 HER2 2+/ISH+ tumors with a median size of 1.95 cm (range 1-3 cm) and 10 patients had tumors >2 cm. Seven patients were pre-menopausal. Six received tamoxifen and 8 letrozole. Eleven patients completed 6 cycles and 9 patients will receive 10 cycles of zanidatamab. Eleven patients already had surgery the remainder patients will have surgery by Oct 30, 2023. Four (36%) had pCR, 3 RCB1 (28%) and 4 RCB2 (36%). Treatment was tolerated well. There were no grade 3 or 4 toxicities. One patient had minor infusion related reaction and grade 2 acne, and 2 grade 2 diarrhea.

Conclusions:

Neoadjuvant zanidatamab demonstrates significant preliminary efficacy, (pCR/RCB-1 64%) with a good safety profile in patients with stage I node negative HER2+ BC. An update of efficacy and safety of all patients will be presented at the time of meeting

Disclosure(s):

Vicente Valero, MD, FACP: Advisory Committee/Board Member: Astra Zeneca (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Novartis (Ongoing), Roche Pharma (Ongoing)

Jason Mouabbi, MD: Advisory Committee/Board Member: AstraZeneca PLC (Ongoing), GE Healthcare (Ongoing); Consulting Fees (e.g., advisory boards): BostonGene Corporation (Ongoing), Gilead Science (Ongoing), Novartis Pharma GmbH (Ongoing)

Gaiane M. Rauch, MD PhD: No financial relationships to disclose

PS09-04

The benefit of adjuvant pertuzumab and trastuzumab according to estrogen receptor and HER2 expression: sub-analysis of the APHINITY trial

Presenting Author(s) and Co-Author(s):

E. de Azambuja. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Brussels Hoofdstedelijk Gewest, Belgium

E. Agostinetto. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Bruxelles, Brussels Hoofdstedelijk Gewest, Belgium

F. Samy. Frontier Science Scotland, Kincaig, Kingussie, United Kingdom

S. Di Cosimo. Biomarker Unit, Department of Applied Research and Technological Development, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

P. Aftimos. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium

N. Pondé. Department of Medical Oncology, A.C. Camargo Cancer Center, São Paulo, Brazil

D. Eiger. F. Hoffmann-La Roche Ltd, Basel, Switzerland

M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy

D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom

A. Kiermaier. F.Hoffmann-La Roche Ltd, Basel, Switzerland

A. Bailey. Frontier Science Scotland, Kincaig, Kingussie, United Kingdom

G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

M. Piccart. Institut Jules Bordet, Anderlecht, Brussels Hoofdstedelijk Gewest, Belgium

Background:

Some studies suggest that response to HER2-targeting agents may differ according to estrogen receptor (ER) and HER2 expression levels. This study aimed to investigate the magnitude of benefit from the addition of pertuzumab to trastuzumab and chemotherapy according to ER and HER2 expression levels in the APHINITY trial.

Methods:

APHINITY (NCT01358877; BIG 4-11) was a randomized, double-blind, phase III study comparing the addition of pertuzumab or placebo to adjuvant trastuzumab and chemotherapy in an ITT population of 4804 patients with HER2-positive early breast cancer. The primary objective of this exploratory, unplanned analysis was to compare whether the addition of pertuzumab to trastuzumab had an impact in invasive disease-free survival (IDFS) within different subgroups defined by HER2 FISH amplification ratio and/or ER percentage of positivity on immunohistochemistry (IHC) (centrally assessed). Patients with a FISH ratio less than 2 were excluded from this analysis, leaving 4782 patients. IDFS was defined as the time from randomization until the date of the first occurrence of an IDFS event. HER2 FISH amplification ratio was categorized as low ($2 \leq \text{FISH ratio} < 5$) vs. high ($\text{FISH ratio} \geq 5$). ER expression on IHC was categorized as negative ($< 1\%$) vs. positive ($\geq 1\%$). A subgroup analysis using Cox proportional hazards regression models was used to model IDFS, assessing four categories formed by cross classifying the FISH ratio and ER groups. The model was adjusted for randomized arm, adjuvant chemotherapy regimen received, and a combined variable of nodal status and protocol version.

Results:

The 4782 patients had a median age of 51 years old (IQR 44-59), with a median follow up time of 73.6 months (IQR 63.0-75.2). Most patients received an anthracycline-based chemotherapy (n=3712, 77.6%). ER expression was positive in 3047 patients (63.7%). HER2 FISH amplification ratio was high in 2479 patients (51.8%). All FISH ratio/ER subgroups seem to derive IDFS benefit from the addition of pertuzumab (HR < 1) (Table 1). The HER2 FISH ratio-low/ER positive subgroup had the largest reduction in risk of an IDFS event, 30% for the pertuzumab arm (HR=0.70, 95% CI 0.51-0.95) versus placebo. Smaller differences in IDFS events were observed between the treatment arms in the other subgroups. The subgroup of tumors with HER2 FISH ratio-high/ER-negative expression showed the numerically smallest benefit in IDFS events with the addition of pertuzumab (HR 0.85, 95% CI 0.59-1.25), see Table 1.

Conclusions:

In this APHINITY sub-analysis, patients treated with pertuzumab/trastuzumab derive similar benefit regardless of ER and HER2 expression levels. More research is needed to find predictive biomarkers to escalate or de-escalate treatments.

Table 1.

Subgroup	Number of patients Piz + Tiz + chemo vs Pbo + Tiz + chemo	Number of events Piz + Tiz + chemo vs Pbo + Tiz + chemo	Percentage of IDFS at 6 years from randomization (95% CI) Piz + Tiz + chemo vs Pbo + Tiz + chemo	Adjusted HR (95% CI)
FISH high/ER+	746 vs 696	64 vs 75	91.0 (88.8-93.1) vs. 89.3 (86.9-91.7)	0.79 (0.54 - 1.10)
FISH high/ER-	515 vs 520	53 vs 58	90.2 (87.4-92.8) vs. 88.4 (85.5-91.2)	0.85 (0.59 - 1.23)
FISH low/ER+	777 vs 826	67 vs 102	91.2 (89.3-93.2) vs. 87.4 (85.0-89.7)	0.70 (0.51 - 0.95)
FISH low/ER-	355 vs 347	39 vs 50	88.6 (85.2-92.0) vs. 84.8 (80.9-88.7)	0.74 (0.47 - 1.13)

Abbreviations: FISH: fluorescence in situ hybridization, ER: estrogen receptor; IDFS: invasive disease-free survival; CI: confidence interval; HR: hazard ratio

Disclosure(s):

Evandro de Azambuja, MD/PhD: Advisory Committee/Board Member: F. Hoffman La Roche Ltd (Ongoing); Consulting Fees (e.g., advisory boards): AstraZenca (Terminated), Eli Lilly and Co (Terminated), F. Hoffman La Roche Ltd (Terminated), Gilead Science (Terminated), Libs (Terminated), MSD Co., Ltd. (Terminated), Novartis Pharma GmbH (Terminated), PierreFabre (Terminated), SeaGen (Terminated), Zodiac (Terminated)

Elisa Agostinetti, MD: Honorarium: Sandoz (Terminated); meeting/travel grants: Novartis, Roche, Eli Lilly, Genetic, Istituto Gentili, Daiichi Sankyo, AstraZeneca (Terminated); Research grant to my Institution: Gilead (Terminated); speaking fee: AstraZeneca (Terminated), Eli Lilly (Terminated)

Matteo Lambertini, MD, PhD: Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Eli Lilly and Co (Ongoing), Exact Sciences Corporation (Ongoing), Gilead (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), SeaGen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Daiichi-Sankyo (Ongoing), Eli Lilly and Co (Ongoing), Gilead (Ongoing), IPSEN (Ongoing), Knights Pharmaceuticals (Ongoing), Libbs (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), Sandoz (Ongoing), Takeda Pharmaceuticals, Ltd. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Gilead (Ongoing); Travel grant: Daiichi-Sankyo (Ongoing), Gilead (Ongoing)

Sherene Loi, MD, PhD: Advisory Committee/Board Member: Bristol-Myers Squibb Company (Ongoing), MSD Co., Ltd. (Ongoing); Consulting Fees (e.g., advisory boards): Aduro Biotech (Ongoing), Amunix (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), MSD Co., Ltd. (Ongoing), Nektar Therapeutics (Ongoing), Novartis International AG (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics (Ongoing); Uncompensated consultant: Aduro Biotech (Ongoing), Amunix (Ongoing), Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing)

Martine J. Piccart, MD, PhD: Advisory Committee/Board Member: Oncolytics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Camel-IDS/Precirix (Ongoing), Gilead (Ongoing), Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Roche-Genentech (Ongoing), Seattle Genetics, Seagen, NBE Therapeutics, Frame Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing), Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Roche-Genentech (Ongoing), Servier, Synthron (Ongoing)

PS09-06

Tumor infiltrating lymphocytes as a predictor of pathologic complete response to neoadjuvant therapy in HER2 positive breast cancer

Presenting Author(s) and Co-Author(s):

A. Monroy Chargoy. Hospital Regional de Alta Especialidad de Ixtapaluca, Ciudad de Mexico, Mexico City, Mexico

H. Verduzco-Aguirre. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

J. Monroy Chargoy. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, United States

J. Espinosa-Fernandez. INSTITUTO NACIONAL DE CANCEROLOGIA, United States

J. Martinez Ojeda. Universidad de Sonora, United States

P. Cabrera-Galeana. Instituto Nacional de Cancerologia, CDMX, Distrito Federal, Mexico

Background

The presence of tumor infiltrating lymphocytes (TILs) has shown positive prognostic relevance for certain subtypes of breast cancer, although its value as a predictive biomarker is still uncertain. The purpose of this study was to study the association between TILs expression with the pathologic complete response (pCR) following neoadjuvant therapy in Mexican patients with HER2+ breast cancer.

Methods

Retrospective cohort of patients with stage I-III HER2+ breast cancer who received neoadjuvant therapy between 2017 and 2020 at Instituto Nacional de Cancerología (INCan). We collected demographic and clinico-pathological characteristics. Stage was assigned using AJCC 7th criteria; hormone receptor (HR) and HER2 status were determined according to ASCO-CAP guidelines. Quantification of TILs was made by microscopy and stained with hematoxylin-eosin. TIL levels were defined as low (1-10%) intermediate (11-40%) and high (>40%). Complete pathologic response was defined as the absence of invasive disease in breast and axilla (ypT0/is N0). pCR rates were compared using X2 and Fisher's exact tests according to demographic and clinicopathologic characteristics. Univariate logistic regression analysis was performed to estimate the probability of pCR according to relevant characteristics. Those parameters with $p \leq 0.10$ on univariate analysis were included in a multivariate logistic regression model. A $p < 0.05$ was considered as statistically significant.

Results

We included 164 patients (mean age 51.0 years, SD 11.4). 86 patients (54.1%) were postmenopausal, 75 patients (47.2%) had T3-T4 tumors, 129 patients (81.1%) had positive lymph nodes, 133 patients (83.6%) presented Ki67 $\geq 30\%$, 59 patients (37.1%) had negative hormone receptors, 136 patients (85.5%) were treated with anthracyclines and 20 patients (12.6%) received dual anti-HER2 therapy with trastuzumab/pertuzumab. TIL expression was low in 84 patients (52.8%), intermediate in 47 (29.6%), and high in 28 patients (17.6%). The pathologic complete response (pCR) rate in the overall population was 50.9%. pCR rates according to the demographic and clinico-pathological features are listed in Table 1. In patients with intermediate-high TILs, pCR rates were 73.1% with trastuzumab, and 75.0% with dual HER2 blockade ($p=0.91$). Among patients with low TILs, pCR rates were 23.6% and 75.0%, respectively ($p < 0.001$).

On univariate analysis, intermediate TILs (OR 3.59; 95% C.I 1.70-7.59; p= < 0.001), high TILs (OR 29.00; 95% C.I 6.40-131.37; p= < 0.001), Ki67 \geq 30% (OR 2.73, 95% C.I 1.11-6.73; p=0.02), and dual anti-HER2 therapy (OR 3.31; 95% C.I 1.14-9.63 p= 0.021) were associated with a higher probability of pCR. T3/T4 tumor size (OR 0.43; 95% C.I 0.22-0.81; p = 0.009) was associated with a lower probability of pCR. Positive lymph nodes, HR status , and use of anthracyclines were not significantly associated. On multivariate analysis, intermediate TILs (OR 3.28; 95% C.I 1.46-7.32 p=.004), high TILs (OR 32.37; 95% C.I 6.84-153.04 p= < 0.001), and dual anti-HER2 therapy (OR 6.58; 95% CI 2.01-21.47 p= .002) remained significantly associated with pCR.

Conclusions

Intermediate/high TIL expression was significantly associated with pCR. Our results suggest that TIL expression could help select patients with locally advanced HER2+ breast cancer for treatment intensification with dual HER2 blockade in resource-limited settings. However, these findings require confirmation in larger, prospective studies before implementation into routine practice.

TABLE 1. Pathologic complete response (pCR) rates according to demographic and clinical pathological features (n=164).

	pCR (n,%)	p
Age in years		
<65 years	70 (49.0%)	0.13
\geq 65 years	11 (68.8%)	
Menopausal status		
Premenopausal	33 (45.2%)	0.18
Postmenopausal	48 (55.8%)	
Tumor size		
T1-T2	51 (60.7%)	0.009
T3-T4	30 (40.0%)	
Lymph Nodes		
Negative	17 (56.7%)	0.48
Positive	64 (49.6%)	
TILs		
Low	26 (31.0%)	<0.001
Intermediate	29 (61.7%)	
High	26 (92.9%)	
Ki67		
< 30%	8 (30.8%)	0.02
\geq 30%	73 (54.9%)	
Grade		
1-2	37 (45.7%)	0.17
3	43 (56.6%)	
Hormone receptors (HR)		
HR negative	35 (59.3%)	0.10
HR positive	46 (46.0%)	
Use of anthracyclines		
No	12 (52.2%)	0.89
Yes	69 (50.7%)	
Dual anti-HER2 therapy		
No	66 (47.5%)	0.021
Yes	15 (75.0%)	

Disclosure(s):

Alberto Monroy Chargoy, MD: Consulting Fees (e.g., advisory boards): Roche, Janssen, and MSD (Ongoing)

PS09-07

SPAG5 as a companion prognostic and predictive test for management of early stage HER2 positive breast cancer (BCs)

Presenting Author(s) and Co-Author(s):

T. ABDEL-Fatah. Nottingham University Hospital NHS Trust, Nottingham, England, United Kingdom

G. Ball. Intellomx Limited, United States

D. Yeo. Nottingham University Hospital NHS Trust, United States

G. Hickman. Nottingham Trent University, United States

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

I. Ellis. University of Nottingham, United Kingdom

S. Chan. Nottingham University Hospital NHS Trust, United States

Background:

SPAG5 is a novel oncogene that is amplified in 40% of HER2+BC. Herein, we evaluated the prognostic and predictive significance of SPAG5 in HER2+ BC

Methods:

This retrospective cohort study included 2454 patients with HER2+BC derived from 6 cohorts in adjuvant (Adj) and neoadjuvant (NACT) settings.

Adj cohorts: The association between SPAG5 and survivals were evaluated in 1354 HER2+ BC who received Adj therapy: 1) HER2+ Adj transcript cohort (n=448): 31% (137/448) did not receive Anthracycline (AC), Taxane (TX), Trastuzumab (TZ) or Pertuzuman (PZ) whereas 20% (89/448) had received AC alone and 35% (155/448) received TZ + AC +/- TX (Median follow-up (MFU): 60 months (m)). 2) HER2+ Adj Molecular Taxonomy of BC International Consortium cohort (n=240): patients with ER- and lymph node (LN) + received Adj chemotherapy but none received TZ (MFU: 109 m). 3) HER2+ Adj Historical cohort (n=206): no TZ, AC or TX was received (MFU: 143 m). 4) HER2+/ER- cohort (n=101): AC alone was received; MFU: 62 m. 5) HER+ Adj TZ cohort (n=359): patients received TZ +TX +/-AC (MFU: 90 m).

Neo-Adjuvant cohort: the associations of SPAG5 protein expression with pathological complete response (pCR) was evaluated in 1100 BCs (MFU: 67 m) including 200 local cases participated in ROSCO trial. In this cohort; 73% (803/1100) received AC+TX. AC alone was given to 187/1100 (17%) whereas 88/1100 (8%) received TX alone. Of HER2+ BC, 14% (54/399) received AC +/- TX and 63% received TZ + TX +/-AC and 23% (92/399) received TZ + PZ + TX +/- AC.

Sections were IHC profiled for HER2, ER, PR, Ki67 and SPAG5 and stained for Fluorescent in situ hybridisation (FISH) using a novel triple colour probe (HER2/SPAG5/Ch17). ASCO guidelines recommendations were followed.

Results:

In univariate survival analysis, High SPAG5 (+) transcript was associated with shorter 5- year distant metastases free survival (5-y DRFS); $p < 0.0001$, compared to SPAG5 low (-) in HER2+ patients who did not receive TZ or AC whereas in those who received AC alone, SPAG5+ was associated with lower risk of 5-y DRFS than SPAG5- ($p < 0.001$). Multivariable Cox regression analysis showed that SPAG5+ transcript ; as well as LN status, was independently associated

with poor prognosis (HR (95% CI): 4.9 (2.0-12.0), $p < 0.001$). The interaction term between SPAG5 and AC was significantly associated with lower risk of DR. Multivariable Cox regression analysis for 10-year relapse free survival (10y-RFS) in HER2+ patients who did not receive AC or TZ confirmed that SPAG5+ protein expression ; as well as LN status and tumour size, were independently associated with poor prognosis (HR (95% CI): 2.1 (1.3, 3.5), $p=0.002$).

SPAG5+ predicted response for NACT +/- HER2 targeting agents. For instance; None of HER2 IHC 2+ with SPAG5- expression/ (0/191) either with HER2 FISH- (0/121) or HER2 FISH+ (0/70) achieved pCR whereas 51% (48/95) of those of HER2 IHC 2+/SPAG5+ achieved pCR ($p < 0.0001$). Similarly patients with HER2+ IHC 3+ /SPAG5+ achieved higher pCR rate compared to those with SPAG5- expression [73% (107/146) vs., 10% (14/135); respectively]; $p < 0.0001$. Noteworthy, after receiving TZ+ PZ +Texans +/- AC, patients with SPAG5+ achieved higher pCR rate compared to those with SPAG5- expression [85% (50/59) vs., 0% (0/51); respectively, $p < 0.001$]. Similarly in HER2 + BC patients who received TZ + TX +/- AC, SPAG5+ expression was associated with higher pCR [67% (67/101)] compared to those with SPAG5- [10% (11/107)]; $p < 0.001$. In HER2+ who received AC alone, SPAG5+ cases achieved higher pCR compared to those with SPAG5- [56% (20/36) vs., 6% (3/47); $p < 0.001$; respectively]. Multivariable logistic regression analysis showed that SPAG5+ expression as well as ER, HER2 IHC, grade, clinical TNM and HER2 targeting agents were independent predictors for pCR (OR (95% CI): 13.74 (5.76-32.79; $p < 0.001$).

Conclusions

SPAG5 is an independent poor prognostic factor in HER2+ BC and could help in distinguishing those who would and would not benefit from NACT and HER2 targeting agents.

Disclosure(s):

TAREK TMA ABDEL-Fatah, PhD, MD: No financial relationships to disclose

Arlene Chan, MBBS, FRACP, MMED: No financial relationships to disclose

PS09-08

Genomic characterization of endocrine resistance in ER+HER2+ breast cancers in the POETIC Trial

Presenting Author(s) and Co-Author(s):

M. Cheang. The Institute of Cancer Research, London, England, United Kingdom

X. Zhu. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

O. Sipos. The Institute of Cancer Research, Clinical Trials and Statistics Unit, London, United Kingdom.

A. Alataki. Breast Cancer Research, The Institute of Cancer Research, London, United States

M. Feldbauer. University of North Carolina, United States

E. López-Knowles. Breast Cancer Research, The Institute of Cancer Research, London, United States

H. Tovey. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

L. Kilburn. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

M. Bergamino Sirvén. Clinical Trial and Statistics Unit, The Institute of Cancer Research, London, United States

D. Patel. The Institute of Cancer Research, Clinical Trials and Statistics Unit, London, United Kingdom.

H. Xiao. Clinical Trial and Statistics Unit, The Institute of Cancer Research, London, United States

P. Maxwell. School of Medicine, Dentistry and Biomedical Sciences Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, United States

A. Skene. Royal Bournemouth and Christchurch NHS Foundation Trust, Bournemouth, United Kingdom

C. Holcombe. Liverpool University Hospital NHS Foundation Trust, United States

M. Salto-Tellez. The Institute of Cancer Research, London; Queen's University Belfast, Belfast, United Kingdom.

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

A. Dodson. UK NEQAS ICC & ISH, London, United Kingdom

I. Smith. The Royal Marsden NHS Foundation Trust, London, United States

J. Robertson. University of Nottingham, Nottingham, UK; University Hospitals of Derby and Burton, Derby, England, United Kingdom

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

G. Schuster. Breast Cancer Research, The Institute of Cancer Research, London, United States

R. Salgado. GZA-ZNA-Hospitals, Antwerp, Belgium; Peter Mac Callum Cancer Centre, Temse, Belgium

M. Dowsett. The Royal Marsden NHS Foundation Trust, London, UK; The Institute of Cancer Research, London, United Kingdom

K. Hoadley. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, United States

Background:

Mechanisms of resistance to endocrine therapy are not well understood within ER+HER2+ breast cancer (BC). Our prior work suggested that intrinsic HER2-Enriched (HER2E) molecular subtype predicts early resistance to aromatase inhibitors (AI) (Bergamino eBioMedicine 2022) and high on-treatment (on-Txt) Ki67 levels predict poor survival (Smith Lancet Oncol 2020). Improved early detection of persistent proliferating tumor cells with endocrine resistance pathways could be targeted by pre-emptive personalized therapy and reduction in recurrence. In this study, we proposed to further identify additional alterations/features from genomic and spatial data to provide unprecedented new insight into intrinsic and adaptive resistant pathways in tumor cells that may assist to identify molecular targets for treatment.

Materials:

POETIC was a phase III trial of post-menopausal patients with ER/PR+ invasive BC (n = 4480) randomized 2:1 to 2 weeks of peri-operative AI (POAI) vs control, followed by standard-of-care treatment. Ki67 was assessed by IHC and intra-tumor heterogeneity was evaluated (5-15 regions) for all the POETIC POAI samples (N = 2487). ER+HER2+ samples were classified as good responders (GR) or poor responders (PR) based on a reduction in Ki67 between pre-treatment (pre-Txt) and 2-week on-Txt samples. Tumor-infiltrating lymphocytes were assessed; multiplex Immunofluorescence (mIF) was performed to measure immune cell densities in tumor and stroma compartments (CD3, CD20, CD68, FOXP3, and CD3 FOXP3 co-expression). Gene expression profiles by BC360™ (Nanostring) on all 210 pairs of POAI treated ER+/HER2+; whole exome sequencing (WES, 100X) were performed on pre-Txt tumor and blood samples from 13 GR, 17 PR, and 9 HER2E GR. We performed GeoMx Whole Transcriptome on 4 pairs (pre-Txt and on-Txt) of GR and GeoMx Proteins (77 including IO proteins) on 6 pairs of GRs and 6 pairs of PRs.

Results:

The most frequently mutated genes were TP53, PIK3CA, GATA3, and CHD4. Only TP53 was associated with PR (Fisher's exact p=0.01). TP53 mutated cases had higher expression of TP53 mutant-like gene expression signature compared to wild-type cases (Wilcoxon test p=0.001), mIF FOXP3 (Wilcoxon test p = 0.0005), and CD68 (Wilcoxon test p = 0.019) density score. However, within the HER2-E subset, we found that TP53 mutations were associated with GR (Fisher's exact p=0.02).

We found spatial heterogeneity of Ki67 IHC levels across POAI samples. Examining IHC, while there was higher heterogeneity of Ki67 in the ER+HER2- samples (n = 2264) with 3% of pre-Txt and 9% on-Txt, 6% of ER+HER2+ samples (13/223, 6 LumA, 5 LumB, and 2 HER2E) showed heterogeneity of Ki67 exclusively on-Txt. Even in GR tumors with Ki67 < 10% on-Txt, we identified hotspots with retained proliferating Ki67+ cells after 2 weeks of POAI. The lobular tumors were GR and had characteristic CDH1 mutations. Importantly, cases with persistent areas of Ki67+ cells, regardless of Her2 status, were associated with late relapse.

To further explore intratumoral heterogeneity, we performed spatial whole transcriptomics profiling on 95 regions from 4 pairs of GR samples (Ki67 > 10% at baseline and Ki67 < 10% on-Txt) and found low intratumoral heterogeneity in the pre-Txt samples that increased at 2 weeks on-Txt. In a larger set of samples including both GR and PR with the GeoMx protein method, we found increased intratumoral heterogeneity in the PR vs GR.

Conclusion:

While TP53 mutation was generally a predictor of poor response; in HER2-E it paradoxically was associated with a good early response to aromatase inhibitor which warrants further investigation. Ki67 levels in ER+HER2+ showed higher intratumoral heterogeneity in a subset of patients on treatment suggesting the potential of persistent, proliferating cells leading to later recurrence. Our spatial RNA and protein data further observe the intratumoral heterogeneity that identifies pathways for use as potential spatial biomarkers.

Disclosure(s):

Maggie Chon U Cheang, PhD: Royalty: Veracyte (Ongoing)

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Guardant Health (Ongoing), Invitae (Ongoing), Natera (Ongoing), Personalis (Ongoing)

John Robertson, MB ChB BSc MD FRCS: Advisory Committee/Board Member: Carrick Therapeutics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): AstraZeneca (Terminated, October 29, 2023), Takeda (Terminated, October 29, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Carrick Therapeutics (Ongoing), FaHRAS (Ongoing), Oncimmune (Ongoing)

Roberto Salgado, MD, PhD: Advisory Committee/Board Member: Astra Zeneca (Terminated), BMS (Terminated), Daichii Sankyo (Terminated), Exact Sciences (Terminated); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Daichii Sankyo (Ongoing), Roche (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Terminated), BMS (Terminated), Merck (Terminated), Puma Biotechnology, Inc (Terminated)

PS09-09

Multiomics profiling and molecular classification refine precision treatment strategies for HER2-positive breast cancer

Presenting Author(s) and Co-Author(s):

Y. Li. Fudan University Shanghai Cancer Center, China (People's Republic)
D. Ma. Fudan University Shanghai Cancer Center, China (People's Republic)
X. Wu. Fudan University Shanghai Cancer Center, China (People's Republic)
L. Dai. Fudan University Shanghai Cancer Center, China (People's Republic)
S. Zhao. Fudan University Shanghai Cancer Center, China (People's Republic)
Y. Xu. Fudan University Shanghai Cancer Center, China (People's Republic)
X. Jin. Fudan University Shanghai Cancer Center, China (People's Republic)
X. Yi. Fudan University Shanghai Cancer Center, China (People's Republic)
Y. Wang. Fudan University Shanghai Cancer Center, China (People's Republic)
C. Lin. Fudan University Shanghai Cancer Center, China (People's Republic)
Y. Zhou. Fudan University Shanghai Cancer Center, China (People's Republic)
T. Fu. Fudan University Shanghai Cancer Center, China (People's Republic)
W. Yang. Fudan University Shanghai Cancer Center, China (People's Republic)
M. Li. Fudan University Shanghai Cancer Center, China (People's Republic)
H. Lv. Fudan University Shanghai Cancer Center, China (People's Republic)
Y. Jiang. Fudan University Shanghai Cancer Center, SHANGHAI, Shanghai, China (People's Republic)
Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

Background:

Anti-HER2 targeted therapy has achieved a series of breakthroughs. However, the current treatment strategy regarding HER2-positive breast cancer remains indiscriminate and lacks specificity, which limits the further improvement of overall treatment response and may lead to overtreatment and extra cost for some patients. Our study aims to reveal the molecular heterogeneity of HER2-positive breast cancer to guide a more precise treatment.

Patients and methods:

We selected HER2-positive breast cancer patients treated at Fudan University Shanghai Cancer Center between 2013 and 2014 and conducted genomic, transcriptomic, proteomic and metabolomic profiling. We then applied a non-negative matrix factorization algorithm on transcriptomic data to obtain an unsupervised classification. And we further studied the correlation between subtypes and corresponding treatment strategies in multiple cohorts of adjuvant and neoadjuvant therapy. For clinical accessibility, we developed convolutional neural network models through deep learning algorithm based on digital pathology to identify different subtypes. Additionally, we explored novel treatment strategies using the patient-derived organoids (PDOs) models.

Results: We established a novel multimomics cohort of 180 HER2- breast cancer patients and

classified them into four clinically significant molecular subtypes: (1) A classical HER2-enriched (HER2-CLA, N=51) subtype characterized by strong ERBB2 signaling and remarkable sensitivity to anti-HER2-targeted therapy (pathologic complete response with dual-targeted therapy: 93%). (2) an immunomodulatory (HER2-IM, N=36) subtype characterized by an immune-activated microenvironment and excellent prognosis with current treatment (no relapse in 97% of patients with a median follow-up of 86 months). Tumors of this subtype were therefore candidates for de-escalatory treatment. (3) A luminal-like (HER2-LUM, N=55) subtype distinguished by activated estrogen receptor signaling and (4) a basal/mesenchymal-like (HER2-BM, N=38) subtype enriched in activated receptor tyrosine kinase pathways. HER2-LUM and HER2-BM showed limited benefit from anti-HER2 therapy, and thus, add-on therapies might be needed. The overall area under the curve (AUC) of the convolutional neural network model based on digital pathology for identifying different subtypes is 0.77. In the exploration of novel treatment strategies, we found in the PDO model that the HER2-LUM subtype is more sensitive to a treatment regimen combining standard (chemotherapy and targeted therapy) with subsequent endocrine therapy and CDK4/6 inhibitors compared to other subtypes. Additionally, the HER2-BM subtype demonstrated greater sensitivity to treatment with a combination of EGFR inhibitors, PDGFR inhibitors or VEGFR inhibitors.

Conclusion:

We uncovered a high degree of molecular heterogeneity in HER2-positive breast cancer and illustrated its impact on treatment response. More precise treatment can be given according to the characteristics of different subtypes, which may achieve good efficacy and simultaneously reduce overtreatment and extra cost. The comprehensive profiling of HER2-positive breast cancers could also serve as an important resource for further exploration.

Key Words: HER2-positive breast cancer cohort; molecular classification; targeted therapy; precision treatment; de-escalatory treatment.

Disclosure(s):

Yi-Zhou Jiang, MD: No financial relationships to disclose

Zhi-Ming Shao, MD Ph.D: No financial relationships to disclose

PS12-02

Exploration of ctDNA Dynamics in the PACE Trial: A Randomized Phase II Study of Fulvestrant, Palbociclib, and Avelumab for HR+/HER2- Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
J. Fu. Dana-Farber Cancer Institute, United States
Y. Ren. Department of Biostatistics, Dana-Farber Cancer Institute, United States
R. Mahtani. Miami Cancer Institute, Plantation, Florida, United States
C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States
A. DeMichele. University of Pennsylvania, Philadelphia, Pennsylvania, United States
M. Cristofanilli. Weill Cornell Medicine, United States
J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States
K. Miller. Indiana University, United States
Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States
E. Riley. University of Louisville Health - Brown Cancer Center, United States
R. Qamar. Advocate Aurora Health, United States
P. Sharma. University of Kansas Medical Center Westwood, Westwood, Kansas City, Kansas, United States
S. Reid. Vanderbilt-Ingram Cancer Center, United States
N. Ko. Boston Medical Center, United States
Y. Liu. Pfizer Inc, San Diego, California, United States
H. Burstein. Dana-Farber Cancer Institute, United States
M. DeMeo. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

Background The PACE trial for HR+/HER2- metastatic breast cancer (MBC) prospectively evaluated whether continuation of the CDK4/6 inhibitor (CDK4/6i) palbociclib (P) beyond progression on prior CDK4/6i and aromatase inhibitor (AI), with a change in endocrine therapy (ET) to fulvestrant (F), improved outcomes beyond change to F alone, as well as explored the activity of a palbociclib, fulvestrant, and avelumab (P+F+A) triplet. The primary analysis did not show improvement in progression-free survival (PFS) with F+P versus F alone. In this analysis, an evaluation of serial translational PACE samples was performed to gain insights into the mutational landscape of HR+/HER2- MBC after prolonged exposure to CDK4/6i, evaluate early mutational dynamics with ongoing therapy, and identify potential genetic markers predictive of treatment response. Additionally, the identification of acquired mutations at the time of tumor progression could provide valuable information about mechanisms of treatment resistance.

Methods PACE is a multicenter randomized open-label investigator-initiated phase II trial. Eligible patients (pts) had HR+/HER2- evaluable MBC with prior progression on AI and any CDK4/6i after > 6 months (mo) of therapy in the MBC setting, or during/within 12 mo in the adjuvant setting, with no more than 1 prior line of chemotherapy for MBC. Pts were randomized 1:2:1 to F alone, F+P, or F+P+A, with tumor assessments every 8 weeks. Correlative samples

including circulating tumor DNA (ctDNA) were collected at baseline (BL), times of tumor assessments (C3D1), and end of study/progression (EOT). Targeted NGS (Guardant360) to evaluate mutations (somatic single nucleotide variants and indels) was performed. Kaplan-Meier survival curves were used for assessing PFS and the log-rank test for comparisons. McNemar's test with continuity correction was used to test the changes in the frequency of mutations. Results Of the 220 randomized pts, 211 contributed ctDNA samples (200 at BL, 129 at C3D1, 146 at EOT). Characteristics of the correlative science population were similar to the intention to treat population. At BL, the most common mutations observed were ESR1 (57%), TP53 (38%), PIK3CA (36%), GATA3 (20%) ATM (12%) and Rb1 (12%). The presence of a PIK3CA mutation vs WT-PIK3CA at BL was associated with shorter PFS in the F alone arm ($p=0.001$) but not in the F+P or F+P+A arms. ESR1 mutations present at baseline were D538G (34%), Y537S (21%), Y537N (15%), E380Q (10%) and L536H (4%). At C3D1, the most common mutations observed were ESR1 (47%), TP53 (33%), PIK3CA (26.1), GATA3 (18.1), ATM (13%) and PTEN (8.6%). Including only BL and C3D1 matched samples (N=124), the prevalence of ESR1 mutations decreased after 2 cycles of treatment (57% at BL vs 44% at C3D1), predominantly observed in the F+P+A arm. For those in any arm with at least 6 months of disease stability on study (N=53), the presence of an ESR1 D538G mutation decreased during therapy, with 38% having a mutation at BL, 24% at C3D1, and no pts gaining ESR1 D538G at C3D1. The prevalence of PIK3CA mutations also decreased on treatment (32% at BL to 24% at C3D1), with the greatest decrease in the F+P arm. A predictive model correlating early genomic dynamics and associations with outcome will be presented. Conclusions The PACE trial offers one of the largest clinical trial cohorts describing the genomic landscape of HR+/HER2- MBC post-CDK4/6 exposure. Results from this correlative study provide a comprehensive mutational landscape post-CDK4/6i, demonstrate associations between mutations and clinical outcomes, and suggest the potential value of early ctDNA dynamics in this setting.

PS12-03

p53 loss enables HR+ breast cancer escape from CDK4/6 inhibitor-induced quiescence via CDK2

Presenting Author(s) and Co-Author(s):

- R. Kudo. Memorial Sloan Kettering Cancer Center, Koto-City, Tokyo, Japan
- A. Safonov. Memorial Sloan Kettering Cancer Center, New York, United States
- E. da Silva. Memorial Sloan Kettering Cancer Center, New York, New York, United States
- Q. Li. Memorial Sloan Kettering Cancer Center, United States
- H. Shao. Memorial Sloan Kettering Cancer Center, United States
- M. will. Memorial Sloan Kettering Cancer Center, United States
- H. Nakshatri. Indiana University School of Medicine, Indianapolis, Indiana, United States
- J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States
- S. Goel. The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia
- A. Koff. Department of Molecular Biology, Memorial Sloan Kettering Cancer Center, United States
- B. Weigelt. Memorial Sloan Kettering Cancer Center, New York, New York, United States
- Q. Khan. University of Kansas Medical Center, United States
- P. Razavi. Memorial Sloan Kettering Cancer Center, New York, New York, United States
- S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

Background: Inhibition of CDK4/6 kinases has led to improved clinical outcomes in hormone receptor positive (HR+) breast cancer. While these are highly effective therapies, only a minority of patients experience long-term disease control. We sought to determine the genomic configurations and underlying mechanisms associated with long-term response. **Methods:** To identify genomic patterns associated with clinical outcomes, we analyzed a cohort of 447 patients with metastatic HR+ breast cancer treated at MSK with first-line CDK4/6 inhibitors (CDK4/6i) for which tumor-normal sequencing and long-term clinical follow up were available. To identify the pattern of genomic features associated with longer, intermediate, and short response, we implemented an elastic net Cox regression on binary pathogenic variant status of each gene as well as select clinical features (prior endocrine therapy, endocrine therapy partner, de novo metastatic status). Our principal aim was variable interpretability over pure predictive accuracy. Human HR+ breast cancer models including human breast cancer organoids and cell lines were utilized for mechanistic studies. For validation in a clinical setting, we analyzed the association between Ki67 score after neoadjuvant ribociclib plus endocrine therapy and pre-treatment gene mutation from the FELINE trial [NCT02712723] using a Fisher exact test. **Results:** Our model identified a “longer response” group (n = 124, 27.7%) from patients with a median progression free survival (PFS) of 32.5 months, compared with an “intermediate” (n = 224, 50.1%, median PFS = 13.7 months) and “short response” group (n = 99, 22.1%, median PFS = 5.84 months). TP53 and MDM2 pathogenic variant status were the most important variables to stratify between these groups, obtaining variable selection frequencies of 1.0 and 0.93 and mean hazard ratios of 2.02 and 1.38, respectively. To elucidate the mechanisms whereby the p53 pathway supports long term response, we generated isogenic and patient derived models of TP53 loss or MDM2 overexpression. Using immunoblotting and cell cycle assays, we found that drug-treated p53 KO cells and MDM2

overexpressing cells effectively suppressed RB1 phosphorylation and blocked in G1 after 24-48 hours. However, upon drug withdrawal, these cells could reenter the cell cycle and promote long-term tumor outgrowth. These effects we observed both in vitro and in vivo. Measures of long-term CDK4/6i response such as expression of senescence associated secretory phenotype genes was abrogated by TP53 loss. Mechanistically, we found persistent phosphorylation of the p130 RB1-like protein in the p53 KO cells. Phosphorylation of p130 impaired its interaction with E2F4, thereby blocking DREAM complex assembly and promoting cell cycle reentry. Inhibition of phosphorylation of p130 via p21 overexpression or by selective CDK2 inhibitors could restore irreversible cell cycle arrest in p53 KO cells. The combination of CDK2 and CDK4/6 inhibition led to long-term tumor growth suppression in models with mutant TP53. To validate the human relevance of TP53 mediating CDK4/6i response, we analyzed longitudinal samples from the FELINE trial that evaluated efficacy and feasibility of neoadjuvant ribociclib plus endocrine therapy. Of 45 evaluable patients, 13 (28.9%) harbored a pre-treatment TP53 loss of function variant. Of these 13 cases, 7 (53.8%) did not achieve a low (< 10%) Ki-67 upon surgical resection as compared to TP53 wildtype tumors (n=32), only one (3.2%) of which did not achieve a low Ki-67 [OR 32.1, 95% CI 3.28 – 1660.3, p = 0.00026]. Conclusion: Loss of p53 was strongly associated with lack of long-term response to CDK4/6i in patients. Complete inhibition of both CDK4/6 and CDK2 appears to be necessary in order to convert quiescent HR+ tumors cells into durably inhibited and effectively dormant cancers.

PS12-04

Inhibition of GPX4 enhances CDK4/6 inhibitor activity in breast cancer.

Presenting Author(s) and Co-Author(s):

M. Herrera Abreu. Institute of Cancer Research, London, England, United Kingdom

U. khalid. Institute of Cancer Research, United States

J. Ning. Institute of Cancer Research, United States

R. Cutts. The Institute of Cancer Research, United Kingdom

G. Wilson. Institute of Cancer Research, United States

C. Lord. Institute of Cancer Research, London, United States

A. Swain. Institute of Cancer Research, United Kingdom

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background: Cyclin D-dependent kinases 4 and 6 (CDK4/6) inhibitors (CDK4/6i) including palbociclib, ribociclib and abemaciclib in combination with endocrine therapy are the standard of care for patients with estrogen receptor-positive (ER+). Despite the success of these treatments, cytostasis is frequently observed, and novel strategies that enhance efficacy are required to eradicate residual cancer in the clinic. Methods: In the search of an effective drug combinations to enhance the efficacy of CDK4/6 inhibitors in breast cancer, we performed a whole genome CRISPR-Cas9 suppressor screen in MCF-7, an ER+ model. We also carried out transcriptomics, proteomics, and functional molecular biology analysis of breast cancer models treated with palbociclib to identify resistant mechanisms. Results: The whole genome CRISPR-Cas9 screen revealed that multiple genes involved in oxidative stress and ferroptosis modulated palbociclib sensitivity, being GPX4 the top sensitizing hit. GPX4 is a key glutathione peroxidase that protects against ferroptosis by catalysing the reduction of phospholipid and cholesterol hydroperoxides. CRISPR-depletion or drug inhibition of GPX4 increased sensitivity to palbociclib in ER+ breast cancer models, and in addition sensitised triple negative breast cancer models to palbociclib. Moreover, GPX4 null xenografts were highly sensitive to palbociclib in vivo. Transcriptomics and proteomics analysis showed that palbociclib upregulate pathways involved in oxidative stress and lipid metabolism promoting a redox-lipid imbalance. Palbociclib induced lipid peroxidation leading to a ferroptosis vulnerable state with GPX4 preventing cell death. Polyunsaturated fatty acids (PUFAs) are highly susceptible of lipid peroxidation, and pathways that regulate their abundance in membrane phospholipids were explored. Interestingly, in ER+ breast cancer models, lipid peroxidation relied on a peroxisome AGPAT3-dependent pathway rather than the classical ACSL4 pathway. Conclusion: Our studies demonstrate that quiescence induced by palbociclib results in a ferroptosis-vulnerable state that could be exploited through combination with GPX4 inhibitors to enhance sensitivity to CDK4/6 inhibition in breast cancer.

PS12-06

A phase 2 study of abemaciclib monotherapy for patients with retinoblastoma-positive (Rb+), triple-negative metastatic breast cancer

Presenting Author(s) and Co-Author(s):

S. Goel. The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia

B. Jovanović. Dana-Farber Cancer Institute, United States

X. Chu. Dana Farber Cancer Institute, United States

M. Hughes. Dana Farber Cancer Institute, United States

A. Mohammed-Abreu. Dana Farber Cancer Institute, United States

J. Kasparian. Dana-Farber Cancer Institute, United States

T. Erick. Dana-Farber Cancer Institute, United States

M. DiLullo. Dana-Farber Cancer Center, United States

E. Wrabel. Dana-Farber Cancer Institute, United States

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Schnitt. Harvard Medical School, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Cyclin-dependent kinase (CDK) 4/6 inhibitors can significantly extend survival when given in combination with endocrine therapy as treatment for hormone receptor-positive metastatic breast cancer. Preclinical studies suggest CDK4/6 inhibitor monotherapy might also be effective in a subset of triple-negative breast cancers (TNBCs), including those that express a functional retinoblastoma (RB) protein and/or those of the Luminal Androgen Receptor (LAR) subtype. Currently, the clinical activity of CDK4/6 inhibitor therapy in TNBC has not been reported. Methods: We conducted a single-arm phase II study of abemaciclib monotherapy in patients with locally advanced or metastatic TNBC. Key eligibility criteria included: (i) Measurable disease by RECIST 1.1; (ii) Between 1-3 prior lines of systemic therapy for advanced TNBC; (iii) RB-positive tumor (defined as $\geq 50\%$ of tumor cells staining positive for RB by immunohistochemistry [archival or fresh sample] on central testing); (iv) ECOG PS 0/1. Patients were treated with abemaciclib 200 mg orally (28-day cycles) twice daily until disease progression, unacceptable toxicity, withdrawal of consent, or death. Tumor biopsies were mandatory at baseline and C2D1 if tumor tissue was safely accessible. The primary outcome was objective response rate (ORR). Key secondary endpoints included progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR: CR + PR + SD ≥ 24 weeks), and safety and tolerability. The study had a two-stage design. Thirteen patients were enrolled in the first stage, with the plan to enrol a further 25 patients if at least one objective response was observed. Results: One unconfirmed partial response was observed in stage 1, and a total of 27 patients were enrolled before the trial was closed early due to slow accrual. The median age was 61 years and patients had received a median of 2 prior lines of systemic therapy for metastatic disease. Twelve patients had received prior immunotherapy. After a median follow-up of 28.5 months, the confirmed ORR was 0% and the CBR was 15%, with 4 of 27 patients experiencing stable disease for ≥ 24 weeks. The median PFS was 1.94 months (95% CI: 1.8 –

11.5 months), and the median OS was 8.44 months (95% CI: 4.6 – 15.6 months). There was no significant difference in PFS or OS between patients with PD-L1-positive versus PD-L1-negative disease, or Androgen Receptor (AR) positive versus negative tumors by immunohistochemistry. The most common adverse events of grade 2 or higher were diarrhea (41%), neutropenia (41%), anemia (30%), and nausea (30%). RNA-sequencing of baseline biopsies has been performed to identify biomarkers associated with clinical benefit, and results will be presented at the meeting. Conclusions: Abemaciclib monotherapy did not show clinical activity in patients with Rb+ metastatic TNBC. This finding suggests that future trials of CDK4/6 inhibition as monotherapy in TNBC are not warranted.

PS12-07

Phase II clinical trial of palbociclib and binimetinib in advanced triple-negative breast cancer (TNBC) with hyperactivation of ERK and/or CDK4/6

Presenting Author(s) and Co-Author(s):

R. Sánchez-Bayona. Medical Oncology Department, Hospital 12 de Octubre, Madrid. SOLTI Cancer Research Group, Barcelona, Spain

A. Cortes. Hospital Universitario Ramon y Cajal, Madrid, Spain

J. Cejalvo. Hospital Clínico Universitario de Valencia, Valencia, Spain

L. Manso. Hospital 12 de Octubre, Madrid, Spain

S. Morales. Hospital Universitario Arnau Villanova, Catalonia, Spain

J. Garcia-Saenz. Hospital Clínico San Carlos, Madrid, Spain

J. Silva. Hospital Universitario Fuenlabrada, Madrid, Spain

J. Guerra. Hospital Universitario de Fuenlabrada, Madrid, Spain

D. Malón-Giménez. Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain

S. Mouron. CNIO - Spanish National Cancer Research Center, United States

E. Caleiras. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

M. Quintela-Fandino. CNIO - Spanish National Cancer Research Center, Madrid, Spain

Background: We previously demonstrated that a kinase-based taxonomy of TNBC was most parsimonious than next-generation sequencing in defining TNBC subtypes associated with prognostic categories in early disease. The most aggressive TNBC variants were driven by a heterogeneous set of genetic aberrations that converged in the increased activity of 6 kinases: KIT, PNKP, PRKCE, P70S6K, ERK and CDK6 (Nat Commun; 9:3501-18). The combined inhibition of these kinases in pairs led to potent tumor regression in preclinical models, being the most powerful combination that one directed against CDK6 and ERK. This prompted us to design a phase II trial testing the combination of palbociclib (against CDK6) and binimetinib (against the ERK upstream kinase MEK, since no ERK inhibitor was available at that moment outside phase I trials) in advanced TNBC. Hyperactivation of CDK6 and/or ERK was selected as entry criterion. Trial design: This was a single-arm, prospective, multicentric, open-label, phase II investigator-initiated trial. CDK6 and phospho-ERK levels were measured in tumor samples by immunohistochemistry and normalized with a reference sample collection to a Z-score. Patients with scores for either kinase above the median were candidates for the trial. Key inclusion criteria included metastatic >18-year-old TNBC, adequate organ function, measurable disease, and progression to 1-2 prior treatment lines (including immunotherapy, and a PARP inhibitor in case of germline BRCA1/2 mutation). Patients started continuous oral binimetinib at 45 mg/BID and palbociclib 100 mg/day from days 1 to 21, in 28-day cycles. Patients experiencing \leq grade 1 tolerable side effects as the greatest toxicity were escalated to palbociclib to 125 in cycle 2. RECIST 1.1 and NCI CTC AE V 5.0 were used for assessing disease control (q8 weeks) and toxicity. The primary aims were to assess the efficacy and toxicity of this combination, and the secondary one to detect biomarkers of activity. At the time of trial design, in absence of available Sacituzumab for prescription, the reference PFS to beat in advanced lines for physician's choice in TNBC was 1.7 month (NEJM; 384:1529-41, 2021). With alpha and beta errors of 0.05 and 0.2, the minimum number of patients to demonstrate a 30% improvement in PFS to 2.5 months was 25. Results: From November 2020 to April 2023, 69 patients were screened and 24 entered the trial (5 positive for phospho-ERK; 2 for CDK6; 17 for both). Toxicity was generally mild and included grade 1-2 diarrhea (33% of the patients),

grade 1-2 asthenia (50%), grade 1-3 neutropenia (75%), grade 2 retinal toxicity (8.3%) and grade 3 rash (4.2%); no grade 4/5 toxicities were observed. Median PFS was 1.83 months (range 0.3 to 11.3+). Phospho-ERK and CDK6 levels were not correlated (Pearson's $R = -0.089$; $P = 0.68$); CDK6 levels did not show association with PFS time ($R = -0.120$; $P = 0.58$). Interestingly, however, phospho-ERK levels in the baseline tumor sample showed correlation with PFS time ($R = 0.428$; $P = 0.037$). Conclusion: The combination of palbociclib and binimetinib was generally safe, and PFS time showed correlation with baseline phosphorylation levels of ERK. However, the trial did not meet its primary endpoint.

PS12-08

MORPHEUS Hormone Receptor-Positive Breast Cancer: interim analysis of a Phase Ib/II, study of fulvestrant ± atezolizumab and abemaciclib triplet treatment in patients metastatic disease

Presenting Author(s) and Co-Author(s):

K. Jung. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Not Applicable, Republic of Korea

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

D. Yardley. Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, United States

S. Hurvitz. Fred Hutchinson Cancer Center, Seattle, Washington, United States

K. Lee. Center for Breast Cancer, National Cancer Center, Goyang, Republic of Korea

A. Sonnenblick. Oncology Division, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

S. Shachar. Tel Aviv University, Tel Aviv, Israel

A. Tan. Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, United States

E. Comen. MSKCC, United States

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

J. Zhu. Genentech, Inc., South San Francisco, California, United States

K. DuPree. Genentech, Inc., South San Francisco, California, United States

V. Breton. F. Hoffmann-La Roche Ltd, Canada

F. Young. Roche Products Ltd, Welwyn Garden City, United Kingdom

R. Schwab. Genentech, Inc., South San Francisco, California, United States

E. Cha. Genentech, Inc., South San Francisco, California, United States

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

BACKGROUND Endocrine therapy (ET) is the mainstay of treatment for metastatic hormone receptor-positive breast cancer (HR+ BC). ET resistance and disease progression are expected, thus novel therapies, like cancer immunotherapy, are needed. Prior data suggest that abemaciclib (abema), a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, has immunomodulatory activity. In the MORPHEUS HR+ BC study (NCT03280563), atezolizumab (atezo; anti-programmed death-ligand 1 [PD-L1]) was tested in combination with fulvestrant (FUL), with and without abema, in patients (pts) with HR+ metastatic BC. We present 24-week interim analyses. **METHODS** Pts with measurable disease progression during first- or second-line therapy for metastatic or inoperable locally advanced HR+ BC and prior treatment with a CDK4/6 inhibitor were randomized to receive FUL (control) or FUL + atezo (1200 mg intravenous every 3 weeks) or FUL + atezo + abema (150 mg twice a day); prior FUL was not permitted. Pts were treated

until loss of clinical benefit or unacceptable toxicity. Primary endpoints were objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and safety. Progression-free survival (PFS) was a secondary endpoint. Baseline tumor samples were analyzed for PD-L1 expression (SP263), CD8 T cell infiltration, and gene expression by RNAseq. RESULTS As of Dec 2022, 40, 31, and 25 pts (38, 30, and 20 evaluable pts) were randomized to atezo + abema + FUL, atezo + FUL, and FUL, respectively. Pts were followed for ≥ 24 weeks. Demographics were similar among the groups, with most pts receiving prior palbociclib (palbo) as part of their only prior metastatic therapy. Details and best confirmed ORRs are shown in the table. Median PFS was 6.34 months (95% confidence interval [CI] 5.52, 16.03) in the atezo + abema + FUL arm, 3.15 months (95% CI 1.51, 7.79) in the atezo + FUL arm, and 1.95 months (95% CI 1.45, 4.93) in the FUL arm. The hazard ratio of atezo + abema + FUL vs FUL was 0.43 (95% CI 0.24, 0.78). Safety data are shown in the table. Mild/moderate (grade 1/2) interstitial lung disease (ILD)/pneumonitis (7.7%) was observed in the atezo + abema + FUL arm. At baseline, tumors exhibited low prevalence of PD-L1 (median immune cells: 0.5%, tumor cells: 0%) and CD8 infiltration (12% inflamed phenotype), which did not associate with response in any arm. RNAseq analysis indicated that response to atezo + abema + FUL was strongly associated with low baseline expression levels of proliferation and metabolism signatures and trended with high expression of some immune signatures. CONCLUSIONS The triplet therapy of atezo + abema + FUL showed improved ORR and PFS compared with FUL monotherapy in the second- or third-line setting post-CDK4/6 inhibitor. This combination of atezo + abema + FUL was tolerable, with no unexpected safety signals, including no high-grade ILD/pneumonitis.

Efficacy and safety

Baseline characteristics	FUL n = 25	Atezo + FUL n = 31	Atezo + abema + FUL n = 40
Number of prior lines of therapy in a metastatic or locally advanced setting			
1L	24 (96.0%)	25 (80.6%)	35 (87.5%)
2L	1 (4.0%)	5 (16.1%)	5 (12.5%)
3L	0	1 (3.2%)*	0
Prior CDK4/6 inhibitor therapy			
Median duration (months)	13.31	14.36	15.28
25 th and 75 th percentiles	8.54–21.16	8.15–23.52	5.75–22.85
Palbociclib	23 (92.0%)	24 (77.4%)	35 (87.5%)
Efficacy			
	n = 20	n = 30	n = 38
ORR	2 (10.0%)	3 (10.0%)	10 (26.3%)
95% CI	(1.23, 31.79)	(2.11, 26.53)	(13.49, 43.10)
Clinical benefit rate	3 (15.0%)	13 (43.3%)	28 (73.7%)
95% CI	(3.21, 37.89)	(9.93, 42.28)	(26.31, 59.18)
Median PFS, months	1.95	3.15	6.34
95% CI	(1.45, 4.93)	(1.51, 7.79)	(5.52, 16.03)
Safety			
	n = 20	n = 30	n = 39
TRAEs (all grade)	35.0%	76.7%	97.4%
AEs Grade 3–4	15.0%	26.7%	82.1%
AEs leading to treatment discontinuation	0	6.7%	20.5%
AEs leading to dose modification/interruption	5%	16.7%	89.7%
Fatal AEs	0	0	0
Most common TRAEs ($\geq 20\%$ incidence rate)	0	Fatigue: 8 (26.7%); arthralgia: 6 (20.0%)	Diarrhea: 34 (87.2%); fatigue: 17 (43.6%); nausea: 13 (33.3%); vomiting: 10 (25.6%); anemia: 11 (28.2%); neutropenia: 10 (25.6%); hypothyroidism: 9 (23.1%); AST increased: 8 (20.5%); neutrophil count decreased: 8 (20.5%); rash: 8 (20.5%)
Most common irAEs ($\geq 20\%$ incidence rate)	0	0	AST increased (28.2%); ALT increased (20.5%); rash (25.6%); hypothyroidism (23.1%)

Data are number of patients (%), unless otherwise specified. * Patient was treated in the second line and incorrectly included in this group. Abema, abemaciclib; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; atezo, atezolizumab; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; ful, fulvestrant; irAE, immune-related adverse event; L, line; ORR, objective response rate; PFS, progression-free survival; TRAE, treatment-related adverse event.

PS12-09

Capivasertib plus cyclin-dependent kinase 4/6 inhibitor and fulvestrant in hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: updated Phase 1b analysis from CAPItello-292

Presenting Author(s) and Co-Author(s):

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

M. Beeram. The START Center, United States

V. Borges. University of Colorado Anschutz Medical Center, United States

M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France

J. Guimarães. Sherbrooke University and Integrated University Health and Social Services Center (CIUSS) of Saguenay-Lac-Saint-Jean, Quebec, Canada

T. Foukakis. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer Theme, Karolinska University Hospital, Karolinska Comprehensive Cancer Center, Solna, Sweden

A. Raskov Kodahl. Odense University Hospital, Odense, Denmark

P. Lau. Linear Clinical Research, Perth, Australia and University of Western Australia, Perth, Washington, Australia

E. Lim. Garvan Institute of Medical Research, St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia

I. Ługowska. Maria Skłodowska-Curie National Institute of Oncology, Warsaw, Poland

G. Rychlik. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. Gresty. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. Miller. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

R. Somnavilla. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

D. Sudhan. Research and Early Development, Oncology R&D, AstraZeneca, Waltham, Massachusetts, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

Background AKT pathway activation is implicated in endocrine therapy (ET) and cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) resistance in patients (pts) with HR+/HER2– advanced breast cancer (ABC). In CAPItello-291, capivasertib (C, a potent inhibitor of all 3 AKT isoforms) + fulvestrant (F) significantly improved PFS versus placebo F in pts with aromatase inhibitor-resistant HR+/HER2– ABC. Simultaneous inhibition of AKT and CDK4/6 pathways may delay CDK4/6i resistance or re-sensitize tumors to ET plus CDK4/6i, leading to improved clinical outcomes. CAPItello-292 (NCT04862663) is an ongoing Phase 1b/3 study examining the efficacy and safety of C + CDK4/6i (palbociclib [P], ribociclib [R]) + F in HR+/HER2– ABC. The recommended Phase 3 dose (RP3D) of C+P+F has been determined (C 400 mg BID, 4 days on/3 days off, P 125 mg, F 500 mg). Here we report ongoing Phase 1b data on C+P+F and C+R+F. Methods: Phase 1b of CAPItello-292 uses a keyboard design (mTPI-2) with the following planned doses: C 200 mg, 320 mg, 400 mg; P 75 mg, 100 mg, 125 mg; R 200 mg, 400 mg, 600 mg; F is fixed at 500 mg every 28 days + loading dose on cycle 1 day 15. Starting

doses for C+P+F were C 320 mg BID, 4 days on/3 days off, P 125 mg QD) for 21 days of each 28-day cycle. Starting doses for C+R+F (ongoing) are C 400 mg BID, 4 days on/3 days off, R 400 mg QD for 21 days of each 28-day cycle. Eligible pts have HR+/HER2- ABC and ≥ 1 prior ET in the advanced setting or disease recurrence within 12 months of completing (neo)adjuvant ET (HER2- defined as immunohistochemistry [IHC] 0, or 1-positive or IHC2-positive/in situ hybridization-negative). Prior use of CDK4/6i, selective estrogen receptor degraders, and chemotherapy is permitted in Phase 1b. Phase 1b primary objectives: assess safety/tolerability; confirm RP3D. Objective response and clinical benefit rates (24 weeks; RECIST v1.1) were also assessed. Results: At data cut-off (Apr 21, 2023), 40 pts (median age: 58.5 years [range 38–82]) who were heavily pre-treated (as follows: 82.5% [33/40] prior CDK4/6i; 47.5% [19/40] prior F; 70.0% [28/40] prior chemotherapy [median 1.5 lines]) were treated with C+P+F. No new dose-limiting toxicities (DLTs) were observed since determination of RP3D. The most frequent adverse events (AEs) occurring in $>40\%$ of pts were diarrhea (70.0% [28/40]; 1/28 grade [G] ≥ 3), neutropenia (55.0% [22/40]; 20/22 G ≥ 3), fatigue, and nausea (both 42.5% [17/40]; all G1/2). Hyperglycemia occurred in 17.5% (7/40) pts (1/7 G3). No treatment-related deaths or new safety risks were identified. At the RP3D, the median (range) duration of exposure to C was 8.6 months (1.7–14.1); 5/8 pts with measurable disease at baseline had confirmed partial response (objective response rate: 62.5%, 95% confidence interval [CI] 24.5–91.5). Two additional pts had stable disease ≥ 7 weeks as a best objective response. At 24 weeks, the clinical benefit rate was 53.8% (7/13; 95% CI 25.1–80.8). Enrollment into C+R+F is ongoing: as of May 05, 2023, 8 pts had been dosed (6/8 pts had completed cycle 1). Based on clinical and safety review, the safety review committee has endorsed dose escalation to the highest dose level of R; no DLTs have been reported so far, although data are preliminary. Preliminary ctDNA analyses of pts treated with C+P/R+F will be presented. Conclusions: C+P+F was tolerable in heavily pre-treated pts with HR+/HER2- ABC at all dose levels; AEs were as expected, given the known safety profile of the individual treatments. Evidence of clinical activity has been observed in pts treated with the RP3D; data collection is ongoing. Preliminary safety analysis of C+R+F suggests no critical tolerability concerns; more pts and longer follow-up is required to characterize the safety of the combination. Updated data will be presented. Funding: AstraZeneca Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited)

PS10-01

Hormonal Contraception and Breast Cancer Risk for Carriers of Germline Pathogenic Variants in BRCA1 and BRCA2

Presenting Author(s) and Co-Author(s):

K. Phillips. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

J. Kotsopoulos. University of Toronto, Toronto, Ontario, Canada

S. Domchek. University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, United States

J. Chamberlain. Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Australia

J. Bassett. Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Australia

A. Aeilts. Division of Human Genetics, Department of Internal Medicine, The Ohio State University, Columbus, Ohio, United States

I. Andrulis. University of Toronto, United States

S. Buys. Huntsman Cancer Institute at the University of Utah, Utah, United States

W. Cui. Department of Medical Oncology, Peter MacCallum Cancer Centre and The Sir Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia

M. Daly. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Eisen. Sunnybrook Health Sciences Center, United States

W. Foulkes. McGill University Medical School, Department of Human Genetics, Canada

M. Friedlander. Department of Medical Oncology Prince of Wales Hospital and Clinical School UNSW, Sydney, Australia

J. Gronwald. International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Poland

J. Hopper. University of Melbourne, United States

E. John. Stanford University, United States

B. Karlan. UCLA Jonsson Comprehensive Cancer Center and David Geffen School of Medicine at UCLA, California, United States

R. Kim. Division of Medical Oncology and Hematology, University Health Network, Sinai Health System, Ontario Institute for Cancer Research, Toronto, Ontario, Canada

J. Lubiński. Pomeranian Medical University, Szczecin, Poland

K. Metcalfe. University of Toronto, Toronto, Ontario, Canada

K. Nathanson. University of Pennsylvania School of Medicine, Pennsylvania, United States

C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria

H. Symecko. Basser Center for BRCA, University of Pennsylvania, United States

N. Tung. Beth Israel Deaconess Medical Center, Boston, United States

S. Narod. Women's College Research Institute, Toronto, Ontario, Canada

M. Terry. Columbia University, United States

R. Milne. Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Australia

BACKGROUND: Current use of hormonal contraception is associated with a 20-30% relative increase in the risk of breast cancer (BC) for women in the general population compared with never using. Longer duration of use is associated with higher risk, and the risk remains elevated above that of never users for at least 5 years after cessation. Most published data are for various formulations of the combined oral contraceptive pill, but associations are similar for progestogen-only contraceptives, including intrauterine devices. For women in the general population who use hormonal contraceptives in their 20s and 30s, when baseline BC risk for most women is low, these increased relative risks translate into only small increases in absolute risk. It is unclear whether use of hormonal contraceptives increases BC risk for women carrying a germline BRCA1 or BRCA2 pathogenic variant (PV). These women are at markedly higher risk of early-onset BC, so even slightly increased relative risks could translate to important increases in their absolute risk of BC. This study assessed the association between use of any hormonal contraception and BC risk for BRCA1 and BRCA2 PV carriers using individual participant data from four prospective cohorts. **METHODS:** Data from females born after 1920 with a PV in BRCA1 or BRCA2 and no history of cancer or bilateral mastectomy at cohort entry were analyzed. Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for BC (invasive disease or ductal carcinoma in situ) associated with use of hormonal contraceptives for at least 1 year, with age as the timescale, entry at cohort enrolment, and censoring at the earlier of bilateral mastectomy, death, diagnosis of another cancer or last follow-up. Analyses were adjusted for study, birth cohort, first-degree family history of BC, parity, premenopausal bilateral oophorectomy and menopausal status. Current use of hormonal contraceptives was defined as use within the previous year, to account for cessation of use due to BC symptoms or clinical investigation. **RESULTS:** Of 3,882 BRCA1 and 1,509 BRCA2 PV carriers, 53% and 71%, respectively had ever used hormonal contraceptives (for at least one year). The median cumulative duration of hormonal contraceptive use was 4.8 and 5.7 years, respectively. Overall, 488 BRCA1 and 191 BRCA2 PV carriers developed incident BC during a median of 5.9 and 5.6 years of follow-up, respectively. For BRCA1 PV carriers, use of hormonal contraceptives for at least 1 year was associated with increased BC risk (HR [95% CI]: 1.29 [1.04-1.60] $p=0.019$). BC risk increased with longer cumulative duration of hormonal contraceptive use (HR [95% CI]: 1.13 [0.88-1.45] $p=0.35$, 1.48 [1.11-1.96] $p=0.007$ and 1.56 [1.13-2.17] $p=0.007$ for 1-5, 6-10 and >10 years of use, respectively), with an estimated proportional increase in risk of 3% (1%-5%, $p=0.002$) for each additional year of use. For BRCA2 PV carriers, there was no evidence that current or past use, or cumulative duration of use, were associated with increased risk of BC, but confidence intervals on the HRs were wide. **CONCLUSION:** Hormonal contraceptive use is associated with an increased risk of BC for women carrying PVs in BRCA1 and risk increases with cumulative duration of use. Hormonal contraceptives are an important healthcare option for women; they provide excellent contraceptive efficacy and reduce risks of ovarian and endometrial cancer. Decisions about use of hormonal contraceptives in women at increased risk for BC due to BRCA1 PVs need to carefully weigh the risks and benefits; while shorter-term use may result in only small increases, prolonged cumulative use may result in larger increases in absolute BC risk that may not be acceptable to some women.

PS10-02

Association between Germline Mutation Status and Overall Survival among Women with Breast Cancer in Population-based Studies in the United States

Presenting Author(s) and Co-Author(s):

S. Yadav. Mayo Clinic, Rochester, Minnesota, United States

C. Hu. Mayo Clinic, United States

N. Boddicker. Mayo Clinic, United States

C. CONSORTIUM. NA, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

Background: The influence of germline pathogenic variants (PVs) in breast cancer predisposition genes on overall survival (OS) after breast cancer diagnosis is not well defined, particularly for PVs in genes other than BRCA1 and BRCA2, and in the context of estrogen-receptor (ER) positive breast cancer. Even for BRCA1/2, OS estimates in women with breast cancer have primarily been derived from high-risk women qualifying for genetic testing due to young age at diagnosis or family history of cancer, and OS estimates by germline PV status from population-based studies are lacking. Methods: The study included 16,797 prospectively followed women with locoregional breast cancer within the population-based CARRIERS study who underwent surgical resection of the primary tumor. OS was compared between germline PV carriers and non-carriers (negative for germline PVs in 12 breast cancer predisposition genes) from the time of breast cancer diagnosis in a multivariable Cox proportional hazard regression analysis adjusting for age and menopausal status at diagnosis, race/ethnicity, ER status, type of surgery, use of adjuvant radiation, chemotherapy and endocrine agents, and prophylactic oophorectomy. Further subset analyses by race/ethnicity ER status of the primary tumor and adjusting for relevant covariates were also performed. Results: Germline PVs in ATM, BRCA1, BRCA2, CHEK2, or PALB2 were detected in 5.6% of the women in the study [ATM: 142 (0.8%), BRCA1: 206 (1.2%), BRCA2: 260 (1.5%), CHEK2:167 (1.0%) and PALB2:116 (0.7%)]. Compared to non-carriers, a significant difference in OS was not observed for germline PV carriers in ATM, BRCA1, BRCA2, or CHEK2 in the overall study population. However, a trend towards worse OS was noted for PALB2 PV carriers compared to non-carriers although this was not statistically significant (Hazard Ratio (HR): 1.36, 95%CI: 0.98 – 1.89, p=0.06). Further subset analysis by race/ethnicity demonstrated that the OS was significantly worse among Black PALB2 PV carriers (HR: 3.11, 95%CI: 1.74 – 5.55, p< 0.001) but not in non-Hispanic White PALB2 PV carriers (HR: 1.00, 95%CI: 0.59 – 1.70, p=0.98) compared to non-carriers within the same race/ethnicity. Among 12,780 women with ER+ breast cancer, compared to non-carriers, OS was significantly worse in BRCA2 PV carriers (HR: 1.51, 95%CI: 1.06 – 2.16, p=0.02) and a trend towards worse OS was observed in BRCA1 PV carriers (HR:1.53, 95%CI:0.93 – 2.51, p=0.09). Among women with ER-negative breast cancer, a significant difference in OS was not observed between PV carriers in each of the five genes and non-carriers. Conclusions: The differences in OS by race/ethnicity in PALB2 PV carriers and by ER status of the tumor in BRCA2 PV carriers warrant further investigation of underlying tumor biology and assessment of endocrine sensitivity of breast cancer in germline PV carriers.

PS10-03

Impact of Baseline Oestradiol and Testosterone on the Preventive Effect of Anastrozole

Presenting Author(s) and Co-Author(s):

J. Cuzick. Queen Mary University of London, London, England, United Kingdom

K. Chu. Queen Mary University of London, United States

b. keevil. Manchester University NHS Foundation Trust, United States

A. Howell. University of Manchester, United States

B. Bonanni. 4. Division of Cancer Prevention and Genetics, European Institute of Oncology, IRCCS, Milan, Italy

E. Gareth. University of Manchester, United States

K. Holli. University of Tamoere, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

N. Zdenkowski. Breast Cancer Trials, Newcastle, New South Wales, Australia

S. Cummings. UCSF, San Francisco, California, United States

M. Dowsett. The Royal Marsden NHS Foundation Trust, London, UK; The Institute of Cancer Research, London, United Kingdom

It is well known that serum levels of oestradiol and testosterone, esp free hormone levels, influence the risk of developing breast cancer in postmenopausal women (Thomas et al 1997, Hankinson et al 1998, Kaaks et al 2005, Tin Tin et al 2021). However very little is known about how these hormone levels influence the effectiveness of aromatase inhibitors. In the IBIS-II Prevention Trial we compared anastrozole to placebo in 3864 women at high risk of breast cancer (Cuzick et al 2020). Of these women 3644 (94.3%) had a baseline blood sample. In those with a valid blood sample, 72 in the anastrozole arm and 142 in the placebo arm developed breast cancer (including DCIS) after 12.9 years of follow up (OR = 0.49, 95% CI 0.37–0.66 $P < 0.0001$). For each case two controls were selected, matched on age, treatment arm and follow up longer than the matching case. In these women oestradiol (E2), testosterone (Testo) and SHBG were measured by liquid chromatography – tandem mass spectroscopy, and E2/SHBG and Testo/SHBG ratios were computed to approximate free hormone levels, and analysed in quartiles. Hormone replacement therapy was not allowed during the trial, and women with use within 3 months prior to entry or outlier hormone values were excluded from these analyses. In the placebo arm higher levels of both of these ratios were associated with a higher breast cancer rate (OR per quartile 1.25 (1.04-1.59), $P = 0.018$) for E2/SHBG and (OR per quartile 1.22 (1.02-1.47), $P = 0.032$) for Testo/SHBG), whereas no significant effect was seen in the anastrozole arm (OR = 1.05 (0.81-1.37), and 1.16 (0.90-1.49), resp) (Table). Neither treatment interaction was significant. Absolute numbers of cases were similar between the anastrozole and placebo arms in the lowest quartile of E2/SHBG (18 anastrozole, 22 placebo), but higher numbers were seen in the placebo arm for the other quartiles. Similar results were seen for testo/SHBG, and supportive, but weaker results were seen for these two hormones without an SHBG adjustment, SHBG and BMI at entry. Adjusting for other risk factors had no influence on these findings. Effect sizes were similar during the 5 year treatment period and thereafter. There were too few ER negative cases to compare results by receptor status. Vasomotor side effects were higher with increasing E2/SHBG levels in both arms, but no other hormone showed an effect, and no hormone level was significantly associated with gynaecologic or musculoskeletal side effects. As aromatase inhibitors effectively eliminate the

production of oestradiol in postmenopausal women, these results suggest they may be more effective in postmenopausal women with high oestradiol or testosterone levels, and raise questions about their value in women in the lower quartile of serum levels for these hormones for prevention and possibly adjuvant treatment. Table: Risk of breast cancer by quartiles of the oestradiol/SHBG in ratio high risk women treated with anastrozole or placebo.

Quartile	Anastrozole			Placebo		
	N		OR (95% CI)	N		OR (95% CI)
	Case	Control		Case	Control	
Q1 (<0.167)	18	31	1.0 (ref)	22	72	1.0 (ref)
Q2 (0.167 to <0.279)	14	38	0.63 (0.27-1.48)	31	66	1.54 (0.81-2.92)
Q3 (0.279 to <0.617)	21	40	0.90 (0.41-1.98)	46	63	2.39 (1.30-4.40)
Q4 (=0.617)	19	31	1.06 (0.47-2.38)	43	73	1.93 (1.05-3.54)
Total	72	140	1.21 (0.69-2.15)*	142	274	1.70 (1.13-2.58)*
OR per quartile	1.05 (0.81-1.37) P = 0.70 (trend)			1.25 (1.04-1.50) P = 0.018 (trend)		
P-value treatment interaction term				0.30		

*Q3+Q4 vs Q1+Q2

PS10-04

The Landscape of Somatic Genetic Alterations in Breast Cancers from Carriers of Germline Pathogenic Variants in DNA-repair Genes

Presenting Author(s) and Co-Author(s):

S. Yadav. Mayo Clinic, Rochester, Minnesota, United States

A. Arafa. University of Minnesota Masonic Cancer Center, United States

E. Teslow. Tempus Labs, Inc., United States

M. Huang. Tempus Labs, Inc., United States

M. Stoppler. Tempus Labs, Inc., United States

C. Chao. Tempus Labs, United States

E. Antonarakis. University of Minnesota Masonic Cancer Center, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

Background: Hereditary breast cancer in carriers of germline pathogenic or likely pathogenic variants (PVs) in ATM, BRCA1, BRCA2, CHEK2, and PALB2 have unique clinicopathological characteristics compared to sporadic breast cancer. However, very little is known about the underlying differences in somatic genetic alterations between hereditary and sporadic breast cancer. **Methods:** The study included 7,533 individuals with breast cancer subjected to Tempus xT tumor-normal matched sequencing (596-648 genes). The frequencies of the somatic genetic alterations in each gene were compared separately between tumors arising in individuals with incidental germline PVs (gATM, gBRCA1, gBRCA2, gCHEK2, gPALB2) and sporadic breast tumors. Sporadic tumors were identified as individuals with no detected incidental germline PVs in these 5 genes. Comparisons were made by either Pearson's Chi-squared or Fisher's exact test, with false discovery rate (FDR) correction for multiple testing. Breast cancer subtype was determined based on the record of IHC positivity for ER, PR, or HER2. Detection of ERBB2 (HER2) gene amplifications via DNA sequencing was also used to classify samples as HER2+ in the absence of available IHC data. **Results:** The median age at breast cancer diagnosis for the cohort was 56 years. More than two-thirds of the patients were White (73%) while 14% identified as Black or African American. The overall frequency of incidental germline PVs in each gene was 0.8% for gATM, 1.4% for gBRCA1, 2.1% for gBRCA2, 1.0% for CHEK2, and 0.7% for PALB2. A total of 3,648 (48.4%) tumors were ER+/PR+/HER2-, 1,297 (17.2%) were triple-negative (TNBC), 841 (11.2%) were HER2+ and 1,747 (23.2%) could not be classified due to missing ER, PR or HER2 status, or absence of detected ERBB2 amplifications. Among ER+/PR+/HER2- breast cancers, compared to sporadic tumors, ESR1 mutations were significantly enriched in gATM carriers (33% vs. 11%, q-value 0.05), TP53 alterations were significantly enriched in gBRCA1 PV carriers (69% vs. 30%, q-value < 0.001) but depleted in gATM (12% vs. 30%, q-value 0.4) and gCHEK2 PV carriers (5.4% vs. 30%, q-value 0.06), and PIK3CA (14% vs. 35%, q-value 0.001) and CCND1 (3.4% vs. 17%, q-value 0.02) alterations were significantly lower in gBRCA2 PV carriers. Among TNBC, TP53 alterations were also significantly higher in gBRCA1 PV carriers compared to sporadic tumors (96% vs. 69%, q-value 0.004). In HER2+ breast cancers, ERBB2 alterations were observed in approximately two-thirds of the tumors, and a significant difference was not observed between incidental hereditary and sporadic tumors. Among ER+/PR+/HER2- tumors, although not statistically significant, the frequency of ESR1 (3.1% vs. 11%, q-value >0.9), PIK3CA (12% vs. 35%, q-value 0.2) alterations were lower in incidental gBRCA1 versus sporadic tumors, FGFR1 alterations were lower in incidental gBRCA1 (6.2% vs. 13%, q-value >0.9) and incidental gBRCA2 (3.4% vs. 13%, q-value 0.13) but enriched in incidental gATM (33% vs. 13%, q-value 0.05). **Conclusions:**

The observed differences in the frequencies of CCND1, ESR1, PIK3CA, TP53, and other key genetic alterations between incidental hereditary and sporadic breast cancer highlight the unique tumor biology of breast cancer in germline PV carriers and have significant implications for understanding tumorigenesis and identifying therapeutic strategies for the management of hereditary breast cancer.

PS10-06

Contribution of a breast cancer polygenic risk score to mammography artificial intelligence models and breast density for long term breast cancer risk prediction

Presenting Author(s) and Co-Author(s):

C. Vachon. Mayo Clinic, Rochester, Minnesota, United States

C. Scott. Mayo Clinic, United States

I. Banerjee. Mayo Clinic, United States

R. Correa Moderno. Mayo Clinic, United States

D. Hursh. Mayo Clinic, United States

M. Jensen. Mayo Clinic, United States

Y. Wang. Mayo Clinic, United States

K. Brandt. Mayo Clinic, United States

K. Kerlikowske. University of California, San Francisco, United States

S. Pruthi. Mayo Clinic, Rochester, Minnesota, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

S. Winham. Mayo Clinic, United States

Artificial intelligence (AI) models based on deep learning of mammogram images have been developed for lesion detection and diagnosis as well as breast cancer (BC) risk. We and others have shown that these AI models, coupled with breast density, predict long-term breast cancer risk. Common germline genetic variation, in particular a polygenic risk score (PRS) that captures the cumulative impact of hundreds of common risk variants, has been shown associated with 3-fold increased BC risk. The BC-PRS may complement imaging risk factors to improve identification of women at high BC risk and better target prevention strategies. We evaluated the contribution of a BC-PRS to two imaging-based AI models (Transpara AI cancer detection system and Mirai 5-year risk) and breast density measures to long-term BC risk. We hypothesized that the BC-PRS will improve long-term risk prediction above AI and density measures. We examined this hypothesis within a cohort of 10,271 women enrolled to the Mayo Clinic Biobank between 2009 and 2015. Eligible women had no prior cancer, were ages 35 to 85, had a full-field digital screening mammogram within two years of enrollment and genotyping by Regeneron. Incident invasive and DCIS BC was identified through the Mayo tumor registry and follow-up questionnaires, and person years were calculated from date of mammogram through date of BC, last mammogram at Mayo or last questionnaire. We estimated Transpara AI malignancy score (1-10), 5-year Mirai risk and Volpara volumetric density measures (volumetric percent density, dense volume) on screening mammograms at enrollment and obtained clinical BI-RADS density. We calculated the BC-PRS using 268 SNPs (of the 313-SNP score) and the weighted sum of the SNPs using odds ratios from the largest BC GWAS of European ancestry to date. We performed cox proportional hazards regression adjusting for age and BMI to estimate hazard ratios (HRs), 95% confidence intervals (CI), and C-statistics (AUC) to describe the contribution of BC-PRS (per standard deviation (SD)) to the association of AI scores and breast density with BC risk. Likelihood ratio tests (LRT) and bootstrapping were used to compare model performance with vs. without inclusion of BC-PRS, at 10-years follow-up. Comparisons to the Tyrer-Cuzick model are ongoing. Over a median of 9.1 years (Interquartile range, 6.8 to 10.6), 446 incident BC were identified of which 285 invasive and 103 DCIS were confirmed by pathology report (60 were self-reported); 399 (256 invasive) occurred within 10 years and were used in primary analyses. Transpara score [HR per 1 unit=1.18 (1.14,

1.23), AUC=0.655 (0.628, 0.682)] and Mirai risk [HR per SD log risk=1.54 (1.43, 1.65), AUC=0.681 (0.655, 0.706)] were both associated with BC. All three breast density measures were also significantly associated with BC, including in models with AI scores (Table). Addition of the BC-PRS to models with AI scores and breast density improved both model fit (All $P_{LRT} < 0.001$; Table) and discrimination, with increases in AUC ranging from 0.033 to 0.034 for models with Transpara and density and 0.025 to 0.026 for models with Mirai and density (all P-values < 0.001 ; Table). Analyses restricted to invasive BC showed identical results. But, the BC-PRS contribution at 5-year follow-up was attenuated. In this cohort study, we found BC-PRS contributed to long-term risk prediction of BC above imaging AI models and breast density. Imaging and genetic risk factors are complementary and may outperform existing risk models and provide more accurate risk assessment to aid in precision prevention strategies.

Table. Contribution of a polygenic risk score for breast cancer (BC-PRS) to association of AI scores (Transpara, Mirai), breast density measures and BC risk at 10-years

Model variables	Models without BC-PRS		Models with BC-PRS	
	HR (95% CI)	AUC (95% CI)	HR (95% CI)	AUC (95% CI)
Transpara (per unit)	1.17 (1.12, 1.20)	0.670 (0.644, 0.696)	1.15 (1.11, 1.20)	0.703 (0.679, 0.728)
VBD% (log)*	1.41 (1.25, 1.60)		1.40 (1.23, 1.58)	
BC-PRS*	-----		1.51 (1.37, 1.67)	
Transpara (per unit)	1.16 (1.12, 1.21)	0.670 (0.644, 0.697)	1.15 (1.11, 1.20)	0.704 (0.679, 0.728)
DV (log)*	1.31 (1.18, 1.45)		1.29 (1.17, 1.43)	
BC-PRS*	-----		1.51 (1.37, 1.67)	
Transpara (per unit)	1.16 (1.12, 1.20)	0.668 (0.642, 0.694)	1.15 (1.11, 1.19)	0.703 (0.678, 0.727)
BI-RADS a	0.74 (0.54, 1.02)		0.77 (0.56, 1.06)	
BI-RADS b	1.0 (ref)		1.0 (ref)	
BI-RADS c	1.64 (1.30, 2.05)		1.61 (1.29, 2.02)	
BI-RADS d	1.72 (0.83, 3.56)		1.64 (0.79, 3.39)	
BC-PRS*	-----		1.51 (1.37, 1.67)	
MIRAI 5 yr Risk (log)*	1.48 (1.37, 1.60)	0.681 (0.655, 0.706)	1.44 (1.33, 1.56)	0.711 (0.687, 0.736)
VBD% (log)*	1.37 (1.21, 1.55)		1.36 (1.20, 1.54)	
BC-PRS*	-----		1.50 (1.36, 1.65)	
MIRAI 5 yr Risk (log)*	1.48 (1.37, 1.60)	0.686 (0.661, 0.712)	1.44 (1.33, 1.56)	0.710 (0.685, 0.735)
DV (log)*	1.26 (1.14, 1.40)		1.25 (1.13, 1.39)	
BC-PRS*	-----		1.50 (1.36, 1.66)	
MIRAI 5 yr Risk (log)*	1.46 (1.35, 1.58)	0.682 (0.657, 0.708)	1.43 (1.32, 1.54)	0.709 (0.684, 0.734)
BI-RADS a	0.75 (0.54, 1.03)		0.76 (0.55, 1.05)	
BI-RADS b	1.0 (ref)		1.0 (ref)	
BI-RADS c	1.51 (1.20, 1.90)		1.51 (1.20, 1.90)	
BI-RADS d	1.53 (0.74, 3.17)		1.44 (0.69, 2.97)	
BC-PRS*	-----		1.50 (1.36, 1.66)	

*per standard deviation

PS10-07

A second-generation polygenic risk score (PRS) based on genetic ancestry improves breast cancer (BC) risk prediction for all ancestries

Presenting Author(s) and Co-Author(s):

T. Simmons. Myriad Genetics, Inc., Salt Lake City, Utah, United States

E. Hughes. Myriad Genetics, Inc., United States

D. Pruss. Myriad Genetics, Inc., United States

M. Kucera. Myriad Genetics, Inc., United States

B. Roa. Myriad Genetics, Inc., United States

T. Judkins. Myriad Genetics, Inc., United States

T. Slavin. Myriad Genetics, Inc., United States

V. Abkevich. Myriad Genetics, Inc., United States

R. Hoff. Myriad Genetics, Inc., United States

S. Jammulapati. Myriad Genetics, Inc., United States

S. Wagner. Myriad Genetics, Inc., United States

D. Muzzey. Myriad Genetics, Inc., United States

J. Lanchbury. Myriad Genetics, Inc., United States

A. Gutin. Myriad Genetics, Inc., United States

Background: Common genetic variants, mainly single-nucleotide polymorphisms (SNPs) explain substantial genetic susceptibility to BC. PRS have been developed to quantify the combined effects of BC-associated SNPs, providing important information about BC risk. Historically, genome-wide association studies have been conducted in predominantly European populations, resulting in miscalibrated and inaccurate PRS for non-Europeans. We previously described a multiple-ancestry PRS (MA-PRS-149) based on 56 ancestry-informative and 93 BC-associated SNPs. The MA-PRS-149 achieved accuracy for all women by characterizing the genetic ancestry of each BC-associated SNP in terms of three reference ancestries (African, East Asian, and European), applying ancestry-specific SNP risks and frequencies, and combining the results as a weighted sum of three ancestry-specific PRS. Here, we aimed to improve the predictive accuracy of MA-PRS-149, particularly for non-Europeans, through the inclusion of additional BC-associated SNPs. Methods: Women referred for hereditary cancer testing and negative for pathogenic variants in BC-associated genes were divided into consecutive study cohorts to (1) quantify ancestry-specific SNP risks, (2) combine the three ancestry-specific PRS, and (3) pre-specified clinical validation. To select an optimal set of BC-associated SNPs, we developed a novel synthetic stepwise regression methodology that accounts for linkage disequilibrium. Ancestry-specific SNP risks were determined from meta-analyses of literature with clinical cohorts of 57,827 Black/African and 26,992 East Asian women. Ancestry-specific PRS were combined based on a diverse cohort of 157,740 women. Clinical validation was conducted in an independent cohort of 77,774 women. We used multivariable logistic regression adjusted for age, ancestry, and cancer history to test for improved BC risk prediction over clinical factors. We tested for improvement over the MA-PRS-149, and a European PRS, by including additional PRS as covariates. Calibration was assessed through goodness-of-fit tests. All analyses were conducted within the full cohort and ancestral subpopulations. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported per standard deviation within the corresponding population. Results: An optimal set of 383

SNPs (56 ancestry-informative and 327 BC-associated) was included in the final PRS (MA-PRS-383). MA-PRS-383 added significant predictive information to clinical factors in the full cohort and within each ancestry (Table 1). MA-PRS-383 had greater predictive accuracy than MA-PRS-149 or a 383-SNP PRS with European weights. Goodness-of-fit tests showed that MA-PRS-383 was well-calibrated and predicted risk accurately in the tails of the distribution for both European and non-European women. Conclusion: MA-PRS-383 was well-calibrated and substantially improved upon existing PRS in all tested ancestral populations. Incorporation of MA-PRS-383 into BC risk assessment may lead to more accurate identification of women who are most likely to benefit from screening and preventive medications.

Table 1: Association of MA-PRS-383 with BC risk after accounting for clinical factors

Table 1: Association of MA-PRS-383 with BC risk after accounting for clinical factors			
Self-reported ancestry	N	OR (95% CI)	P-value
All	77,774	1.56 (1.53, 1.60)	<10 ⁻³⁰⁰
Asian	2,012	1.37 (1.20, 1.56)	1.3×10 ⁻⁰⁶
Black/African	9,416	1.40 (1.31, 1.49)	7.7×10 ⁻²⁷
European ^a	50,881	1.61 (1.56, 1.65)	8.9×10 ⁻²⁶⁴
Hispanic	6,718	1.67 (1.53, 1.81)	2.1×10 ⁻³⁶
Mixed ^b	4,152	1.58 (1.40, 1.79)	1.7×10 ⁻¹³
Non-European ^c	19,616	1.48 (1.41, 1.55)	9.2×10 ⁻⁶⁸
^a White/non-Hispanic and/or Ashkenazi Jewish			
^b More than one ancestry excluding White/non-Hispanic and/or Ashkenazi Jewish			
^c Any combination of Asian, Black/African, Hispanic, Middle Eastern, Native American, and/or Pacific Islander			

a White/non-Hispanic and/or Ashkenazi Jewish

b More than one ancestry excluding White/non-Hispanic and/or Ashkenazi Jewish

c Any combination of Asian, Black/African, Hispanic, Middle Eastern, Native American, and/or Pacific Islander

PS10-08

Validation of a clinical image-based AI-risk model for individualized breast cancer screening in a multi-national setting

Presenting Author(s) and Co-Author(s):

M. Eriksson. Karolinska Institutet, Stockholm, Not Applicable, United Kingdom

M. Román. IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

A. Gräwingholt. Mammographiescreening Paderborn, Paderborn, Germany

S. Heywang-Köbrunner. Technical University Munich, Munich, Germany, United States

P. Rossi. Azienda Unitá Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy (P.G.R.), United States

P. Hall. Karolinska Institutet, Stockholm, Not Applicable, Sweden

Background: Image-derived AI risk models for breast cancer have shown high discriminatory performances compared with clinical risk models based on family history and lifestyle factors. However, little is known about their generalizability across different screening settings and clinical feasibility. **Purpose:** To investigate the predictive performance of a clinically used image-derived AI-based breast cancer risk model in multiple European screening populations.

Methods: Four European mammographic screening populations in three countries screened between 2009-2020 for women aged 45-69 was used to perform a nested case-control study. In total, 739 women with incident breast cancers were included together with 7,812 controls matched to cases on year of study-entry. Mammographic features (density, microcalcifications, masses, left-right breast asymmetries of these features) for risk assessment were extracted using AI from full-field digital mammograms. Breast cancer occurrence was assessed after two years of follow-up. Absolute risks of breast cancer were predicted using the risk model from negative mammograms at study-entry. Adjusted Area Under the receiver operating characteristic Curves (aAUC) estimated discriminatory performance and, adjusted risk-ratios estimated the stratification performance of women at high/general risk per the clinical guidelines. **Results:** The overall aAUC of the AI risk model was 0.72 (95%CI 0.70-0.75), range 0.71 (95%CI 0.67-0.75) to 0.74 (95%CI 0.69-0.78) for breast cancers developed in four screening populations. In the 4.6% of women classified at high risk using the NICE guidelines thresholds, cancers were more likely diagnosed after 2 years follow-up, risk-ratio (RR) 6.7 (95%CI 5.6-8.0), compared with the 71% of women classified at general risk by the model. Similar risk-ratios were observed across tertiles of mammographic density. In the high-risk group, 22% of the 2-year future cancers were diagnosed, and 29% of stage 2 and higher cancers, $p < 0.01$. **Conclusions:** The AI risk model showed generalizable discriminatory performances across European populations and, captured ~30% of clinically relevant stage 2 and higher breast cancers in ~5% of high-risk women who were sent home with a negative mammogram. Similar results were seen in fatty and dense breasts. An image-derived AI model

is feasible for personalized screening to improve screening outcomes.

Table 1. Discriminatory performance of the PFAI Risk model by study population. AUCs were adjusted for mammography vendor, year of mammogram, and age at study-entry (aAUC). The aAUC for studies combined were additionally adjusted for study population.

Study population	N cases/controls	aAUC (95% CI)
RETomato, arm 1	89/984	0.73 (0.67-0.79)
RETomato, arm 2	91/915	0.73 (0.68-0.79)
Hospital Del Mar	158/1,550	0.71 (0.67-0.75)
München Süd	232/3,124	0.71 (0.67-0.74)
Paderborn	169/1,239	0.74 (0.69-0.78)
All studies combined	739/7,812	0.72 (0.70-0.75)

Arm 1 – Risk measured on DM mammograms at baseline in our study in the women who were examined at follow-up for breast cancer using DM.

Arm 2 – Risk measured on DM mammograms at baseline in our study in the women who were examined at follow-up for breast cancer using DM + DBT.

aAUC – Adjusted Area Under the receiver operating characteristic Curve

DM – full-field Digital Mammogram

DBT – Digital Breast Tomosynthesis

PS10-09

Development of an absolute risk prediction model for premenopausal breast cancer in an international consortium

Presenting Author(s) and Co-Author(s):

K. Brantley. Harvard TH Chan School of Public Health, Boston, Massachusetts, United States

M. Jones. The Institute of Cancer Research, United States

M. Schoemaker. IQVIA Real World Data, United States

H. Nichols. University of North Carolina Gillings School of Public Health, United States

A. Swerdlow. The Institute of Cancer Research, United States

R. MacInnis. University of Melbourne, United States

R. Milne. Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia

T. Clendenen. Department of Population Health, NYU Grossman School of Medicine, New York, New York, United States

Y. Chen. Department of Population Health, NYU Grossman School of Medicine, New York, New York, United States

X. Shu. Vanderbilt University Medical Center, United States

W. Zheng. Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, United States

W. Koh. Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

J. Yuan. University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

C. Kitahara. Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, United States

M. Linet. Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, United States

D. Sandler. National Institute of Environmental Health Sciences, United States

B. Rosner. Brigham and Women's Hospital and Harvard Medical School, United States

P. Kraft. Division of Cancer Epidemiology and Genetics, National Cancer Institute, United States

A. Eliassen. Harvard TH Chan School of Public Health, United States

Risk prediction models that have been developed for overall breast cancer risk are based on a limited number of premenopausal cases in individual cohorts. As some risk factors differ in their associations with pre- versus postmenopausal breast cancer, a distinct risk prediction model is needed for premenopausal breast cancer. We developed a risk prediction model for premenopausal breast cancer using 779,601 participants and 9,665 incident cases from 18 prospective studies within the Premenopausal Breast Cancer Collaborative Group (PBCCG), across North America (N=9), Europe (N=6), Australia (N=1), and Asia (N=2). Data were split, within each cohort, into training (2/3) and testing (1/3) datasets. Individual risk was assessed in five-year intervals, using variables reported at the start of the time interval. Cox proportional hazards regression was used to model risk factors in a backwards-selection method, stratified by cohort: age at menarche, age at first birth, parity, breastfeeding (months), height (cm), BMI

(kg/m²), BMI at age 18, recent weight change (kg), alcohol consumption (drinks/week), first-degree family history of breast cancer, and personal history of benign breast disease. To enable the use of information from all cohorts despite differences in missing variables by design, cohorts were grouped by available variables and risk models were fit for each group. In cohorts with incomplete data, model coefficients were adjusted based on the correlation of covariates with the missing variables in the complete case dataset. Coefficients were meta-analyzed with inverse variance weighting to obtain final coefficients. Discrimination was evaluated in the testing dataset by calculation of the c-index. Work is ongoing to calibrate the model based on five-year absolute risk using GLOBOCAN continent- and age-specific incidence rates to represent baseline risk. The final model included age at menarche, parity, height, BMI, BMI at age 18, first-degree family history of breast cancer, and history of benign breast disease. Young adulthood BMI and BMI (at start of the 5-year risk interval) were associated with a decreased risk (Hazard Ratio (HR) (95% confidence interval (CI)) per 5 kg/m² = 0.87 (0.81-0.93) and 0.90 (0.86-0.95), respectively) as was parity (HR (95% CI) = 0.92 (0.90-0.94)). Height was associated with increased risk (HR (95% CI) per 10 cm = 1.14 (1.07-1.21)), while history of benign breast disease and family history were associated with larger increases in risk (HR (95% CI) = 1.64 (1.30-2.06) and 1.76 (1.63-1.90), respectively). Model discrimination was higher than that reported for women under 50 years in existing breast cancer risk prediction models considering clinical factors (AUC (95% CI) = 0.61 (0.59-0.62)). Calibration of absolute 5-year risk is ongoing. Several factors driving risk prediction of postmenopausal breast cancer have similar influence on risk of premenopausal breast cancer, while family history has a stronger influence on premenopausal breast cancer risk. Our model demonstrates acceptable discrimination and will enable individual 5-year absolute risk prediction for premenopausal breast cancer.

PS10-01

Hormonal Contraception and Breast Cancer Risk for Carriers of Germline Pathogenic Variants in BRCA1 and BRCA2

Presenting Author(s) and Co-Author(s):

K. Phillips. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

J. Kotsopoulos. University of Toronto, Toronto, Ontario, Canada

S. Domchek. University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, United States

J. Chamberlain. Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Australia

J. Bassett. Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Australia

A. Aeilts. Division of Human Genetics, Department of Internal Medicine, The Ohio State University, Columbus, Ohio, United States

I. Andrulis. University of Toronto, United States

S. Buys. Huntsman Cancer Institute at the University of Utah, Utah, United States

W. Cui. Department of Medical Oncology, Peter MacCallum Cancer Centre and The Sir Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia

M. Daly. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Eisen. Sunnybrook Health Sciences Center, United States

W. Foulkes. McGill University Medical School, Department of Human Genetics, Canada

M. Friedlander. Department of Medical Oncology Prince of Wales Hospital and Clinical School UNSW, Sydney, Australia

J. Gronwald. International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Poland

J. Hopper. University of Melbourne, United States

E. John. Stanford University, United States

B. Karlan. UCLA Jonsson Comprehensive Cancer Center and David Geffen School of Medicine at UCLA, California, United States

R. Kim. Division of Medical Oncology and Hematology, University Health Network, Sinai Health System, Ontario Institute for Cancer Research, Toronto, Ontario, Canada

J. Lubiński. Pomeranian Medical University, Szczecin, Poland

K. Metcalfe. University of Toronto, Toronto, Ontario, Canada

K. Nathanson. University of Pennsylvania School of Medicine, Pennsylvania, United States

C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria

H. Symecko. Basser Center for BRCA, University of Pennsylvania, United States

N. Tung. Beth Israel Deaconess Medical Center, Boston, United States

S. Narod. Women's College Research Institute, Toronto, Ontario, Canada

M. Terry. Columbia University, United States

R. Milne. Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Australia

BACKGROUND:

Current use of hormonal contraception is associated with a 20-30% relative increase in the risk of breast cancer (BC) for women in the general population compared with never using. Longer duration of use is associated with higher risk, and the risk remains elevated above that of never users for at least 5 years after cessation. Most published data are for various formulations of the combined oral contraceptive pill, but associations are similar for progestogen-only contraceptives, including intrauterine devices. For women in the general population who use hormonal contraceptives in their 20s and 30s, when baseline BC risk for most women is low, these increased relative risks translate into only small increases in absolute risk. It is unclear whether use of hormonal contraceptives increases BC risk for women carrying a germline BRCA1 or BRCA2 pathogenic variant (PV). These women are at markedly higher risk of early-onset BC, so even slightly increased relative risks could translate to important increases in their absolute risk of BC. This study assessed the association between use of any hormonal contraception and BC risk for BRCA1 and BRCA2 PV carriers using individual participant data from four prospective cohorts.

METHODS:

Data from females born after 1920 with a PV in BRCA1 or BRCA2 and no history of cancer or bilateral mastectomy at cohort entry were analyzed. Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for BC (invasive disease or ductal carcinoma in situ) associated with use of hormonal contraceptives for at least 1 year, with age as the timescale, entry at cohort enrolment, and censoring at the earlier of bilateral mastectomy, death, diagnosis of another cancer or last follow-up. Analyses were adjusted for study, birth cohort, first-degree family history of BC, parity, premenopausal bilateral oophorectomy and menopausal status. Current use of hormonal contraceptives was defined as use within the previous year, to account for cessation of use due to BC symptoms or clinical investigation.

RESULTS:

Of 3,882 BRCA1 and 1,509 BRCA2 PV carriers, 53% and 71%, respectively had ever used hormonal contraceptives (for at least one year). The median cumulative duration of hormonal contraceptive use was 4.8 and 5.7 years, respectively. Overall, 488 BRCA1 and 191 BRCA2 PV carriers developed incident BC during a median of 5.9 and 5.6 years of follow-up, respectively. For BRCA1 PV carriers, use of hormonal contraceptives for at least 1 year was associated with increased BC risk (HR [95% CI]: 1.29 [1.04-1.60] $p=0.019$). BC risk increased with longer cumulative duration of hormonal contraceptive use (HR [95% CI]: 1.13 [0.88-1.45] $p=0.35$, 1.48 [1.11-1.96] $p=0.007$ and 1.56 [1.13-2.17] $p=0.007$ for 1-5, 6-10 and >10 years of use, respectively), with an estimated proportional increase in risk of 3% (1%-5%, $p=0.002$) for each additional year of use. For BRCA2 PV carriers, there was no evidence that current or past use, or cumulative duration of use, were associated with increased risk of BC, but confidence intervals on the HRs were wide.

CONCLUSION:

Hormonal contraceptive use is associated with an increased risk of BC for women carrying PVs in BRCA1 and risk increases with cumulative duration of use. Hormonal contraceptives are an important healthcare option for women; they provide excellent contraceptive efficacy and reduce risks of ovarian and endometrial cancer. Decisions about use of hormonal contraceptives in women at increased risk for BC due to BRCA1 PVs need to carefully weigh the risks and benefits; while shorter-term use may result in only small increases, prolonged cumulative use may result in larger increases in absolute BC risk that may not be acceptable to some women.

Disclosure(s):

Kelly-Anne Phillips, MBBS (Hons) MD FRACP FAHMS: No financial relationships to disclose

Joanne Kotsopoulos, PhD: No financial relationships to disclose

Kelly Metcalfe, RN, PhD: Consulting Fees (e.g., advisory boards): Astra Zeneca, Roche, Novartis, Biocad, R-Pharm, Eisai, Eli Lilly, Pfizer, MSD, BMS (Ongoing)

Steven Narod, MD: No financial relationships to disclose

Poster Spotlight Session 10: Refining Prediction of Cancer Risk and Outcomes

Presenting Author(s) and Co-Author(s):

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

Disclosure(s):

Fergus J. Couch, PhD: No financial relationships to disclose

PS10-03

Impact of Baseline Oestradiol and Testosterone on the Preventive Effect of Anastrozole

Presenting Author(s) and Co-Author(s):

J. Cuzick. Queen Mary University of London, London, England, United Kingdom

K. Chu. Queen Mary University of London, United States

b. keevil. Manchester University NHS Foundation Trust, United States

A. Howell. University of Manchester, United States

B. Bonanni. 4. Division of Cancer Prevention and Genetics, European Institute of Oncology, IRCCS, Milan, Italy

E. Gareth. University of Manchester, United States

K. Holli. University of Tamoere, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

N. Zdenkowski. Breast Cancer Trials, Newcastle, New South Wales, Australia

S. Cummings. UCSF, San Francisco, California, United States

M. Dowsett. The Royal Marsden NHS Foundation Trust, London, UK; The Institute of Cancer Research, London, United Kingdom

It is well known that serum levels of oestradiol and testosterone, esp free hormone levels, influence the risk of developing breast cancer in postmenopausal women (Thomas et al 1997, Hankinson et al 1998, Kaaks et al 2005, Tin Tin et al 2021). However very little is known about how these hormone levels influence the effectiveness of aromatase inhibitors. In the IBIS-II Prevention Trial we compared anastrozole to placebo in 3864 women at high risk of breast cancer (Cuzick et al 2020). Of these women 3644 (94.3%) had a baseline blood sample. In those with a valid blood sample, 72 in the anastrozole arm and 142 in the placebo arm developed breast cancer (including DCIS) after 12.9 years of follow up (OR = 0.49, 95% CI 0.37–0.66 P< 0.0001). For each case two controls were selected, matched on age, treatment arm and follow up longer than the matching case. In these women oestradiol (E2), testosterone (Testo) and SHBG were measured by liquid chromatography – tandem mass spectroscopy, and E2/SHBG and Testo/SHBG ratios were computed to approximate free hormone levels, and analysed in quartiles. Hormone replacement therapy was not allowed during the trial, and women with use within 3 months prior to entry or outlier hormone values were excluded from these analyses.

In the placebo arm higher levels of both of these ratios were associated with a higher breast cancer rate (OR per quartile 1.25 (1.04-1.59), P=0.018) for E2/SHBG and (OR per quartile 1.22 (1.02-1.47), P = 0.032) for Testo/SHBG), whereas no significant effect was seen in the anastrozole arm (OR = 1.05 (0.81-1.37), and 1.16 (0.90-1.49), resp) (Table). Neither treatment interaction was significant. Absolute numbers of cases were similar between the anastrozole and placebo arms in the lowest quartile of E2/SHBG (18 anastrozole, 22 placebo), but higher numbers were seen in the placebo arm for the other quartiles. Similar results were seen for testo/SHBG, and supportive, but weaker results were seen for these two hormones without an SHBG adjustment, SHBG and BMI at entry. Adjusting for other risk factors had no influence on these findings. Effect sizes were similar during the 5 year treatment period and thereafter. There were too few ER negative cases to compare results by receptor status. Vasomotor side effects were higher with increasing E2/SHBG levels in both arms, but no other hormone

showed an effect, and no hormone level was significantly associated with gynaecologic or musculoskeletal side effects.

As aromatase inhibitors effectively eliminate the production of oestradiol in postmenopausal women, these results suggest they may be more effective in postmenopausal women with high oestradiol or testosterone levels, and raise questions about their value in women in the lower quartile of serum levels for these hormones for prevention and possibly adjuvant treatment.

Table: Risk of breast cancer by quartiles of the oestradiol/SHBG in ratio high risk women treated with anastrozole or placebo.

Quartile	Anastrozole			Placebo		
	N		OR (95% CI)	N		OR (95% CI)
	Case	Control		Case	Control	
Q1 (<0.167)	18	31	1.0 (ref)	22	72	1.0 (ref)
Q2 (0.167 to <0.279)	14	38	0.63 (0.27-1.48)	31	66	1.54 (0.81-2.92)
Q3 (0.279 to <0.617)	21	40	0.90 (0.41-1.98)	46	63	2.39 (1.30-4.40)
Q4 (≥0.617)	19	31	1.06 (0.47-2.38)	43	73	1.93 (1.05-3.54)
Total	72	140	1.21 (0.69-2.15)*	142	274	1.70 (1.13-2.58)*
OR per quartile	1.05 (0.81-1.37) P = 0.70 (trend)			1.25 (1.04-1.50) P = 0.018 (trend)		
P-value treatment interaction term				0.30		

*Q3+Q4 vs Q1+Q2

Disclosure(s):

Jack M. Cuzick, CBE, PhD, FRS, FMedSci, FRCP (hon): Royalty: Cancer Research UK (Royalty payments from licenses for commercial use of the Tyrer-Cuzick/IBIS algorithm) (Ongoing), Cancer Research UK (Royalty payments from licenses for commercial use of the Tyrer-Cuzick/IBIS algorithm) (Ongoing), Cancer Research UK (Royalty payments from licenses for commercial use of the Tyrer-Cuzick/IBIS algorithm) (Ongoing)

Sibylle Loibl, MD, PhD: Advisory Committee/Board Member: GSK, Pfizer, Novartis (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Consulting Fees (e.g., advisory boards): GSK, Pfizer, Novartis (Ongoing), Menarini/Stemline (Ongoing), MSD Co., Ltd. (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Licences for VM Ki67 Quantifier: VM Scope GmbH (Ongoing); patents pending: EP14153692.0 , EP21152186.9 , EP19808852.8 , (Ongoing)

Nicholas Zdenkowski, B Med, FRACP, PhD: Advisory Committee/Board Member: Novartis Pharmaceuticals (Terminated, June 5, 2023); Consulting Fees (e.g., advisory boards): AstraZenca (Terminated, June 13, 2023), Lilly Australia Pty Ltd (Terminated, June 13, 2023), MSD Co., Ltd. (Terminated, June 13, 2023), Pfizer, Inc. (Terminated, June 13, 2023); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Eisai Co.Ltd (Terminated, August 18, 2023), Gilead (Terminated, August 18, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): BMS (Terminated, October 14, 2022), Roche/Genentech (Terminated, October 14, 2022)

PS10-02

Association between Germline Mutation Status and Overall Survival among Women with Breast Cancer in Population-based Studies in the United States

Presenting Author(s) and Co-Author(s):

S. Yadav. Mayo Clinic, Rochester, Minnesota, United States

C. Hu. Mayo Clinic, United States

N. Boddicker. Mayo Clinic, United States

C. CONSORTIUM. NA, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

Background:

The influence of germline pathogenic variants (PVs) in breast cancer predisposition genes on overall survival (OS) after breast cancer diagnosis is not well defined, particularly for PVs in genes other than BRCA1 and BRCA2, and in the context of estrogen-receptor (ER) positive breast cancer. Even for BRCA1/2, OS estimates in women with breast cancer have primarily been derived from high-risk women qualifying for genetic testing due to young age at diagnosis or family history of cancer, and OS estimates by germline PV status from population-based studies are lacking.

Methods:

The study included 16,797 prospectively followed women with locoregional breast cancer within the population-based CARRIERS study who underwent surgical resection of the primary tumor. OS was compared between germline PV carriers and non-carriers (negative for germline PVs in 12 breast cancer predisposition genes) from the time of breast cancer diagnosis in a multivariable Cox proportional hazard regression analysis adjusting for age and menopausal status at diagnosis, race/ethnicity, ER status, type of surgery, use of adjuvant radiation, chemotherapy and endocrine agents, and prophylactic oophorectomy. Further subset analyses by race/ethnicity ER status of the primary tumor and adjusting for relevant covariates were also performed.

Results:

Germline PVs in ATM, BRCA1, BRCA2, CHEK2, or PALB2 were detected in 5.6% of the women in the study [ATM: 142 (0.8%), BRCA1: 206 (1.2%), BRCA2: 260 (1.5%), CHEK2:167 (1.0%) and PALB2:116 (0.7%)]. Compared to non-carriers, a significant difference in OS was not observed for germline PV carriers in ATM, BRCA1, BRCA2, or CHEK2 in the overall study population. However, a trend towards worse OS was noted for PALB2 PV carriers compared to non-carriers although this was not statistically significant (Hazard Ratio (HR): 1.36, 95%CI: 0.98 – 1.89, p=0.06). Further subset analysis by race/ethnicity demonstrated that the OS was significantly worse among Black PALB2 PV carriers (HR: 3.11, 95%CI: 1.74 – 5.55, p< 0.001) but not in non-Hispanic White PALB2 PV carriers (HR: 1.00, 95%CI: 0.59 – 1.70, p=0.98) compared to non-carriers within the same race/ethnicity. Among 12,780 women with ER+ breast cancer, compared to non-carriers, OS was significantly worse in BRCA2 PV carriers (HR: 1.51, 95%CI: 1.06 – 2.16, p=0.02) and a trend towards worse OS was observed in BRCA1 PV carriers (HR:1.53, 95%CI:0.93 – 2.51, p=0.09). Among women with ER-negative breast cancer, a significant difference in OS was not observed between PV carriers in each of the five genes and non-carriers.

Conclusions:

The differences in OS by race/ethnicity in PALB2 PV carriers and by ER status of the tumor in BRCA2 PV carriers warrant further investigation of underlying tumor biology and assessment of endocrine sensitivity of breast cancer in germline PV carriers.

Disclosure(s):

Siddhartha Yadav, MD: Advisory Board (no personal compensation): AstraZeneca (Terminated); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZenca (Ongoing), REPARE Therapeutics (Ongoing)

Fergus J. Couch, PhD: No financial relationships to disclose

PS10-04

The Landscape of Somatic Genetic Alterations in Breast Cancers from Carriers of Germline Pathogenic Variants in DNA-repair Genes

Presenting Author(s) and Co-Author(s):

S. Yadav. Mayo Clinic, Rochester, Minnesota, United States

A. Arafa. University of Minnesota Masonic Cancer Center, United States

E. Teslow. Tempus Labs, Inc., United States

M. Huang. Tempus Labs, Inc., United States

M. Stoppler. Tempus Labs, Inc., United States

C. Chao. Tempus Labs, United States

E. Antonarakis. University of Minnesota Masonic Cancer Center, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

Background:

Hereditary breast cancer in carriers of germline pathogenic or likely pathogenic variants (PVs) in ATM, BRCA1, BRCA2, CHEK2, and PALB2 have unique clinicopathological characteristics compared to sporadic breast cancer. However, very little is known about the underlying differences in somatic genetic alterations between hereditary and sporadic breast cancer.

Methods:

The study included 7,533 individuals with breast cancer subjected to Tempus xT tumor-normal matched sequencing (596-648 genes). The frequencies of the somatic genetic alterations in each gene were compared separately between tumors arising in individuals with incidental germline PVs (gATM, gBRCA1, gBRCA2, gCHEK2, gPALB2) and sporadic breast tumors. Sporadic tumors were identified as individuals with no detected incidental germline PVs in these 5 genes. Comparisons were made by either Pearson's Chi-squared or Fisher's exact test, with false discovery rate (FDR) correction for multiple testing. Breast cancer subtype was determined based on the record of IHC positivity for ER, PR, or HER2. Detection of ERBB2 (HER2) gene amplifications via DNA sequencing was also used to classify samples as HER2+ in the absence of available IHC data.

Results:

The median age at breast cancer diagnosis for the cohort was 56 years. More than two-thirds of the patients were White (73%) while 14% identified as Black or African American. The overall frequency of incidental germline PVs in each gene was 0.8% for gATM, 1.4% for gBRCA1, 2.1% for gBRCA2, 1.0% for CHEK2, and 0.7% for PALB2. A total of 3,648 (48.4%) tumors were ER+/PR+/HER2-, 1,297 (17.2%) were triple-negative (TNBC), 841 (11.2%) were HER2+ and 1,747 (23.2%) could not be classified due to missing ER, PR or HER2 status, or absence of detected ERBB2 amplifications. Among ER+/PR+/HER2- breast cancers, compared to sporadic tumors, ESR1 mutations were significantly enriched in gATM carriers (33% vs. 11%, q-value 0.05), TP53 alterations were significantly enriched in gBRCA1 PV carriers (69% vs. 30%, q-value < 0.001) but depleted in gATM (12% vs. 30%, q-value 0.4) and gCHEK2 PV carriers (5.4% vs. 30%, q-value 0.06), and PIK3CA (14% vs. 35%, q-value 0.001) and CCND1 (3.4% vs. 17%, q-value 0.02) alterations were significantly lower in gBRCA2 PV carriers. Among TNBC, TP53 alterations were also significantly higher in gBRCA1 PV carriers compared to sporadic tumors (96% vs. 69%, q-value 0.004). In HER2+ breast cancers, ERBB2 alterations were observed in approximately two-thirds of the tumors, and a significant difference was not

observed between incidental hereditary and sporadic tumors. Among ER+/PR+/HER2- tumors, although not statistically significant, the frequency of ESR1 (3.1% vs. 11%, q-value >0.9), PIK3CA (12% vs. 35%, q-value 0.2) alterations were lower in incidental gBRCA1 versus sporadic tumors, FGFR1 alterations were lower in incidental gBRCA1 (6.2% vs. 13%, q-value >0.9) and incidental gBRCA2 (3.4% vs. 13%, q-value 0.13) but enriched in incidental gATM (33% vs. 13%, q-value 0.05).

Conclusions:

The observed differences in the frequencies of CCND1, ESR1, PIK3CA, TP53, and other key genetic alterations between incidental hereditary and sporadic breast cancer highlight the unique tumor biology of breast cancer in germline PV carriers and have significant implications for understanding tumorigenesis and identifying therapeutic strategies for the management of hereditary breast cancer.

Disclosure(s):

Siddhartha Yadav, MD: Advisory Board (no personal compensation): AstraZeneca (Terminated); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZenca (Ongoing), REPARE Therapeutics (Ongoing)
Fergus J. Couch, PhD: No financial relationships to disclose

PS10-06

Contribution of a breast cancer polygenic risk score to mammography artificial intelligence models and breast density for long term breast cancer risk prediction

Presenting Author(s) and Co-Author(s):

C. Vachon. Mayo Clinic, Rochester, Minnesota, United States

C. Scott. Mayo Clinic, United States

I. Banerjee. Mayo Clinic, United States

R. Correa Moderno. Mayo Clinic, United States

D. Hursh. Mayo Clinic, United States

M. Jensen. Mayo Clinic, United States

Y. Wang. Mayo Clinic, United States

K. Brandt. Mayo Clinic, United States

K. Kerlikowske. University of California, San Francisco, United States

S. Pruthi. Mayo Clinic, Rochester, Minnesota, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

S. Winham. Mayo Clinic, United States

Artificial intelligence (AI) models based on deep learning of mammogram images have been developed for lesion detection and diagnosis as well as breast cancer (BC) risk. We and others have shown that these AI models, coupled with breast density, predict long-term breast cancer risk. Common germline genetic variation, in particular a polygenic risk score (PRS) that captures the cumulative impact of hundreds of common risk variants, has been shown associated with 3-fold increased BC risk. The BC-PRS may complement imaging risk factors to improve identification of women at high BC risk and better target prevention strategies. We evaluated the contribution of a BC-PRS to two imaging-based AI models (Transpara AI cancer detection system and Mirai 5-year risk) and breast density measures to long-term BC risk. We hypothesized that the BC-PRS will improve long-term risk prediction above AI and density measures.

We examined this hypothesis within a cohort of 10,271 women enrolled to the Mayo Clinic Biobank between 2009 and 2015. Eligible women had no prior cancer, were ages 35 to 85, had a full-field digital screening mammogram within two years of enrollment and genotyping by Regeneron. Incident invasive and DCIS BC was identified through the Mayo tumor registry and follow-up questionnaires, and person years were calculated from date of mammogram through date of BC, last mammogram at Mayo or last questionnaire. We estimated Transpara AI malignancy score (1-10), 5-year Mirai risk and Volpara volumetric density measures (volumetric percent density, dense volume) on screening mammograms at enrollment and obtained clinical BI-RADS density. We calculated the BC-PRS using 268 SNPs (of the 313-SNP score) and the weighted sum of the SNPs using odds ratios from the largest BC GWAS of European ancestry to date. We performed cox proportional hazards regression adjusting for age and BMI to estimate hazard ratios (HRs), 95% confidence intervals (CI), and C-statistics (AUC) to describe the contribution of BC-PRS (per standard deviation (SD)) to the association of AI scores and breast density with BC risk. Likelihood ratio tests (LRT) and bootstrapping were used to compare model performance with vs. without inclusion of BC-PRS, at 10-years follow-up. Comparisons to the Tyrer-Cuzick model are ongoing.

Over a median of 9.1 years (Interquartile range, 6.8 to 10.6), 446 incident BC were identified of which 285 invasive and 103 DCIS were confirmed by pathology report (60 were self-reported); 399 (256 invasive) occurred within 10 years and were used in primary analyses. Transpara score [HR per 1 unit=1.18 (1.14, 1.23), AUC=0.655 (0.628, 0.682)] and Mirai risk [HR per SD log risk=1.54 (1.43, 1.65), AUC=0.681 (0.655, 0.706)] were both associated with BC. All three breast density measures were also significantly associated with BC, including in models with AI scores (Table). Addition of the BC-PRS to models with AI scores and breast density improved both model fit (All $P_{LRT} < 0.001$; Table) and discrimination, with increases in AUC ranging from 0.033 to 0.034 for models with Transpara and density and 0.025 to 0.026 for models with Mirai and density (all P-values < 0.001; Table). Analyses restricted to invasive BC showed identical results. But, the BC-PRS contribution at 5-year follow-up was attenuated.

In this cohort study, we found BC-PRS contributed to long-term risk prediction of BC above imaging AI models and breast density. Imaging and genetic risk factors are complementary and may outperform existing risk models and provide more accurate risk assessment to aid in precision prevention strategies.

Table. Contribution of a polygenic risk score for breast cancer (BC-PRS) to association of AI scores (Transpara, Mirai), breast density measures and BC risk at 10-years

Model variables	Models without BC-PRS		Models with BC-PRS	
	HR (95% CI)	AUC (95% CI)	HR (95% CI)	AUC (95% CI)
Transpara (per unit)	1.17 (1.12, 1.20)	0.670 (0.644, 0.696)	1.15 (1.11, 1.20)	0.703 (0.679, 0.728)
VBD% (log)*	1.41 (1.25, 1.60)		1.40 (1.23, 1.58)	
BC-PRS*	-----		1.51 (1.37, 1.67)	
Transpara (per unit)	1.16 (1.12, 1.21)	0.670 (0.644, 0.697)	1.15 (1.11, 1.20)	0.704 (0.679, 0.728)
DV (log)*	1.31 (1.18, 1.45)		1.29 (1.17, 1.43)	
BC-PRS*	-----		1.51 (1.37, 1.67)	
Transpara (per unit)	1.16 (1.12, 1.20)	0.668 (0.642, 0.694)	1.15 (1.11, 1.19)	0.703 (0.678, 0.727)
BI-RADS a	0.74 (0.54, 1.02)		0.77 (0.56, 1.06)	
BI-RADS b	1.0 (ref)		1.0 (ref)	
BI-RADS c	1.64 (1.30, 2.05)		1.61 (1.29, 2.02)	
BI-RADS d	1.72 (0.83, 3.56)		1.64 (0.79, 3.39)	
BC-PRS*	-----		1.51 (1.37, 1.67)	
MIRAI 5 yr Risk (log)*	1.48 (1.37, 1.60)	0.681 (0.655, 0.706)	1.44 (1.33, 1.56)	0.711 (0.687, 0.736)
VBD% (log)*	1.37 (1.21, 1.55)		1.36 (1.20, 1.54)	
BC-PRS*	-----		1.50 (1.36, 1.65)	
MIRAI 5 yr Risk (log)*	1.48 (1.37, 1.60)	0.686 (0.661, 0.712)	1.44 (1.33, 1.56)	0.710 (0.685, 0.735)
DV (log)*	1.26 (1.14, 1.40)		1.25 (1.13, 1.39)	
BC-PRS*	-----		1.50 (1.36, 1.66)	
MIRAI 5 yr Risk (log)*	1.46 (1.35, 1.58)	0.682 (0.657, 0.708)	1.43 (1.32, 1.54)	0.709 (0.684, 0.734)
BI-RADS a	0.75 (0.54, 1.03)		0.76 (0.55, 1.05)	
BI-RADS b	1.0 (ref)		1.0 (ref)	
BI-RADS c	1.51 (1.20, 1.90)		1.51 (1.20, 1.90)	
BI-RADS d	1.53 (0.74, 3.17)		1.44 (0.69, 2.97)	
BC-PRS*	-----		1.50 (1.36, 1.66)	

*per standard deviation

Disclosure(s):

Celine M. Vachon, PhD: No financial relationships to disclose

Fergus J. Couch, PhD: No financial relationships to disclose

PS10-07

A second-generation polygenic risk score (PRS) based on genetic ancestry improves breast cancer (BC) risk prediction for all ancestries

Presenting Author(s) and Co-Author(s):

T. Simmons. Myriad Genetics, Inc., Salt Lake City, Utah, United States

E. Hughes. Myriad Genetics, Inc., United States

D. Pruss. Myriad Genetics, Inc., United States

M. Kucera. Myriad Genetics, Inc., United States

B. Roa. Myriad Genetics, Inc., United States

T. Judkins. Myriad Genetics, Inc., United States

T. Slavin. Myriad Genetics, Inc., United States

V. Abkevich. Myriad Genetics, Inc., United States

R. Hoff. Myriad Genetics, Inc., United States

S. Jammulapati. Myriad Genetics, Inc., United States

S. Wagner. Myriad Genetics, Inc., United States

D. Muzzey. Myriad Genetics, Inc., United States

J. Lanchbury. Myriad Genetics, Inc., United States

A. Gutin. Myriad Genetics, Inc., United States

Background:

Common genetic variants, mainly single-nucleotide polymorphisms (SNPs) explain substantial genetic susceptibility to BC. PRS have been developed to quantify the combined effects of BC-associated SNPs, providing important information about BC risk. Historically, genome-wide association studies have been conducted in predominantly European populations, resulting in miscalibrated and inaccurate PRS for non-Europeans. We previously described a multiple-ancestry PRS (MA-PRS-149) based on 56 ancestry-informative and 93 BC-associated SNPs. The MA-PRS-149 achieved accuracy for all women by characterizing the genetic ancestry of each BC-associated SNP in terms of three reference ancestries (African, East Asian, and European), applying ancestry-specific SNP risks and frequencies, and combining the results as a weighted sum of three ancestry-specific PRS. Here, we aimed to improve the predictive accuracy of MA-PRS-149, particularly for non-Europeans, through the inclusion of additional BC-associated SNPs.

Methods:

Women referred for hereditary cancer testing and negative for pathogenic variants in BC-associated genes were divided into consecutive study cohorts to (1) quantify ancestry-specific SNP risks, (2) combine the three ancestry-specific PRS, and (3) pre-specified clinical validation.

To select an optimal set of BC-associated SNPs, we developed a novel synthetic stepwise regression methodology that accounts for linkage disequilibrium. Ancestry-specific SNP risks were determined from meta-analyses of literature with clinical cohorts of 57,827 Black/African and 26,992 East Asian women. Ancestry-specific PRS were combined based on a diverse cohort of 157,740 women.

Clinical validation was conducted in an independent cohort of 77,774 women. We used

multivariable logistic regression adjusted for age, ancestry, and cancer history to test for improved BC risk prediction over clinical factors. We tested for improvement over the MA-PRS-149, and a European PRS, by including additional PRS as covariates. Calibration was assessed through goodness-of-fit tests. All analyses were conducted within the full cohort and ancestral subpopulations. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported per standard deviation within the corresponding population.

Results:

An optimal set of 383 SNPs (56 ancestry-informative and 327 BC-associated) was included in the final PRS (MA-PRS-383). MA-PRS-383 added significant predictive information to clinical factors in the full cohort and within each ancestry (Table 1). MA-PRS-383 had greater predictive accuracy than MA-PRS-149 or a 383-SNP PRS with European weights. Goodness-of-fit tests showed that MA-PRS-383 was well-calibrated and predicted risk accurately in the tails of the distribution for both European and non-European women.

Conclusion:

MA-PRS-383 was well-calibrated and substantially improved upon existing PRS in all tested ancestral populations. Incorporation of MA-PRS-383 into BC risk assessment may lead to more accurate identification of women who are most likely to benefit from screening and preventive medications.

Table 1: Association of MA-PRS-383 with BC risk after accounting for clinical factors

Table 1: Association of MA-PRS-383 with BC risk after accounting for clinical factors			
Self-reported ancestry	N	OR (95% CI)	P-value
All	77,774	1.56 (1.53, 1.60)	<10 ⁻³⁰⁰
Asian	2,012	1.37 (1.20, 1.56)	1.3×10 ⁻⁰⁶
Black/African	9,416	1.40 (1.31, 1.49)	7.7×10 ⁻²⁷
European ^a	50,881	1.61 (1.56, 1.65)	8.9×10 ⁻²⁶⁴
Hispanic	6,718	1.67 (1.53, 1.81)	2.1×10 ⁻³⁶
Mixed ^b	4,152	1.58 (1.40, 1.79)	1.7×10 ⁻¹³
Non-European ^c	19,616	1.48 (1.41, 1.55)	9.2×10 ⁻⁶⁸
^a White/non-Hispanic and/or Ashkenazi Jewish			
^b More than one ancestry excluding White/non-Hispanic and/or Ashkenazi Jewish			
^c Any combination of Asian, Black/African, Hispanic, Middle Eastern, Native American, and/or Pacific Islander			

a White/non-Hispanic and/or Ashkenazi Jewish

b More than one ancestry excluding White/non-Hispanic and/or Ashkenazi Jewish

c Any combination of Asian, Black/African, Hispanic, Middle Eastern, Native American, and/or Pacific Islander

Disclosure(s):

Timothy Simmons, MStat: Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Myriad Genetics, Inc. (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Myriad Genetics, Inc. (Ongoing)

PS10-08

Validation of a clinical image-based AI-risk model for individualized breast cancer screening in a multi-national setting

Presenting Author(s) and Co-Author(s):

M. Eriksson. Karolinska Institutet, Stockholm, Not Applicable, United Kingdom

M. Román. IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

A. Gräwingholt. Mammographiescreening Paderborn, Paderborn, Germany

S. Heywang-Köbrunner. Technical University Munich, Munich, Germany, United States

P. Rossi. Azienda Unitá Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy (P.G.R.), United States

P. Hall. Karolinska Institutet, Stockholm, Not Applicable, Sweden

Background:

Image-derived AI risk models for breast cancer have shown high discriminatory performances compared with clinical risk models based on family history and lifestyle factors. However, little is known about their generalizability across different screening settings and clinical feasibility.

Purpose:

To investigate the predictive performance of a clinically used image-derived AI-based breast cancer risk model in multiple European screening populations.

Methods:

Four European mammographic screening populations in three countries screened between 2009-2020 for women aged 45-69 was used to perform a nested case-control study. In total, 739 women with incident breast cancers were included together with 7,812 controls matched to cases on year of study-entry. Mammographic features (density, microcalcifications, masses, left-right breast asymmetries of these features) for risk assessment were extracted using AI from full-field digital mammograms. Breast cancer occurrence was assessed after two years of follow-up. Absolute risks of breast cancer were predicted using the risk model from negative mammograms at study-entry. Adjusted Area Under the receiver operating characteristic Curves (aAUC) estimated discriminatory performance and, adjusted risk-ratios estimated the stratification performance of women at high/general risk per the clinical guidelines.

Results:

The overall aAUC of the AI risk model was 0.72 (95%CI 0.70-0.75), range 0.71 (95%CI 0.67-0.75) to 0.74 (95%CI 0.69-0.78) for breast cancers developed in four screening populations. In the 4.6% of women classified at high risk using the NICE guidelines thresholds, cancers were more likely diagnosed after 2 years follow-up, risk-ratio (RR) 6.7 (95%CI 5.6-8.0), compared with the 71% of women classified at general risk by the model. Similar risk-ratios were observed across tertiles of mammographic density. In the high-risk group, 22% of the 2-year future cancers were diagnosed, and 29% of stage 2 and higher cancers, $p < 0.01$.

Conclusions:

The AI risk model showed generalizable discriminatory performances across European populations and, captured ~30% of clinically relevant stage 2 and higher breast cancers in ~5% of high-risk women who were sent home with a negative mammogram. Similar results were seen in fatty and dense breasts. An image-derived AI model is feasible for personalized

screening to improve screening outcomes.

Table 1. Discriminatory performance of the PFAI Risk model by study population. AUCs were adjusted for mammography vendor, year of mammogram, and age at study-entry (aAUC). The aAUC for studies combined were additionally adjusted for study population.

Study population	N cases/controls	aAUC (95% CI)
RETom, arm 1	89/984	0.73 (0.67-0.79)
RETom, arm 2	91/915	0.73 (0.68-0.79)
Hospital Del Mar	158/1,550	0.71 (0.67-0.75)
München Süd	232/3,124	0.71 (0.67-0.74)
Paderborn	169/1,239	0.74 (0.69-0.78)
All studies combined	739/7,812	0.72 (0.70-0.75)

Arm 1 – Risk measured on DM mammograms at baseline in our study in the women who were examined at follow-up for breast cancer using DM.

Arm 2 – Risk measured on DM mammograms at baseline in our study in the women who were examined at follow-up for breast cancer using DM + DBT.

aAUC – Adjusted Area Under the receiver operating characteristic Curve

DM – full-field Digital Mammogram

DBT – Digital Breast Tomosynthesis

Disclosure(s):

Mikael Eriksson: Receipt of Intellectual Property Rights / Patent Holder: iCAD Inc. (Ongoing)

Per FL Hall, MD, PhD: Consulting Fees (e.g., advisory boards): Atossa (Ongoing);

Independent Contractor: Atossa (Ongoing); Industry Grant Support (Principal Investigators

must provide information on research funding from ineligible companies, even if received/managed by the institution): iCAD (Ongoing); Royalty: iCAD (Ongoing)

PS10-09

Development of an absolute risk prediction model for premenopausal breast cancer in an international consortium

Presenting Author(s) and Co-Author(s):

K. Brantley. Harvard TH Chan School of Public Health, Boston, Massachusetts, United States

M. Jones. The Institute of Cancer Research, United States

M. Schoemaker. IQVIA Real World Data, United States

H. Nichols. University of North Carolina Gillings School of Public Health, United States

A. Swerdlow. The Institute of Cancer Research, United States

R. MacInnis. University of Melbourne, United States

R. Milne. Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia

T. Clenenden. Department of Population Health, NYU Grossman School of Medicine, New York, New York, United States

Y. Chen. Department of Population Health, NYU Grossman School of Medicine, New York, New York, United States

X. Shu. Vanderbilt University Medical Center, United States

W. Zheng. Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, United States

W. Koh. Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

J. Yuan. University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

C. Kitahara. Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, United States

M. Linet. Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, United States

D. Sandler. National Institute of Environmental Health Sciences, United States

B. Rosner. Brigham and Women's Hospital and Harvard Medical School, United States

P. Kraft. Division of Cancer Epidemiology and Genetics, National Cancer Institute, United States

A. Eliassen. Harvard TH Chan School of Public Health, United States

Risk prediction models that have been developed for overall breast cancer risk are based on a limited number of premenopausal cases in individual cohorts. As some risk factors differ in their associations with pre- versus postmenopausal breast cancer, a distinct risk prediction model is needed for premenopausal breast cancer.

We developed a risk prediction model for premenopausal breast cancer using 779,601 participants and 9,665 incident cases from 18 prospective studies within the Premenopausal Breast Cancer Collaborative Group (PBCCG), across North America (N=9), Europe (N=6), Australia (N=1), and Asia (N=2). Data were split, within each cohort, into training (2/3) and testing (1/3) datasets. Individual risk was assessed in five-year intervals, using variables reported at the start of the time interval. Cox proportional hazards regression was used to

model risk factors in a backwards-selection method, stratified by cohort: age at menarche, age at first birth, parity, breastfeeding (months), height (cm), BMI (kg/m^2), BMI at age 18, recent weight change (kg), alcohol consumption (drinks/week), first-degree family history of breast cancer, and personal history of benign breast disease. To enable the use of information from all cohorts despite differences in missing variables by design, cohorts were grouped by available variables and risk models were fit for each group. In cohorts with incomplete data, model coefficients were adjusted based on the correlation of covariates with the missing variables in the complete case dataset. Coefficients were meta-analyzed with inverse variance weighting to obtain final coefficients. Discrimination was evaluated in the testing dataset by calculation of the c-index. Work is ongoing to calibrate the model based on five-year absolute risk using GLOBOCAN continent- and age-specific incidence rates to represent baseline risk.

The final model included age at menarche, parity, height, BMI, BMI at age 18, first-degree family history of breast cancer, and history of benign breast disease. Young adulthood BMI and BMI (at start of the 5-year risk interval) were associated with a decreased risk (Hazard Ratio (HR) (95% confidence interval (CI)) per $5 \text{ kg}/\text{m}^2 = 0.87 (0.81-0.93)$ and $0.90 (0.86-0.95)$, respectively) as was parity (HR (95% CI) = $0.92 (0.90-0.94)$). Height was associated with increased risk (HR (95% CI) per 10 cm = $1.14 (1.07-1.21)$), while history of benign breast disease and family history were associated with larger increases in risk (HR (95% CI) = $1.64 (1.30-2.06)$ and $1.76 (1.63-1.90)$, respectively). Model discrimination was higher than that reported for women under 50 years in existing breast cancer risk prediction models considering clinical factors (AUC (95% CI) = $0.61 (0.59-0.62)$). Calibration of absolute 5-year risk is ongoing.

Several factors driving risk prediction of postmenopausal breast cancer have similar influence on risk of premenopausal breast cancer, while family history has a stronger influence on premenopausal breast cancer risk. Our model demonstrates acceptable discrimination and will enable individual 5-year absolute risk prediction for premenopausal breast cancer.

Disclosure(s):

Kristen D. Brantley, PhD: No financial relationships to disclose

PS11-01

Brain metastases in metastatic breast cancer: prevalence per line of treatment and cumulative incidence in a cohort of 18075 real-world patients

Presenting Author(s) and Co-Author(s):

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Leone. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

T. Sanglier. F. Hoffmann-La Roche Ltd, Basel, Basel-Stadt, Switzerland

P. Lambert. Genentech, Inc., South San Francisco, California, United States

F. Montemurro. F. Hoffmann-La Roche Ltd, Basel 4070, Switzerland

R. Poppe. F. Hoffmann-La Roche Ltd, Basel 4070, Switzerland

E. Restuccia. F. Hoffmann-La Roche Ltd, Basel, Switzerland, Basel-Stadt, Switzerland

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

BACKGROUND Historic data suggest that incidence of brain metastasis (BM) is relatively distributed over time in HER2-positive (HER2+) breast cancer (BC), occurs early in triple negative BC (TNBC), and occurs late in hormone receptor-positive (HR+) metastatic BC (mBC). However, the timing of BM relative to line of therapy has not been well described. We describe the prevalence per line of therapy and cumulative incidence of BM in a large real-world cohort of patients (pts) with mBC, by BC subtype and line of therapy. **METHODS** This analysis used data from the longitudinal US Flatiron Health de-identified database, which provides unstructured and structured electronic health record-derived data from >2.6 million pts with cancer in ~800 unique sites of care. Eligible pts had initiated a first line of treatment (index data) for mBC up to March 1, 2021, to allow for ≥2 years potential follow-up time. Baseline characteristics were assessed, and pts categorized by HER2 and HR status: 1) HR+, HER2+; 2) HR+, HER2-, 3) HR-, HER2+ and 4) TNBC (i.e., negative for HR and HER2). For the last two categories, HER2-low subsets were defined based on immunohistochemistry results (1+, 2+, or equivocal). Lines of therapy were derived using both treatment regimens and progression data. The primary outcome was the first diagnosis of BM. The prevalence of BM was evaluated by subtype, at the index date, and by the line of therapy. The cumulative incidence function (CIF) of BM was used to estimate the risk of BM in pts free of BM at the index date, and death was treated as a competing event. **RESULTS** Overall, 18075 pts were included (HR+, HER2+: 3062 pts [16.9%]; HR-, HER2+: 902 pts [5.0%]; HR+, HER2-: 12331 pts [68.2%] [HR+, HER2-low: 7062 (39.1%)]); TNBC: 1780 pts [9.8%] [HR-, HER2-low: 725 pts (4.0%)]. Median age at the index date was 64 years (interquartile range: 54, 73) and 10271 pts (56.8%) had visceral metastasis. In total, 5951 pts (32.9%) had de novo disease, 12090 (66.9%) had recurrent disease, and 34 (0.2%) did not have available data for mBC type. The table shows the number of pts by line of therapy, prevalence of BM, and cumulative incidence of BM from the index date. Of the included pts, 1306 (7.2%) had a BM at the index date; the CIF was run on the remaining 16973 pts. Overall, 2248 pts (13.2%) had an incident BM event during follow-up (HR+, HER2+: 578 events; HR-, HER2+: 237 events; HR+, HER2-: 1119 events [HR+, HER2-low: 619 events]; TNBC: 314 events [HR-, HER2-low: 124 events]), 9314 had a competing event, and 5411 were censored. By fourth-line therapy, the prevalence of BM was 26.1% in HR+, HER2+; 37.1% in HR-, HER2+; 24.7% in TNBC (HR-, HER2-low: 27.9%); but remained low at 7.2% in HR+, HER2- (HR+, HER2-low: 9.4%). The cumulative incidence of BM at 60

months was 23% in HR+, HER2+, 34% in HR-, HER2+, 10% in HR+, HER2-, and, 22% in TNBC. Overall, the HER2-low subsets had BM prevalence and cumulative incidence that were very close to those that were HER2-. CONCLUSIONS This large analysis of real-world data demonstrates that the prevalence of BM across pts with mBC differs by tumor subtype and by line of therapy. Conversely, HER2-low status may have limited impact. The cumulative incidence of BM was highest in the HR-, HER2+ and TNBC subgroups, and lowest in the HR+, HER2- subgroup; despite this, due to the high proportion of HER2-, HR+ mBC cases, the HR+, HER2- group represented the largest number of BM events. These data emphasize the need for clinical and biologic predictors of BM and for strategies to prevent their onset, and provide information on the impact of BM inclusion and exclusion criteria in clinical trials for pts with mBC.

Number of patients by line of therapy, prevalence of BM, and cumulative incidence of BM from the index date

Line of therapy	HR+, HER2+	HR-, HER2+	HR+, HER2- [HR+, HER2-low]	TNBC [HR-, HER2-low]
Number of pts, n				
1	3062	902	12331 [7062]	1780 [725]
2	1936	478	8120 [4721]	972 [422]
3	1232	281	5303 [3101]	526 [240]
4	761	159	3454 [2002]	283 [129]
5+	453	103	2191 [1276]	141 [70]
Prevalence of BM, %				
1	193 (6.3)	101 (11.2)	134 (2.5) [199 (2.8)]	109 (10.3) [88 (12.1)]
2	341 (17.6)	149 (31.2)	150 (4.4) [275 (5.8)]	97 (17.6) [73 (17.3)]
3	265 (21.5)	102 (36.3)	125 (6.7) [231 (7.4)]	63 (22.0) [50 (20.8)]
4	199 (26.1)	59 (37.1)	104 (7.2) [189 (9.4)]	38 (24.7) [36 (27.9)]
5+	120 (26.5)	38 (36.9)	78 (8.5) [134 (10.5)]	23 (32.4) [18 (25.7)]
Cumulative incidence of BM from the index date in the first line, % (95% confidence interval)				
12 months	7.2 (6-8)	13 (11-16)	3.1 (3-3) [3 (3-3)]	14 (12-15) [14 (11-17)]
24 months	14 (13-15)	25 (22-28)	6 (5-6) [6 (5-6)]	20 (18-22) [20 (17-23)]
36 months	19 (17-34)	30 (27-34)	8 (7-8) [8 (7-8)]	21 (19-23) [21 (18-24)]
60 months	23 (21-24)	34 (30-37)	10 (10-11) [10 (9-11)]	22 (20-26) [22 (19-26)]

BM, brain metastasis; HR, hormone receptor, pts, patients; TNBC, triple negative breast cancer.

PS11-02

Clinical risk factors of Central Nervous System (CNS)-related death in patients with HER2-positive metastatic breast cancer

Presenting Author(s) and Co-Author(s):

E. Ferraro. Memorial Sloan Kettering Cancer Center/Breast Medicine Service, New York City, New York, United States

R. Bou Nassif. Neurosurgery, Memorial Sloan Kettering Cancer Center, United States

A. Reiner. Memorial Sloan Kettering Cancer Center, United States

S. Brown. Memorial Sloan Kettering Cancer Center, United States

U. Tosi. Neurosurgery, Memorial Sloan Kettering Cancer Center, United States

K. Panageas. Memorial Sloan Kettering Cancer Center, United States

C. Dang. Breast Medicine Service, Memorial Sloan-Kettering Cancer Center, United States

A. Seidman. Memorial Sloan Kettering Cancer Center, United States

N. Moss. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Central nervous system (CNS) relapse represents a challenge in the management of patients with HER2-positive (+) metastatic breast cancer. Data regarding the impact of brain metastases (BrM) and CNS involvement on mortality are sparse. In this study we sought to determine the proportion of HER2+ MBC patients in which CNS disease is the cause of death and identify risk factors associated with CNS-related mortality. Methods: We reviewed medical records of 294 consecutive patients with HER2+ MBC and diagnosis of CNS disease including parenchymal BrM, leptomeningeal disease (LMD) or dural metastases (DM), treated at Memorial Sloan Kettering Cancer Center between August 2010 and April 2022. HER2-positivity was assessed at the first diagnosis of metastatic disease (any site). Clinicopathologic characteristics including disease burden at presentation, timing of CNS disease and extracranial metastases (ECM), neurologic complications, and local and systemic treatments were collected. CNS-related death was defined as any death caused by BrM or LMD or DM progression or CNS treatment-associated complications. CNS-related death was estimated using cumulative incidence in the competing risks setting (with death due to other causes as a competing event) and overall survival (OS) was estimated using Kaplan Meier methodology. Risk factors associated with CNS-related death were assessed using sub-distribution hazards regression modeling. Treatments given after CNS disease diagnosis were treated as time-varying variables. Tests were two-sided with statistical significance < 0.05. Results: After excluding 19 patients (11 for discordant HER2 status, 5 for concomitant second solid tumor, and 3 for missing data), 275 patients were included in these analyses (258 patients with parenchymal BrM +/- LMD, 8 patients with DM only, 2 patients with DM concomitantly with LMD, and 6 patients with LMD only). Overall, 63/275 (23%) presented with CNS as first and only site of metastasis, 210 (76%) patients developed CNS disease synchronously with or following ECM, and 2 had unknown timing. 125/275 (45%) had de novo MBC, and nearly all patients were treated with CNS local therapies (92% ≥ 1 radiation treatment and 28% underwent ≥ 1 BrM resection). The median number of lines of systemic therapy after CNS disease diagnosis was 1 (range: 0-14); 105/275 (38%) patients received a HER2 tyrosine kinase inhibitor (lapatinib: 21%, neratinib: 4.4%, and tucatinib: 12%). The median follow-up was 3.6 years for survivors (range: 0.22 years-12 years). 193/275 (70%) patients died, of whom 105 (54%) died of CNS-related cause. The 3-year OS rate was 40% (95% CI=34%-46%), which varied for patients with BrM only at the diagnosis of metastatic disease [56% (95% CI=43%-

69%] compared to patients with ECM +/- BrM [35% (95% CI=28%-42%)] ($p=0.05$). The cumulative incidence of CNS-related death at 3 years was 33% (95% CI=27%-39%). Upon univariable modeling, LMD and CNS radiation treatment (RT) were associated with CNS-related death, and these associations remained statistically significant in a multivariable model [LMD: HR=2.49 (95% CI=1.62-3.83), $p < 0.0001$, and RT: HR=2.91 (95% CI=1.27-6.64), $p=0.01$]. Conclusions: Greater than half of patients with HER2+ with CNS involvement suffered of CNS-related death, with greatest risk among patients with LMD. We hypothesize that the association between radiotherapy and CNS-related death may reflect upfront response to systemic cancer-directed treatments of those in patients with DM only or limited CNS disease extension. CNS-only relapse at metastatic presentation portended improved survival than intra-plus extracranial progression, supporting an approach of aggressive local therapy for selected patients. Multimodality approaches using HER2-directed agents effective against parenchymal BrM, LMD along with extracranial metastases, in combination with local CNS-directed therapies need to be optimized.

PS11-03

Comparison of next-generation sequencing (NGS) results from the cerebrospinal fluid, peripheral blood, and systemic metastatic tumor tissue of patients with metastatic breast cancer (MBC) and leptomeningeal disease (LMD)

Presenting Author(s) and Co-Author(s):

L. Huppert. University of California, San Francisco, Oakland, California, United States

L. Her. University of California, San Francisco, United States

C. Hodgdon. GRASP - Guiding Researchers & Advocates To Scientific Partnerships, Baltimore, Maryland, United States

S. Brain. I-SPY 2 Advocacy Group, United States

C. Simmons. I-SPY 2 Advocacy Group, United States

J. Chien. University of California, San Francisco, San Francisco, California, United States

M. Majure. University of California, San Francisco, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

M. Magbanua. University of California San Francisco, San Francisco, California, United States

R. Balassanian. University of California, San Francisco, United States

M. Melisko. University of California at San Francisco, San Francisco, California, United States

Introduction. Leptomeningeal disease (LMD) is a devastating complication of advanced malignancies and occurs in 5-15% of patients (pts) with metastatic breast cancer (MBC). Molecular characterization of the primary tumor to identify actionable mutations is standard of care, and targeted therapies have significantly improved survival. In contrast, metastatic tumors to the central nervous system (CNS) are not routinely assessed for the presence of actionable mutations, so the frequency and concordance of actionable mutations centrally vs. peripherally is not well characterized. In this single-center prospective study, we collected cerebrospinal fluid (CSF) in pts with known or suspected LMD and performed next generation sequencing (NGS) to evaluate the status of actionable mutations in the CSF and compared these results with NGS from matched peripheral blood and systemic metastatic tumor samples. **Methods.** We enrolled sixteen (16) pts with MBC and suspected or confirmed LMD at a single academic center from 2021-2023 in this non-therapeutic prospective study and collected CSF, peripheral blood, and archival systemic tumor samples from each pt. We used NGS to evaluate the status of actionable biomarkers in the CSF, blood, and tissue using the following NGS platforms: CNSide (Biocept) for CSF; Guardant 360, Foundation One CDx and CNSide for blood; and Caris and the UCSF CLIA-validated UCSF500 panel for the systemic metastatic tumor samples. We also evaluated CSF tumor cell enumeration and HER2 status in a subset of pts (CNSide). **Results.** Of the sixteen pts with MBC and suspected or confirmed LMD, 81% (13/16) were ultimately determined to be LMD-positive based on positive CSF cytology and/or convincing MRI imaging, including 6 pts with HR+/HER2- MBC, 6 pts with metastatic triple negative breast cancer (mTNBC), and 1 pt with HR+/HER2+ MBC; 3 pts were determined to be LMD-negative based on similar criteria. Of the 6 pts with HR+/HER2- MBC and LMD, NGS detected actionable mutations in the CSF in 67% (4/6), including two pts with PIK3CA E545E, one pt with both PIK3CA E542K and ERBB2 amplification, and 1 pt with ESR1 Y537S. Matched NGS analysis of the peripheral blood and/or systemic metastatic tissue showed concordance with PIK3CA E542K detected across tissue types in two pts, but discordance across tissue types in the other pts, including ESR1 detected systemically in two pts but not in the CSF. Of

the 6 pts with mTNBC and LMD, CSF NGS detected actionable mutations in the CSF in 17% (1/6) of pts, including one pt with PIK3CA E542K; analysis of blood NGS for this pt is pending. 3 pts (50%) had mutations in TP53 in the CSF (1 pt with R273H and two pts with K132R), which were concordant across tissue types in all 3 pts. NGS did not detect any variants in the CSF of the one pt with HR+/HER2+ MBC and LMD. CSF tumor cell enumeration and central HER2 status will also be reported. Conclusion. This study demonstrates that NGS can detect actionable mutations in the CSF of pts with MBC and LMD. We observed concordance and heterogeneity in the status of actionable mutations between the CSF, peripheral blood, and systemic metastatic tumor tissue. Larger studies are needed to assess the clinical utility of these observations, particularly with the development of several novel targeted agents that are CNS-penetrant.

PS11-05

Trastuzumab Deruxtecan in patients with HER2[+] or HER2-Low Advanced Breast Cancer and Pathologically Confirmed Leptomeningeal Carcinomatosis: Results from Cohort 5 of the DEBBRAH Study

Presenting Author(s) and Co-Author(s):

M. Vaz Batista. Hospital Professor Doutor Fernando Fonseca EPE, Lisbon, Portugal. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Amadora , Lisboa, Portugal

J. Pérez-García. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Catalonia, Spain

L. Garrigós. International Breast Cancer Center (IBCC), Quiron Group, Barcelona, Spain. Hospital Universitari Dexeus, Barcelona, Spain

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

P. Cortez-Castedo. IOB Institute of Oncology, Hospital Ruber Internacional, Quiron Group, Madrid, Spain

F. Racca. IOB Institute of Oncology, Quiron Group, Madrid and Barcelona, Spain

S. Blanch. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US. Fundación Instituto Valenciano de Oncología, Valencia, Spain, United States

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

A. Fernández. Medical Oncology Department, Hospital Ramon y Cajal, Madrid, Spain; Alcalá de Henares University, Faculty of Medicine, Madrid, Spain

M. Fernández-Abad. Hospital Universitario Ramón y Cajal, Madrid (Spain); Universidad de Alcalá de Henares, ONCARE, Madrid, Spain

V. Iranzo. Hospital General Universitario de Valencia. GEICAM Spanish Breast Cancer Group, Spain

M. Gion. Ramón y Cajal University Hospital, Madrid, Madrid, Spain

G. Martrat. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

D. Alcalá-López. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

J. Pérez-Escuredo. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

M. Sampayo-Cordero. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

A. Llombart-Cussac. Arnau de Vilanova Hospital, Valencia, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US, Comunidad Valenciana, Spain

S. Braga. Hospital Professor Doutor Fernando Fonseca EPE, Lisbon, Portugal

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

Background: Leptomeningeal carcinomatosis (LMC) occurs in approximately 5-15% of patients (pts) with advanced breast cancer (ABC) and is associated with poor survival and a significant reduction in quality of life. The antibody-drug conjugate trastuzumab deruxtecan (T-DXd) has shown remarkable intracranial and extracranial activity, leading to its widespread clinical use. DEBBRAH is evaluating the efficacy and safety of T-DXd in pts with HER2[+] and HER2-low ABC with a history of brain metastases (BM) and/or LMC. Here, we report results from cohort 5 that included pts with pathologically confirmed LMC. Methods: DEBBRAH (NCT04420598) is a single-arm, open-label, five-cohort, phase 2 study conducted across 18 sites in Spain and Portugal. A total of 39 pts aged ≥ 18 years with pretreated HER2[+] or HER2-low ABC with stable, progressing, or untreated BM and/or LMC were enrolled in 5 cohorts: (1) HER2[+] ABC with non-progressing BM after radiotherapy and/or surgery; (2) HER2[+] or HER2-low ABC with asymptomatic untreated BM; (3) HER2[+] ABC with progressing BM after local treatment; (4) HER2-low ABC with progressing BM after local treatment; (5) HER2[+] or HER2-low ABC and LMC with positive cerebrospinal fluid cytology. Pts received 5.4 mg/kg T-DXd intravenously once every 21 days until disease progression, unacceptable toxicity, or consent withdrawal. Primary endpoint for cohort 5 was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response, clinical benefit rate (CBR) according to RANO-BM (intracranial lesions) and RECIST v.1.1 (extracranial and overall lesions); and safety and tolerability as per NCI-CTCAE v.5.0. OS was tested with the maximum likelihood exponential method (H_0 : median OS ≤ 2 months; H_1 : median OS ≥ 6 months). We estimate that 7 pts are needed to attain an 80% power at the nominal level of one-sided α of 0.05. Results: Between Apr 14, 2021, and Apr 5, 2022, 7 pts were allocated into cohort 5. Median age was 57 (range, 42–69) years, 3 (42.9%) pts were HER2[+], 6 (85.7%) pts had synchronous extracranial metastases, 2 of whom (28.6%) also presented BM, and 3 (42.9%) pts had measurable disease. Median number of previous lines of therapy for advanced disease was 4 (range, 1-8) and no patient received prior local treatment for central nervous system involvement. At data cut-off (Apr 4, 2023), median follow-up was 12 months (range, 2.5-18.6). Median duration of treatment was 9.0 months (range, 2.1-18.6). Two (28.6%) pts remained on treatment: 1 HER2[+] and 1 HER2-low, after 18.6 and 12.0 months, respectively. Median OS rate was 13.3 months (95% CI, 5.7-NA, $p < 0.001$) meeting the primary endpoint. Among 5 pts with disease progression, none had intracranial progression. A total of 4 (57.1%) pts presented extracranial progression and 1 (14.3%) patient had clinical worsening. No objective responses were observed, but 5 out of 7 pts had prolonged stabilization (≥ 24 weeks) for an overall CBR of 71.4% (95% CI, 29.0-96.3) and a median PFS of 8.9 months (95% CI, 4.9-NA) according to RECIST v.1.1. The most common non-hematological treatment emergent adverse events (TEAEs) of any grade (G) were nausea (57.1%; 14.3% G3), fatigue (42.9%; 0% G3), vomiting (42.9%; 0% G3), headache (42.9%; 0% G3), and urinary tract infection (42.9%; 0% G3). Anemia (42.9%; 0% G3) and thrombocytopenia (28.6%; 14.3% G3) were the most frequent hematological TEAEs. No cases of interstitial lung disease/pneumonitis were reported. Serious unrelated TEAEs occurred in 4 (57.1%) of 7 pts, and 1 patient experienced a related serious TEAE (nausea G3). No treatment-related deaths were reported. Conclusions: T-DXd showed promising activity with no new safety concerns in HER2[+] and HER2-low pts with previously untreated, pathologically confirmed LMC. These encouraging data warrant further investigation to address the unmet need in this difficult-to-treat condition.

PS11-06

Analysis of HER2 expression changes from breast primary to brain metastases including HER2 Low and impact on overall survival

Presenting Author(s) and Co-Author(s):

A. Pereslete. Herbert Wertheim College of Medicine/Dana-Farber Cancer Institute, Miami, Florida, United States

M. Hughes. Dana Farber Cancer Institute, United States

A. Patterson. Dana Farber Cancer Institute, United States

J. Files. Medical Oncology, Dana-Farber Cancer Institute, Hull, Massachusetts, United States

K. Nguyen. Dana Farber Cancer Institute, United States

L. Buckley. Dana Farber Cancer Institute, United States

A. Patel. Dana Farber Cancer Institute, United States

A. Moore. Dana Farber Cancer Institute, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

T. Li. Dana-Farber Cancer Institute, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Previous studies have shown that breast cancer receptor subtype switching between matched primary and metastatic brain metastases (BrM) is common. HER2 expression at low levels, termed “HER2 Low”, has emerged as a new therapeutic biomarker for highly active antibody drug conjugates with potential intracranial activity. Trastuzumab deruxtecan is FDA approved for the treatment of HER2 Low and HER2 positive breast cancer with emerging evidence of CNS responses and clinical benefit in patients with BrM. This study aimed to investigate the relationship between HER2 expression including HER2-Low between matched breast cancer primary tumors and brain metastases. We also sought to evaluate the impact of low HER2 expression on overall survival in breast cancer brain metastases. **Methods:** We identified pts with MBC seen at least once at a single, NCI-designated center and had a diagnosis of BrM between 2003 and 2023. Of 1252 MBC pts with a diagnosis of BrM, 265 pts underwent resection/biopsy for BrM with available ER/PR/HER2 status. Only pts with available matched primary and BrM tissue were analyzed. HER2 expression was defined as: HER2+ (3+ or 2+/ISH amplified), HER2-Low (1+, 2+/ISH neg) or HER2-0 [by ASCO-CAP guidelines]. Estrogen receptor (ER) status was defined as ER \geq 1%. Multivariate overall survival (OS) analyses by Cox proportional hazard models were determined from time of BrM resection to death or last follow-up between HER2+, HER2-Low and HER2-0 patients controlling for ER and age. **Results:** 197 matched breast cancer primary and BrMs with available ER, PR, and HER2 testing were evaluated. Median age at BrM resection was 51 yrs. ER was positive in 48% (N=95) of BrMs. Of 265 resected BrMs, HER2 expression was found in 72%: 49.8% HER2+ (N=132), 22.2% HER2-Low (N=59), and 27.9% HER2-0 (N=74). HER2 expression by 197 primary tumors was: 57% HER2+ (N=112), 24% HER2-Low (N=48), 19% HER2 0 (N=37). Amongst 112 HER2+ primary tumors, 97% (N=109) had concordant HER2+ BrMs, 3 (2.6%) switched to HER2-Low, with 100% retaining some HER2 expression. Of 37 HER2-0 primaries, 35% (13/37) gained HER2-Low expression and 5.4% (2/37) gained HER2+ expression in the

BrM. Amongst 48 HER2-Low primary tumors, half (52%) changed expression to either HER2+ (21%) or HER2-0 (31.2%) in the brain. 66 tumors had extracranial tissue biopsied prior to BrM resection available for HER2 analysis. Of 15 HER2-0 extracranial tumors, 47% gained HER2-Low and 13% gained HER2+ at time of BrMs. After adjusting for age and ER status at the time of BrMs, patients with HER2+ BrM had a statistically significant lower risk of death at time of follow up than those with HER2-Low BrM (HR=0.41, P=0.0006). The risk of death between patients with HER2-0 BrM did not differ from HER2-Low BrM after adjustment for ER and age (HR=0.96, p =0.9). Median survival from BrM resection was 12.4m, 16.1m, 47.6m for HER2-Low, HER2-0 and HER2+ respectively (p = .0004). Conclusions: HER2 expression amongst primary, extracranial and brain metastases is dynamic with frequent change. Over 40% of HER2-0 primary or extracranial tumors gain HER2 expression in the brain. These changes have therapeutic implications given HER2 targeting antibody drug conjugates with improved OS and emerging evidence of CNS activity, highlighting the need for better diagnostics, including those that do not require invasive tissue sampling, to determine HER2 status in the brain. Patients with HER2-Low and HER2-0 BrMs have inferior survival and are a clinical unmet need.

PS11-07

High prevalence of HER2-Low and AR expression in breast cancer brain metastases provide novel therapeutic options

Presenting Author(s) and Co-Author(s):

G. Garcia. Vanderbilt University Medical Center, Nashville, Tennessee, United States

P. Gonzalez-Ericsson. Vanderbilt University Medical Center, United States

B. Lehmann. Vanderbilt-Ingram Cancer Center, United States

B. Mobley. Vanderbilt University Medical Center, Tennessee, United States

J. Pietenpol.

L. Kennedy. Vanderbilt University Medical Center, Nashville, Tennessee, United States

B. Park. Vanderbilt University Medical Center, NASHVILLE, Tennessee, United States

M. Sanders. Vanderbilt University Medical Center, Nashville, Tennessee, United States

Background: Although survival rates for patients with advanced breast cancer (BC) have improved overall, rates of BC brain metastases (BCBM) have increased over the past two decades, occurring in up to 15% to 30% of patients. BCBM greatly reduce quality of life and overall survival (OS) and are now the leading cause of BC patient mortality. Patients with primary HER2+ and triple negative BC (TNBC) are at highest risk for BM. Locoregional therapy with surgery and radiation are currently standard of care (SOC), but these treatments have significant morbidity and BCBM progressing despite these interventions are hard to treat. Systemic therapies to reduce cognitive impairment and increase survival are desperately needed, particularly in HER2-negative patients. Currently, immune checkpoint inhibitors (ICIs) and small molecules such as PARP inhibitors are among the limited systemic options that have BCBM activity in HER2-negative BC. However, the benefit of these therapies is limited to a select group of patients. For example, androgen receptor (AR) is expressed in 60-80% of all BC and, in our recently completed clinical trial (NCT03206203), patients with AR+ metastatic TNBC treated with carboplatin +/- atezolizumab received no clinical benefit from the addition of atezolizumab. Alternatives to ICIs are needed for patients with AR+ TNBC. HER2-low (H2L) BC is a newly defined subset of HER2-negative BC with a HER2 immunohistochemical (IHC) score of 1+ (>10%) or 2+/in situ hybridization (ISH) negative phenotype. Recent clinical trials have demonstrated significant clinical benefit from novel HER2 antibody-drug conjugates (ADCs) in treating H2L BC. Trastuzumab-deruxtecan (T-DXd), a HER2-directing ADC (topoisomerase I inhibitor conjugated to a humanized HER2-targeted antibody) was recently FDA approved as the first targeted therapy to treat H2L BC and can penetrate the blood-brain barrier. DESTINY-Breast04 demonstrated notable PFS and OS benefit of T-DXd compared to SOC in patients with H2L metastatic BC and included 61 patients with BCBM (results anticipated shortly). The overall rates of AR and H2L expression in patients with BCBM is unknown. The goal of this study is to investigate the prevalence of AR and HER2-low expression in a large cohort of BCBM treated at our institution. Methods: We retrospectively assessed rates of H2L and AR positivity (AR+) among patients with BCBM whose treatment included surgery at our institution between 2005-2023. Results were correlated with clinical receptor status (HR+/HER2-, HER2+/HR+, HER2+/HR- and TNBC) and clinical characteristics. Results of ER, PR, and HER2 testing performed for clinical purposes on the brain metastases and primary tumors were obtained from pathology reports. We retrieved formalin-fixed paraffin-embedded tissue blocks of the brain metastases and performed IHC for AR (SP107) and prognostic markers for cases with missing data. Results: We identified 101 cases of BCBM. Based on clinical prognostic markers, BCBM subtypes were HR+/HER2- (22%), HR+/HER2+ (14%), HER2+/HR- (21%) and

TNBC (43%). Forty-five percent of the BCBM (n=45) were AR+ (>10%) and 24% (n=24) demonstrated > 50% AR+. Among tumors with >50% AR+, 42% (n=10) are H2L (7 HR+[30%] and 3 TNBC [13%]). Forty-two percent of BCBM were H2L. Among the HER2-negative BCBM (n= 66), 64% (n=42) were H2L, including 23 of 44 TNBC (52%) and 19 of 22 HR+ (86%). Fifteen percent of BMBC changed clinical subtype from the primary, including conversion to TNBC and H2L. Conclusion: AR+ positive (24% > 50% expression) and HER2-Low expressing (42%) tumors represent a significant proportion of our BCBM cohort providing exciting new options for treatment. Trials re-evaluating AR antagonists in combination with SOC utilizing high AR+ thresholds may benefit patients with BCBM. At least 10% of BCBM are both H2L and demonstrate >50% AR positivity providing the rationale for the combination of ADCs such as T-DXd and AR-targeted therapies for BCBM.

PS11-01

Brain metastases in metastatic breast cancer: prevalence per line of treatment and cumulative incidence in a cohort of 18075 real-world patients

Presenting Author(s) and Co-Author(s):

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Leone. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

T. Sanglier. F. Hoffmann-La Roche Ltd, Basel, Basel-Stadt, Switzerland

P. Lambert. Genentech, Inc., South San Francisco, California, United States

F. Montemurro. F. Hoffmann-La Roche Ltd, Basel 4070, Switzerland

R. Poppe. F. Hoffmann-La Roche Ltd, Basel 4070, Switzerland

E. Restuccia. F. Hoffmann-La Roche Ltd, Basel, Switzerland, Basel-Stadt, Switzerland

S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

BACKGROUND

Historic data suggest that incidence of brain metastasis (BM) is relatively distributed over time in HER2-positive (HER2+) breast cancer (BC), occurs early in triple negative BC (TNBC), and occurs late in hormone receptor-positive (HR+) metastatic BC (mBC). However, the timing of BM relative to line of therapy has not been well described. We describe the prevalence per line of therapy and cumulative incidence of BM in a large real-world cohort of patients (pts) with mBC, by BC subtype and line of therapy.

METHODS

This analysis used data from the longitudinal US Flatiron Health de-identified database, which provides unstructured and structured electronic health record-derived data from >2.6 million pts with cancer in ~800 unique sites of care. Eligible pts had initiated a first line of treatment (index data) for mBC up to March 1, 2021, to allow for ≥2 years potential follow-up time. Baseline characteristics were assessed, and pts categorized by HER2 and HR status: 1) HR+, HER2+; 2) HR+, HER2-, 3) HR-, HER2+ and 4) TNBC (i.e., negative for HR and HER2). For the last two categories, HER2-low subsets were defined based on immunohistochemistry results (1+, 2+, or equivocal). Lines of therapy were derived using both treatment regimens and progression data. The primary outcome was the first diagnosis of BM. The prevalence of BM was evaluated by subtype, at the index date, and by the line of therapy. The cumulative incidence function (CIF) of BM was used to estimate the risk of BM in pts free of BM at the index date, and death was treated as a competing event.

RESULTS

Overall, 18075 pts were included (HR+, HER2+: 3062 pts [16.9%]; HR-, HER2+: 902 pts [5.0%]; HR+, HER2-: 12331 pts [68.2%] [HR+, HER2-low: 7062 (39.1%)]); TNBC: 1780 pts [9.8%] [HR-, HER2-low: 725 pts (4.0%)]. Median age at the index date was 64 years (interquartile range: 54, 73) and 10271pts (56.8%) had visceral metastasis. In total, 5951 pts (32.9%) had de novo disease, 12090 (66.9%) had recurrent disease, and 34 (0.2%) did not have available data for mBC type. The table shows the number of pts by line of therapy, prevalence of BM, and cumulative incidence of BM from the index date. Of the included pts, 1306 (7.2%) had a BM at the index date; the CIF was run on the remaining 16973 pts. Overall,

2248 pts (13.2%) had an incident BM event during follow-up (HR+, HER2+: 578 events; HR-, HER2+: 237 events; HR+, HER2-: 1119 events [HR+, HER2-low: 619 events]; TNBC: 314 events [HR-, HER2-low: 124 events]), 9314 had a competing event, and 5411 were censored. By fourth-line therapy, the prevalence of BM was 26.1% in HR+, HER2+; 37.1% in HR-, HER2+; 24.7% in TNBC (HR-, HER2-low: 27.9%); but remained low at 7.2% in HR+, HER2- (HR+, HER2-low: 9.4%). The cumulative incidence of BM at 60 months was 23% in HR+, HER2+, 34% in HR-, HER2+, 10% in HR+, HER2-, and, 22% in TNBC. Overall, the HER2-low subsets had BM prevalence and cumulative incidence that were very close to those that were HER2-.

CONCLUSIONS

This large analysis of real-world data demonstrates that the prevalence of BM across pts with mBC differs by tumor subtype and by line of therapy. Conversely, HER2-low status may have limited impact. The cumulative incidence of BM was highest in the HR-, HER2+ and TNBC subgroups, and lowest in the HR+, HER2- subgroup; despite this, due to the high proportion of HER2-, HR+ mBC cases, the HR+, HER2- group represented the largest number of BM events. These data emphasize the need for clinical and biologic predictors of BM and for strategies to prevent their onset, and provide information on the impact of BM inclusion and exclusion criteria in clinical trials for pts with mBC.

Number of patients by line of therapy, prevalence of BM, and cumulative incidence of BM from the index date

Line of therapy	HR+, HER2+	HR-, HER2+	HR+, HER2- [HR+, HER2-low]	TNBC [HR-, HER2-low]
Number of pts, n				
1	3062	902	12331 [7062]	1780 [725]
2	1936	478	8120 [4721]	972 [422]
3	1232	281	5303 [3101]	526 [240]
4	761	159	3454 [2002]	283 [129]
5+	453	103	2191 [1276]	141 [70]
Prevalence of BM, %				
1	193 (6.3)	101 (11.2)	134 (2.5) [199 (2.8)]	109 (10.3) [88 (12.1)]
2	341 (17.6)	149 (31.2)	150 (4.4) [275 (5.8)]	97 (17.6) [73 (17.3)]
3	265 (21.5)	102 (36.3)	125 (6.7) [231 (7.4)]	63 (22.0) [50 (20.8)]
4	199 (26.1)	59 (37.1)	104 (7.2) [189 (9.4)]	38 (24.7) [36 (27.9)]
5+	120 (26.5)	38 (36.9)	78 (8.5) [134 (10.5)]	23 (32.4) [18 (25.7)]
Cumulative incidence of BM from the index date in the first line, % (95% confidence interval)				
12 months	7.2 (6-8)	13 (11-16)	3.1 (3-3) [3 (3-3)]	14 (12-15) [14 (11-17)]
24 months	14 (13-15)	25 (22-28)	6 (5-6) [6 (5-6)]	20 (18-22) [20 (17-23)]
36 months	19 (17-34)	30 (27-34)	8 (7-8) [8 (7-8)]	21 (19-23) [21 (18-24)]
60 months	23 (21-24)	34 (30-37)	10 (10-11) [10 (9-11)]	22 (20-26) [22 (19-26)]

BM, brain metastasis; HR, hormone receptor, pts, patients; TNBC, triple negative breast cancer.

Disclosure(s):

Sarah L. Sammons, MD: Advisory Committee/Board Member: : Roche, Astra Zeneca, Pfizer, GSK, Novartis (Ongoing), Loxo@Lilly (Ongoing); Consulting Fees (e.g., advisory boards): : Roche, Astra Zeneca, Pfizer, GSK, Novartis (Ongoing), Loxo@Lilly (Ongoing), Novartis AG (Ongoing); Industry Grant Support (Principal Investigators must provide information on research

funding from ineligible companies, even if received/managed by the institution): Loxo@Lilly (Ongoing), SeaGen (Ongoing)

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

Nancy U. Lin, MD: Consulting Fees (e.g., advisory boards): Affinia Therapeutics (Ongoing), Aleta Biopharma (Ongoing), AstraZeneca (Ongoing), Blueprint Medicine (Ongoing), Daiichi-Sankyo (Ongoing), Genetech / Roche (Ongoing), Janssen (Ongoing), Menarini/Stemline (Ongoing), Olema Pharmaceuticals (Ongoing), Prelude Therapeutics (Ongoing), Reverie Labs (Ongoing), SeaGen (Ongoing), Voyager Therapeutics (Ongoing); Independent Contractor: Artera (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Genetech / Roche (Ongoing), Menarini/Stemline (Ongoing), Merck (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing), SeaGen (Ongoing), Zion Pharmaceuticals (Ongoing)

Poster Spotlight Session 11: CNS Disease in Breast Cancer: Where are We Now and Can We do Better?

Presenting Author(s) and Co-Author(s):

E. Stringer-Reasor. University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Hoover, AL, United States

Disclosure(s):

Erica Stringer-Reasor, MD: Consulting Fees (e.g., advisory boards): AstraZeneco (Ongoing), Elly Lilly (Ongoing), Gilead (Ongoing), Immunomedics Inc (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing)

PS11-02

Clinical risk factors of Central Nervous System (CNS)-related death in patients with HER2-positive metastatic breast cancer

Presenting Author(s) and Co-Author(s):

E. Ferraro. Memorial Sloan Kettering Cancer Center/Breast Medicine Service, New York City, New York, United States

R. Bou Nassif. Neurosurgery, Memorial Sloan Kettering Cancer Center, United States

A. Reiner. Memorial Sloan Kettering Cancer Center, United States

S. Brown. Memorial Sloan Kettering Cancer Center, United States

U. Tosi. Neurosurgery, Memorial Sloan Kettering Cancer Center, United States

K. Panageas. Memorial Sloan Kettering Cancer Center, United States

C. Dang. Breast Medicine Service, Memorial Sloan-Kettering Cancer Center, United States

A. Seidman. Memorial Sloan Kettering Cancer Center, United States

N. Moss. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background:

Central nervous system (CNS) relapse represents a challenge in the management of patients with HER2-positive (+) metastatic breast cancer. Data regarding the impact of brain metastases (BrM) and CNS involvement on mortality are sparse. In this study we sought to determine the proportion of HER2+ MBC patients in which CNS disease is the cause of death and identify risk factors associated with CNS-related mortality.

Methods:

We reviewed medical records of 294 consecutive patients with HER2+ MBC and diagnosis of CNS disease including parenchymal BrM, leptomeningeal disease (LMD) or dural metastases (DM), treated at Memorial Sloan Kettering Cancer Center between August 2010 and April 2022. HER2-positivity was assessed at the first diagnosis of metastatic disease (any site). Clinicopathologic characteristics including disease burden at presentation, timing of CNS disease and extracranial metastases (ECM), neurologic complications, and local and systemic treatments were collected. CNS-related death was defined as any death caused by BrM or LMD or DM progression or CNS treatment-associated complications. CNS-related death was estimated using cumulative incidence in the competing risks setting (with death due to other causes as a competing event) and overall survival (OS) was estimated using Kaplan Meier methodology. Risk factors associated with CNS-related death were assessed using sub-distribution hazards regression modeling. Treatments given after CNS disease diagnosis were treated as time-varying variables. Tests were two-sided with statistical significance < 0.05 .

Results:

After excluding 19 patients (11 for discordant HER2 status, 5 for concomitant second solid tumor, and 3 for missing data), 275 patients were included in these analyses (258 patients with parenchymal BrM +/- LMD, 8 patients with DM only, 2 patients with DM concomitantly with LMD, and 6 patients with LMD only). Overall, 63/275 (23%) presented with CNS as first and only site of metastasis, 210 (76%) patients developed CNS disease synchronously with or following ECM, and 2 had unknown timing. 125/275 (45%) had de novo MBC, and nearly all patients were treated with CNS local therapies (92% ≥ 1 radiation treatment and 28% underwent ≥ 1 BrM resection). The median number of lines of systemic therapy after CNS disease

diagnosis was 1 (range: 0-14); 105/275 (38%) patients received a HER2 tyrosine kinase inhibitor (lapatinib: 21%, neratinib: 4.4%, and tucatinib: 12%). The median follow-up was 3.6 years for survivors (range: 0.22 years-12 years). 193/275 (70%) patients died, of whom 105 (54%) died of CNS-related cause. The 3-year OS rate was 40% (95% CI=34%-46%), which varied for patients with BrM only at the diagnosis of metastatic disease [56% (95% CI=43%-69%)] compared to patients with ECM +/- BrM [35% (95% CI=28%-42%)] ($p=0.05$). The cumulative incidence of CNS-related death at 3 years was 33% (95% CI=27%-39%). Upon univariable modeling, LMD and CNS radiation treatment (RT) were associated with CNS-related death, and these associations remained statistically significant in a multivariable model [LMD: HR=2.49 (95% CI=1.62-3.83), $p< 0.0001$, and RT: HR=2.91 (95% CI=1.27-6.64), $p=0.01$].

Conclusions:

Greater than half of patients with HER2+ with CNS involvement suffered of CNS-related death, with greatest risk among patients with LMD. We hypothesize that the association between radiotherapy and CNS-related death may reflect upfront response to systemic cancer-directed treatments of those in patients with DM only or limited CNS disease extension. CNS-only relapse at metastatic presentation portended improved survival than intra- plus extracranial progression, supporting an approach of aggressive local therapy for selected patients. Multimodality approaches using HER2-directed agents effective against parenchymal BrM, LMD along with extracranial metastases, in combination with local CNS-directed therapies need to be optimized.

Disclosure(s):

Emanuela Ferraro, MD: No financial relationships to disclose

Nelson Moss, MD: Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing), GT Medical Technology (Ongoing)

PS11-03

Comparison of next-generation sequencing (NGS) results from the cerebrospinal fluid, peripheral blood, and systemic metastatic tumor tissue of patients with metastatic breast cancer (MBC) and leptomeningeal disease (LMD)

Presenting Author(s) and Co-Author(s):

L. Huppert. University of California, San Francisco, Oakland, California, United States

L. Her. University of California, San Francisco, United States

C. Hodgdon. GRASP - Guiding Researchers & Advocates To Scientific Partnerships, Baltimore, Maryland, United States

S. Brain. I-SPY 2 Advocacy Group, United States

C. Simmons. I-SPY 2 Advocacy Group, United States

J. Chien. University of California, San Francisco, San Francisco, California, United States

M. Majure. University of California, San Francisco, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

M. Magbanua. University of California San Francisco, San Francisco, California, United States

R. Balassanian. University of California, San Francisco, United States

M. Melisko. University of California at San Francisco, San Francisco, California, United States

Introduction.

Leptomeningeal disease (LMD) is a devastating complication of advanced malignancies and occurs in 5-15% of patients (pts) with metastatic breast cancer (MBC). Molecular characterization of the primary tumor to identify actionable mutations is standard of care, and targeted therapies have significantly improved survival. In contrast, metastatic tumors to the central nervous system (CNS) are not routinely assessed for the presence of actionable mutations, so the frequency and concordance of actionable mutations centrally vs. peripherally is not well characterized. In this single-center prospective study, we collected cerebrospinal fluid (CSF) in pts with known or suspected LMD and performed next generation sequencing (NGS) to evaluate the status of actionable mutations in the CSF and compared these results with NGS from matched peripheral blood and systemic metastatic tumor samples.

Methods.

We enrolled sixteen (16) pts with MBC and suspected or confirmed LMD at a single academic center from 2021-2023 in this non-therapeutic prospective study and collected CSF, peripheral blood, and archival systemic tumor samples from each pt. We used NGS to evaluate the status of actionable biomarkers in the CSF, blood, and tissue using the following NGS platforms: CNSide (Biocept) for CSF; Guardant 360, Foundation One CDx and CNSide for blood; and Caris and the UCSF CLIA-validated UCSF500 panel for the systemic metastatic tumor samples. We also evaluated CSF tumor cell enumeration and HER2 status in a subset of pts (CNSide).

Results.

Of the sixteen pts with MBC and suspected or confirmed LMD, 81% (13/16) were ultimately determined to be LMD-positive based on positive CSF cytology and/or convincing MRI imaging, including 6 pts with HR+/HER2- MBC, 6 pts with metastatic triple negative breast cancer (mTNBC), and 1 pt with HR+/HER2+ MBC; 3 pts were determined to be LMD-negative based

on similar criteria. Of the 6 pts with HR+/HER2- MBC and LMD, NGS detected actionable mutations in the CSF in 67% (4/6), including two pts with PIK3CA E545E, one pt with both PIK3CA E542K and ERBB2 amplification, and 1 pt with ESR1 Y537S. Matched NGS analysis of the peripheral blood and/or systemic metastatic tissue showed concordance with PIK3CA E542K detected across tissue types in two pts, but discordance across tissue types in the other pts, including ESR1 detected systemically in two pts but not in the CSF. Of the 6 pts with mTNBC and LMD, CSF NGS detected actionable mutations in the CSF in 17% (1/6) of pts, including one pt with PIK3CA E542K; analysis of blood NGS for this pt is pending. 3 pts (50%) had mutations in TP53 in the CSF (1 pt with R273H and two pts with K132R), which were concordant across tissue types in all 3 pts. NGS did not detect any variants in the CSF of the one pt with HR+/HER2+ MBC and LMD. CSF tumor cell enumeration and central HER2 status will also be reported.

Conclusion.

This study demonstrates that NGS can detect actionable mutations in the CSF of pts with MBC and LMD. We observed concordance and heterogeneity in the status of actionable mutations between the CSF, peripheral blood, and systemic metastatic tumor tissue. Larger studies are needed to assess the clinical utility of these observations, particularly with the development of several novel targeted agents that are CNS-penetrant.

Disclosure(s):

Laura Huppert, MD: Consulting Fees (e.g., advisory boards): AstraZenica (Ongoing)

Jo Chien, MD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Amgen Inc. (Ongoing), Merck & Co., Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), SeaGen (Ongoing)

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

PS11-05

Trastuzumab Deruxtecan in patients with HER2[+] or HER2-Low Advanced Breast Cancer and Pathologically Confirmed Leptomeningeal Carcinomatosis: Results from Cohort 5 of the DEBBRAH Study

Presenting Author(s) and Co-Author(s):

M. Vaz Batista. Hospital Professor Doutor Fernando Fonseca EPE, Lisbon, Portugal. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Amadora, Lisboa, Portugal

J. Pérez-García. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Catalonia, Spain

L. Garrigós. International Breast Cancer Center (IBCC), Quiron Group, Barcelona, Spain. Hospital Universitari Dexeus, Barcelona, Spain

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

P. Cortez-Castedo. IOB Institute of Oncology, Hospital Ruber Internacional, Quiron Group, Madrid, Spain

F. Racca. IOB Institute of Oncology, Quiron Group, Madrid and Barcelona, Spain

S. Blanch. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US. Fundación Instituto Valenciano de Oncología, Valencia, Spain, United States

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

A. Fernández. Medical Oncology Department, Hospital Ramon y Cajal, Madrid, Spain; Alcalá de Henares University, Faculty of Medicine, Madrid, Spain

M. Fernández-Abad. Hospital Universitario Ramón y Cajal, Madrid (Spain); Universidad de Alcalá de Henares, ONCARE, Madrid, Spain

V. Iranzo. Hospital General Universitario de Valencia. GEICAM Spanish Breast Cancer Group, Spain

M. Gion. Ramón y Cajal University Hospital, Madrid, Madrid, Spain

G. Martrat. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

D. Alcalá-López. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

J. Pérez-Escuredo. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

M. Sampayo-Cordero. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

A. Llombart-Cussac. Arnau de Vilanova Hospital, Valencia, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US, Comunidad Valenciana, Spain

S. Braga. Hospital Professor Doutor Fernando Fonseca EPE, Lisbon, Portugal

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US; Department of Medicine, Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Madrid, Spain., Barcelona, Catalonia, Spain

Background:

Leptomeningeal carcinomatosis (LMC) occurs in approximately 5-15% of patients (pts) with advanced breast cancer (ABC) and is associated with poor survival and a significant reduction in quality of life. The antibody-drug conjugate trastuzumab deruxtecan (T-DXd) has shown remarkable intracranial and extracranial activity, leading to its widespread clinical use. DEBBRAH is evaluating the efficacy and safety of T-DXd in pts with HER2[+] and HER2-low ABC with a history of brain metastases (BM) and/or LMC. Here, we report results from cohort 5 that included pts with pathologically confirmed LMC.

Methods:

DEBBRAH (NCT04420598) is a single-arm, open-label, five-cohort, phase 2 study conducted across 18 sites in Spain and Portugal. A total of 39 pts aged ≥ 18 years with pretreated HER2[+] or HER2-low ABC with stable, progressing, or untreated BM and/or LMC were enrolled in 5 cohorts: (1) HER2[+] ABC with non-progressing BM after radiotherapy and/or surgery; (2) HER2[+] or HER2-low ABC with asymptomatic untreated BM; (3) HER2[+] ABC with progressing BM after local treatment; (4) HER2-low ABC with progressing BM after local treatment; (5) HER2[+] or HER2-low ABC and LMC with positive cerebrospinal fluid cytology. Pts received 5.4 mg/kg T-DXd intravenously once every 21 days until disease progression, unacceptable toxicity, or consent withdrawal. Primary endpoint for cohort 5 was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response, clinical benefit rate (CBR) according to RANO-BM (intracranial lesions) and RECIST v.1.1 (extracranial and overall lesions); and safety and tolerability as per NCI-CTCAE v.5.0. OS was tested with the maximum likelihood exponential method (H_0 : median OS ≤ 2 months; H_1 : median OS ≥ 6 months). We estimate that 7 pts are needed to attain an 80% power at the nominal level of one-sided α of 0.05.

Results:

Between Apr 14, 2021, and Apr 5, 2022, 7 pts were allocated into cohort 5. Median age was 57 (range, 42–69) years, 3 (42.9%) pts were HER2[+], 6 (85.7%) pts had synchronous extracranial metastases, 2 of whom (28.6%) also presented BM, and 3 (42.9%) pts had measurable disease. Median number of previous lines of therapy for advanced disease was 4 (range, 1-8) and no patient received prior local treatment for central nervous system involvement. At data cut-off (Apr 4, 2023), median follow-up was 12 months (range, 2.5-18.6). Median duration of treatment was 9.0 months (range, 2.1-18.6). Two (28.6%) pts remained on treatment: 1 HER2[+] and 1 HER2-low, after 18.6 and 12.0 months, respectively. Median OS rate was 13.3 months (95% CI, 5.7-NA, $p < 0.001$) meeting the primary endpoint. Among 5 pts with disease progression, none had intracranial progression. A total of 4 (57.1%) pts presented extracranial progression and 1 (14.3%) patient had clinical worsening. No objective responses were observed, but 5 out of 7 pts had prolonged stabilization (≥ 24 weeks) for an overall CBR of 71.4% (95% CI, 29.0-96.3) and a median PFS of 8.9 months (95% CI, 4.9-NA) according to RECIST v.1.1.

The most common non-hematological treatment emergent adverse events (TEAEs) of any grade (G) were nausea (57.1%; 14.3% G3), fatigue (42.9%; 0% G3), vomiting (42.9%; 0% G3), headache (42.9%; 0% G3), and urinary tract infection (42.9%; 0% G3). Anemia (42.9%; 0% G3) and thrombocytopenia (28.6%; 14.3% G3) were the most frequent hematological TEAEs. No cases of interstitial lung disease/pneumonitis were reported. Serious unrelated TEAEs occurred in 4 (57.1%) of 7 pts, and 1 patient experienced a related serious TEAE (nausea G3). No treatment-related deaths were reported.

Conclusions:

T-DXd showed promising activity with no new safety concerns in HER2[+] and HER2-low pts

with previously untreated, pathologically confirmed LMC. These encouraging data warrant further investigation to address the unmet need in this difficult-to-treat condition.

Disclosure(s):

Marta Vaz Batista, MD: Consulting Fees (e.g., advisory boards): Novartis Pharma GmbH (Ongoing)

Maria Gion, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo/Astra Zeneca (Terminated), Gilead Science (Terminated), Novartis (Terminated), Pfizer (Terminated); Travel: F. Hoffman La Roche Ltd (Terminated)

Javier Cortés, MD, PhD: No relevant disclosure to display

PS11-06

Analysis of HER2 expression changes from breast primary to brain metastases including HER2 Low and impact on overall survival

Presenting Author(s) and Co-Author(s):

A. Pereslete. Herbert Wertheim College of Medicine/Dana-Farber Cancer Institute, Miami, Florida, United States

M. Hughes. Dana Farber Cancer Institute, United States

A. Patterson. Dana Farber Cancer Institute, United States

J. Files. Medical Oncology, Dana-Farber Cancer Institute, Hull, Massachusetts, United States

K. Nguyen. Dana Farber Cancer Institute, United States

L. Buckley. Dana Farber Cancer Institute, United States

A. Patel. Dana Farber Cancer Institute, United States

A. Moore. Dana Farber Cancer Institute, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

T. Li. Dana-Farber Cancer Institute, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background:

Previous studies have shown that breast cancer receptor subtype switching between matched primary and metastatic brain metastases (BrM) is common. HER2 expression at low levels, termed "HER2 Low", has emerged as a new therapeutic biomarker for highly active antibody drug conjugates with potential intracranial activity. Trastuzumab deruxtecan is FDA approved for the treatment of HER2 Low and HER2 positive breast cancer with emerging evidence of CNS responses and clinical benefit in patients with BrM. This study aimed to investigate the relationship between HER2 expression including HER2-Low between matched breast cancer primary tumors and brain metastases. We also sought to evaluate the impact of low HER2 expression on overall survival in breast cancer brain metastases.

Methods:

We identified pts with MBC seen at least once at a single, NCI-designated center and had a diagnosis of BrM between 2003 and 2023. Of 1252 MBC pts with a diagnosis of BrM, 265 pts underwent resection/biopsy for BrM with available ER/PR/HER2 status. Only pts with available matched primary and BrM tissue were analyzed. HER2 expression was defined as: HER2+ (3+ or 2+/ISH amplified), HER2-Low (1+, 2+/ISH neg) or HER2-0 [by ASCO-CAP guidelines]. Estrogen receptor (ER) status was defined as ER \geq 1%. Multivariate overall survival (OS) analyses by Cox proportional hazard models were determined from time of BrM resection to death or last follow-up between HER2+, HER2-Low and HER2-0 patients controlling for ER and age.

Results:

197 matched breast cancer primary and BrMs with available ER, PR, and HER2 testing were evaluated. Median age at BrM resection was 51 yrs. ER was positive in 48% (N=95) of BrMs.

Of 265 resected BrMs, HER2 expression was found in 72%: 49.8% HER2+ (N=132), 22.2% HER2-Low (N=59), and 27.9% HER2-0 (N=74). HER2 expression by 197 primary tumors was: 57% HER2+ (N=112), 24% HER2-Low (N=48), 19% HER2 0 (N=37). Amongst 112 HER2+ primary tumors, 97% (N=109) had concordant HER2+ BrMs, 3 (2.6%) switched to HER2-Low, with 100% retaining some HER2 expression. Of 37 HER2-0 primaries, 35% (13/37) gained HER2-Low expression and 5.4% (2/37) gained HER2+ expression in the BrM. Amongst 48 HER2-Low primary tumors, half (52%) changed expression to either HER2+ (21%) or HER2-0 (31.2%) in the brain. 66 tumors had extracranial tissue biopsied prior to BrM resection available for HER2 analysis. Of 15 HER2-0 extracranial tumors, 47% gained HER2-Low and 13% gained HER2+ at time of BrMs. After adjusting for age and ER status at the time of BrMs, patients with HER2+ BrM had a statistically significant lower risk of death at time of follow up than those with HER2-Low BrM (HR=0.41, P=0.0006). The risk of death between patients with HER2-0 BrM did not differ from HER2-Low BrM after adjustment for ER and age (HR=0.96, p =0.9). Median survival from BrM resection was 12.4m, 16.1m, 47.6m for HER2-Low, HER2-0 and HER2+ respectively (p = .0004).

Conclusions:

HER2 expression amongst primary, extracranial and brain metastases is dynamic with frequent change. Over 40% of HER2-0 primary or extracranial tumors gain HER2 expression in the brain. These changes have therapeutic implications given HER2 targeting antibody drug conjugates with improved OS and emerging evidence of CNS activity, highlighting the need for better diagnostics, including those that do not require invasive tissue sampling, to determine HER2 status in the brain. Patients with HER2-Low and HER2-0 BrMs have inferior survival and are a clinical unmet need.

Disclosure(s):

Alyssa M. Pereslete, BA: No financial relationships to disclose

Eric Winer, MD: No financial relationships to disclose

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

Nancy U. Lin, MD: Consulting Fees (e.g., advisory boards): Affinia Therapeutics (Ongoing), Aleta Biopharma (Ongoing), AstraZeneca (Ongoing), Blueprint Medicine (Ongoing), Daiichi-Sankyo (Ongoing), Genetech / Roche (Ongoing), Janssen (Ongoing), Menarini/Stemline (Ongoing), Olema Pharmaceuticals (Ongoing), Prelude Therapeutics (Ongoing), Reverie Labs (Ongoing), SeaGen (Ongoing), Voyager Therapeutics (Ongoing); Independent Contractor: Artera (Ongoing); Industry Grant Support (Principal Investigators must provide information on

research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Genetech / Roche (Ongoing), Menarini/Stemline (Ongoing), Merck (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing), SeaGen (Ongoing), Zion Pharmaceuticals (Ongoing)

Sarah L. Sammons, MD: Advisory Committee/Board Member: : Roche, Astra Zeneca, Pfizer, GSK, Novartis (Ongoing), Loxo@Lilly (Ongoing); Consulting Fees (e.g., advisory boards): : Roche, Astra Zeneca, Pfizer, GSK, Novartis (Ongoing), Loxo@Lilly (Ongoing), Novartis AG (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Loxo@Lilly (Ongoing), SeaGen (Ongoing)

PS11-07

High prevalence of HER2-Low and AR expression in breast cancer brain metastases provide novel therapeutic options

Presenting Author(s) and Co-Author(s):

G. Garcia. Vanderbilt University Medical Center, Nashville, Tennessee, United States

P. Gonzalez-Ericsson. Vanderbilt University Medical Center, United States

B. Lehmann. Vanderbilt-Ingram Cancer Center, United States

B. Mobley. Vanderbilt University Medical Center, Tennessee, United States

J. Pietenpol.

L. Kennedy. Vanderbilt University Medical Center, Nashville, Tennessee, United States

B. Park. Vanderbilt University Medical Center, NASHVILLE, Tennessee, United States

M. Sanders. Vanderbilt University Medical Center, Nashville, Tennessee, United States

Background:

Although survival rates for patients with advanced breast cancer (BC) have improved overall, rates of BC brain metastases (BCBM) have increased over the past two decades, occurring in up to 15% to 30% of patients. BCBM greatly reduce quality of life and overall survival (OS) and are now the leading cause of BC patient mortality. Patients with primary HER2+ and triple negative BC (TNBC) are at highest risk for BM. Locoregional therapy with surgery and radiation are currently standard of care (SOC), but these treatments have significant morbidity and BCBM progressing despite these interventions are hard to treat. Systemic therapies to reduce cognitive impairment and increase survival are desperately needed, particularly in HER2-negative patients. Currently, immune checkpoint inhibitors (ICIs) and small molecules such as PARP inhibitors are among the limited systemic options that have BCBM activity in HER2-negative BC. However, the benefit of these therapies is limited to a select group of patients. For example, androgen receptor (AR) is expressed in 60-80% of all BC and, in our recently completed clinical trial (NCT03206203), patients with AR+ metastatic TNBC treated with carboplatin +/- atezolizumab received no clinical benefit from the addition of atezolizumab. Alternatives to ICIs are needed for patients with AR+ TNBC. HER2-low (H2L) BC is a newly defined subset of HER2-negative BC with a HER2 immunohistochemical (IHC) score of 1+ (>10%) or 2+/in situ hybridization (ISH) negative phenotype. Recent clinical trials have demonstrated significant clinical benefit from novel HER2 antibody-drug conjugates (ADCs) in treating H2L BC. Trastuzumab-deruxtecan (T-DXd), a HER2-directing ADC (topoisomerase I inhibitor conjugated to a humanized HER2-targeted antibody) was recently FDA approved as the first targeted therapy to treat H2L BC and can penetrate the blood-brain barrier. DESTINY-Breast04 demonstrated notable PFS and OS benefit of T-DXd compared to SOC in patients with H2L metastatic BC and included 61 patients with BCBM (results anticipated shortly). The overall rates of AR and H2L expression in patients with BCBM is unknown. The goal of this study is to investigate the prevalence of AR and HER2-low expression in a large cohort of BCBM treated at our institution.

Methods:

We retrospectively assessed rates of H2L and AR positivity (AR+) among patients with BCBM whose treatment included surgery at our institution between 2005-2023. Results were correlated with clinical receptor status (HR+/HER2-, HER2+/HR+, HER2+/HR- and TNBC) and clinical characteristics. Results of ER, PR, and HER2 testing performed for clinical purposes on the brain metastases and primary tumors were obtained from pathology reports. We retrieved

formalin-fixed paraffin-embedded tissue blocks of the brain metastases and performed IHC for AR (SP107) and prognostic markers for cases with missing data.

Results:

We identified 101 cases of BCBM. Based on clinical prognostic markers, BCBM subtypes were HR+/HER2- (22%), HR+/HER2+ (14%), HER2+/HR- (21%) and TNBC (43%). Forty-five percent of the BCBM (n=45) were AR+ (>10%) and 24% (n=24) demonstrated > 50% AR+. Among tumors with >50% AR+, 42% (n=10) are H2L (7 HR+[30%] and 3 TNBC [13%]). Forty-two percent of BCBM were H2L. Among the HER2-negative BCBM (n= 66), 64% (n=42) were H2L, including 23 of 44 TNBC (52%) and 19 of 22 HR+ (86)%. Fifteen percent of BCBM changed clinical subtype from the primary, including conversion to TNBC and H2L.

Conclusion:

AR+ positive (24% > 50% expression) and HER2-Low expressing (42%) tumors represent a significant proportion of our BCBM cohort providing exciting new options for treatment. Trials re-evaluating AR antagonists in combination with SOC utilizing high AR+ thresholds may benefit patients with BCBM. At least 10% of BCBM are both H2L and demonstrate >50% AR positivity providing the rationale for the combination of ADCs such as T-DXd and AR-targeted therapies for BCBM.

Disclosure(s):

Guadalupe Ailin Garcia, MD: No financial relationships to disclose

Ben H. Park, MD, PhD: Advisory Committee/Board Member: Celcuity Inc. (Ongoing); Consulting Fees (e.g., advisory boards): CARIS life science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Adela (Ongoing), Guardant Health Inc. (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Celcuity Inc. (Ongoing); Royalty: Horizon Discovery (Ongoing); Unpaid advisor: Tempus Labs Inc. (Terminated, October 21, 2023)

Melinda Sanders, MD: No financial relationships to disclose

Poster Spotlight Session 12: Putting Brakes on the Cell Cycle: Understanding Mechanisms Governing CDK 4/6 Inhibitor Resistance and Role for Novel Therapeutic Strategies

Presenting Author(s) and Co-Author(s):

A. Waks. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Disclosure(s):

Adrienne G. Waks, MD: Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Genentech (Ongoing), Gilead (Ongoing), MacroGenics (Ongoing), Merck (Ongoing)

PS12-02

Exploration of ctDNA Dynamics in the PACE Trial: A Randomized Phase II Study of Fulvestrant, Palbociclib, and Avelumab for HR+/HER2- Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
J. Fu. Dana-Farber Cancer Institute, United States
Y. Ren. Department of Biostatistics, Dana-Farber Cancer Institute, United States
R. Mahtani. Miami Cancer Institute, Plantation, Florida, United States
C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States
A. DeMichele. University of Pennsylvania, Philadelphia, Pennsylvania, United States
M. Cristofanilli. Weill Cornell Medicine, United States
J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States
K. Miller. Indiana University, United States
Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States
E. Riley. University of Louisville Health - Brown Cancer Center, United States
R. Qamar. Advocate Aurora Health, United States
P. Sharma. University of Kansas Medical Center Westwood, Westwood, Kansas City, Kansas, United States
S. Reid. Vanderbilt-Ingram Cancer Center, United States
N. Ko. Boston Medical Center, United States
Y. Liu. Pfizer Inc, San Diego, California, United States
H. Burstein. Dana-Farber Cancer Institute, United States
M. DeMeo. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States
E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

Background

The PACE trial for HR+/HER2- metastatic breast cancer (MBC) prospectively evaluated whether continuation of the CDK4/6 inhibitor (CDK4/6i) palbociclib (P) beyond progression on prior CDK4/6i and aromatase inhibitor (AI), with a change in endocrine therapy (ET) to fulvestrant (F), improved outcomes beyond change to F alone, as well as explored the activity of a palbociclib, fulvestrant, and avelumab (P+F+A) triplet. The primary analysis did not show improvement in progression-free survival (PFS) with F+P versus F alone. In this analysis, an evaluation of serial translational PACE samples was performed to gain insights into the mutational landscape of HR+/HER2- MBC after prolonged exposure to CDK4/6i, evaluate early mutational dynamics with ongoing therapy, and identify potential genetic markers predictive of treatment response. Additionally, the identification of acquired mutations at the time of tumor progression could provide valuable information about mechanisms of treatment resistance.

Methods

PACE is a multicenter randomized open-label investigator-initiated phase II trial. Eligible patients (pts) had HR+/HER2- evaluable MBC with prior progression on AI and any CDK4/6i

after > 6 months (mo) of therapy in the MBC setting, or during/within 12 mo in the adjuvant setting, with no more than 1 prior line of chemotherapy for MBC. Pts were randomized 1:2:1 to F alone, F+P, or F+P+A, with tumor assessments every 8 weeks. Correlative samples including circulating tumor DNA (ctDNA) were collected at baseline (BL), times of tumor assessments (C3D1), and end of study/progression (EOT). Targeted NGS (Guardant360) to evaluate mutations (somatic single nucleotide variants and indels) was performed. Kaplan-Meier survival curves were used for assessing PFS and the log-rank test for comparisons. McNemar's test with continuity correction was used to test the changes in the frequency of mutations.

Results

Of the 220 randomized pts, 211 contributed ctDNA samples (200 at BL, 129 at C3D1, 146 at EOT). Characteristics of the correlative science population were similar to the intention to treat population. At BL, the most common mutations observed were ESR1 (57%), TP53 (38%), PIK3CA (36%), GATA3 (20%) ATM (12%) and Rb1 (12%). The presence of a PIK3CA mutation vs WT-PIK3CA at BL was associated with shorter PFS in the F alone arm ($p=0.001$) but not in the F+P or F+P+A arms. ESR1 mutations present at baseline were D538G (34%), Y537S (21%), Y537N (15%), E380Q (10%) and L536H (4%). At C3D1, the most common mutations observed were ESR1 (47%), TP53 (33%), PIK3CA (26.1), GATA3 (18.1), ATM (13%) and PTEN (8.6%). Including only BL and C3D1 matched samples ($N=124$), the prevalence of ESR1 mutations decreased after 2 cycles of treatment (57% at BL vs 44% at C3D1), predominantly observed in the F+P+A arm. For those in any arm with at least 6 months of disease stability on study ($N=53$), the presence of an ESR1 D538G mutation decreased during therapy, with 38% having a mutation at BL, 24% at C3D1, and no pts gaining ESR1 D538G at C3D1. The prevalence of PIK3CA mutations also decreased on treatment (32% at BL to 24% at C3D1), with the greatest decrease in the F+P arm. A predictive model correlating early genomic dynamics and associations with outcome will be presented.

Conclusions

The PACE trial offers one of the largest clinical trial cohorts describing the genomic landscape of HR+/HER2- MBC post-CDK4/6 exposure. Results from this correlative study provide a comprehensive mutational landscape post-CDK4/6i, demonstrate associations between mutations and clinical outcomes, and suggest the potential value of early ctDNA dynamics in this setting.

Disclosure(s):

Reshma L. Mahtani, DO: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing)

Cynthia Ma, MD, PhD: Advisory Committee/Board Member: Puma Biotechnology, Inc (Ongoing); Authorship/Article Publication: Wolters Kluwer/UpToDate (Ongoing); Consulting Fees (e.g., advisory boards): Agendia (Ongoing), AstraZeneca (Ongoing), Athenex (Ongoing), Bayer Healthcare (Ongoing), Biovica (Ongoing), Eisai (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), Inivata (Ongoing), Jacobio (Ongoing), Natera (Ongoing), Novartis (Ongoing), Olaris (Ongoing), OncoSignal (Ongoing), Pfizer (Ongoing), Phillips Electronics (Ongoing), Puma Biotechnology, Inc (Ongoing), Sanofi (Ongoing), Seattle Genetics (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): PlusOne Heath GmbH (Ongoing); Filled out Surveys for Tempus regarding these tests. Did not impact clinical or research activity.: Tempus (Ongoing); Royalty: Wolters Kluwer/UpToDate (Ongoing)

Priyanka Sharma, MD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Boston Scientific (Ongoing), Cipla Limited (Ongoing), Gilead Sciences (Ongoing), GlaxoSmithKline (GSK) (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Salient Pharmaceuticals (Ongoing), Sanofi (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol Meyer Squibb (Ongoing), Gilead Sciences (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Amgen (Ongoing), Gilead Sciences (Ongoing), Janssen (Johnson and Johnson) (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), Sanofi (Ongoing)

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

Erica L. Mayer, MD, MPH: Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Novartis Pharma GmbH (Ongoing)

PS12-03

p53 loss enables HR+ breast cancer escape from CDK4/6 inhibitor-induced quiescence via CDK2

Presenting Author(s) and Co-Author(s):

- R. Kudo. Memorial Sloan Kettering Cancer Center, Koto-City, Tokyo, Japan
A. Safonov. Memorial Sloan Kettering Cancer Center, New York, United States
E. da Silva. Memorial Sloan Kettering Cancer Center, New York, New York, United States
Q. Li. Memorial Sloan Kettering Cancer Center, United States
H. Shao. Memorial Sloan Kettering Cancer Center, United States
M. will. Memorial Sloan Kettering Cancer Center, United States
H. Nakshatri. Indiana University School of Medicine, Indianapolis, Indiana, United States
J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States
S. Goel. The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia
A. Koff. Department of Molecular Biology, Memorial Sloan Kettering Cancer Center, United States
B. Weigelt. Memorial Sloan Kettering Cancer Center, New York, New York, United States
Q. Khan. University of Kansas Medical Center, United States
P. Razavi. Memorial Sloan Kettering Cancer Center, New York, New York, United States
S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

Background:

Inhibition of CDK4/6 kinases has led to improved clinical outcomes in hormone receptor positive (HR+) breast cancer. While these are highly effective therapies, only a minority of patients experience long-term disease control. We sought to determine the genomic configurations and underlying mechanisms associated with long-term response.

Methods:

To identify genomic patterns associated with clinical outcomes, we analyzed a cohort of 447 patients with metastatic HR+ breast cancer treated at MSK with first-line CDK4/6 inhibitors (CDK4/6i) for which tumor-normal sequencing and long-term clinical follow up were available. To identify the pattern of genomic features associated with longer, intermediate, and short response, we implemented an elastic net Cox regression on binary pathogenic variant status of each gene as well as select clinical features (prior endocrine therapy, endocrine therapy partner, de novo metastatic status). Our principal aim was variable interpretability over pure predictive accuracy. Human HR+ breast cancer models including human breast cancer organoids and cell lines were utilized for mechanistic studies. For validation in a clinical setting, we analyzed the association between Ki67 score after neoadjuvant ribociclib plus endocrine therapy and pre-treatment gene mutation from the FELINE trial [NCT02712723] using a Fisher exact test.

Results:

Our model identified a “longer response” group (n = 124, 27.7%) from patients with a median progression free survival (PFS) of 32.5 months, compared with an “intermediate” (n = 224, 50.1%, median PFS = 13.7 months) and “short response” group (n = 99, 22.1%, median PFS =

5.84 months). TP53 and MDM2 pathogenic variant status were the most important variables to stratify between these groups, obtaining variable selection frequencies of 1.0 and 0.93 and mean hazard ratios of 2.02 and 1.38, respectively. To elucidate the mechanisms whereby the p53 pathway supports long term response, we generated isogenic and patient derived models of TP53 loss or MDM2 overexpression. Using immunoblotting and cell cycle assays, we found that drug-treated p53 KO cells and MDM2 overexpressing cells effectively suppressed RB1 phosphorylation and blocked in G1 after 24-48 hours. However, upon drug withdrawal, these cells could reenter the cell cycle and promote long-term tumor outgrowth. These effects we observed both in vitro and in vivo. Measures of long-term CDK4/6i response such as expression of senescence associated secretory phenotype genes was abrogated by TP53 loss. Mechanistically, we found persistent phosphorylation of the p130 RB1-like protein in the p53 KO cells. Phosphorylation of p130 impaired its interaction with E2F4, thereby blocking DREAM complex assembly and promoting cell cycle reentry. Inhibition of phosphorylation of p130 via p21 overexpression or by selective CDK2 inhibitors could restore irreversible cell cycle arrest in p53 KO cells. The combination of CDK2 and CDK4/6 inhibition led to long-term tumor growth suppression in models with mutant TP53. To validate the human relevance of TP53 mediating CDK4/6i response, we analyzed longitudinal samples from the FELINE trial that evaluated efficacy and feasibility of neoadjuvant ribociclib plus endocrine therapy. Of 45 evaluable patients, 13 (28.9%) harbored a pre-treatment TP53 loss of function variant. Of these 13 cases, 7 (53.8%) did not achieve a low (< 10%) Ki-67 upon surgical resection as compared to TP53 wildtype tumors (n=32), only one (3.2%) of which did not achieve a low Ki-67 [OR 32.1, 95% CI 3.28 – 1660.3, p = 0.00026].

Conclusion:

Loss of p53 was strongly associated with lack of long-term response to CDK4/6i in patients. Complete inhibition of both CDK4/6 and CDK2 appears to be necessary in order to convert quiescent HR+ tumors cells into durably inhibited and effectively dormant cancers.

Disclosure(s):

Rei Kudo, MD, PhD: No financial relationships to disclose

Jorge Reis-Filho, MD, PhD: No relevant disclosure to display

Shom Goel, B Med Sci (Hons), MBBS (Hons), FRACP, PhD: Advisory Committee/Board Member: G1-Therapeutics (Ongoing), Loxo@Lilly | Eli Lilly and Company (Ongoing); Consulting Fees (e.g., advisory boards): Novartis Pharma GmbH (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): G1-Therapeutics (Ongoing), Incyclix Bio (Ongoing), Loxo@Lilly | Eli Lilly and Company (Ongoing)

Pedram Razavi, MD, PhD: Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing), Chromcode (Ongoing), Epic Sciences (Ongoing), Foundation Medicine (Ongoing), Guardant (Ongoing), Lilly/Loxo (Ongoing), Natera (Ongoing), NeoGenomics/Invitae (Ongoing), Novartis (Ongoing), Paige (Ongoing), Pfizer (Ongoing), Prelude Therapeutics (Ongoing), SAGA Diagnostics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Biothernostics (Ongoing), Biovica (Ongoing), Epic Sciences (Ongoing), Grail/Illumina (Ongoing), Guardant (Ongoing), Invitae/.Archer Dx (Ongoing), NeoGenomics/Invitae (Ongoing), Novartis (Ongoing), Tempus (Ongoing)

PS12-04

Inhibition of GPX4 enhances CDK4/6 inhibitor activity in breast cancer.

Presenting Author(s) and Co-Author(s):

M. Herrera Abreu. Institute of Cancer Research, London, England, United Kingdom

U. khalid. Institute of Cancer Research, United States

J. Ning. Institute of Cancer Research, United States

R. Cutts. The Institute of Cancer Research, United Kingdom

G. Wilson. Institute of Cancer Research, United States

C. Lord. Institute of Cancer Research, London, United States

A. Swain. Institute of Cancer Research, United Kingdom

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background:

Cyclin D-dependent kinases 4 and 6 (CDK4/6) inhibitors (CDK4/6i) including palbociclib, ribociclib and abemaciclib in combination with endocrine therapy are the standard of care for patients with estrogen receptor-positive (ER+). Despite the success of these treatments, cytostasis is frequently observed, and novel strategies that enhance efficacy are required to eradicate residual cancer in the clinic.

Methods:

In the search of an effective drug combinations to enhance the efficacy of CDK4/6 inhibitors in breast cancer, we performed a whole genome CRISPR-Cas9 suppressor screen in MCF-7, an ER+ model. We also carried out transcriptomics, proteomics, and functional molecular biology analysis of breast cancer models treated with palbociclib to identify resistant mechanisms.

Results:

The whole genome CRISPR-Cas9 screen revealed that multiple genes involved in oxidative stress and ferroptosis modulated palbociclib sensitivity, being GPX4 the top sensitizing hit. GPX4 is a key glutathione peroxidase that protects against ferroptosis by catalysing the reduction of phospholipid and cholesterol hydroperoxides. CRISPR-depletion or drug inhibition of GPX4 increased sensitivity to palbociclib in ER+ breast cancer models, and in addition sensitised triple negative breast cancer models to palbociclib. Moreover, GPX4 null xenografts were highly sensitive to palbociclib in vivo. Transcriptomics and proteomics analysis showed that palbociclib upregulate pathways involved in oxidative stress and lipid metabolism promoting a redox-lipid imbalance. Palbociclib induced lipid peroxidation leading to a ferroptosis vulnerable state with GPX4 preventing cell death. Polyunsaturated fatty acids (PUFAs) are highly susceptible of lipid peroxidation, and pathways that regulate their abundance in membrane phospholipids were explored. Interestingly, in ER+ breast cancer models, lipid peroxidation relied on a peroxisome AGPAT3-dependent pathway rather than the classical ACSL4 pathway.

Conclusion:

Our studies demonstrate that quiescence induced by palbociclib results in a ferroptosis-vulnerable state that could be exploited through combination with GPX4 inhibitors to enhance sensitivity to CDK4/6 inhibition in breast cancer.

Disclosure(s):

Maria Teresa Herrera Abreu, PhD: No financial relationships to disclose

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Guardant Health (Ongoing), Invitae (Ongoing), Natera (Ongoing), Personalis (Ongoing)

PS12-06

A phase 2 study of abemaciclib monotherapy for patients with retinoblastoma-positive (Rb+), triple-negative metastatic breast cancer

Presenting Author(s) and Co-Author(s):

S. Goel. The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia

B. Jovanović. Dana-Farber Cancer Institute, United States

X. Chu. Dana Farber Cancer Institute, United States

M. Hughes. Dana Farber Cancer Institute, United States

A. Mohammed-Abreu. Dana Farber Cancer Institute, United States

J. Kasparian. Dana-Farber Cancer Institute, United States

T. Erick. Dana-Farber Cancer Institute, United States

M. DiLullo. Dana-Farber Cancer Center, United States

E. Wrabel. Dana-Farber Cancer Institute, United States

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Schnitt. Harvard Medical School, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

Background:

Cyclin-dependent kinase (CDK) 4/6 inhibitors can significantly extend survival when given in combination with endocrine therapy as treatment for hormone receptor-positive metastatic breast cancer. Preclinical studies suggest CDK4/6 inhibitor monotherapy might also be effective in a subset of triple-negative breast cancers (TNBCs), including those that express a functional retinoblastoma (RB) protein and/or those of the Luminal Androgen Receptor (LAR) subtype. Currently, the clinical activity of CDK4/6 inhibitor therapy in TNBC has not been reported.

Methods:

We conducted a single-arm phase II study of abemaciclib monotherapy in patients with locally advanced or metastatic TNBC. Key eligibility criteria included: (i) Measurable disease by RECIST 1.1; (ii) Between 1-3 prior lines of systemic therapy for advanced TNBC; (iii) RB-positive tumor (defined as $\geq 50\%$ of tumor cells staining positive for RB by immunohistochemistry [archival or fresh sample] on central testing); (iv) ECOG PS 0/1. Patients were treated with abemaciclib 200 mg orally (28-day cycles) twice daily until disease progression, unacceptable toxicity, withdrawal of consent, or death. Tumor biopsies were mandatory at baseline and C2D1 if tumor tissue was safely accessible. The primary outcome was objective response rate (ORR). Key secondary endpoints included progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR: CR + PR + SD ≥ 24 weeks), and safety and tolerability. The study had a two-stage design. Thirteen patients were enrolled in the first stage, with the plan to enrol a further 25 patients if at least one objective response was observed.

Results:

One unconfirmed partial response was observed in stage 1, and a total of 27 patients were enrolled before the trial was closed early due to slow accrual. The median age was 61 years and patients had received a median of 2 prior lines of systemic therapy for metastatic disease. Twelve patients had received prior immunotherapy. After a median follow-up of 28.5 months, the confirmed ORR was 0% and the CBR was 15%, with 4 of 27 patients experiencing stable disease for ≥ 24 weeks. The median PFS was 1.94 months (95% CI: 1.8 – 11.5 months), and the median OS was 8.44 months (95% CI: 4.6 – 15.6 months). There was no significant difference in PFS or OS between patients with PD-L1-positive versus PD-L1-negative disease, or Androgen Receptor (AR) positive versus negative tumors by immunohistochemistry. The most common adverse events of grade 2 or higher were diarrhea (41%), neutropenia (41%), anemia (30%), and nausea (30%). RNA-sequencing of baseline biopsies has been performed to identify biomarkers associated with clinical benefit, and results will be presented at the meeting.

Conclusions:

Abemaciclib monotherapy did not show clinical activity in patients with Rb+ metastatic TNBC. This finding suggests that future trials of CDK4/6 inhibition as monotherapy in TNBC are not warranted.

Disclosure(s):

Shom Goel, B Med Sci (Hons), MBBS (Hons), FRACP, PhD: Advisory Committee/Board Member: G1-Therapeutics (Ongoing), Loxo@Lilly | Eli Lilly and Company (Ongoing); Consulting Fees (e.g., advisory boards): Novartis Pharma GmbH (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): G1-Therapeutics (Ongoing), Incyclix Bio (Ongoing), Loxo@Lilly | Eli Lilly and Company (Ongoing)

Nancy U. Lin, MD: Consulting Fees (e.g., advisory boards): Affinia Therapeutics (Ongoing), Aleta Biopharma (Ongoing), AstraZeneca (Ongoing), Blueprint Medicine (Ongoing), Daiichi-Sankyo (Ongoing), Genentech / Roche (Ongoing), Janssen (Ongoing), Menarini/Stemline (Ongoing), Olema Pharmaceuticals (Ongoing), Prelude Therapeutics (Ongoing), Reverie Labs (Ongoing), SeaGen (Ongoing), Voyager Therapeutics (Ongoing); Independent Contractor: Artera (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Genentech / Roche (Ongoing), Menarini/Stemline (Ongoing), Merck (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing), SeaGen (Ongoing), Zion Pharmaceuticals (Ongoing)

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing),

NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

PS12-07

Phase II clinical trial of palbociclib and binimetinib in advanced triple-negative breast cancer (TNBC) with hyperactivation of ERK and/or CDK4/6

Presenting Author(s) and Co-Author(s):

R. Sánchez-Bayona. Medical Oncology Department, Hospital 12 de Octubre, Madrid. SOLTI Cancer Research Group, Barcelona, Spain

A. Cortes. Hospital Universitario Ramon y Cajal, Madrid, Spain

J. Cejalvo. Hospital Clínico Universitario de Valencia, Valencia, Spain

L. Manso. Hospital 12 de Octubre, Madrid, Spain

S. Morales. Hospital Universitario Arnau Villanova, Catalonia, Spain

J. Garcia-Saenz. Hospital Clínico San Carlos, Madrid, Spain

J. Silva. Hospital Universitario Fuenlabrada, Madrid, Spain

J. Guerra. Hospital Universitario de Fuenlabrada, Madrid, Spain

D. Malón-Giménez. Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain

S. Mouron. CNIO - Spanish National Cancer Research Center, United States

E. Caleiras. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

M. Quintela-Fandino. CNIO - Spanish National Cancer Research Center, Madrid, Spain

Background:

We previously demonstrated that a kinase-based taxonomy of TNBC was most parsimonious than next-generation sequencing in defining TNBC subtypes associated with prognostic categories in early disease. The most aggressive TNBC variants were driven by a heterogeneous set of genetic aberrations that converged in the increased activity of 6 kinases: KIT, PNKP, PRKCE, P70S6K, ERK and CDK6 (Nat Commun; 9:3501-18). The combined inhibition of these kinases in pairs led to potent tumor regression in preclinical models, being the most powerful combination that one directed against CDK6 and ERK. This prompted us to design a phase II trial testing the combination of palbociclib (against CDK6) and binimetinib (against the ERK upstream kinase MEK, since no ERK inhibitor was available at that moment outside phase I trials) in advanced TNBC. Hyperactivation of CDK6 and/or ERK was selected as entry criterion.

Trial design:

This was a single-arm, prospective, multicentric, open-label, phase II investigator-initiated trial. CDK6 and phosphor-ERK levels were measured in tumor samples by immunohistochemistry and normalized with a reference sample collection to a Z-score. Patients with scores for either kinase above the median were candidates for the trial. Key inclusion criteria included metastatic >18-year-old TNBC, adequate organ function, measurable disease, and progression to 1-2 prior treatment lines (including immunotherapy, and a PARP inhibitor in case of germline BRCA1/2 mutation). Patients started continuous oral binimetinib at 45 mg/BID and palbociclib 100 mg/day from days 1 to 21, in 28-day cycles. Patients experiencing \leq grade 1 tolerable side effects as the greatest toxicity were escalated to palbociclib to 125 in cycle 2. RECIST 1.1 and NCI CTC AE V 5.0 were used for assessing disease control (q8 weeks) and toxicity. The primary aims were to assess the efficacy and toxicity of this combination, and the secondary one to detect biomarkers of activity. At the time of trial design, in absence of available Sacituzumab for prescription, the reference PFS to beat in advanced lines for physician's choice in TNBC was 1.7 month (NEJM; 384:1529-41, 2021). With alpha and beta errors of 0.05 and 0.2, the

minimum number of patients to demonstrate a 30% improvement in PFS to 2.5 months was 25.

Results:

From November 2020 to April 2023, 69 patients were screened and 24 entered the trial (5 positive for phospho-ERK; 2 for CDK6; 17 for both). Toxicity was generally mild and included grade 1-2 diarrhea (33% of the patients), grade 1-2 asthenia (50%), grade 1-3 neutropenia (75%), grade 2 retinal toxicity (8.3%) and grade 3 rash (4.2%); no grade 4/5 toxicities were observed. Median PFS was 1.83 months (range 0.3 to 11.3+). Phospho-ERK and CDK6 levels were not correlated (Pearson's $R = -0.089$; $P = 0.68$); CDK6 levels did not show association with PFS time ($R = -0.120$; $P = 0.58$). Interestingly, however, phospho-ERK levels in the baseline tumor sample showed correlation with PFS time ($R = 0.428$; $P = 0.037$).

Conclusion:

The combination of palbociclib and binimetinib was generally safe, and PFS time showed correlation with baseline phosphorylation levels of ERK. However, the trial did not meet its primary endpoint.

Disclosure(s):

Miguel Quintela-Fandino, MD, PhD: Consulting Fees (e.g., advisory boards): Ellipses Pharma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bayer Pharmaceuticals (Ongoing), Circle Pharma (Ongoing), MECO Diagnostics (Ongoing), Pfizer, Inc. (Ongoing); Travel Grant: Pfizer, Inc. (Ongoing)

PS12-08

MORPHEUS Hormone Receptor-Positive Breast Cancer: interim analysis of a Phase Ib/II, study of fulvestrant ± atezolizumab and abemaciclib triplet treatment in patients metastatic disease

Presenting Author(s) and Co-Author(s):

K. Jung. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Not Applicable, Republic of Korea

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

D. Yardley. Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, United States

S. Hurvitz. Fred Hutchinson Cancer Center, Seattle, Washington, United States

K. Lee. Center for Breast Cancer, National Cancer Center, Goyang, Republic of Korea

A. Sonnenblick. Oncology Division, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

S. Shachar. Tel Aviv University, Tel Aviv, Israel

A. Tan. Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, United States

E. Comen. MSKCC, United States

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

J. Zhu. Genentech, Inc., South San Francisco, California, United States

K. DuPree. Genentech, Inc., South San Francisco, California, United States

V. Breton. F. Hoffmann-La Roche Ltd, Canada

F. Young. Roche Products Ltd, Welwyn Garden City, United Kingdom

R. Schwab. Genentech, Inc., South San Francisco, California, United States

E. Cha. Genentech, Inc., South San Francisco, California, United States

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

BACKGROUND

Endocrine therapy (ET) is the mainstay of treatment for metastatic hormone receptor-positive breast cancer (HR+ BC). ET resistance and disease progression are expected, thus novel therapies, like cancer immunotherapy, are needed. Prior data suggest that abemaciclib (abema), a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, has immunomodulatory activity. In the MORPHEUS HR+ BC study (NCT03280563), atezolizumab (atezo; anti-programmed death-ligand 1 [PD-L1]) was tested in combination with fulvestrant (FUL), with and without abema, in patients (pts) with HR+ metastatic BC. We present 24-week interim analyses.

METHODS

Pts with measurable disease progression during first- or second-line therapy for metastatic or

inoperable locally advanced HR+ BC and prior treatment with a CDK4/6 inhibitor were randomized to receive FUL (control) or FUL + atezo (1200 mg intravenous every 3 weeks) or FUL + atezo + abema (150 mg twice a day); prior FUL was not permitted. Pts were treated until loss of clinical benefit or unacceptable toxicity. Primary endpoints were objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and safety. Progression-free survival (PFS) was a secondary endpoint. Baseline tumor samples were analyzed for PD-L1 expression (SP263), CD8 T cell infiltration, and gene expression by RNAseq.

RESULTS

As of Dec 2022, 40, 31, and 25 pts (38, 30, and 20 evaluable pts) were randomized to atezo + abema + FUL, atezo + FUL, and FUL, respectively. Pts were followed for ≥ 24 weeks. Demographics were similar among the groups, with most pts receiving prior palbociclib (palbo) as part of their only prior metastatic therapy. Details and best confirmed ORRs are shown in the table. Median PFS was 6.34 months (95% confidence interval [CI] 5.52, 16.03) in the atezo + abema + FUL arm, 3.15 months (95% CI 1.51, 7.79) in the atezo + FUL arm, and 1.95 months (95% CI 1.45, 4.93) in the FUL arm. The hazard ratio of atezo + abema + FUL vs FUL was 0.43 (95% CI 0.24, 0.78). Safety data are shown in the table. Mild/moderate (grade 1/2) interstitial lung disease (ILD)/pneumonitis (7.7%) was observed in the atezo + abema + FUL arm. At baseline, tumors exhibited low prevalence of PD-L1 (median immune cells: 0.5%, tumor cells: 0%) and CD8 infiltration (12% inflamed phenotype), which did not associate with response in any arm. RNAseq analysis indicated that response to atezo + abema + FUL was strongly associated with low baseline expression levels of proliferation and metabolism signatures and trended with high expression of some immune signatures.

CONCLUSIONS

The triplet therapy of atezo + abema + FUL showed improved ORR and PFS compared with FUL monotherapy in the second- or third-line setting post-CDK4/6 inhibitor. This combination of atezo + abema + FUL was tolerable, with no unexpected safety signals, including no high-grade ILD/pneumonitis.

Efficacy and safety

Baseline characteristics	FUL n = 25	Atezo + FUL n = 31	Atezo + abema + FUL n = 40
Number of prior lines of therapy in a metastatic or locally advanced setting			
1L	24 (96.0%)	25 (80.6%)	35 (87.5%)
2L	1 (4.0%)	5 (16.1%)	5 (12.5%)
3L	0	1 (3.2%)*	0
Prior CDK4/6 inhibitor therapy			
Median duration (months)	13.31	14.36	15.28
25 th and 75 th percentiles	8.54–21.16	8.15–23.52	5.75–22.85
Palbociclib	23 (92.0%)	24 (77.4%)	35 (87.5%)
Efficacy			
	n = 20	n = 30	n = 38
ORR	2 (10.0%)	3 (10.0%)	10 (26.3%)
95% CI	(1.23, 31.70)	(2.11, 26.53)	(13.40, 43.10)
Clinical benefit rate	3 (15.0%)	13 (43.3%)	28 (73.7%)
95% CI	(3.21, 37.89)	(9.93, 42.28)	(26.31, 59.18)
Median PFS, months	1.95	3.15	6.34
95% CI	(1.45, 4.93)	(1.51, 7.79)	(5.52, 16.03)
Safety			
	n = 20	n = 30	n = 39
TRAEs (all grade)	35.0%	76.7%	97.4%
AEs Grade 3–4	15.0%	26.7%	82.1%
AEs leading to treatment discontinuation	0	6.7%	20.5%
AEs leading to dose modification/interruption	5%	16.7%	89.7%
Fatal AEs	0	0	0
Most common TRAEs ($\geq 20\%$ incidence rate)	0	Fatigue: 8 (26.7%); arthralgia: 6 (20.0%)	Diarrhea: 34 (87.2%); fatigue: 17 (43.6%); nausea: 13 (33.3%); vomiting: 10 (25.6%); anemia: 11 (28.2%); neutropenia: 10 (25.6%); hypothyroidism: 9 (23.1%); AST increased: 8 (20.5%); neutrophil count decreased: 8 (20.5%); rash: 8 (20.5%)
Most common irAEs ($\geq 20\%$ incidence rate)	0	0	AST increased (28.2%); ALT increased (20.5%); rash (25.6%); hypothyroidism (23.1%)

Data are number of patients (%), unless otherwise specified.

* Patient was treated in the second line and incorrectly included in this group.

Abema, abemaciclib; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; atezo, atezolizumab; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; ful, fulvestrant; irAE, immune-related adverse event; L, line; ORR, objective response rate; PFS, progression-free survival; TRAE, treatment-related adverse event.

Disclosure(s):

Kyung Hae Jung, MD, MS, PhD: Consulting Fees (e.g., advisory boards): Gilead Science (Terminated, May 26, 2023)

Antoinette R. Tan, MD, MHSc, FACP, FASCO: Consulting Fees (e.g., advisory boards): Arvinas (Ongoing), Astra Zeneca (Ongoing), G1 Therapeutics (Ongoing), Genentech-Roche (Ongoing), Jazz Pharmaceuticals (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Arvinas (Ongoing), Astra Zeneca (Ongoing), G1-Therapeutics (Ongoing), Genentech-Roche (Ongoing), GSK (Ongoing), Incyclix Bio (Ongoing), Merck & Co., Inc. (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing)

Einav Nili Gal-Yam, MD, PhD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated, November 14, 2023), Eli Lilly & Company (Terminated, November 14, 2023), F. Hoffman La Roche Ltd (Terminated, November 14, 2023), MSD Co., Ltd. (Terminated, November 14, 2023), Novartis Pharmaceuticals (Terminated, November 14, 2023), Pfizer, Inc. (Terminated, November 14, 2023); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): F. Hoffman La Roche Ltd (Ongoing); Honoraria: Astra Zeneca (Terminated, November 14, 2023); Honoraria: Eli Lilly & Company (Terminated, November 14, 2023), MSD Co., Ltd. (Terminated, November 14, 2023), Novartis Pharmaceuticals (Terminated, November 14, 2023), Pfizer, Inc. (Terminated, November 14, 2023)

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

Melinda Telli, MD: Advisory Committee/Board Member: Blueprint Medicine (Terminated, July 20, 2023), Natera, Inc. (Terminated, July 20, 2023), Novartis Pharma GmbH (Terminated, July 20, 2023), Reflexion Medical (Terminated, July 20, 2023), Replicate (Terminated, July 20, 2023), Sanofi Aventis (Terminated, July 20, 2023); Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated, July 20, 2023), Daiichi-Sankyo (Terminated, July 20, 2023), G1 Therapeutics (Terminated, July 20, 2023), Gilead Science (Terminated, July 20, 2023), Guardanth health (Terminated, July 20, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Arvinas (Ongoing), Astra Zeneca (Ongoing), Bayer

Pharmaceuticals (Ongoing), Genentech-Roche (Ongoing), Hummingbird Biosciences (Ongoing), Merck & Co., Inc. (Ongoing), OncoSec (Ongoing), Pfizer, Inc. (Ongoing)

PS12-09

Capivasertib plus cyclin-dependent kinase 4/6 inhibitor and fulvestrant in hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: updated Phase 1b analysis from CAPItello-292

Presenting Author(s) and Co-Author(s):

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

M. Beeram. The START Center, United States

V. Borges. University of Colorado Anschutz Medical Campus, Aurora, Colorado, United States

M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France

J. Guimarães. Sherbrooke University and Integrated University Health and Social Services Center (CIUSS) of Saguenay-Lac-Saint-Jean, Quebec, Canada

T. Foukakis. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer Theme, Karolinska University Hospital, Karolinska Comprehensive Cancer Center, Solna, Sweden

A. Raskov Kodahl. Odense University Hospital, Odense, Denmark

P. Lau. Linear Clinical Research, Perth, Australia and University of Western Australia, Perth, Washington, Australia

E. Lim. Garvan Institute of Medical Research, St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia

I. Ługowska. Maria Skłodowska-Curie National Institute of Oncology, Warsaw, Poland

G. Rychlik. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. Gresty. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. Miller. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

R. Somnavilla. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

D. Sudhan. Research and Early Development, Oncology R&D, AstraZeneca, Waltham, Massachusetts, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

Background

AKT pathway activation is implicated in endocrine therapy (ET) and cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) resistance in patients (pts) with HR+/HER2- advanced breast cancer (ABC). In CAPItello-291, capivasertib (C, a potent inhibitor of all 3 AKT isoforms) + fulvestrant (F) significantly improved PFS versus placebo F in pts with aromatase inhibitor-resistant HR+/HER2- ABC. Simultaneous inhibition of AKT and CDK4/6 pathways may delay CDK4/6i resistance or re-sensitize tumors to ET plus CDK4/6i, leading to improved clinical outcomes. CAPItello-292 (NCT04862663) is an ongoing Phase 1b/3 study examining the efficacy and safety of C + CDK4/6i (palbociclib [P], ribociclib [R]) + F in HR+/HER2- ABC. The recommended Phase 3 dose (RP3D) of C+P+F has been determined (C 400 mg BID, 4 days on/3 days off, P 125 mg, F 500 mg). Here we report ongoing Phase 1b data on C+P+F and C+R+F.

Methods:

Phase 1b of CAPItello-292 uses a keyboard design (mTPI-2) with the following planned doses: C 200 mg, 320 mg, 400 mg; P 75 mg, 100 mg, 125 mg; R 200 mg, 400 mg, 600 mg; F is fixed at 500 mg every 28 days + loading dose on cycle 1 day 15. Starting doses for C+P+F were C 320 mg BID, 4 days on/3 days off, P 125 mg QD) for 21 days of each 28-day cycle. Starting doses for C+R+F (ongoing) are C 400 mg BID, 4 days on/3 days off, R 400 mg QD for 21 days of each 28-day cycle. Eligible pts have HR+/HER2- ABC and ≥ 1 prior ET in the advanced setting or disease recurrence within 12 months of completing (neo)adjuvant ET (HER2- defined as immunohistochemistry [IHC] 0, or 1-positive or IHC2-positive/in situ hybridization-negative). Prior use of CDK4/6i, selective estrogen receptor degraders, and chemotherapy is permitted in Phase 1b. Phase 1b primary objectives: assess safety/tolerability; confirm RP3D. Objective response and clinical benefit rates (24 weeks; RECIST v1.1) were also assessed.

Results:

At data cut-off (Apr 21, 2023), 40 pts (median age: 58.5 years [range 38–82]) who were heavily pre-treated (as follows: 82.5% [33/40] prior CDK4/6i; 47.5% [19/40] prior F; 70.0% [28/40] prior chemotherapy [median 1.5 lines]) were treated with C+P+F. No new dose-limiting toxicities (DLTs) were observed since determination of RP3D. The most frequent adverse events (AEs) occurring in $>40\%$ of pts were diarrhea (70.0% [28/40]; 1/28 grade [G] ≥ 3), neutropenia (55.0% [22/40]; 20/22 G ≥ 3), fatigue, and nausea (both 42.5% [17/40]; all G1/2). Hyperglycemia occurred in 17.5% (7/40) pts (1/7 G3). No treatment-related deaths or new safety risks were identified. At the RP3D, the median (range) duration of exposure to C was 8.6 months (1.7–14.1); 5/8 pts with measurable disease at baseline had confirmed partial response (objective response rate: 62.5%, 95% confidence interval [CI] 24.5–91.5). Two additional pts had stable disease ≥ 7 weeks as a best objective response. At 24 weeks, the clinical benefit rate was 53.8% (7/13; 95% CI 25.1–80.8). Enrollment into C+R+F is ongoing: as of May 05, 2023, 8 pts had been dosed (6/8 pts had completed cycle 1). Based on clinical and safety review, the safety review committee has endorsed dose escalation to the highest dose level of R; no DLTs have been reported so far, although data are preliminary. Preliminary ctDNA analyses of pts treated with C+P/R+F will be presented.

Conclusions:

C+P+F was tolerable in heavily pre-treated pts with HR+/HER2- ABC at all dose levels; AEs were as expected, given the known safety profile of the individual treatments. Evidence of clinical activity has been observed in pts treated with the RP3D; data collection is ongoing. Preliminary safety analysis of C+R+F suggests no critical tolerability concerns; more pts and longer follow-up is required to characterize the safety of the combination. Updated data will be presented.

Funding: AstraZeneca

Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited)

Disclosure(s):

Erika P. Hamilton, MD: Consulting Fees (e.g., advisory boards): Arcus, Arvinas, AstraZeneca, Daiichi Sankyo, Deciphera Pharmaceuticals, Ellipses Pharma, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo, Mersana, Novartis, Orum Therapeutics, Pfizer, Relay Therapeutics, Roche/Genentech, SeaGen, Verascity Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if

received/managed by the institution): Abbvie, Acerta Pharma, Accutar Biotechnology ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, (Ongoing)

Barbara Pistilli, MD: Advisory Committee/Board Member: LILLY (Ongoing), Novartis Pharma GmbH (Ongoing)

Virginia F. Borges, MD: Advisory Committee/Board Member: Seagen Inc (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): DAIICHI-ASTRAZENECA (Ongoing), Olema Oncology (Ongoing), Seagen Inc (Ongoing)

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

General Session 2

Presenting Author(s) and Co-Author(s):

A. Tan. Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, United States

R. Rao. Columbia University Vagelos College of Physicians and Surgeons, New York City, New York, United States

Disclosure(s):

Antoinette R. Tan, MD, MHSc, FACP, FASCO: Consulting Fees (e.g., advisory boards): Arvinas (Ongoing), Astra Zeneca (Ongoing), G1 Therapeutics (Ongoing), Genentech-Roche (Ongoing), Jazz Pharmaceuticals (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Arvinas (Ongoing), Astra Zeneca (Ongoing), G1-Therapeutics (Ongoing), Genentech-Roche (Ongoing), GSK (Ongoing), Incyclix Bio (Ongoing), Merck & Co., Inc. (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing)

Roshni Rao, MD, FACS: No financial relationships to disclose

GS02-01

Randomized phase 3 study of datopotamab deruxtecan vs chemotherapy for patients with previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative breast cancer: Results from TROPION-Breast01b>

Presenting Author(s) and Co-Author(s):

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

M. De Laurentiis. Istituto Nazionale dei Tumori IRCCS 'Fondazione Pascale, Napoli, Italy

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

S. Pernas. SOLTI Cancer Research Group, Barcelona, Spain Institut Catala d'Oncologia; IDIBELL, L'Hospitalet, Barcelona, Spain

G. Borges. Tapirama, Brazil, United States

D. Cescon. Princess Margaret Cancer Centre/UHN, Toronto, Ontario, Canada

M. Hattori. Aichi Cancer Center, United States

Y. Lu. National Taiwan University Hospital, Taipei, Taiwan.

N. Martínez-Jáñez. Medical Oncology Hospital Universitario Ramón y Cajal. Madrid. Spain. GEICAM Spanish Breast Cancer Group., TRES CANTOS, Madrid, Spain

E. Hamilton. Sarah Cannon Research Institute / Tennessee Oncology-Nashville, Nashville, Tennessee, United States

S. Wang. Sun yat-sen university cancer center, United States

J. Tsurutani. Advanced Cancer Translational Research Institute at Showa University, Tokyo, Shinagawa, Japan

K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

L. Xu. AstraZeneca, United States

S. Khan. AstraZeneca, Gaithersburg, MD, United States

N. Denduluri. AstraZeneca, Gaithersburg, Maryland, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

B. Pistilli. Gustave Roussy, Villejuif, France

Background: The global, phase 3 TROPION-Breast01 trial (NCT05104866) assessed the TROP2-directed antibody-drug conjugate (ADC) datopotamab deruxtecan (Dato-DXd) compared with investigator's choice of chemotherapy (ICC) in patients (pts) with inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer (BC). Primary results were presented at ESMO 2023 (Bardia A, et al. Abstract LBA11). Here we report expanded data from TROPION-Breast01. Methods: Pts aged ≥18 years who had inoperable or metastatic HR+/HER2- BC, had disease progression on endocrine therapy (ET) and for whom ET was unsuitable, and had received 1–2 prior lines of systemic chemotherapy (CT), were eligible. Pts were randomized 1:1 to Dato-DXd (6 mg/kg Q3W) or ICC (eribulin,

vinorelbine, capecitabine, or gemcitabine) until progression or unacceptable toxicity. The dual primary endpoints were progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1, and overall survival (OS). Results: In total, 732 pts were randomized: 365 to the Dato-DXd arm and 367 to ICC. At data cut-off (Jul 17, 2023), 93/39 pts in the Dato-DXd/ICC groups were ongoing treatment. Pts receiving Dato-DXd had significantly improved PFS vs ICC (HR 0.63 [95% CI 0.52–0.76]; $p < 0.0001$). Hazard ratios for PFS favored Dato-DXd over ICC across prespecified pt subgroups, including prior lines of CT in the metastatic setting (1 vs 2), prior use of CDK4/6 inhibitor (≤ 12 months vs > 12 months), prior use of endocrine therapy in the metastatic setting (< 6 months vs ≥ 6 months) and brain metastases (yes vs no). OS data were not mature at this data cut-off. In the Dato-DXd vs ICC arms, 192 (53%) vs 247 (67%) pts had received a subsequent therapy after study treatment discontinuation, including 15 (4%) vs 52 (14%) who received subsequent ADC therapy, and 165 (45%) vs 186 (51%) who received subsequent CT. Median time to first subsequent therapy was 8.2 months in the Dato-DXd arm vs 5.0 months in the ICC arm (HR 0.53 [95% CI 0.45–0.64]). Overall, rate of grade ≥ 3 treatment-related adverse events (TRAEs) with Dato-DXd was less than half that with ICC. The secondary patient-reported outcome endpoints showed that time to deterioration in physical functioning, pain, and global health status/quality of life were delayed in the Dato-DXd arm compared with ICC. Conclusions: TROPION-Breast01 met its dual primary endpoint of PFS, demonstrating statistically significant and clinically meaningful improvement in PFS with Dato-DXd compared with ICC across all subgroups. Overall, the safety profile and QoL with Dato-DXd was favorable compared with ICC. These data support Dato-DXd as a potential new therapeutic option for pts with inoperable or metastatic HR+/HER2– BC who have received 1–2 prior lines of CT.

Disclosure(s):

Aditya Bardia, MD, MPH: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution):

Menarini/Stemline (Ongoing)

Komal Jhaveri, MD, FACP: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), AstraZeneca (Ongoing), Blueprint Medicines (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Jounce Therapeutics (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Menarini/Stemline (Ongoing), Novartis (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing), Sun Pharma Advanced Research Company Ltd (Ongoing), TAIHO Oncology (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Context Therapeutics (Ongoing), Debio Pharmaceuticals (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck Pharmaceuticals (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Puma Biotechnology, Inc (Ongoing), Zymeworks Inc. (Ongoing)

David W. Cescon, MD, PhD: Advisory Committee/Board Member: Inivata/NeoGenomics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co. Ltd. (Ongoing), Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), GlaxoSmithKline (Ongoing), Inflex Ltd (Ongoing), Lilly (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer, Inc. (Ongoing), SAGA Diagnostics (Ongoing); Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Gilead Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing), GlaxoSmithKline (Ongoing), Guardant Health Inc. (Ongoing), Inivata/NeoGenomics (Ongoing), Knight

Therapeutics (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), ProteinQure (Ongoing), Roche (Ongoing)

Erika P. Hamilton, MD: Consulting Fees (e.g., advisory boards): Accutar Biotechnology (Ongoing), AstraZeneca Pharmaceutical (Ongoing), Daiichi Sankyo (Ongoing), Ellipses Pharma (Ongoing), Entos (Ongoing), Fosun Pharma (Ongoing), Gilead Sciences (Ongoing), Greenwich Lifesciences (Ongoing), Jazz Pharmaceuticals (Ongoing), Lilly (Ongoing), Medical Pharma Services (Ongoing), Mersana Therapeutics (Ongoing), Novartis (Ongoing), Olema (Ongoing), Orum Therapeutics (Ongoing), Pfizer (Ongoing), Roche/Genentech (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing), Theratechnologies (Ongoing), Tubulis (Ongoing), Verascity Science (Ongoing), Zantalis Pharmaceuticals (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AbbVie Inc (Ongoing), Accutar Biotechnology (Ongoing), Acerta Pharma (Ongoing), ADC Therapeutics (Ongoing), Akesobio (Ongoing), Amgen (Ongoing), Aravive (Ongoing), ArQule (Ongoing), Artios (Ongoing), Arvinas (Ongoing), AstraZeneca Pharmaceutical (Ongoing), AtlasMedx (Ongoing), BeiGene (Ongoing), Black Diamond (Ongoing), Bliss BioPharmaceuticals (Ongoing), Boehringer Ingelheim (Ongoing), Bristol-Myers Squibb Company (Ongoing), Cascadian Therapeutics (Ongoing), Clovis Oncology (Ongoing), Compugen (Ongoing), Context Therapeutics (Ongoing), Cullinan (Ongoing), Curis (Ongoing), CytomX (Ongoing), Daiichi Sankyo (Ongoing), Dana Farber Cancer Inst (Ongoing), Dantari Pharmaceuticals (Ongoing), Deciphera (Ongoing), Duality Biologics (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai (Ongoing), Ellipses Pharma (Ongoing), Elucida Oncology (Ongoing), EMD Serono (Ongoing), Fochon (Ongoing), FUJIFILM Pharmaceuticals U.S.A (Ongoing), G1 Therapeutics (Ongoing), Gilead Sciences (Ongoing), H3 Biomedicine (Ongoing), Harpoon Therapeutics (Ongoing), Hutchinson MediPharma (Ongoing), Immunogen (Ongoing), Immunomedics Inc (Ongoing), Incyte (Ongoing), Infinity Pharmaceuticals (Ongoing), Inspira Inc (Ongoing), InventisBio (Ongoing), Jacobio Pharmaceuticals Co., Ltd. (Ongoing), Karyopharm (Ongoing), K-Group Beta (Ongoing), Kind Pharmaceuticals (Ongoing), Leap Therapeutics (Ongoing), Lilly (Ongoing), Loxo Oncology (Ongoing), Lycera (Ongoing), Mabspace Biosciences (Ongoing), Macrogenics (Ongoing), MedImmune (Ongoing), Mersana Therapeutics (Ongoing), Merus (Ongoing), Millennium (Ongoing), Molecular Templates (Ongoing), Myriad Genetics Inc. (Ongoing), Novartis (Ongoing), Nucana (Ongoing), Olema (Ongoing), OncoMed (Ongoing), Onconova Therapeutics (Ongoing), Oncothyreon (Ongoing), ORIC Pharmaceuticals (Ongoing), Orinove (Ongoing), Orum Therapeutics (Ongoing), Pfizer (Ongoing), PharmaMar (Ongoing), Pieris Pharmaceuticals (Ongoing), Pionyr Immunotherapeutics (Ongoing), Plexxikon (Ongoing), Prelude Therapeutics (Ongoing), Profound Bio (Ongoing), Radius Health (Ongoing), Regeneron Pharmaceuticals Inc. (Ongoing), Relay Therapeutics (Ongoing), Repertoire Immune Medicine (Ongoing), Rgenix (Ongoing), Roche/Genentech (Ongoing), SeaGen (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Shattuck Labs (Ongoing), Silverback Therapeutics (Ongoing), StemCentRx (Ongoing), Stemline Therapeutics (Ongoing), Sutro (Ongoing), Syndax Pharmaceuticals (Ongoing), Syros (Ongoing), Taiho (Ongoing), TapImmune (Ongoing), Tesaro (Ongoing), Tolmar (Ongoing), Torque Therapeutics (Ongoing), Treadwell Therapeutics (Ongoing), Verastem (Ongoing), Zenith Epigenetics (Ongoing), Zymeworks Inc. (Ongoing)

Kevin Kalinsky, MD, MS: Consulting Fees (e.g., advisory boards): Merck Foundation (Terminated), Takeda Pharmaceuticals, Ltd. (Terminated); spouse is employee: EQRX (Ongoing)

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis

Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

Barbara Pistilli, MD: Advisory Committee/Board Member: LILLY (Ongoing), Novartis Pharma GmbH (Ongoing)

GS02-02

Are nodal ITCs after neoadjuvant chemotherapy an indication for axillary dissection? The OPBC05/EUBREAST-14R/ICARO study

Presenting Author(s) and Co-Author(s):

G. Montagna. Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, United States

A. Laws. Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, United States

M. Ferrucci. Padua, Italy

M. Mrdutt. Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, United States

N. Polidorio. Memorial Sloan Kettering Cancer Center, New York, New York, United States

V. Sevilimedu. Memorial Sloan Kettering Cancer Center, United States

T. Moo. Memorial Sloan Kettering Cancer Center, New York, NY, United States

A. Barrio. Memorial Sloan Kettering Cancer Center, New York, New York, United States

M. Boyle. Cedars-Sinai Medical Center, Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA, United States

F. Cabero. Santa Paula Hospital, Sao Paulo, SP, Brazil

D. Cocco. Valleywise Health Medical Center, Phoenix, AZ, United States

F. Corsi. Breast Unit, Department of Surgery, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy; Department of Biomedical and Clinical Sciences "Luigi Sacco", Università di Milano, Milan, Italy

A. Crown. True Family Women's Cancer Center, Swedish Cancer Institute, United States

M. Flanagan. University of Washington / Fred Hutchinson Cancer Center, Seattle, Washington, United States

M. Gulcelik. University of Health Sciences, Gulhane Hospital, Department of Surgery, Turkey

C. Hlavin. University of Pittsburgh Medical Center, Pittsburgh, PA, United States

J. Jelinska. Poland, United States

H. Karanlik. Istanbul University Institute of Oncology, Department of Surgical Oncology, Istanbul, Turkey

S. Kesmodel. University of Miami DeWitt Daughtry Dept. Surgery, United States

H. Kuerer. The University of Texas MD Anderson Cancer Center, Houston, TX, United States

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

C. Leo. Breast Center, Cantonal Hospital Baden, Baden, Switzerland

T. Menes. Sheba Medical Center, Tel Hashomer, Israel; Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

M. Pilewskie. University of Michigan, Ann Arbor, Michigan, United States

N. Pisljar. Institute of Oncology Ljubljana, Slovenia

N. Rocco. Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy

J. Ryu. Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam, Ulsan-gwangyoksi, Republic of Korea

L. Soares. Federal University of Goiás, Seoul, Brazil

C. Tausch. Breast Center Zurich, Zurich, Switzerland

M. Ugurlu. Marmara University School of Medicine, Department of Surgery, Istanbul, Turkey

C. URBAN. Centro de Doenças da Mama- Breast Unit Nossa Senhora das Graças Hospital, United States

A. Botty van de bruele. Duke University School of Medicine, North Carolina, United States

D. Vorburger. Breast Cancer Unit, Comprehensive Cancer Center Zurich, University Hospital Zurich, Zurich, Switzerland

F. Wärnberg. Gothenburg University, Gothenburg, Sweden

A. Weiss. Division of Surgical Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States

A. Williams. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

S. Wong. Segal cancer centre, Jewish General Hospital, Lady Davis institute, United States

S. Woodward. Department of Surgery, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, PA, United States

S. Sun. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Zhang. Department of Surgery, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, Pennsylvania, United States

M. Ziauddin. Guthrie Cancer Center, Sayre, PA, United States

G. Karadeniz Cakmak. Zonguldak Bulent Ecevit University, Department of Surgery, Turkey

N. Bese. Research Institute of Senology Acibadem, Istanbul, Turkey, United States

T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany

J. Boughey. Division of Breast and Melanoma Surgical Oncology, Department of Surgery, Mayo Clinic, Rochester, Minnesota, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

N. Ditsch. Department of Gynaecology and Obstetrics, University Hospital Augsburg, Augsburg, Germany

M. Banys-Paluchowski. Department of Obstetrics and Gynecology, Asklepios Hospital Barmbek, Hamburg, Germany

M. Morrow. Memorial Sloan Kettering Cancer Center, New York, New York, United States

W. Weber. Breast Center, University Hospital of Basel, Basel-Stadt, Switzerland

Background: In patients with micro- and macrometastases in the sentinel lymph node (SLN) after neoadjuvant chemotherapy (NAC), additional positive nodes are found in >60% of cases and axillary lymph node dissection (ALND) is currently considered standard of care. The likelihood of finding additional positive lymph nodes in patients with residual isolated tumor cells (ITCs) is unknown, and the benefit of ALND is unclear. As a consequence, surgical management of the axilla in these patients is not standardized. We sought to evaluate how often additional positive lymph nodes are found, to determine factors associated with ALND, and to compare oncological outcomes in patients treated with and without ALND after identification of residual ITCs in the SLN. Methods: Data were collected from 42 centers: 20 in

the Oncoplastic Breast Consortium (OPBC) and EUBREAST networks, and 22 in North and South America. We included patients with cT1-4 N0-3 breast cancer at diagnosis who underwent NAC followed by axillary staging with either SLN biopsy (SLNB) or targeted axillary dissection (TAD) and were found to have residual ITCs [ypN0(i+)]. Single-tracer mapping was allowed for cN0 patients, while dual mapping or TAD was required for cN+ cases. Axillary treatment included completion ALND and/or nodal radiotherapy (RT). Competing risk analysis was performed to assess the cumulative incidence rates of any axillary recurrence (AR), locoregional recurrence (LRR), and any invasive (locoregional or distant) recurrence. Five-year cumulative incidence rates were compared between patients who underwent ALND and those who did not using the Gray's test. Type I error rate was set to 0.05 (α). Results: We included 412 patients treated with NAC followed by surgery from 01/2009-05/2022. 146 (35.4%) had completion ALND and 266 (64.6%) did not. Median patient age was 48 years. The majority (57%) of patients had clinical T2 tumors, and 68% had biopsy-proven N1 disease. Most were HR+/HER2- (41%) or HER2+ (39%). Most patients (80%) received anthracycline and taxane-based chemotherapy regimens. Nodal RT was administered to 83% of patients. The median number of SLNs with ITCs was 1. Patients treated with ALND were more likely to have ITCs detected on frozen section (61% v 6.7%, $p < 0.001$), to have N2/3 disease at presentation (15.1% v 5.6%, $p = 0.001$) and to have LVI (40% v 26%, $p = 0.004$) (Table 1). There was no significant trend over time in the proportion of patients undergoing completion ALND during the study period ($p = 0.5$). In the ALND group, additional positive nodes were found in 43/146 (29.5%) of cases, and consisted of macrometastases in 11/146 (7.5%), micrometastases in 9/146 (6.2%), and ITCs in 23/146 (15.8%). 5-year rates of any AR, LRR, and any invasive recurrence in the entire cohort were 2.7% (95% CI 1.2-5.4), 2.8% (95% CI 1.2-5.4) and 16% (95% CI 11-21), respectively. There was no statistical difference between patients who underwent ALND and those who did not in any of the 3 endpoints (2.2% v 3.1%, $p = 0.6$), (2.6% v 3.0%, $p = 0.4$) and (14% v 18%, $p = 0.12$), respectively. Conclusion: The likelihood of finding additional positive lymph nodes in patients with ITCs after NAC is lower than in patients with residual micro- and macrometastases, and in the majority of cases, they contain ITCs. Nodal recurrence after omission of ALND is rare in this population. Overall, these results do not support routine ALND in patients with residual ITCs.

Table 1. Clinicopathological Features of the Study Cohort, Stratified by Type of Axillary Surgery

	Full cohort n = 412	SLNB/TAD only n = 266	SLNB/TAD + ALND n = 146	p-value
Age, median, years (IQR)	48 (41, 57)	48 (40, 57)	49 (43, 58)	0.2
Race/ethnicity				<0.001
Asian	31 (7.5)	19 (7.1)	12 (8.2)	
Black	17 (4.1)	12 (4.5)	5 (3.4)	
Hispanic	19 (4.6)	12 (4.5)	7 (4.8)	
White	245 (59.2)	219 (82.3)	136 (92.9)	
Other/unknown	7 (1.7)	4 (1.5)	3 (2.1)	
Clinical T category				0.086
1	79 (19)	53 (19)	26 (18)	
2	244 (59.2)	144 (54)	100 (68)	
3	90 (22)	66 (25)	24 (16)	
4	12 (2.9)	6 (2.3)	6 (4.1)	
5	1 (0.2)	0 (0)	1 (0.7)	
Clinical N category				0.001
0	86 (21)	74 (27)	12 (8)	
1	279 (68)	178 (67)	101 (69)	
2	31 (7.5)	12 (4.5)	19 (13)	
3	6 (1.5)	3 (1.1)	3 (2.1)	
Staging technique				0.3
SLNB	286 (69)	180 (68)	106 (73)	
TAD	126 (31)	86 (32)	40 (27)	
Number of SLNs removed, median (IQR)	3 (2, 4)	3 (2, 4.75)	3 (1, 4)	<0.001
ITCs detected on frozen section				<0.001
Yes	100 (24)	17 (6.4)	83 (57)	
No	292 (70)	249 (93)	63 (43)	
Not performed/unknown	20	13	9	0.5
Number of SLNs with ITCs, median (IQR)	1 (1, 1)	1 (1, 1)	1 (1, 1)	<0.001
Total number of ITCs removed, median (IQR)	6 (1, 12)	4 (1, 5)	14 (1, 19)	<0.001
Total number of positive ITCs, median (IQR)	1 (1, 1)	1 (1, 1)	1 (1, 1)	0.9
Breast pCR (ypT0/i)	119 (29)	76 (29)	43 (29)	0.4
Yes	299 (73)	190 (71)	109 (74)	
NAC regimens HER2- tumors*				
ACT	208 (50)	137 (51)	71 (49)	
ACT + Platinum	17 (4.1)	8 (3)	9 (6)	
ACT + Platinum with Pembrolizumab	7 (1.7)	4 (1.5)	3 (2)	
AC-Free regimen	7 (1.7)	6 (2.3)	1 (0.7)	
Other	13 (3.1)	9 (3.4)	4 (2.7)	
NAC regimens HER2+ tumors**				0.2
ACT+T	43 (27)	25 (25)	18 (13)	
ACT+HP	54 (34)	36 (35)	18 (13)	
TC+HP	31 (20)	24 (24)	7 (5)	
Other	32 (20)	17 (17)	15 (11)	
Histology				0.066
Ductal	365 (89)	232 (88)	133 (92)	
Lobular or mixed	38 (9.3)	30 (11)	8 (5)	
Other	7 (1.7)	3 (1.1)	4 (2.8)	
Unknown	2	1	1	
Tumor differentiation				0.2
Well	25 (6)	20 (8)	5 (4)	
Moderately	137 (33)	95 (36)	42 (29)	
Poorly	235 (57)	136 (51)	99 (68)	
Unknown	35	15	25	
Subtype				0.6
HR+/HER2-	169 (41)	107 (40)	62 (42)	
HR+/HER2+	136 (33)	71 (27)	65 (45)	
HR-/HER2+	44 (11)	31 (12)	13 (9)	
HR-/HER2-	83 (20)	57 (21)	26 (18)	
LVI				0.004
Yes	127 (31)	69 (26)	58 (40)	
No	179 (43)	130 (49)	99 (67)	
Unknown	237 (58)	150 (56)	87 (59)	
Whole breast radiotherapy*				0.3
Yes	173 (42)	112 (42)	59 (40)	
No	4 (1)	4 (1)	0 (0)	
Unknown	235 (57)	150 (56)	87 (59)	
Postmastectomy radiotherapy†				0.056
Yes	173 (42)	112 (42)	59 (40)	
No	235 (57)	150 (56)	87 (59)	
Unknown	32 (8)	25 (9)	7 (5)	
Nodal radiotherapy				0.3
Yes	338 (82)	214 (80)	124 (85)	
No	70 (17)	49 (18)	21 (14)	
Unknown	4	3	1	

Frequency (row percent) reported for categorical variables, and median (IQR) reported for continuous variables. SLNB sentinel lymph node biopsy; TAD targeted axillary dissection; SLNs sentinel lymph nodes; LNs lymph nodes; pCR pathologic complete response; ACT anthracycline and taxane; AC anthracycline; H Herceptin, HP, Herceptin and Perjeta; TC taxol (or Taxotere) and carboplatinum; LVI lymphovascular invasion; BCS breast-conserving surgery. ^ Applied to HER2- tumors only (n=252). ^^ Applies to HER2+ tumors only (n=160). # LVI was present on core biopsy or final pathology. * Applies to BCS patients only (n=175). ** Applies to mastectomy patients only (n=237).

Disclosure(s):

Giacomo Montagna, MD, MPH: No financial relationships to disclose

Natalia Polidorio, MD, PhD: No financial relationships to disclose

Andrea V. Barrio, MD, FACS: No financial relationships to disclose

Melissa Pilewskie, MD, FACS: No financial relationships to disclose

Jai Min Ryu, MD, PhD: No financial relationships to disclose

Tari A. King, MD: Consulting Fees (e.g., advisory boards): Exact Sciences (Genomic Health) (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Exact Sciences (Genomic Health) (Ongoing)

Monica Morrow, MD: No financial relationships to disclose

GS02-04

Surgical Treatment of Women with Breast Cancer and a BRCA1 Mutation: An International Analysis of the Impact of Bilateral Mastectomy on Survival

Presenting Author(s) and Co-Author(s):

K. Metcalfe. University of Toronto, Toronto, Ontario, Canada
J. Lubinski. Pomeranian Medical University, Szczecin, Poland
J. Soukupová. First Faculty of Medicine, Charles University, Prague, Czech Republic
R. Bernstein-Molho. Chaim Sheba Medical Center, Israel
M. Lee. Memorial Sloan Kettering Cancer Center, United States
E. Gareth. University of Manchester, United States
A. Irmejs. Riga Stradins University and Pauls Stradins Clinical University Hospital, Latvia
R. Fruscio. University of Milan Bicocca, Italy
C. Villarreal Garza. Tecnológico de Monterrey, Monterrey, Mexico
J. Ngeow. National Cancer Centre Singapore, Singapore
J. Plichta. Duke University School of Medicine, Durham, North Carolina, United States
R. Yerushalmi. Rabin Medical Center, Israel
S. Narod. Women's College Research Institute, Toronto, Ontario, Canada

Background: Women with breast cancer and a BRCA1 mutation face a high risk of contralateral breast cancer. For this reason, many women with a unilateral breast cancer opt for bilateral mastectomies. Some will have a contralateral prophylactic mastectomy as a second surgery. However, it is not clear to what extent this operation impacts breast cancer mortality. The objective of the current study was to evaluate the differences in survival by surgical treatment in an international cohort of women with a BRCA1 mutation and unilateral breast cancer.

Methods: Eligible participants were identified from a large international cohort of women with breast cancer and a BRCA1 mutation, from 26 collaborating centres. Patients with DCIS and stage IV breast cancer were excluded. Patients with synchronous bilateral cancer were excluded. Demographic data were patient reported and clinical and treatment data were collected from medical records. Women were followed from date of breast cancer diagnosis to either date of last follow-up or date of death.

Results: There were 2482 eligible participants from 26 centres from 11 countries. The mean age of breast cancer diagnosis was 43.1 years (range 18-70 years). Among those who had a unilateral mastectomy or lumpectomy, the risk of contralateral breast cancer at 20 years was 27.5%. After experiencing a contralateral cancer the hazard ratio for breast cancer death was 2.14 (95%CI 1.43-3.18), $P=0.0002$. The fifteen-year breast cancer specific survival in the entire cohort was 82.9%. The survival was 78.7% for those who had a unilateral mastectomy, 86.2% for those who had a lumpectomy, and 88.7% for those who had bilateral mastectomies. 529 of the women who initially underwent a unilateral surgery subsequently had a contralateral or bilateral preventive mastectomy in the follow up period. 529 of the women with unilateral surgery had a contralateral or bilateral preventive mastectomy in the follow up period. After adjusting for age of diagnosis, tumor size, nodal status, chemotherapy (yes/no) and preventive mastectomy (time dependent) the hazard ratio for breast cancer mortality for bilateral surgery versus unilateral surgery was 0.78 (95% CI 0.55-1.13), $p = 0.19$.

Discussion: Women with a BRCA1 mutation and breast cancer who develop a contralateral breast cancer have double the risk of mortality compared to women who do not develop contralateral breast cancer. We observed a small non-significant reduction in mortality

for those who had bilateral mastectomies as initial treatment, but the cohort will require longer follow up for definitive results. Women with a BRCA1 mutation should be counselled on the risks of contralateral breast cancer and make surgical decisions with this knowledge.

Disclosure(s):

Kelly Metcalfe, RN, PhD: Consulting Fees (e.g., advisory boards): Astra Zeneca, Roche, Novartis, Biocad, R-Pharm, Eisai, Eli Lilly, Pfizer, MSD, BMS (Ongoing)

Steven Narod, MD: No financial relationships to disclose

GS02-05

Overview of Axillary Treatment in Early Breast Cancer: patient-level meta-analysis of long-term outcomes among 20,273 women in 29 randomised trials

Presenting Author(s) and Co-Author(s):

- G. Mannu. University of Oxford, Oxford, England, United Kingdom
G. Beake. University of Oxford, Oxford, England, United Kingdom
R. Berry. University of Oxford, Oxford, England, United Kingdom
D. Dodwell. University of Oxford, Oxford, England, United Kingdom
R. Hills. University of Oxford, Oxford, England, United Kingdom
P. McGale. University of Oxford, Oxford, England, United Kingdom
S. Anderson. University of Pittsburgh, Pittsburgh, Pennsylvania, United States
I. Campbell. University of Auckland, United States
A. Giuliano. Cedars-Sinai Medical Center, WEST HOLLYWOOD, CA, United States
R. Jagsi. Emory University, Ann Arbor, Michigan, United States
T. Kuehn. Women's Hospital, Klinikum Esslingen, United States
R. Llewellyn-Bennett. Southmead Hospital, United States
E. Mamounas. NSABP Foundation and Orlando Health Cancer Institute, Orlando, FL, USA, Windermere, Florida, United States
R. Mansel. Cardiff University, United States
P. Roy. Université de Lyon, United States
E. Rutgers. Department of Surgical Oncology, Netherlands Cancer Institute, United States
N. Sharma. Leeds Teaching Hospitals NHS Trust, United States
S. Swain. Georgetown University Medical Center, Lombardi Comprehensive Cancer Center and MedStar Health, Washington, DC, USA, United States
J. Bergh. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Breast Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden
O. EBCTCG. University of Oxford, Oxford, England, United Kingdom

Background: In early breast cancer, the optimal management of the axilla is uncertain. To better understand the long-term benefits and risks of different approaches, we undertook an individual patient data meta-analysis of randomised trials comparing varying types of axillary treatment. Methods: Information was available on 20,273 women in 29 trials of axillary surgery or axillary radiotherapy. The trial comparisons included in this overview are summarised in Table 1. Randomisation took place during 1958–2009. Median follow-up was 10.0 years (IQR 7.4–11.5). Findings: In the trials of more extensive versus less extensive axillary treatment, the rate ratios (RR) for locoregional recurrence varied by site ($p=0.003$), however, 82% of these locoregional recurrences (552/670) occurred either in the breast or were of unspecified location (Table 2). Considering locoregional recurrence at any site, there was little difference in the risk from more versus less axillary treatment (10-year risk 4.3% vs 4.7%; RR 0.90 95% CI 0.77–1.05; $p = 0.20$), even in women treated for node-positive disease (3.7% vs 3.6%; RR 1.01, 95% CI 0.74–1.36, $p=0.97$). There was, however, a substantial difference in lymphoedema for trials of more versus less axillary surgery (odds ratio (OR) 2.35, 95% CI 2.05–2.70; $p<0.00001$) and for trials of axillary treatment (surgery or radiotherapy) compared with no further axillary

treatment (OR 3.08, 95% CI 2.01–4.71; $p < 0.00001$). In the four trials comparing axillary node clearance to axillary radiotherapy, the risk of locoregional recurrence appeared to be somewhat reduced in women allocated to clearance (43 vs. 56 events, 10-year risk 4.4% vs. 6.9%; RR 0.64, 95% CI 0.43-0.96, $p=0.03$) whilst their risk of lymphoedema was increased (OR 1.79, 95% CI 1.42–2.27; $p < 0.00001$). The risks of distant recurrence, breast cancer, non-breast-cancer, or all-cause mortality did not differ significantly by extent of axillary treatment or when comparing axillary clearance to radiotherapy. Interpretation: This is the most comprehensive overview of axillary treatment to date. Less extensive surgery, such as sentinel lymph node biopsy, or using axillary radiotherapy, resulted in a substantial reduction in lymphoedema compared to axillary node clearance. While there was no evidence of a difference in locoregional recurrence, a moderate effect cannot be excluded. Funding: Cancer Research UK, British Heart Foundation, Medical Research Council

Table 1: Summary of the trials of treatment of the axilla in early breast cancer that began prior to 2012.

	More vs. less axillary treatment	Trials	Women
Pre-sentinel lymph node biopsy era (1958-1995)			
Axillary node clearance vs. not	Yes	4	1558
Axillary node clearance vs. not*	Yes	1	773
Axilla supraclavicular fossa RT vs. not	Yes	2	652
Axillary node clearance vs. axilla supraclavicular fossa RT	No	2	534
More vs. less surgery to axilla	Yes	1	82
More vs. less surgery to axilla*	Yes	3	4509
Axilla supraclavicular fossa RT + axillary node clearance vs. axilla supraclavicular fossa RT *	Yes	1	233
Sentinel lymph node biopsy era (1998-2004)			
Axillary sampling/node clearance vs. not (cN0/sN-)	Yes	10	8010
Axilla RT or surgery vs. not: (sN+)	Yes	3	2023
Axillary node clearance vs. axilla RT: (sN+)	No	2	1899
Total		29	20273

* confounded by extent of breast surgery
cN0=clinical node negative, sN-=sentinel node negative, sN+=sentinel node positive, RT=radiotherapy

Table 2: Numbers of locoregional recurrences as first event and rate ratios in the trials of more versus less axillary treatment.

Recurrence site	More axillary treatment (n=8347*)	Less axillary treatment (n=8401*)	Rate ratio (95% CI) (p-het: 0.003)
Breast	188	169	1.13 (0.92-1.40)
Isolated ipsilateral axilla	17	38	0.43 (0.25-0.73)
Isolated IMC-SCF	6	15	0.41 (0.17-0.98)
Regional, but site uncertain	15	24	0.62 (0.33-1.18)
Multiple sites/unspecified	89	109	0.87 (0.65-1.16)
Total	315	355	0.90 (0.77-1.05)

* two (1099 women) of these 25 trials did not provide data on locoregional recurrence

p-het: p for heterogeneity in the ratio of annual event rates between sites of recurrence

IMC=internal mammary chain, SCF= supraclavicular fossa

Disclosure(s):

Gurdeep S. Mannu, DPhil FRCS: No financial relationships to disclose

Reshma Jagsi, MD, DPhil: No financial relationships to disclose

Eleftherios P. Mamounas, MD: Consulting Fees (e.g., advisory boards): TerSera (Terminated, October 8, 2022); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Olaris, Novartis, Gilead, AstraZeneca, Sanofi-Genzyme, Biovica, Jacobio, Natera, Inivata, Athenex, Bayer, OncoSignal (Terminated, October 13, 2022)

GS02-06

Recurrence-free survival following sentinel node-positive breast cancer without completion axillary lymph node dissection – first results from the international randomized SENOMAC trial.

Presenting Author(s) and Co-Author(s):

J. de Boniface. Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, and Department of Surgery, Capio St. Göran's Hospital, Stockholm, Stockholms Lan, Sweden

T. Tvedskov. Herlev-Gentofte Hospital, Hovedstaden, Denmark

B. Leif. Uppsala University, United States

J. Frisell. Karolinska Institutet, Stockholm, Sweden

Y. Andersson. Västmanland Hospital and Uppsala University, United States

S. Alkner. Lund University, United States

M. Sund. Umeå University, United States

R. Olofsson Bagge. Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden

D. Lundstedt. Gothenburg University, Gothenburg, Sweden

O. Gentilini. Breast Surgery Unit, San Raffaele University Hospital, Milan, Italy

M. Kontos. 1st Department of Surgery, Laiko Hospital, National and Kapodistrian University of Athens, Greece

T. Reimer. University Hospital Rostock, Rostock, Germany

B. Offersen. Aarhus University Hospital, United States

T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany

L. Rydén. Region Skane / Lund University, United States

P. Christiansen. Aarhus University Hospital, Denmark, United States

Background

The omission of a completion axillary lymph node dissection (cALND) after a positive sentinel lymph node (SLN) biopsy in patients with clinically node-negative breast cancer has been demonstrated to yield survival outcomes non-inferior to routine cALND in breast-conserving surgery followed by whole-breast irradiation (ACOSOG Z0011 and IBCSG 23-01 trials), and to axillary radiotherapy (RT) regardless of breast surgery (EORTC AMAROS trial). Mainly due to the under-representation of mastectomy patients, and a limited number of observed events compromising statistical power, the international randomized SENOMAC trial was initiated in 2015. The main aim of this non-inferiority trial was to address knowledge gaps relating to individuals treated by mastectomy, those with larger tumors and those with SLN extracapsular extension. Method

The SENOMAC trial (NCT 02240472) enrolled patients with cT1-3cN0 primary breast cancer and 1-2 SLN macrometastases at 67 sites in five countries between January 27, 2015, and December 31, 2021. Participants were randomized 1:1 between cALND (standard) and omission of cALND (intervention). Stratification was per country. Breast-conserving surgery and mastectomy were eligible surgical interventions. Preoperative axillary ultrasound was mandatory; patients with non-palpable suspicious axillary lymph nodes, even if proven metastatic by biopsy, were eligible. SLN extracapsular extension was allowed. Adjuvant

radiotherapy was dictated by national guidelines and not by the trial protocol. Statistical sample size calculation was based on the primary outcome overall survival. Non-inferiority was defined as a 5-year overall survival not worsened by more than 2.5% when refraining from cALND after the observation of 190 all-cause deaths in a target sample size of 3000 included patients. In the present analysis, the pre-specified secondary outcome of recurrence-free survival is reported.

Results

Out of 2766 randomized individuals, 2539 comprised the per-protocol population: 1204 in the standard and 1335 in the intervention group. Median follow-up was 37.1 months (1.5-75.0) and median age at inclusion 61 years (range 20-94). Most tumors belonged to the luminal subtype (93.6%); tumor stage was T1 in 1358 (53.5%), T2 in 1034 (40.7%) and T3 in 146 participants (5.8%). Out of 347 participants with suspicious lymph nodes on ultrasound, 36 had confirmed non-palpable metastasis. SLN extracapsular extension was reported in 866 (34.1%). The breast was conserved in 1621 (63.8%) and a mastectomy performed in 918 (36.2%) patients. Most patients (2127, 83.8%) received radiotherapy including nodal target volumes. In 34.1% of the standard group, additional non-SLN metastases were identified on cALND. Overall, 104 recurrences were reported, 54 (4.5%) in the standard and 50 (3.7%) in the intervention group. Of these, 11 recurrences were found in the ipsilateral axilla: 5 (0.4%) and 6 (0.5%), respectively. Recurrence-free survival did not differ between groups (country-adjusted HR 0.89, 95% CI 0.65-1.20). Conclusion

Despite extended inclusion criteria, there was no difference in recurrence-free survival whether cALND was omitted (intervention) or not (standard). Patients undergoing mastectomy will specifically be addressed in subgroup analyses. Long-term follow-up is crucial considering the high proportion of luminal cancers.

Disclosure(s):

Jana de Boniface, MD, PhD: No financial relationships to disclose

GS02-07**Loco-Regional Irradiation in Patients with Biopsy-proven Axillary Node Involvement at Presentation Who Become Pathologically Node-negative After Neoadjuvant Chemotherapy: Primary Outcomes of NRG Oncology/NSABP B-51/RTOG 1304**

Presenting Author(s) and Co-Author(s):

E. Mamounas. NSABP Foundation and Orlando Health Cancer Institute, Orlando, FL, USA, Windermere, Florida, United States

H. Bandos. NRG Oncology Biostatistical Center, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

J. White. Ohio State University, Columbus, Ohio, United States

T. Julian. Allegheny Health Network Cancer Institute, Pittsburgh, Pennsylvania, United States

A. Khan. MSKCC, United States

S. Shaitelman. University of Texas MD Anderson Cancer Center, United States

M. Torres. Winship Cancer Institute of Emory University, Atlanta, Georgia, United States

F. Vicini. GenesisCare, United States

P. Ganz. UCLA Jonsson Comprehensive Cancer Center, and UCLA Fielding School of Public Health, Los Angeles, California, United States

S. McCloskey. Santa Monica UCLA Department of Radiation Oncology, United States

N. Gupta. Ohio State University Comprehensive Cancer Center-James Cancer Hospital, Solove Research Institute, United States

X. Li. Medical College of Wisconsin, United States

P. Lucas. UPMC Hillman Cancer Center / NSABP Foundation, Pittsburgh, Pennsylvania, United States

N. Abu-Rustum. Memorial Sloan-Kettering Cancer Center LAPS, United States

S. Gandhi. University of Texas MD Anderson Cancer Center LAPS, United States

R. Tendulkar. CWRU Case Comprehensive Cancer Center LAPS/Tau Taussig Cancer Center, Cleveland Clinic, United States

R. Coleman. The US Oncology Network, United States

K. Fujiwara. Saitama Medical University International Medical Center, United States

S. Seaward. Kaiser Permanente NCORP, United States

W. Irvin. Bon Secours Saint Francis Medical Center Cancer Institute/Southeast Clinical Oncology Research (SCOR), Midlothian, Virginia, United States

K. Higgins. Emory University - Winship Cancer Institute LAPS, United States

R. Mutter. Mayo Clinic LAPS, United States

J. Boileau. Jewish General Hospital Segal Cancer Centre, McGill University, Montréal, Quebec, Canada

A. Muskovitz. William Beaumont Hospital-Royal Oak, United States

R. Jagsi. Emory University, Ann Arbor, Michigan, United States

A. Weiss. Division of Surgical Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States

C. Walter. Winship Cancer Institute of Emory University, Atlanta, GA, United States

N. Wolmark. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

Disclosure(s):

Eleftherios P. Mamounas, MD: Consulting Fees (e.g., advisory boards): TerSera (Terminated, October 8, 2022); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Olaris, Novartis, Gilead, AstraZeneca, Sanofi-Genzyme, Biovica, Jacobio, Natera, Inivata, Athenex, Bayer, OncoSignal (Terminated, October 13, 2022)

Mylin A. Torres, MD: Consulting Fees (e.g., advisory boards): Genentech-Roche (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Genentech-Roche (Ongoing)

Reshma Jagsi, MD, DPhil: No financial relationships to disclose

GS02-08

Five-year outcomes of the IDEA trial of endocrine therapy without radiotherapy after breast-conserving surgery for postmenopausal patients age 50-69 with genomically-selected favorable Stage I breast cancer

Presenting Author(s) and Co-Author(s):

R. Jagsi. Emory University, Ann Arbor, Michigan, United States
K. Griffith. University of Michigan, United States
E. Harris. University Hospitals Case Western Reserve University, Cleveland, Ohio, United States
J. Wright. Johns Hopkins, United States
A. Recht. Harvard Medical School, United States
A. Taghian. Harvard Medical School, Boston, MA, United States
L. Lee. Northwell, United States
M. Moran. Yale, United States
W. Small. Loyola, United States
C. Johnstone. Medical College of Wisconsin, United States
A. Rahimi. University of Texas Southwestern Medical Center, Dallas, Texas, United States
G. Freedman. University of Pennsylvania, United States
M. Muzaffar. East Carolina University, United States
B. Haffty. Rutgers Cancer Institute of New Jersey, United States
K. Horst. Stanford University, United States
S. Powell. MSKCC, United States
J. Sharp. University of Michigan, United States
M. Sabel. University of Michigan, United States
A. Schott. Rogel Cancer Center, University of Michigan Health, Ann Arbor, Michigan, United States
M. El-Tamer. Memorial Sloan Kettering Cancer Center, Weill Cornell Medical School, New York, New York, United States

Disclosure(s):

Reshma Jagsi, MD, DPhil: No financial relationships to disclose

Asal Rahimi, MD, MS: Ad Board: Accuray (Ongoing); Consulting Fees (e.g., advisory boards): Accuray (Terminated, June 24, 2021), GE Health (Terminated, June 24, 2021); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Accuray (Ongoing)

GS02-10

Effects of a structured and individualized exercise program on fatigue and health-related quality of life in patients with metastatic breast cancer: the multinational randomized controlled PREFERABLE-EFFECT study

Presenting Author(s) and Co-Author(s):

A. May. University Medical Center Utrecht, Utrecht, Not Applicable, Netherlands

A. Hiensch. University Medical Center Utrecht, United States

J. Depenbusch. German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT) Heidelberg, Germany

M. Schmidt. German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT) Heidelberg, Germany

E. Monninkhof. University Medical Center Utrecht, United States

M. Pelaez. OSID-Onkologikoa, Osakidetza, United States

D. Clauss. German Sport University Cologne, Germany

P. Zimmer. German Sport University Cologne and TU Dortmund University, Germany

J. Belloso. Onkologikoa, United States

M. Trevaskis. Australian Catholic University, United States

H. Rundqvist. Karolinska Institutet, Stockholm, Sweden

J. Wiskemann. National Center for Tumor Diseases (NCT), Heidelberg University Hospital, United States

J. Muller. National Center for Tumor Diseases (NCT), Heidelberg University Hospital, United States

C. Fremd. Medical Oncology, National Center for Tumor Diseases Heidelberg, NCT (DKFZ and University Hospital), Heidelberg, Baden-Wurtemberg, Germany

R. Altena. Karolinska Institutet, Stockholm, Sweden

J. Kufel-Grabowska. Medical University of Gdańsk, United States

R. Bijlsma. University Medical Center Utrecht, United States

L. van Leeuwen-Snoeks. Diakonessenhuis Utrecht, United States

D. ten Bokkel-Huinink. Alexander Monro Hospital, United States

G. Sonke. Netherlands Cancer Institute, Amsterdam, Netherlands

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

P. Francis. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

G. Richardson. Cabrini, United States

I. Álvarez. Hospital Universitario Donostia-BioDonostia. GEICAM Spanish Breast Cancer Group., Spain

W. Malter. Universitätsklinikum Köln, United States

E. Van der Wall. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

N. Aaronson. The Netherlands Cancer Institute, United States

E. Senkus. Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland

A. Urriticoechea. Oncologikoa, United States

E. Zopf. Cabrini Health and Australian Catholic University, United States

W. Bloch. German Sport University Cologne, Germany

M. Stuiver. The Netherlands Cancer Institute, United States

Y. Wengström. Karolinska Institutet, Stockholm, Sweden

K. Steindorf. German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT) Heidelberg, Germany

Disclosure(s):

Anne M. May, PhD: No financial relationships to disclose

Bruce Mann, MBBS, PhD, FRACS: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution); Prelude corporation (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Prelude corporation (Ongoing)

GS02-11

Fertility preservation and assisted reproductive technologies (ART) in breast cancer (BC) patients (pts) interrupting endocrine therapy (ET) to attempt pregnancy

Presenting Author(s) and Co-Author(s):

H. Azim. School of Medecine, Monterrey Institute of Technology, Monterrey, Nuevo Leon, Mexico

S. Niman. Dana-Farber Cancer Institute, United States

A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

I. Demeestere. Research Laboratory on Human Reproduction and Gynecology and Obstetrics Department, Fertility Clinic, HUB-Erasme Hospital, Université Libre de Bruxelles (ULB),, Belgium

M. Ruggieri. ETOP IBCSG Partners Foundation, Bern, Bern, Switzerland

M. Colleoni. Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Lombardia, Italy

C. Saura. Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology and SOLTI Breast Cancer Research Group, Barcelona, Spain

C. Shimizu. Department of Breast and Medical Oncology, National Center for Global Health and Medicine, Tokyo, Japan

A. Saetersdal. Oslo University Hospital, Oslo, Norway

J. Kroep. Leiden University Medical Center, United States

A. Mailliez. Oscar LAMBRET Centre, LILLE, France

E. Warner. Sunnybrook Odette Cancer Centre, Toronto, Ontario, Canada

V. Borges. University of Colorado Anschutz Medical Campus, Aurora, Colorado, United States

F. Amant. UZ Leuven, Leuven, Vlaams-Brabant, Belgium

A. Gombos. Institut Jules Bordet, Brussels, Belgium

A. Kataoka. The Cancer Institute Hospital of JFCR, Koto-ku, Tokyo, Japan

C. Rousset-Jablonski. Leon Berard Cancer Center, Lyon, France

S. Borstnar. Institute of Oncology, Ljubljana, Slovenia

J. Takei. Department of Breast Surgical Oncology and Department of Clinical Genetics, St. Luke's international hospital, Chu-o-ku, Tokyo, Japan

J. Lee. Samsung Medical Center, Seoul, Republic of Korea

J. Walshe. Dept. of Medical Oncology St. Vincent's University Hospital and Tallaght University Hospital, United States

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucia, Spain

H. Moore. Cleveland Clinic, United States

C. Saunders. University of Melbourne, United States

V. Bjelic-Radisic. Breast Unit, Helios University Clinic, University Witten/Herdecke, Germany

S. Susnjar. Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

F. Cardoso. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

N. Klar. New York University Langone's Perlmutter Cancer Center, Breast Cancer Center, New York, NY, United States

T. Spanic. Europa Donna, The European Breast Cancer Coalition, Ljubljana, Slovenia

K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States

M. Piccart. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Anderlecht, Brussels Hoofdstedelijk Gewest, Belgium

L. Korde. Division of Cancer Treatment and Diagnosis, National Cancer Institute, United States

A. Goldhirsch. IEO, European Institute of Oncology, United States

R. Gelber. Dana-Farber Cancer Institute, Boston, MA, United States

O. Pagani. Interdisciplinary Cancer Service Hospital Riviera-Chablais Rennaz; Geneva University Hospitals, Lugano University and Swiss Group for Clinical Cancer Research (SAKK), Vaud, Switzerland

F. Peccatori. Fertility and Procreation Unit, IEO European Institute of Oncology IRCCS, Milan, Italy

Disclosure(s):

Hatem A. Azim, MD, PhD, Jr.: Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): PierreFabre (Terminated, May 31, 2022)

Ann Partridge, MD, MPH: Royalty: wolters Kluwer (UpToDate) (Ongoing)

Virginia F. Borges, MD: Advisory Committee/Board Member: Seagen Inc (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): DAIICHI-ASTRAZENECA (Ongoing), Olema Oncology (Ongoing), Seagen Inc (Ongoing)

GS02-13

Pregnancy after breast cancer in young women with germline BRCA pathogenic variants: results from an international cohort study

Presenting Author(s) and Co-Author(s):

- M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy
- E. Blondeaux. IRCCS Ospedale Policlinico San Martino, United States
- E. Agostinetto. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Bruxelles, Brussels Hoofdstedelijk Gewest, Belgium
- A. Hamy-Petit. Institut Curie, United States
- H. Kim. Asan medical center, Seoul, Seoul-t'ukpyolsi, Republic of Korea
- C. Chiodi. Gustave Roussy, Villejuif, France
- R. Bernstein-Molho. Chaim Sheba Medical Center, Israel
- F. Hilbers. NKI, United States
- K. Pogoda. Maria Sklodowska-Curie National Research Institute of Oncology, Warszawa, Mazowieckie, Poland
- E. Carrasco Lopez. Hospital Vall D'Hebron, Catalonia, Spain
- K. Punie. Leuven Cancer Institute, University Hospitals Leuven, United States
- J. Bajpai. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India
- M. Ignatiadis. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Brussels Hoofdstedelijk Gewest, Belgium
- H. Moore. Cleveland Clinic, United States
- K. Phillips. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
- A. Toss. Oncology Department Azienda Ospedaliero Universitaria Policlinico Modena, GOIRC, United States
- C. Rousset-Jablonski. Leon Berard Cancer Center, Lyon, France
- F. Peccatori. Fertility and Procreation Unit, IEO European Institute of Oncology IRCCS, Milan, Italy
- T. Renaud. Bergonie Institute, United States
- A. Ferrari. Fondazione IRCCS Policlinico san Matteo, Pavia, Lombardia, Italy
- S. Paluch-Shimon. Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, and Faculty of Medicine, Hebrew University, Jerusalem, Israel
- R. Fruscio. University of Milan Bicocca, Italy
- W. Cui. Department of Medical Oncology, Peter MacCallum Cancer Centre and The Sir Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia
- S. Wong. Segal cancer centre, Jewish General Hospital, Lady Davis institute, United States
- C. Vernieri. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Lombardia, Italy
- K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States
- M. Dieci. University of Padova, United States
- A. Matikas. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Breast Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden

M. Rozenblit. Yale Cancer Center, New Haven, Connecticut, United States
C. Villarreal Garza. Tecnológico de Monterrey, Monterrey, Mexico
L. De Marchis. "La Sapienza" University of Rome, United States
L. Del Mastro. University of Genova - IRCCS Ospedale Policlinico San Martino, United States
F. Puglisi. Department of Medicine (DAME), University of Udine, Udine, Italy and Department of Medical Oncology - CRO Aviano, National Cancer Institute, IRCCS, Aviano, Friuli-Venezia Giulia, Italy
M. Del Pilar Estevez-Diz. Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil
K. Rodriguez-Wallberg. Karolinska University Hospital, United States
B. Mrinakova. Comenius University & St. Elisabeth Cancer Institute, United States
S. Meister. LMU University Hospital, United States
L. Livraghi. Azienda Ospedaliera "Papa Giovanni XXIII", United States
F. Clatot. Centre Henri Becquerel, France
R. Yerushalmi. Rabin Medical Center-Beilinson Campus, Petah Tikva, Israel
C. De Angelis. University of Naples Federico II., Napoli, Italy
R. Sánchez-Bayona. Medical Oncology Department, Hospital 12 de Octubre, Madrid. SOLTI Cancer Research Group, Barcelona, Spain
I. Meattini. University of Florence, Florence, Toscana, Italy
N. Cichowska-Cwalińska. Medical University of Gdańsk, United States
M. Berlière. Cliniques universitaires Saint-Luc - Institut Roi Albert II, United States
M. Salama. Michigan State University (MSU), United States
U. De Giorgi. Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Italy
A. Sonnenblick. Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
H. Azim. School of Medicine, Monterrey Institute of Technology, Monterrey, Nuevo Leon, Mexico
A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Oncofertility counseling in BRCA carriers has unique challenges due to a possible negative impact of germline pathogenic/likely pathogenic variants (PVs) on reproductive potential and the indication to undergo risk-reducing bilateral salpingo-oophorectomy. While previous studies demonstrated the safety of pregnancy in women with prior breast cancer (BC) history, limited evidence exists in BRCA carriers specifically. We report the results of the largest study to date investigating likelihood of pregnancy after BC, reproductive and disease outcomes specifically in BRCA carriers. Methods: This was an international, multicenter, hospital-based, retrospective cohort study including young BRCA carriers with history of BC (NCT03673306). Eligible patients were women harboring germline PVs in BRCA1 and/or BRCA2 and diagnosed with stage I-III invasive BC at the age of ≤ 40 years between January 2000 and December 2020. BRCA healthy carriers or patients with BRCA variants of unknown significance, non-invasive BC, lack of follow-up, prior ovarian cancer or other malignancies without history of BC were excluded. Primary endpoints were pregnancy rate and disease-free survival (DFS). Overall survival (OS), BC specific survival (BCSS), pregnancy, fetal and obstetric outcomes were secondary endpoints. To mitigate the impact of guaranteed time bias,

two survival analyses were performed: 1) Extended Cox model with occurrence of pregnancy as a time-varying covariate; 2) Case-control analysis by matching 1:3 patients with and without a pregnancy for type of BRCA PV, hormone receptor status, nodal status and year at diagnosis; moreover, each control had to have a disease-free interval longer than the time occurring between BC diagnosis and conception of the matched case. Results: From 78 centers worldwide, 4,732 patients were included, of whom 659 had at least one pregnancy after BC (pregnancy cohort) and 4,073 did not (non-pregnancy cohort). Patients in the pregnancy cohort were significantly more likely to carry BRCA1 PVs, to be younger at BC diagnosis, to have node-negative and hormone receptor-negative (HR-) BC (all $p < 0.01$). Pregnancy rate at 10 years was 22% (95% CI 21%-24%) overall, 18% (95% CI 16%-21%) and 26% (95% CI 24%-26%) in patients with HR+ and HR- BC, respectively ($p < 0.01$). Median time from BC diagnosis to conception was 3.5 years (IQR 2.2-5.3 years), significantly longer in patients with HR+ than HR- BC (4.3 vs 3.2 years, $p < 0.01$). Among 659 patients with a pregnancy after BC, 45 (6.8%) and 63 (9.6%) experienced an induced abortion or a miscarriage, respectively. Of the 517 (78.5%) patients with completed pregnancy, 54 (10.4%) had twins and 406 (78.5%) delivered at term (delivery ≥ 37 weeks). Among the 571 babies born, 5 (0.9%) had congenital anomalies. Median follow-up was 7.8 years (IQR, 4.5-12.6 years). No significant difference in DFS was observed between the pregnancy and non-pregnancy cohorts (unadjusted HR 0.97, 95% CI 0.82-1.15, $p = 0.74$; adjusted HR [aHR] 0.99, 95% CI 0.81-1.20, $p = 0.90$). Patients in the pregnancy cohort showed significantly better BCSS (HR 0.53, 95% CI 0.38-0.74, $p < 0.01$; aHR 0.59, 95% CI 0.41-0.86, $p < 0.01$) and OS (HR 0.52, 95% CI 0.38-0.72, $p < 0.01$; aHR 0.58, 95% CI 0.40-0.85, $p < 0.01$). Similar results were obtained in the case-control analysis. Subgroup analyses of survival endpoints according to patient, tumor and treatment characteristics will be presented at the conference. Conclusions: In this global study, 1 out of 5 young BRCA carriers conceived within 10 years after a BC diagnosis, higher than rates previously reported in unselected young BC populations. Pregnancy following BC in BRCA carriers did not appear to adversely impact maternal prognosis or fetal outcomes. These findings should be incorporated into oncofertility counseling of young BRCA carriers with BC.

Disclosure(s):

Matteo Lambertini, MD, PhD: Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Eli Lilly and Co (Ongoing), Exact Sciences Corporation (Ongoing), Gilead (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), SeaGen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Daiichi-Sankyo (Ongoing), Eli Lilly and Co (Ongoing), Gilead (Ongoing), IPSEN (Ongoing), Knights Pharmaceuticals (Ongoing), Libbs (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), Sandoz (Ongoing), Takeda Pharmaceuticals, Ltd. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Gilead (Ongoing); Travel grant: Daiichi-Sankyo (Ongoing), Gilead (Ongoing)

Elisa Agostinetti, MD: Honorarium: Sandoz (Terminated); meeting/travel grants: Novartis, Roche, Eli Lilly, Genetic, Istituto Gentili, Daiichi Sankyo, AstraZeneca (Terminated); Research grant to my Institution: Gilead (Terminated); speaking fee: AstraZeneca (Terminated), Eli Lilly (Terminated)

Hee Jeong Kim, MD, PhD: No financial relationships to disclose

Jyoti Bajpai, DM Medical Oncology: No financial relationships to disclose

Michail Ignatiadis, MD, PhD: Consulting Fees (e.g., advisory boards): Rejuvenon senescence therapeutics (Ongoing), Seattle Genetics Inc. (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Novartis Pharma GmbH (Terminated, October 31, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed

by the institution): F. Hoffman La Roche Ltd (Ongoing), Inivata/NeoGenomics (Ongoing), Menarini/Stemline (Ongoing), Natera, Inc. (Ongoing)

Kelly-Anne Phillips, MBBS (Hons) MD FRACP FAHMS: No financial relationships to disclose

Claudio Vernieri, MD, PhD: Consulting Fees (e.g., advisory boards): Daiichi-Sankyo (Ongoing), Lilly/Loxo (Ongoing), Menarini/Stemline (Ongoing), Novartis Pharma GmbH (Ongoing), Pfizer, Inc. (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): ISTITUTO GENTILI (Ongoing), Lilly/Loxo (Ongoing), Novartis Pharma GmbH (Ongoing)

Icro Meattini, MD: Consulting Fees (e.g., advisory boards): AstraZeneca (Terminated, July 19, 2023), Daiichi-Sankyo (Terminated, July 19, 2023), Ely Lilly (Terminated, July 19, 2023), Novartis (Terminated, July 19, 2023), Pfizer, Inc. (Terminated, July 19, 2023), Seagen Inc (Terminated, July 19, 2023)

Hatem A. Azim, MD, PhD, Jr.: Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): PierreFabre (Terminated, May 31, 2022)

Ann Partridge, MD, MPH: Royalty: wolters Kluwer (UpToDate) (Ongoing)

Rapid-fire Session 2: Mini-Oral Presentations

Presenting Author(s) and Co-Author(s):

V. Kaklamani. UT Health San Antonio, San Antonio, Texas, United States

Disclosure(s):

Virginia Kaklamani, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo |Astrazeneca (Ongoing), Gilead Science (Ongoing), Loxo@Lilly (Ongoing), Menarini/Stemline (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), SeaGen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Daiichi Sankyo |Astrazeneca (Ongoing), Gilead Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Eisai, Inc (Ongoing)

RF02-01

A Multicenter, Phase I/II Trial of Anastrozole, Palbociclib, Trastuzumab, and Pertuzumab in Hormone Receptor (HR)-Positive, HER2-Positive Metastatic Breast Cancer (ASPIRE)

Presenting Author(s) and Co-Author(s):

R. Patel. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

K. Cascetta. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

P. Klein. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

E. Moshier. Icahn School of Medicine at Mount Sinai, United States

M. Kwa. New York University, United States

J. Fasano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

A. Goel. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

M. Accordino. Columbia University Medical Center, United States

C. Shapiro. Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

R. Vaccaro. Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, United States

G. Joshi. University of Vermont Cancer Center, United States

J. Sparano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

A. Tiersten. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

Background: Among patients (pts) with HR-positive and HER2-positive breast cancer, crosstalk between HER2 and estrogen receptor (ER) signaling pathways may contribute to endocrine resistance but anti-HER2 agents in combination with endocrine therapy can restore endocrine sensitivity. Mechanistically, HER2/HER3 signaling promotes survival by way of PI3K-AKT activation whereas ER-CDK4/6-Rb signaling promotes cell cycle progression. The combination of anti-HER2 therapy with an aromatase inhibitor (AI) and a CDK 4/6 inhibitor would allow for blockade of both pathways and provide a novel, all biologic, and chemotherapy-free approach to the treatment of HR-positive, HER2-positive metastatic breast cancer (MBC). Methods: We conducted a phase I/II multi-institution trial in pts with previously untreated, HR-positive and HER2-positive MBC. In the Phase I portion, pts received escalating doses of palbociclib (100mg, 125mg) in conjunction with trastuzumab, pertuzumab and an AI anastrozole, using a 3+3 dose escalation trial design. In the phase II portion, pts received palbociclib at the maximum tolerated dose (MTD), anastrozole, trastuzumab, and pertuzumab. The primary endpoints of the Phase I and II portions were MTD and clinical benefit rate (CBR) defined as the sum of complete response, partial response, and stable disease for \geq 6 months, respectively. Secondary endpoints included progression free survival (PFS), objective response rate (ORR) and safety. The Phase II portion of this study was powered with 30 pts to show efficacy of palbociclib administered at the MTD in combination with anastrozole, trastuzumab and pertuzumab if the CBR achieved at 6 months exceeded 58%. The Clopper-Pearson method was used to calculate confidence intervals for ORR and CBR. The PFS distribution was estimated using the Kaplan-Meier method. Results: In the Phase I portion, a total of 9 pts were enrolled. No DLTs were observed at the 100mg dose (N=3) or the 125mg dose (N=6) level, and thus, 125mg was established as the MTD. An additional 24 pts were enrolled to the Phase II portion at the MTD, with a total of 30 pts in the modified intention-to-treat population included in

the efficacy analysis. The median age of the population was 57.6 years (range 50.5-63.8) and 27% of pts were premenopausal and received ovarian function suppression as part of treatment. As shown in Table 1, the primary endpoint, CBR, was 97% (95% CI: 0.83-1.0, $p < 0.0001$). ORR was 70% (95% CI: 0.51-0.85). Median time to objective response was 2.8 months with earliest response at 3 months. Median duration of response was not reached with range of 5.1-42.2 months. Median PFS was also not reached with range of 8-44.8 months. Safety data were consistent with known toxicity profiles of agents. Most common adverse events included diarrhea (80%), neutropenia (77%), leukopenia (70%), anemia (67%), and fatigue (60%). Grade 3-4 events occurred in 63% (19/30) of pts and included neutropenia (68%), leukopenia (32%), decrease in absolute neutrophil count (21%), and anemia (21%). Conclusions: The combination of anastrozole, palbociclib, trastuzumab, and pertuzumab was well tolerated and effective with a clinical benefit rate of 97% in pts with previously untreated HR-positive, HER2-positive MBC. The combination provides a chemotherapy-free alternative for pts with triple positive breast cancers. Further follow up will determine impact on PFS.

Table 1. Results in Patients on Anastrozole, Palbociclib, Trastuzumab, and Pertuzumab

Outcome	Patient Population (N=30)
	% (N)
Clinical benefit rate, % [CI]	97% (83%, 100%)
Objective response rate, % [CI]	70% (51%, 85%)
Complete Response	7% (2)
Partial Response	63% (19)
Stable Disease	27% (8)
Progressive Disease	0% (0)
Unevaluable ¹	3% (1)

¹Unevaluable patients treated as non-responders in CBR and ORR calculations.

¹Unevaluable patients treated as non-responders in CBR and ORR calculations.

Disclosure(s):

Amy Tiersten, MD: Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Lilly/Loxo (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing)

RF02-02

BBO-10203, a first-in-class, orally bioavailable, selective covalent small molecule that inhibits RAS-driven PI3K α activity without affecting glucose metabolism

Presenting Author(s) and Co-Author(s):

- P. Beltran. BridgeBio Pharma Oncology Therapeutics, Orinda, California, United States
- S. Dhirendra. NCI RAS Initiative, Frederick National Laboratory for Cancer Research, United States
- R. Xu. BridgeBio Pharma Oncology Therapeutics, United States
- M. Chen. BridgeBio Pharma Oncology Therapeutics, United States
- D. Czyzyk. Frederick National Laboratory for Cancer Research, United States
- S. Donovan. BridgeBio Pharma Oncology Therapeutics, United States
- S. Feng. BridgeBio Pharma Oncology Therapeutics, United States
- C. Feng. BridgeBio Pharma Oncology Therapeutics, United States
- L. Fu. BridgeBio Pharma Oncology Therapeutics, United States
- F. Lightstone. Lawrence Livermore National Laboratory, United States
- K. Lin. BridgeBio Pharma Oncology Therapeutics, United States
- A. Maciag. Frederick National Laboratory for Cancer Research, United States
- D. Nissley. Frederick National Laboratory for Cancer Research, United States
- E. Riegler. BridgeBio Pharma Oncology Therapeutics, United States
- K. Sinkevicius. BridgeBio Pharma Oncology Therapeutics, United States
- A. Stephen. Frederick National Laboratory for Cancer Research, United States
- J. Stice. BridgeBio Pharma Oncology Therapeutics, United States
- D. Turner. Frederick National Laboratory for Cancer Research, United States
- B. Wang. BridgeBio Pharma Oncology Therapeutics, United States
- K. Wang. BridgeBio Pharma Oncology Therapeutics, United States
- Y. Yang. Lawrence Livermore National Laboratory, United States
- C. Zhang. BridgeBio Pharma Oncology Therapeutics, United States
- F. McCormick. UCSF, United States
- E. Wallace. BridgeBio Pharma Oncology Therapeutics, United States

PI3K α is the most mutated kinase and the second most mutated oncogene in human cancer. Activation of PI3K α can be achieved by receptor tyrosine kinases such as insulin receptor and insulin-like growth factor receptor 1 and/or by directly interacting with RAS family members. Previous elegant preclinical studies have established that RAS-driven PI3K α activation is important in tumor cells but may not be involved in cell types controlling glucose metabolism. Alpelisib, a small molecule inhibitor of the kinase activity of PI3K α , has been approved for the treatment of ER⁺ PIK3CA mutant breast cancer in combination with fulvestrant after endocrine therapy in advanced or metastatic breast cancer based on an improvement in PFS versus fulvestrant alone. Inhibition of PI3K α activity by alpelisib in normal tissues resulted in a severe (G3/4) hyperglycemia rate of 37% with frequent dose interruptions and discontinuations. Additionally, preclinical studies have demonstrated that the dysregulation of glucose homeostasis resulting from PI3K α kinase inhibition leads to hyperinsulinemia that increases

pathway flux, rendering kinase inhibitors less effective. Here, we report on a novel covalent small molecule designed to inhibit RAS-mediated activation of the AKT pathway via PI3Ka without the resultant hyperglycemia associated with direct inhibition of PI3Ka kinase activity. BBO-10203 disrupts the physical interaction between RAS and PI3Ka in tumor cells resulting in potent signaling pathway inhibition. This agent selectively binds to PI3Ka and disrupts its interaction with K-, H-, and N-RAS with low single digit nanomolar potency (~5 nM). Breaking the interaction between these two oncogenes inhibits basal pAKT cellular levels (BT-474/KYSE-410 IC₅₀: ~5 nM) in HER2 amplified (HER2^{amp}) and wild-type or mutant PI3Ka cell lines. Even though BBO-10203 does not inhibit the kinase activity of PI3Ka, its effects on cancer cell signaling inhibition and transcriptional regulation highly resemble those of alpelisib. BBO-10203 displays excellent drug-like properties and oral bioavailability. Single dose treatment of KYSE-410 (HER2^{amp}/KRAS^{G12C}) tumor bearing mice with increasing doses (1-100 mg/kg, PO) of BBO-10203 results in dose and time dependent inhibition of pAKT in vivo. Maximal inhibition (~80%) is achieved at 30 mg/kg and lasts for 24 hours. Repeated dose treatment of tumor bearing mice with BBO-10203 is well tolerated and results in significant efficacy in PIK3CA mutant as well as HER2^{amp} human xenograft models. In the KYSE-410 xenograft model, BBO-10203 daily oral dosing of 30 mg/kg results in significant tumor regressions. Importantly, treatment with BBO-10203 does not affect insulin signaling in differentiated adipocytes in vitro, nor does it impact glucose metabolism in vivo at 3-times the maximal efficacious dose level in xenograft studies. In conclusion, we have identified a novel approach to inhibit the PI3Ka signaling pathway by blocking its interaction with, and activation by RAS. This approach can achieve strong pAKT inhibition in tumor cells without changes in glucose metabolism. Clinical investigation of BBO-10203 for the treatment of both ER+ / PIK3CA mutant and HER2^{amp} breast cancer is warranted.

Disclosure(s):

Pedro J. Beltran, PhD: Advisory Committee/Board Member: Fluorish Research (Ongoing); Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): BridgeBio (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Amgen Inc (Ongoing)

RF02-03

Trastuzumab deruxtecan (T-DXd) in combination with anastrozole or fulvestrant in patients with HER2-low HR+ advanced/metastatic breast cancer: a Phase 1b, open-label, multicenter, dose-expansion study (DESTINY-Breast08)

Presenting Author(s) and Co-Author(s):

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

C. Anders. Duke Cancer Institute, Durham, North Carolina, United States

L. Testa. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil

I. Ganshina. N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russia

Y. Lu. National Taiwan University Hospital, Taipei, Taiwan.

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

R. Young. The Center for Cancer and Blood Disorders, TX, United States

M. Wrona. Enhertu, Late Development Oncology, Global Medicines Development, Late Oncology R&D, AstraZeneca, Warsaw, Mazowieckie, Poland

C. Lloyd. Enhertu, Late Development Oncology, Global Medicines Development, Late Oncology R&D, AstraZeneca, New York, NY, United States

Y. Zhang. Late Oncology Statistics, Statistics, Late Oncology R&D, AstraZeneca, Gaithersburg, MD, United States

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Background: Trastuzumab deruxtecan (T-DXd) is approved in over 40 countries for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-low (a score of 1+ on immunohistochemistry [IHC] analysis or an IHC score of 2+ and negative results on in-situ hybridization) breast cancer who have received prior chemotherapy in the metastatic setting or who developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. DESTINY-Breast08 (DB-08) was designed to establish the safety, tolerability, and preliminary activity of T-DXd in combination with widely used standard of care therapies in HER2-low hormone receptor (HR)+ metastatic breast cancer (mBC). Results reported here are from the dose-expansion stage of the Phase 1b, multicenter, open-label, parallel-assignment DB-08 study arms investigating T-DXd–endocrine therapy (ET) combinations [NCT04556773]. Methods: Eligible patients had centrally confirmed HER2-low advanced/mBC with measurable disease per RECIST 1.1 and were documented as HR+. Among patients with mBC, ≤ 1 prior line of ET \pm a targeted therapy was allowed, and prior chemotherapy in the mBC setting was exclusionary. Patients received T-DXd 5.4 mg/kg intravenously (IV) every three weeks (Q3W) + anastrozole 1 mg orally daily (T-DXd + ANA) or T-DXd 5.4 mg/kg IV Q3W + fulvestrant 500 mg intramuscularly Q4W, with a 500 mg loading dose on Cycle 1 Day 15 (T-DXd + FUL). Primary endpoints were safety and tolerability; secondary endpoints included objective response rate (ORR), progression-free survival, duration of response (all evaluated by investigator per RECIST 1.1), and overall survival (OS). Data cutoff (DCO) was ~24 weeks after the last patient in each arm had received study

treatment. Results: As of February 20, 2023, 21 patients in the T-DXd + ANA arm and 20 patients in the T-DXd + FUL arm had received study treatment. Median age was 55 and 66 years, 67% and 75% of patients received a prior line of ET ± a targeted therapy for mBC, 33% and 25% had no prior line of treatment for mBC, and median follow up in censored patients was 12.1 months (range 4.0, 17.3) and 8.5 months (range 1.3, 15.1) in the T-DXd + ANA and T-DXd + FUL arms, respectively. Adverse events (AEs) occurred in 95.2% (20/21) of patients in the T-DXd + ANA arm and 100% (20/20) of patients in the T-DXd + FUL arm, with AEs ≥Grade 3 occurring in 47.6% (10/21) and 55.0% (11/20) of patients in each arm, respectively. The most common any-grade AEs, occurring in ≥30% of patients in either arm, are reported in the Table. Three (15%) adjudicated drug-related interstitial lung disease / pneumonitis events were reported in the T-DXd + FUL arm (all Grade 2; at DCO, one case had resolved, one was resolving, and one was not resolved); none were reported in the T-DXd + ANA arm. AEs were manageable by drug interruption and dose reduction. Confirmed ORR was 71.4% (15/21; 95% confidence interval [CI] 47.8, 88.7) in the T-DXd + ANA arm, and 40.0% (8/20; 95% CI 19.1, 64.0) in the T-DXd + FUL arm (Table). OS data were not mature at this DCO. Conclusions: Safety profiles for T-DXd-ET combinations were generally comparable to T-DXd monotherapy and manageable with dose modification and routine clinical practice. T-DXd in combination with anastrozole or fulvestrant was active in first- or second-line treatment of patients with HER2-low HR+ mBC.

Table. Summary of safety and efficacy data for T-DXd plus anastrozole and T-DXd plus fulvestrant in the total population

	T-DXd + anastrozole (T-DXd + ANA) All (N=21)	T-DXd + fulvestrant (T-DXd + FUL) All (N=20)
Safety data		
Any-grade AEs, n (%)	20 (95.2)	20 (100)
Any-grade AEs occurring in ≥30% of patients in either arm, n (%)		
Nausea	14 (66.7)	17 (85.0)
Alopecia	9 (42.9)	9 (45.0)
Fatigue	9 (42.9)	3 (15.0)
Anemia	7 (33.3)	5 (25.0)
Decreased appetite	7 (33.3)	10 (50.0)
Neutropenia*	7 (33.3)	7 (35.0)
Vomiting	6 (28.6)	6 (30.0)
Any AEs ≥Grade 3, n (%)	10 (47.6)	11 (55.0)
AEs leading to dose interruptions / delays of T-DXd, n (%)	12 (57.1)	8 (40.0)
AEs leading to dose reduction of T-DXd, n (%)	7 (33.3)	6 (30.0)
AEs leading to discontinuation of T-DXd, n (%)	2 (9.5)	3 (15.0)
Median actual treatment duration, months (range)†	10.4 (2.8, 16.9)	6.2 (1.4, 16.1)
Efficacy data		
cORR, % (95% CI)	71.4 (47.8, 88.7)	40.0 (19.1, 64.0)
uORR, % (95% CI)	76.2 (52.8, 91.8)	50.0 (27.2, 72.8)
Median PFS, months (95% CI)‡	13.4 (8.5, 15.1)	NE (5.6, NE)
Median DOR, months (95% CI)‡	9.7 (6.7, NE)	NE (4.1, NE)
Median follow up in censored patients, months (range)	12.1 (4.0, 17.3)	8.5 (1.3, 15.1)

*Grouped term including patients with neutropenia and patients with decreased neutrophil count.
 †Actual treatment duration was reported as total treatment duration, excluding duration of drug interruptions and delays. †NE signifies that DOR/PFS was not reached for these patients at the time of DCO.
 ‡AE, adverse event; ANA, anastrozole; CI, confidence interval; cORR, confirmed overall response rate; DCO, data cutoff; DOR, duration of response; FUL, fulvestrant; NE, not evaluable; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; uORR, unconfirmed overall response rate.

Disclosure(s):

Komal Jhaveri, MD, FACP: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), AstraZeneca (Ongoing), Blueprint Medicines (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Jounce Therapeutics (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Menarini/Stemline (Ongoing), Novartis (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing), Sun Pharma Advanced Research Company Ltd (Ongoing), TAIHO Oncology (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Context Therapeutics (Ongoing), Debio Pharmaceuticals (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck Pharmaceuticals (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Puma Biotechnology, Inc (Ongoing), Zymeworks Inc. (Ongoing)

Erika P. Hamilton, MD: Consulting Fees (e.g., advisory boards): Arcus, Arvinas, AstraZeneca, Daiichi Sankyo, Deciphera Pharmaceuticals, Ellipses Pharma, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo, Mersana, Novartis, Orum Therapeutics, Pfizer, Relay Therapeutics, Roche/Genentech, SeaGen, Verascity Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Abbvie, Acerta Pharma, Accutar Biotechnology ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, (Ongoing)

Peter Schmid, MD, PhD: Consulting Fees (e.g., advisory boards): Eli Lilly & Company (Ongoing), Gilead Science (Ongoing)

Carey K. Anders, MD: Consulting Fees (e.g., advisory boards): Astrazeneka (Ongoing), Athenex (Ongoing), Elucida Oncology (Ongoing), Genentech-Roche (Ongoing), Immunomedics Inc (Ongoing), IPSEN (Ongoing), Novarits (Ongoing), Seattle Genetics/Seagen (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astrazeneka (Ongoing), Caris Life Sciences, Inc. (Ongoing), Elucida Oncology (Ongoing), G1 Therapeutics (Ongoing), Genentech-Roche (Ongoing), GSK/Tesaro (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck Foundation (Ongoing), Nektar (Ongoing), Novarits (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics/Seagen (Ongoing), Zion Pharmaceuticals (Ongoing); Royalty: Jones and Bartlett (Ongoing), UpToDate (Ongoing)

Sherene Loi, MD, PhD: Advisory Committee/Board Member: Bristol-Myers Squibb Company (Ongoing), MSD Co., Ltd. (Ongoing); Consulting Fees (e.g., advisory boards): Aduro Biotech (Ongoing), Amunix (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), MSD Co., Ltd. (Ongoing), Nektar Therapeutics (Ongoing), Novartis International AG (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics (Ongoing); Uncompensated consultant: Aduro Biotech (Ongoing), Amunix (Ongoing), Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing)

RF02-04

A phase III study comparing trastuzumab emtansine with trastuzumab, pertuzumab, and docetaxel in older patients with metastatic HER2-positive breast cancer. (JCOG1607 HERB TEA study)

Presenting Author(s) and Co-Author(s):

A. Shimomura. Department of Breast and Medical Oncology, National Center For Global Health And Medicine, Tokyo, Japan

K. Tamura. Department of Medical Oncology, Shimane University Hospital, Japan

K. Sasaki. JCOG Data Center/Operations Office, National Cancer Center Hospital, tyuoukukitaji, Tokyo, United States

R. Sadate. JCOG Data Center/Operations Office, National Cancer Center Hospital, United States

A. Suto. Department of Breast Surgery, National Cancer Center Hospital, Japan

M. Sawaki. Department of Breast Oncology, Aichi Cancer Center, Japan

N. Yamamoto. Division of Breast Surgery, Chiba Cancer Center, United States

T. Yoshiyama. Department of Breast Surgery, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Japan

T. Hayashi. Department of Breast Surgery, NHO Nagoya Medical Center, Japan

E. Tokunaga. Department of Breast Oncology, NHO Kyushu Cancer Center, Japan

T. Yamanaka. Department of Breast Surgery and Oncology Kanagawa Cancer Center, Japan

C. Shimizu. Department of Breast and Medical Oncology, National Center for Global Health and Medicine, Tokyo, Japan

T. Shien. Okayama University Hospital, Okayama-city, Okayama, United States

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Background A combination of trastuzumab, pertuzumab, and docetaxel (HPD) is recommended as first-line treatment for patients with HER2-positive metastatic breast cancer. For older patients, it is difficult to maintain a relative dose intensity, which often impairs their quality of life. A new standard treatment option for older patients is required with less toxicity and non-inferior efficacy compared to HPD. **Methods** The eligibility criteria were as follows: age 65 years and older, HER2-positive metastatic breast cancer, no previous systemic treatment with chemotherapy and anti-HER2 targeted drugs, ECOG PS 0–2 for 65–74 years or 0–1 for 75 years or older, and adequate organ function. Treatment consisted of trastuzumab emtansine (T-DM1) 3.6 mg/kg every 3 weeks or HPD (trastuzumab 8 mg/kg, then 6 mg/kg, pertuzumab 840 mg, then 420 mg/body, and docetaxel 60 mg/m², could be escalated to 75 mg/m² if there were no unmanageable toxicity) every 3 weeks after a 1:1 ratio randomization. The trial was designed to achieve 70% power to confirm the non-inferiority of T-DM1 to HPD at a one-sided alpha of 5% with a non-inferiority margin of 1.35 in terms of the hazard ratio (HR) for overall survival (OS) as the primary endpoint. With a median OS of 30 months in both arms, 6.5 years of accrual, and 5 years of follow-up, the planned sample size was 250. Secondary endpoints were progression-free survival (PFS), response rate (RR), adverse events, cumulative breast cancer-specific mortality (BCSM), safety, and deterioration of activities of daily living. (Clinical Trial Information: UMIN000030783). **Results** In total, 148 patients were enrolled between January 2018 and March 2023. A total of 135 patients were assessed in the preplanned first interim analysis. The median patient age was 72 years (range 65-88) in the T-DM1 arm and 71

(65-84) in the HPD arm. The proportion of estrogen receptor-positive (10%) patients was well balanced between both arms (49.3 and 55.6%, respectively). Of these patients, 64.8% had stage IV disease and 35.2% had recurrent disease. T-DM1 was not non-inferior to HPD (HR 1.487; 99.9% CI, 0.288 to 7.678) in terms of OS. The median PFS was 9.8 months in the T-DM1 arm and 18.4 months in the HPD arm (HR 1.749; 95%CI, 1.124-2.723). Response rates were lower in the T-DM1 arm than that of the HPD arm (52.7% [95% CI, 38.8-66.4] and 76.8% [95% CI, 63.6-87.0], respectively) ($p=0.099$). BCSM was higher in the T-DM1 arm than that of the HPD arm (HR 1.617; 95% CI, 0.764-3.425). Grade 3 and higher neutropenia were less common in the T-DM1 arm than in the HPD arm (0 vs. 30.4%); however, thrombocytopenia was more common in the T-DM1 arm than in the HPD arm (16.9 vs. 0%). Grade 3 or more non-hematological adverse events were less common and lower in the T-DM1 arm (35.2%) than in the HPD arm (58.6%), including fatigue (5.6% vs. 22.9%), diarrhea (0% vs. 11.4%), appetite loss (8.5% vs. 11.4%), and febrile neutropenia (0% vs. 10.0%), which reduced the quality of life in older patients with HER2-positive metastatic breast cancer. Conclusion T-DM1 was not non-inferior to HPD in terms of OS. However, T-DM1 showed better tolerability in terms of frequency and severity of adverse events. HPD will continue to be the standard of care as the first-line treatment for older patients with HER2-positive metastatic breast cancer. Older patients with breast cancer have heterogeneous health conditions. A subset analysis according to age or geriatric assessment may identify the subpopulation of older patients with HER2-positive metastatic breast cancer for whom T-DM1 is an optional treatment.

Disclosure(s):

Akihiko Shimomura, MD, PhD: Consulting Fees (e.g., advisory boards): Daiichi-Sankyo (Ongoing), Pfizer, Inc. (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): AstraZeneca K.K (Ongoing), Chugai Pharmaceutical Co. Ltd (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly Japan K.K. (Ongoing), MSD Co., Ltd. (Ongoing), Pfizer, Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca K.K (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co.Ltd (Ongoing), Gilead Sciences (Ongoing), Taiho Pharmaceutical Co. Ltd. (Ongoing)

RF02-05

Report on Cohort Expansion of Phase I Study to Investigate the Safety, Tolerability, Pharmacokinetics and Antitumor Activity of BB-1701 in Patients with Locally Advanced/Metastatic HER2 Low Breast Cancer

Presenting Author(s) and Co-Author(s):

F. Ma. Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

P. Munster. University of California San Francisco, San Francisco, California, United States

X. Guan. Jiangsu Province Hospital, Nanjing, United States

J. Wang. Linyi Cancer Hospital, Linyi, United States

H. Yao. Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, United States

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

X. Wang. Sir Run Run Shaw Hospital, United States

Y. Shi. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

X. Liang. Hubei Cancer Hospital, China

N. Xu. The First Affiliated Hospital, Zhejiang University, School of Medicine, United States

H. Tang. Bliss Biopharmaceutical (Hangzhou) Co., Ltd., United States

Y. Zhou. Bliss Biopharmaceutical (Hangzhou) Co., Ltd., United States

Z. Wei. Bliss Biopharmaceutical (Hangzhou) Co., Ltd., United States

Background: BB-1701 is an antibody-drug conjugate (ADC) consisting of a humanized IgG1k monoclonal anti-HER2 antibody with the same sequence as trastuzumab and eribulin linked together by a cathepsin-cleavable valine-citrulline linker. Eribulin is an inhibitor of microtubule approved for the treatment of metastatic breast cancer and advanced liposarcoma, following prior therapies. When BB-1701 targets HER2 expressing cancer cells and it is internalized, free eribulin is cleaved from the ADC by cathepsin b and causes cytotoxicity to cancer cells. The neighboring cells were affected with bystander effects, like cytotoxicity on tumor cells and non-cytotoxic effects on microenvironment, by free eribulin released from dying cancer cells. Here, we report preliminary results from the ongoing cohort expansion of a phase I study of BB-1701 in patients with HER2 low breast cancer (ClinicalTrials.gov Identifier: NCT 04257110). Methods: Patients ≥ 18 years of age with confirmed locally advanced/metastatic HER2 low breast cancer (IHC 2+ and FISH negative or IHC 1+), that had progressed on at least two lines of prior standard therapies, with ECOG PS ≤ 2 and measurable disease (RECIST 1.1) were enrolled. HER2 expressions was determined by IHC and FISH before enrollment. Total of four dose levels of BB-1701 (1.0 mg/kg Q3W, 1.2 mg/kg Q3W, 1.4 mg/kg Q3W and 1.6 mg/kg Q3W) were administered during the cohort expansion. The safety, tolerability and preliminary anti-tumor activity of BB-1701 were assessed during study. Radiographic assessment was conducted every 6 weeks. Results: As of 30 June 2023, 40 patients with HER2 low breast cancer were enrolled in the four dose levels, 5 patients at 1.0 mg/kg Q3W, 20 patients at 1.2 mg/kg Q3W, 5 patients at 1.4 mg/kg Q3W and 10 patients at 1.6 mg/kg Q3W. Median age was 55 years (range 30-74), 97.5% were female, and 30.0%/70.0% patients were ECOG PS 0/1. The median prior lines of systemic therapy were 3 (range 2 – 9). All subjects experienced at least one treatment emergent adverse events and treatment-related adverse events (TRAEs) occurred in 30 subjects. The most common all grade TRAEs ($\geq 20\%$) were peripheral neuropathy, aspartate aminotransferase increased, alanine aminotransferase increased,

anemia, white blood cell count decreased. Grade 3 TRAEs were peripheral neuropathy (3 subjects), peripheral sensory neuropathy (2 subjects), neutrophil count decreased (2 subjects), platelet count decreased (1 subject), white blood cell count decreased (1 subject). There were no grade 4 or grade 5 events. The treatment related serious adverse events (SAEs) were peripheral sensory neuropathy (1 subject) and infusion related reaction (1 subject). There was no interstitial lung disease reported. No patients discontinued the study treatment due to AE. Of the 40 patients enrolled, 38 patients were evaluable for antitumor activity. At 1.0 mg/kg dose level, of 5 patients treated, 2 achieved partial response (PR), 2 had stable disease (SD), best overall response rate (BOR) was 40.0% (2/5) and disease control rate (DCR) was 80.0% (4/5). At 1.2 mg/kg dose level, of 18 patients treated, 5 achieved PR, 11 had SD with BOR of 27.8% (5/18) and DCR of 88.9% (16/18). At 1.4 mg/kg dose level, of 5 patients treated, 2 achieved PR, 2 had SD with BOR of 40.0% (2/5), and DCR was 80.0% (4/5). One patient who achieved PR was previously progressed on sacituzumab govitecan. At 1.6 mg/kg dose level, of 10 patients treated, 1 achieved CR, 3 achieved PR, 2 had SD with BOR of 40.0% (4/10), and DCR of 60.0% (6/10). Among these patients, the patient who achieved CR was previously treated by disitamab vedotin, and one patient who achieved PR was previously treated by trastuzumab deruxtecan. Conclusions: BB-1701 has demonstrated promising preliminary antitumor activity in HER2 low breast cancer including patients who received prior anti-HER2 ADCs, and a manageable safety profile.

Disclosure(s):

Pamela N. Munster, MD: Consulting Fees (e.g., advisory boards): Johnson & Johnson (Terminated, March 1, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Amgen Oncology (Ongoing), BlissBio (Ongoing), Cyteir, Oric, Relay (Ongoing), InventisBio (Ongoing), Merck & Co., Inc. (Ongoing), Revolution Medicines, Inc. (Ongoing), Roche, Novartis, Seagen, DaiichiSankyo, GSK, Clovis, Pfizer (Ongoing), Roche/Blueprint (Ongoing), Tempest, Arvinas, Dragonfly (Ongoing), Xynomics (Ongoing)

Erika P. Hamilton, MD: Consulting Fees (e.g., advisory boards): Arcus, Arvinas, AstraZeneca, Daiichi Sankyo, Deciphera Pharmaceuticals, Ellipses Pharma, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo, Mersana, Novartis, Orum Therapeutics, Pfizer, Relay Therapeutics, Roche/Genentech, SeaGen, Verascity Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Abbvie, Acerta Pharma, Accutar Biotechnology ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, (Ongoing)

RF02-06

AVIATOR/TBCRC045: A randomized phase II study of vinorelbine (N) + trastuzumab (H) alone or combined with avelumab (A) +/- utomilumab (U) in patients (pts) with HER2+ metastatic breast cancer (MBC) (NCT03414658)

Presenting Author(s) and Co-Author(s):

- A. Waks. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
- R. Shi. Dana-Farber Cancer Institute, United States
- M. Regan. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
- C. Dang. Breast Medicine Service, Memorial Sloan-Kettering Cancer Center, United States
- C. Santa-Maria. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, MD & Sibley Memorial Hospital, Johns Hopkins, Washington, DC, Baltimore, Maryland, United States
- K. Westbrook. Duke Cancer Institute, Duke University, United States
- V. Abramson. Vanderbilt University Medical Center, United States
- R. Murthy. MD ANDERSON CANCER CENTER, Houston, Texas, United States
- R. Nanda. University of Chicago Medicine, Chicago, Illinois, United States
- H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States
- A. Clark. University of Pennsylvania, United States
- C. Mainor. Georgetown University, United States
- C. Dees. University of North Carolina, Chapel Hill, North Carolina, United States
- V. Hoyos. Baylor College of Medicine, United States
- K. Miller. Indiana University, United States
- E. Stringer-Reasor. University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, Alabama, United States
- N. Hunter. Fred Hutchinson Cancer Center, Seattle, Washington, United States
- S. Oh. Montefiore Medical Center, United States
- M. DeMeo. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
- A. Okpoebo. Dana-Farber Cancer Institute, United States
- E. Elias. Dana-Farber Cancer Institute, United States
- B. Kurt. Brigham and Women's Hospital, United States
- N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States
- M. Rimawi. Baylor College of Medicine, Houston, Texas, United States
- A. Wolff. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States
- E. Mittendorf. Dana Farber Cancer Institute, Boston, Massachusetts, United States
- S. Goel. The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia
- S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

I. Krop. Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, United States

Background: Chemotherapy (chemo) + H is standard of care therapy for pts with refractory HER2+ MBC. It is unknown whether the addition of immune checkpoint inhibitor (ICI) or a 4-1BB agonist (U) improves efficacy of standard chemo + H for this population. Methods: Eligible pts had HER2+ MBC previously treated with H, pertuzumab (P), and T-DM1. Pts previously treated with N or ICI were excluded. 100 pts were randomized 1:2:2 to tx with NH, NHA, or NHAU. ER status and presence of liver metastases were stratification factors. The original co-primary objectives were to compare progression-free survival (PFS) of (1) NHA vs NH; and (2) NHAU vs NHA. In 2021, due to discontinuation of clinical development of U, an unplanned interim futility analysis reviewed by IDMC led to closure of NHAU and randomization of the final 13 pts to NH or NHA. For the comparison of NH vs NHA, with 60 pts randomized (20 vs 40) there was 88% power for a log-rank test to detect improvement in median PFS (mPFS) from 2 to 4 mos with one-sided alpha of 0.1. Corresponding 2-sided 80% confidence intervals (CI) were reported for the stratified Cox model hazard ratios (HR), along with stratified one-sided log-rank p-value. Secondary endpoints included overall response rate (ORR), duration of response (DOR), and safety/tolerability. Results: 100 pts were randomized from 7/2018-3/2023, and 97 pts started tx on trial: 18 NH, 45 NHA, and 34 NHAU (prior to its closure). Pts were 99% female, with median age 54 yrs (range 26-78 yrs); 70% White, 14% Black, and 8% Asian; 7% were Hispanic. 66% of pts had hormone receptor-positive tumors, and 76% had visceral metastases. All pts were previously treated with H, P, and T-DM1, and 17% had prior trastuzumab deruxtecan. 63% of pts had received ≥ 3 lines of HER2 tx for MBC (range 1-13 lines), and median interval from MBC diagnosis to randomization was 32 mos (interquartile range 22-61 mos). mPFS and ORR results are shown in the Table. One patient remained progression-free on tx at analysis. NHA was associated with a statistically significant improvement in PFS compared to NH (HR=0.56 (80% CI 0.37-0.86, p=0.04)). No difference in PFS was observed between NHAU vs NHA (HR=1.20 (80% CI 0.84-1.73) as final estimate after closure of NHAU for futility). Of 9 pts with confirmed responses in NHA arm, 3 pts had DOR >12 mos. Grade 3-4 treatment-emergent adverse events (AEs) were similar by tx: 61% NH, 62% NHA, and 67% NHAU. There were no grade 5 treatment-related AEs. Immune-related all grade AEs in the A-containing arms (n=79 safety-evaluable pts treated with A) included: AST increase (n=15), ALT increase (n=9), hyper/hypothyroidism (n=8), adrenal insufficiency (n=2), and pneumonitis (n=1), of which two events were grade 3 (adrenal insufficiency and AST increase) and none were grade 4. Only 3 pts (1 in NHA; 2 in NHAU) stopped trial tx for unacceptable AEs. Required baseline and on-tx biopsies were performed; PD-L1 and TIL data will be presented. Conclusions: This trial demonstrated significant improvement in PFS with addition of avelumab to NH among pts with heavily pre-treated HER2+ MBC. 4-1BB agonist did not improve PFS. To our knowledge, this is the first randomized trial to report results of chemo/H +/- ICI in HER2+ MBC. Further investigation of ICI with chemo/H for pts with refractory HER2+ MBC is warranted, and the potential predictive value of immune biomarkers should be explored.

Treatment assignment	Pts	Median PFS (mos) (90% CI)	HR	HR 80% CI	HR 90% CI	p-value*	6-month PFS (%) (90% CI)	12-month PFS (%) (90% CI)	ORR (%) (90% CI)
NH	18	2.0 (1.7,3.9)	18.8 (6.1,36.7)	0	11.1 (2.0-31.0)
NHA	45	3.8 (3.0,5.5)	0.56 (NHA vs NH)	0.37-0.86	0.33-0.97	0.04	31.2 (19.8,43.3)	22.3 (12.4,34.2)	20.0 (10.9-32.3)
NHAU	34	4.0 (3.7,5.5)	1.20 (NHAU vs NHA)	0.84-1.73	0.76-1.91	.	16.8 (5.9,32.5)	0	11.8 (4.1-24.9)

*one-sided stratified log rank test p-value

Disclosure(s):

Adrienne G. Waks, MD: Consulting Fees (e.g., advisory boards): AstraZeneca (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Genentech (Ongoing), Gilead (Ongoing), MacroGenics (Ongoing), Merck (Ongoing)

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

Nancy U. Lin, MD: Consulting Fees (e.g., advisory boards): Affinia Therapeutics (Ongoing), Aleta Biopharma (Ongoing), AstraZeneca (Ongoing), Blueprint Medicine (Ongoing), Daiichi-Sankyo (Ongoing), Genentech / Roche (Ongoing), Janssen (Ongoing), Menarini/Stemline (Ongoing), Olema Pharmaceuticals (Ongoing), Prelude Therapeutics (Ongoing), Reverie Labs (Ongoing), SeaGen (Ongoing), Voyager Therapeutics (Ongoing); Independent Contractor: Artera (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Genentech / Roche (Ongoing), Menarini/Stemline (Ongoing), Merck (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing), SeaGen (Ongoing), Zion Pharmaceuticals (Ongoing)

Mothaffar F. Rimawi, MD: Consulting Fees (e.g., advisory boards): AstraZeneca (Terminated, September 1, 2021), Novartis Pharmaceuticals Corporation (Terminated, September 1, 2021)

Antonio C. Wolff, MD: No financial relationships to disclose

Elizabeth A. Mittendorf, MD, PhD, MHCM: Consulting Fees (e.g., advisory boards): astra Zeneca (Terminated), BioNTech (Terminated), Merck (Terminated); Steering Committee: Roche/GNE (Ongoing); Trial Steering Committee: BMS (Ongoing)

Shom Goel, B Med Sci (Hons), MBBS (Hons), FRACP, PhD: Advisory Committee/Board Member: G1-Therapeutics (Ongoing), Loxo@Lilly | Eli Lilly and Company (Ongoing); Consulting Fees (e.g., advisory boards): Novartis Pharma GmbH (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): G1-Therapeutics (Ongoing), Incyclix Bio (Ongoing), Loxo@Lilly | Eli Lilly and Company (Ongoing)

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

Sherene Loi, MD, PhD: Advisory Committee/Board Member: Bristol-Myers Squibb Company (Ongoing), MSD Co., Ltd. (Ongoing); Consulting Fees (e.g., advisory boards): Aduro Biotech (Ongoing), Amunix (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), MSD Co., Ltd. (Ongoing), Nektar Therapeutics (Ongoing), Novartis International AG (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics (Ongoing); Uncompensated consultant: Aduro Biotech (Ongoing), Amunix (Ongoing), Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing)

RF02-07

Precocious modulation of metabolic and immunological parameters predicts tumor response to fasting-mimicking diet plus chemotherapy in patients with early stage TNBC

Presenting Author(s) and Co-Author(s):

- F. Ligorio. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- G. Fucà. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- A. Vingiani. Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori, United States
- F. Iannelli. IEO - European Institute of Oncology, United States
- R. Lobefaro. Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, United States
- L. Provenzano. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- L. Zanenga. Fondazione IRCCS Istituto dei Tumori, Italy
- C. Ferraris. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- A. Belfiore. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- S. Brich. Fondazione IRCCS Istituto dei Tumori, Italy
- A. Bertolotti. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- G. Scaperrotta. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- C. Depretto. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- A. Martinetti. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- E. Sottotetti. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- P. Corsetto. University of Milan, United States
- G. Bianchi. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- G. Capri. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- S. Folli. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy
- S. Minucci. University of Milan; IEO - European Institute of Oncology, Spain
- M. Foiani. University of Milan; IFOM, the AIRC Institute of Molecular Oncology ETS, Spain
- M. Pagani. University of Milan; IFOM, the AIRC Institute of Molecular Oncology ETS, Spain
- G. Pruneri. University of Milan, Fondazione IRCCS Istituto Nazionale dei Tumori, Spain
- F. De Braud. University of Milan, Fondazione IRCCS Istituto Nazionale dei Tumori, Spain
- C. Vernieri. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Lombardia, Italy

Background: Preclinical studies showed that severely calorie restricted fasting-mimicking diets (FMDs) enhance the antitumor efficacy of chemotherapy (CT) or immunotherapy (IO) in murine triple negative breast cancer (TNBC) models. These effects are mediated by a combination of blood glucose reduction and positive immunomodulatory effects. Moreover, combining fasting and metformin produced synergistic anticancer effects in a broad range of tumor models. The BREAKFAST trial was designed to investigate if FMD, plus/minus metformin, could increase the antitumor activity of neoadjuvant CT in patients with stage I-III TNBC. Methods: BREAKFAST (NCT04248998) is a randomized, non-comparative, phase II, pilot trial that enrolled stage I-III (cT>1 cm) TNBC patients (pts) candidate to receive 4 cycles of neoadjuvant CT with doxorubicin-cyclophosphamide every 3 weeks, followed by 12 cycles of weekly

paclitaxel. Pts were randomized 1:1 to receive: CT plus 5-day FMD every 3 weeks, up to 8 cycles (arm A); CT plus FMD plus daily metformin (1700 mg) (arm B). The primary study endpoint was the rate of pCR in either experimental arm. Secondary/exploratory endpoints included safety, compliance, and biomarker analyses based on blood metabolomics and tumor transcriptomics analyses at different timepoints. Results: Between June 2020 and February 2022 we enrolled 30 pts. Then, the study was interrupted after the introduction of chemo-immunotherapy (CT-IO) as a standard neoadjuvant therapy for early stage TNBC pts. Among 30 pts, 13 were treated with CT plus FMD, while 17 pts received CT plus FMD plus metformin. Overall, pCR rate was 56.6%, i.e., significantly higher than pCR rates reported with anthracycline-taxane CT alone in previous phase II/III trials (26-39%), with no significant differences among treatment arms ($p=0.49$). The FMD acutely reduced blood glucose, insulin and LDH levels, which reflects a reduction in systemic and/or tumor glucose metabolism. Of note, precocious LDH reduction was more pronounced in patients undergoing pCR. RNA-seq analysis of tumor samples revealed a significant downmodulation of glycolysis and TCA cycle pathways after one treatment cycle, paralleled by an increase of intratumor activated T cells, memory T cells and NK cells, as estimated by deconvolution analyses of tumor transcriptomic data. Of note, these changes were observed only in patients achieving pCR. While intratumor metabolic changes were similar in the two treatment arms, the modulation of intratumor immunity was more pronounced in patients not receiving metformin. Conclusion: Preoperative CT plus cyclic FMD (plus/minus metformin) results in excellent pCR rates in localized TNBC patients. Early on-treatment downregulation of systemic and intratumor metabolic parameters related to glucose metabolism predicts pCR, and this is independent of metformin use. Based on results of this study, we recently initiated a large, multicentric trial, namely the BREAKFAST-2 (NCT05763992) study, which will investigate if adding cyclic FMD to neoadjuvant CT-IO increases pCR rates in ~ 145 pts with stage II-III TNBC.

Disclosure(s):

Claudio Vernieri, MD, PhD: Consulting Fees (e.g., advisory boards): Daiichi-Sankyo (Ongoing), Lilly/Loxo (Ongoing), Menarini/Stemline (Ongoing), Novartis Pharma GmbH (Ongoing), Pfizer, Inc. (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): ISTITUTO GENTILI (Ongoing), Lilly/Loxo (Ongoing), Novartis Pharma GmbH (Ongoing)

PO3-01-01

Dysregulation of Phenylalanine-tyrosine Metabolic Signaling Pathway and Neoadjuvant Response in HER2-positive Breast Cancer

Presenting Author(s) and Co-Author(s):

C. Goh. Fudan University Shanghai Cancer Center, United States

B. Xiu. Fudan University Shanghai Cancer Center, United States

J. Xue. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

Y. Chi. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Background: Although trastuzumab and tyrosine inhibitors combined with neoadjuvant chemotherapy could significantly improve patients' pathological complete response (pCR) rate, nearly half of the patients could not achieve complete remission. Our objective was to explore the relationship between metabolic signaling pathway changes and therapeutic efficacy in patients receiving neoadjuvant therapy for HER2-positive breast cancer. **Methods:** Core needle biopsy specimens from HER2-positive breast cancer patients who underwent neoadjuvant therapy and radical mastectomy at Fudan University Shanghai Cancer Center between January 2017 and December 2021 were collected for RNA sequencing. According to pathological evaluation, samples (n=133) were divided into pCR and non-pCR groups. Gene differences between the two groups were further evaluated for KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment analysis. The TCGA (The Cancer Genome Atlas, n=1091) and the HAN ethnic GEO datasets (GSE162228, GSE206, GSE48391, n=305) were used to analyze the metabolic differences between tumors and normal tissues with patients' prognosis. Consensus clustering analysis was performed to divide patients for low and high phenylalanine-tyrosine metabolism dysregulation to analyze patients' outcomes. The IC50 value of cell lines was tested using CCK-8 experiments. Western blot was performed to analyze the protein level changes in mTOR and glycolysis pathway. **Results:** We found that phenylalanine-tyrosine metabolism was significantly enriched in HER2-positive breast cancer patients. Consensus clustering analysis of TCGA and the HAN ethnic GEO datasets showed that patients with low phenylalanine-tyrosine catabolism had a significantly worse survival outcome than patients with high tyrosine metabolism (P= 0.017). In our cohort, phenylalanine-tyrosine pathway metabolic enzyme DDC was upregulated while MAOA was downregulated in non-pCR patients compared to pCR patients, suggesting the increased production of dopamine and reduced catabolism of dopamine (DA) in non-pCR tumors. In vitro experiments showed that dopamine and the knockdown of MAOA decreased cell sensitivity to pyrotinib. In addition, dopamine and clorgyline- an MAOA inhibitor, promoted the proliferation of HER2-positive cell lines under the treatment of pyrotinib. The GSEA analysis of our neoadjuvant cohort and TCGA datasets revealed that MAOA expression was associated with an inverse enrichment of the mTORC1 and glycolysis pathways. Western blot experiment results showed that dopamine or the knockdown of MAOA could activate the mTOR and glycolysis pathway **Conclusions:** Phenylalanine-tyrosine metabolism was significantly enriched in HER2-positive breast cancer patients. The phenylalanine-tyrosine signaling pathway may be dysregulated in HER2-positive

breast cancer and patients with low phenylalanine-tyrosine catabolism have a worse prognosis. Low expression of MAOA promotes tumor resistance to HER2-targeted drugs and could serve as a therapeutic biomarker in breast cancer.

PO3-01-02

Real world outcomes of neoadjuvant therapy with Trastuzumab and Pertuzumab associated with carboplatin and docetaxel (TCHP) in HER2+ early breast cancer patients unfit for anthracyclines: a retrospective cohort comparative study.

Presenting Author(s) and Co-Author(s):

R. Pinto. Department of Medical Oncology - Portuguese Oncology Institute of Porto, Portugal

R. Calisto. Epidemiology Department - Portuguese Oncology Institute of Porto, Portugal

P. Redondo. Group of Epidemiology, Results, Economy and Management in Oncology – GEREMO (GEREMO) – Centro de Investigação | Porto Comprehensive Cancer Center (Porto.CCC) & RISE@CI-IPOP (Health Research Network) - Portuguese Oncology Institute of Porto, Portugal

A. Silva. Group of Epidemiology, Results, Economy and Management in Oncology – GEREMO (GEREMO) – Centro de Investigação | Porto Comprehensive Cancer Center (Porto.CCC) & RISE@CI-IPOP (Health Research Network) - Portuguese Oncology Institute of Porto, Portugal

P. Castro. Department of Biological Engineering - School of Engineering, University of Minho, Porto, Portugal

R. Fernandes. Medical Oncology Department - Portuguese Oncology Institute of Porto, Portugal

R. Teixeira. Medical Oncology Department - Portuguese Oncology Institute of Porto, Portugal

D. Mata. Medical Oncology Department - Portuguese Oncology Institute of Porto, Portugal

A. Ferreira. Medical Oncology Department - Portuguese Oncology Institute of Porto, Portugal

M. Bento. Epidemiology Department - Portuguese Oncology Institute of Porto, Portugal

C. Vieira. Medical Oncology Department - Portuguese Oncology Institute of Porto, Portugal

Background

Neoadjuvant chemotherapy (CT) with anti-HER2 blockade using trastuzumab (H) and pertuzumab (P) is a standard of care for patients (pts) with HER2-positive early-stage Breast Cancer (eBC). Historically, taxanes (T) and anthracyclines (A) have been the mainstays of (neo)adjuvant CT in this setting, but the added benefit of A in the era of anti-HER2 therapy has been questioned. This study aimed to assess the effectiveness, cardiac safety, and cost-effectiveness of an anthracycline-free regimen (TCHP) in a real-world population of pts deemed unfit for A, compared to pts treated with the standard regimen of doxorubicin and cyclophosphamide plus dual-blockade associated with docetaxel (AC-DHP) at a single Portuguese Comprehensive Cancer Center.

Methods

This retrospective cohort study included a consecutive series of female eBC HER2+ pts who initiated primary treatment with TCHP between July 2018 and August 2022. The primary endpoint was pathological complete response (pCR), and secondary endpoints were cardiac safety and disease-free survival (DFS). The outcomes were compared with a historical database of eBC HER2+ pts who started primary treatment with AC-DHP between August 2015 and May 2021. Clinical data was collected from medical and administrative records. Descriptive statistics were used to describe categorical and continuous variables, and the Kaplan-Meier method was used for DFS analysis. Costs analysis employed the micro-costing technique, considering individual medical direct costs from diagnosis until surgery. Multivariate logistic regression models were used for effectiveness analysis and the gamma general model for

costs analysis. The incremental cost-effectiveness ratio (ICER) was calculated using the pCR rate as a measure of effectiveness.

Results

A total of 233 and 23 pts were included in the TCHP and AC-DHP groups respectively. Reasons for choosing the anthracycline-free regimen in the TCHP group were primarily age-related frailty (52%), medical comorbidities (26%), and previous exposure to anthracyclines (22%). The TCHP pts were older (median age 71 years, range [45-77] vs. 47 years [24-70]) and had lower baseline Left Ventricular Ejection Fractions (LVEF) (median 65% [51-80] vs. 60% [56-73]), with a higher proportion of hormone receptor (HR) negative pts (78.3% vs. 33.0%). Clinical stages were balanced between groups, but the TCHP group had a higher nodal involvement (N+) (73.9% vs. 61.8%). The pCR rates were higher in the TCHP group (65.2% vs. 46.1%, HR 0.98 [95% CI 0.36 - 2.70]). Subgroup analysis by HR status showed comparable pCR rates: 77.1% vs. 74.1% in HR- pts and 40% vs. 39.7% in HR+ pts. Cardiac safety analysis indicated a median decrease in LVEF of 9% in both the TCHP and AC-DHP groups, with 43.5% of TCHP pts experiencing a decline of 10% or more, and 13.0% dropping below 50%. In comparison, these figures were 44.2% and 3.9%, respectively, in the AC-DHP group. At the end of the follow-up, only one patient in the TCHP group with a LVEF < 50% persisted with mild symptoms of chronic heart failure. The median follow-up time for DFS events, starting from surgery, was 31.1 months in the TCHP group and 45.7 months in the AC-DHP group, with 1-year DFS rates of 91.3% and 100%, respectively. The ICER analysis indicated that TCHP was cost-effective, as the incremental cost for achieving an additional pCR in similar subgroups can be outweighed by later cost savings, mainly due to further adjuvant treatment with trastuzumab instead of TDM-1.

Conclusions

In a real-world population of HER2+ eBC patients unfit for anthracyclines, the TCHP regimen demonstrated a higher overall pCR rate compared to a historical control treated with the AC-DHP regimen, along with an acceptable cardiac safety profile. These results support the broader use of the TCHP regimen in HER2+ eBC pts, as recommended by current NCCN guidelines. However, larger studies involving similar populations are needed to provide higher levels of evidence.

PO3-01-04

Neoadjuvant compared to adjuvant chemotherapy combined with trastuzumab in patients with HER2-positive breast cancer: a register-based cohort study

Presenting Author(s) and Co-Author(s):

S. Hosseini-Mellner. School of Medical Sciences, Örebro University, Section for Breast Surgery, Department of Surgery, Södersjukhuset Hospital, Stockholm, Stockholms Lan, Sweden

□. Wickberg. Department of Surgery, Faculty of Medicine and Health, Örebro University Hospital Sweden, United States

A. Valachis. Örebro University Hospital, Örebro, Sweden

A. Karakatsanis. Department for Surgical Sciences, Uppsala University, Uppsala, Sweden

Neoadjuvant compared to adjuvant chemotherapy combined with trastuzumab in patients with HER2-positive breast cancer: a register-based cohort study

Servah Hosseini-Mellner, Åsa Wickberg, Andreas Karakatsanis, Antonis Valachis **Introduction** Neoadjuvant therapy (NAT) is considered the standard of care in patients with HER2-positive breast cancer mainly due to the possibility to adjust the post-neoadjuvant treatment based on the tumor response to NAT. However, there is no convincing evidence on a survival benefit with NAT compared to adjuvant therapy (AT) for HER2-positive breast cancer. The aim of the present study was to compare the two therapeutic strategies in a register-based cohort of Swedish patients with primary operable HER2-positive breast cancer. **Method** The research database BCBSa 3.0, which is based on the Swedish National Quality breast cancer register, was used to identify patients with primary operable HER2-positive breast cancer that diagnosed between 2008 and 2020 and received either NAT or AT including chemotherapy and trastuzumab. To mitigate confounding by indication bias, propensity score matching (PSM) with 1:1 matching was applied. The effectiveness of the two therapeutic strategies was investigated through analyzing distant disease-free survival (DDFS), breast-cancer specific survival (BCSS), and overall survival (OS). Multivariate Cox regression analyses were performed for the outcomes of interest to provide Hazard Ratios (HR) and corresponding 95% Confidence Intervals (CI). **Results** In total, 7258 patients with primary operable HER2-positive breast cancer treated with either NAT or AT were identified, 1789 (24.6%) received NAT and 5469 (75.4%) AT. After 1:1 PSM, 1258 patients in each therapeutic strategy were available for comparisons. After a median follow-up of 63 months, no statistically significant differences between NAT and AT were observed in either outcome (HR for DDFS: 0.97; 95% CI: 0.72 – 1.30; HR for BCSS: 0.69; 95% CI: 0.45 – 1.07; HR for OS: 0.72; 95% CI: 0.50 – 1.05). In subgroup analyses, estrogen-receptor status did not impact the results that remained statistically non-significant between NAT and AT whereas in patients with clinically positive lymph node status, NAT resulted in better BCSS (HR: 0.44; 95% CI: 0.22 – 0.89) and OS (HR: 0.49; 95% CI: 0.29 – 0.90). The latter trend was not evident in patients with clinically negative lymph node status. **Conclusion** Our study results confirm the equivalence of NAT and AT in terms of prognosis for patients with operable HER2-positive disease and imply a potential benefit of NAT compared to AT in patients with clinically positive lymph node status. Considering the emerging treatment strategies in HER2-positive breast cancer patients treated with NAT (pertuzumab as a part of NAT, T-DM1 as post-neoadjuvant therapy) that have been shown to improve survival but are not reflected in the study cohort, NAT should be considered as the strategy with the higher possibility to improve long-term prognosis for patients with HER2-positive disease.

PO3-01-05

Enhancing HER2 Evaluation: Correlation between APIS Breast Cancer Subtyping Kit and IHC/ISH for Accurate HER2 Quantification

Presenting Author(s) and Co-Author(s):

A. Gasior. APIS Assay Technologies, Manchester, England, United Kingdom

J. Gorniak. APIS Assay Technologies, United States

S. Rollinson. APIS Assay Technologies, United States

L. Gough. APIS Assay Technologies, United States

A. Wegscheider. MVZ Prof. dr medical A. Niendorf Pathologie Hamburg-West GmbH, United States

A. Niendorf. MVZ Prof. dr medical A. Niendorf Pathologie Hamburg-West GmbH, United States

Background: The quantification of HER2-low in breast cancer (BC) has garnered considerable interest due to emerging evidence of the efficacy of targeted therapies in this patient subgroup. Trastuzumab deruxtecan (T-Dxd), an antibody-drug conjugate targeted at HER2, has recently gained approval in the USA and Europe for treating HER2-low BC, which is currently defined as immunohistochemical (IHC) scores of 1+ or 2+ without HER2/ERBB2 in situ hybridization (ISH) amplification. HER2 quantification using IHC/ISH was primarily designed to identify tumors overexpressing HER2, rather than differentiate between HER2-low and the absence of expression. Consequently, the adequacy of these assays in accurately detecting HER2-low remains uncertain.

Improving the accuracy of HER2 evaluation is crucial to prevent the incorrect selection of patients for T-Dxd treatment. There is a clear need to develop HER2 testing methods that are more precise, reliable, and capable of detecting HER2-low expression with greater sensitivity and reproducibility. This is particularly important as the minimum threshold of HER2 expression required for T-Dxd efficacy is still under investigation, with clinical data suggesting the potential activity of T-Dxd even in patients with IHC 0 HER2 score.

Here, we evaluated the correlation between HER2 mRNA expression levels, detected by APIS Breast Cancer Subtyping Kit, and IHC HER2 classification. Methods: Formalin-fixed paraffin-embedded (FFPE) tumour tissue sections (n=642) obtained by core needle biopsy or resection underwent histological analysis in accordance with laboratory's standard of care methods. Samples with a HER2 score of 2+ were referred to ISH to determine ERBB2 amplification. To evaluate the diagnostic performance, the concordance between HER2 IHC score, and APIS Breast Cancer Subtyping Kit RNA expression level was reported in terms of Overall Percent Agreement (OPA), Negative Percent Agreement (NPA), and Positive Percent Agreement (PPA), along with their corresponding 95% confidence intervals (CI). Results: HER2 expression detected by APIS Breast Cancer Subtyping Kit showed strong correlation with IHC/ISH, with an OPA of 94.2% (95% CI: 92.2-95.8), PPA of 89.2% (95% CI: 80.1-94.4) and NPA of 94.9% (95% CI: 92.8-96.4). The expression of HER2 was detected by APIS Breast Cancer Subtyping Kit in a subset of patients with 0 and 1+ IHC HER2 scores, suggesting its potential as a more sensitive and reliable method for detection of HER2 expression, and providing the opportunity to enhance HER2 stratification. Conclusions: APIS Breast Cancer Subtyping Kit can accurately detect HER2 expression and has the potential to further stratify the HER2-low patients. Further studies examining the relationship between HER2 expression and the response to anti-HER2 therapies could yield valuable insights into treatment administration and identify patients who

could benefit from such therapies. Incorporating continuous quantification of HER2 could optimize patient outcomes.

PO3-01-08

Interaction of Prior Chemotherapy and Addition of Ovarian Function Suppression on Menopausal Symptoms in Tamoxifen-Treated Breast Cancer Patient: A prospective, Observational study

Presenting Author(s) and Co-Author(s):

Y. Lee. Asan Medical Center, United States

J. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea., United States

S. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

B. Son. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

H. Kim. Asan medical center, Seoul, Seoul-t'ukpyolsi, Republic of Korea

B. Ko. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

J. Kim. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea., United States

I. Chung. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

T. Yoo. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Adjuvant endocrine therapy (AET) is commonly used for hormone receptor-positive breast cancer patients. Combining ovarian function suppression (OFS) with tamoxifen improves survival outcomes, but is associated with menopausal symptom-related issues and treatment discontinuation. This study aimed to compare menopausal symptoms between tamoxifen alone and tamoxifen plus OFS over 12 months and identify related factors. **Methods:** This prospective study included 209 premenopausal breast cancer patients on tamoxifen. Menopausal symptoms were assessed using the Menopausal Rating Scale (MRS) at baseline, 3, 6, and 12 months. Statistical analysis involved linear regression and generalized estimating equations. **Results:** Of the participants, 27.8% received tamoxifen plus OFS and were younger and more likely to be unmarried. The tamoxifen plus OFS group had lower baseline MRS scores, but higher scores at 6 and 12 months compared to tamoxifen alone. MRS scores increased significantly in both groups, plateauing at 6 months with tamoxifen alone and at 12 months with tamoxifen plus OFS. Factors associated with higher MRS scores at 6 months were baseline MRS scores and addition of OFS. Impact of OFS on MRS scores varied with prior chemotherapy status, being significant in patients without prior chemotherapy. **Conclusion:** Adding OFS to tamoxifen in premenopausal breast cancer patients was associated with a higher burden of menopausal symptoms compared to tamoxifen alone, particularly in patients who have not undergone prior chemotherapy. Therefore, careful consideration and decision-making regarding this issue are crucial in terms of both treatment outcomes and quality of life.

Table 1. Baseline characteristics, Overall and According to adjuvant endocrine therapy, tamoxifen alone versus tamoxifen plus ovarian function suppression (OFS)

Table 1. Baseline characteristics, Overall and According to adjuvant endocrine therapy, tamoxifen alone versus tamoxifen plus ovarian function suppression (OFS)

Characteristics	Tamoxifen alone (n=183)		Tamoxifen plus OFS (n=58)		p value	Overall (n=269)	
	No.	%	No.	%		No.	%
Age, years							
<30	2	1.3	3	5.2	0.002	5	2.4
30-34	4	2.6	6	10.3		10	4.8
35-39	16	10.6	10	17.2		26	12.4
40-44	58	38.4	18	31.0		76	36.4
45-49	48	31.8	18	31.0		66	31.6
≥50	23	15.2	3	5.2		26	12.4
BMI							
<18.5	5	3.3	1	1.7	0.281	6	2.9
18.5-24.9	113	74.8	47	81.0	0.718	160	76.6
25-29.9	27	17.9	9	15.6		36	17.2
≥30	6	4.0	1	1.7		7	3.3
Marital status							
Single	20	13.2	16	27.6	0.015	36	17.2
Married	130	86.1	42	72.4		172	82.3
Unknown	1	0	0	0		1	0.5
Occupation							
Unemployed	70	46.4	24	41.4	0.517	94	45.0
Employed	81	53.6	34	58.6		115	55.0
Education							
High school & below	51	33.8	14	24.1	0.169	65	31.1
University & above	99	65.6	44	75.9		143	68.4
Unknown	1	0.6	0	0		1	0.5
Surgery type							
Total mastectomy	33	21.9	10	17.2	0.460	43	20.6
Breast conserving surgery	118	78.1	48	82.8		166	79.4
Tumor stage							
Carcinoma in situ	32	21.2	0	0	<0.001	32	15.3
Invasive carcinoma	119	78.8	58	100		177	84.7
Nodal metastases							
Negative	110	72.8	46	79.3	0.925	156	74.6
Positive	41	27.2	12	20.7		53	25.4
Estrogen receptor							
Strong (7-8)	145	96.0	58	100	0.499	203	97.1
Moderate (5-6)	4	2.6	0	0		4	1.9
Weak (3-4)	1	0.7	0	0		1	0.5
Negative (0-2)	1	0.7	0	0		1	0.5
Progesterone receptor							
Strong (7-8)	87	57.6	39	67.2	0.290	126	60.3
Moderate (5-6)	29	19.2	12	20.7		41	19.6
Weak (3-4)	16	10.6	2	3.4		18	8.6
Negative (0-2)	19	12.6	5	8.6		24	11.5
HER2							
Negative	117	77.5	57	98.3	0.002	174	83.3
Positive	21	13.9	0	0		21	10.0
Unknown	13	8.6	1	1.7		14	6.7
Chemotherapy							
No	81	53.6	51	87.9	<0.001	132	63.2
Yes	70	46.4	7	12.1		77	36.8
Radiotherapy							
No	24	15.9	10	17.2	0.813	34	16.3
Yes	127	84.1	48	82.8		175	83.7
Menopausal rating scale (MRS)							
Baseline	9.4 (6.7)		6.4 (4.3)		<0.001	8.6 (6.3)	
3 months after	11.2 (6.8)		12.6 (5.9)		0.192	11.5 (6.6)	
6 months after	11.8 (7.7)		14.9 (7.2)		0.008	12.7 (7.7)	
12 months after	11.6 (6.8)		15.1 (7.6)		0.003	12.6 (7.2)	

Table 2. Multivariable linear regression about MRS scores from the baseline to 6 months, and with interaction between addition of OFS and prior chemotherapy effect

Table 2. Multivariable linear regression about MRS scores from the baseline to 6 months, and with interaction between addition of OFS and prior chemotherapy effect

Multivariable linear regression									
	Estimate	Std. Error	t value	P<0.05	Estimate	Std. Error	P<0.05		
(Intercept)	8.022	4.903	1.636	0.103	(Intercept)	9.623	4.904	1.961	0.051
Age	-0.079	0.084	-0.943	0.347	Age	-0.112	0.084	-1.320	0.188
BMI	0.031	0.136	0.240	0.810	BMI	0.021	0.135	0.158	0.875
Baseline MRS	-0.331	0.077	-4.276	<0.001	Baseline MRS	-0.326	0.077	-4.248	<0.001
Addition of OFS	4.938	1.216	4.062	<0.001	Addition of OFS	6.084	1.306	4.658	<0.001
Education grade	-0.780	1.033	-0.754	0.452	Education grade	-0.849	1.023	-0.828	0.409
Occupation status	0.450	0.947	0.473	0.633	Occupation status	0.414	0.918	0.441	0.660
Tumor stage	0.393	1.481	0.267	0.790	Tumor stage	-0.206	1.490	-0.139	0.890
Nodal metastasis	0.339	1.294	0.262	0.794	Nodal metastasis	0.918	1.306	0.703	0.483
Prior chemotherapy	-0.129	1.333	-0.096	0.923	Prior chemotherapy	0.596	1.338	0.439	0.661
Radiotherapy	0.143	1.255	0.114	0.909	Radiotherapy	0.234	1.243	0.180	0.817
					Addition of OFS : Prior chemotherapy	-6.641	2.046	-2.253	0.025

Table 3. Interaction effect of additional OFS depending on prior chemotherapy; (a) without prior chemotherapy, (b) with prior chemotherapy

Table 3. Interaction effect of additional OFS depending on prior chemotherapy; (a) without prior chemotherapy; (b) with prior chemotherapy

(a) Without prior chemotherapy				
	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	11.291	6.124	1.844	0.068
Age	-0.101	0.102	-0.992	0.321
BMI	-0.104	0.171	-0.607	0.545
Baseline MRS	-2.246	0.116	-2.718	0.008
Addition of OFS	6.293	1.364	4.613	<0.001
Education grade	-0.975	1.368	-0.055	0.954
Occupation status	0.945	1.257	0.751	0.454
Tumor stage	-0.900	1.218	-0.739	0.459
Nodal metastasis	3.053	2.524	1.210	0.229
Radiotherapy	-0.303	1.507	-0.199	0.892

(b) With prior chemotherapy				
	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	0.098	10.359	0.009	0.993
Age	-0.218	0.139	-1.568	0.118
BMI	0.214	0.224	0.944	0.340
Baseline MRS	-0.370	0.105	-3.512	0.001
Addition of OFS	-0.860	2.863	-0.298	0.768
Education grade	-2.277	1.570	-1.450	0.152
Occupation status	0.790	1.487	0.527	0.600
Tumor stage	10.243	6.623	1.547	0.127
Nodal metastasis	-0.289	1.256	-0.230	0.823
Radiotherapy	1.705	2.396	0.712	0.479

PO3-01-09

Results of a prospective observational study evaluating the impact of the Prosigna assay on neoadjuvant treatment decision-making in patients with early-stage HR+/HER2- breast cancer

Presenting Author(s) and Co-Author(s):

C. Corti. European Institute of Oncology, IRCCS, University of Milano, Milan, Italy, Pusiano (CO), Lombardia, Italy

X. Chu. Department of Data Science, Dana-Farber Cancer Centre, Boston, MA, USA, United States

P. Exman. Breast Cancer Unit, Hospital Alemão Oswaldo Cruz, Sao Paulo, Brazil, United States

D. Kline. Breast Oncology Program, Dana-Farber Cancer Centre, Boston, MA, USA, United States

N. Priedigkeit. Dana-Farber Cancer Institute / Broad Institute of MIT and Harvard, Boston, Massachusetts, United States

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

A. Waks. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

M. Hughes. Dana Farber Cancer Institute, United States

A. Giordano. Dana Farber Cancer Institute, Harvard University, Boston, MA, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

D. Dillon. Brigham and Women's Hospital, Breast Oncology Program, Susan F. Smith Center for Women's Cancers, Dana-Farber Brigham Cancer Center; Harvard Medical School, United States

E. Mittendorf. Dana Farber Cancer Institute, Boston, Massachusetts, United States

S. Tolane. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background. Prosigna (PAM50) is an FDA-approved prognostic test that measures the expression of 50 classifier genes in breast cancer tissue samples. It provides intrinsic subtyping, which classifies the biology of an individual patient's tumor, as well as a risk of recurrence (ROR) score that predicts the probability of distant recurrence over 10 years. Currently, the Prosigna assay is only approved for use in postoperative specimens. Given studies demonstrating that Prosigna can identify tumors that are more likely to benefit from chemotherapy, this decision-impact study sought to evaluate whether the assay could influence physicians' choices and patients' confidence in the neoadjuvant treatment plan. Methods. This prospective observational study was conducted at a single institution and included patients with HR+/HER2- breast cancer measuring ≥ 0.5 cm, any nodal status, who were deemed

candidates for neoadjuvant systemic treatment based on physician's choice. Formalin-fixed paraffin-embedded core biopsy specimens were centrally analyzed using Prosigna. Patients' tumors were classified according to intrinsic tumor subtype (Luminal A, Luminal B, HER2-enriched, Basal-like) and ROR score (low, intermediate, or high). Physicians and patients were surveyed before and after performing Prosigna, regarding neoadjuvant therapy recommendations. The primary endpoint was assessment of the effect of Prosigna on oncologists' treatment recommendations and the actual treatment received (neoadjuvant hormonal therapy [NAHT], neoadjuvant chemotherapy [NACT], or upfront surgery). Secondary endpoints included determining whether treatment changes were based on ROR score, intrinsic subtype, or both, as well as assessing physicians' and patients' confidence in the treatment plan. Results. A total of 54 patients were enrolled in the study between March 2019 and April 2023. The distribution of intrinsic tumor subtypes was as follows: 15 patients (28%) had a Luminal A subtype, 34 (63%) had a Luminal B subtype, 3 (6%) had a HER2-enriched subtype, and 2 (4%) had a Basal-like subtype. Thirty-three patients (61%) were classified as ROR-low, 11 (20%) as ROR-intermediate, and 10 (19%) as ROR-high. Out of the 43 patients who had both pre- and post-assay survey results available, a change in the treatment decision was observed in 28% of cases. Specifically, 14% of patients transitioned from NAHT to NACT, 7% from NACT to NAHT, and 5% from NACT to upfront surgery, as shown in the Table. Treatment changes were based on the ROR score, intrinsic subtype, and both in 33%, 3%, and 64% of cases, respectively. Overall, 45% of physicians experienced an increase in confidence for the treatment plan after Prosigna testing, while 16% reported a decrease and 39% maintained the same level of confidence. Sixty-two percent of patients experienced a reduction in anxiety about treatment. Associations of ROR score and intrinsic subtypes will be presented at the meeting. Conclusion. Prosigna performed on presurgical core biopsies influenced oncologists' treatment recommendations regarding neoadjuvant treatment and reduced patient anxiety about treatment among patients with early-stage HR+/HER2- breast cancer.

Table. Neoadjuvant treatment recommendations before and after Prosigna assay, overall and according to nodal status.

Before assay (N=43)	After assay (N=43)		
	NAHT	NACT	Upfront surgery
<i>All evaluable patients, n. (%)</i>			
NAHT	11 (26)	6 (14)	0 (0)
NACT	3 (7)	15 (35)	2 (5)
Upfront surgery	0 (0)	1 (2)	5 (12)
<i>Nodal status</i>			
<i>Node-negative patients, n. (%) (n=16)</i>			
NAHT	4 (9)	2 (5)	0 (0)
NACT	1 (2)	6 (14)	1 (2)
Upfront surgery	0 (0)	0 (0)	2 (5)
<i>Node-positive patients, n. (%) (n=27)</i>			
NAHT	7 (16)	4 (9)	0 (0)
NACT	2 (5)	9 (21)	1 (2)
Upfront surgery	0 (0)	1 (2)	3 (7)

Data are presented as frequencies (%). Abbreviations: NACT, neoadjuvant chemotherapy; NAHT, neoadjuvant hormonal therapy.

PO3-01-10

Changes in Patient-Reported Outcomes with 3 Months of Pre-operative Endocrine Therapy in the POWER Trial

Presenting Author(s) and Co-Author(s):

T. Millard. University of Virginia, Charlottesville, Virginia, United States

L. Turkheimer. University of Virginia, United States

C. Brenin. University of Virginia, United States

D. Brenin. University of Virginia, United States

P. Dillon. University of Virginia, United States

E. Janowski. University of Virginia, United States

A. Schroen. University of Virginia, United States

G. Petroni. University of Virginia, United States

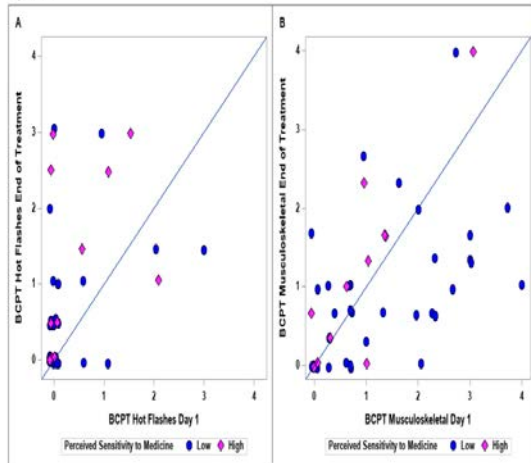
S. Showalter. University of Virginia, United States

Background: The Pre-Operative Window of Endocrine Therapy to Inform Radiation Therapy Decisions Trial (POWER, NCT04272801) aims to determine whether 3 months of pre-operative endocrine therapy (pre-ET) affects decision-making regarding adjuvant radiation therapy (RT) among older women with early-stage, estrogen receptor (ER) positive breast cancer. The goal of the present study is to evaluate changes in patient-reported outcomes (PROs) during the course of pre-ET. We hypothesize that PROs will change over the course of pre-ET and that those changes can be used to identify patients who are at-risk for long-term noncompliance to adjuvant ET and who may benefit from RT. **Methods:** Participants in the POWER Trial receive 3 months of pre-ET prior to breast-conserving surgery and final treatment decisions regarding adjuvant RT. Health-related quality of life (HRQOL) (EORTC QLQ-C30 and QLQ-BR23), depression (Center for Epidemiologic Studies Depression Scale Revised), and general symptom burden (Breast Cancer Prevention Trial Symptom Checklist (BCPT-SCL)) are assessed at baseline and at day 90 after pre-ET. Perceived sensitivity to medicine (Perceived Sensitivity to Medicine (PSM) survey) is assessed at baseline. The BCPT-SCL was used to examine common ET side effects, including hot flashes, musculoskeletal symptoms, cognitive problems, weight gain, and bladder control. Graphical methods are used to display results. **Results:** The first 46 participants who completed pre-ET in the POWER trial were included in this preliminary assessment. From baseline to day 90, there was notable variability in HRQOL and no definitive shift towards worsening HRQOL with a median change (IQR) of 0 (-8.33, 8.33). Similarly, the median change in symptom profiles for the whole cohort was 0 over the 90 days of pre-ET. However, a subset of patients experienced changes in symptom burden throughout the 90-day period. Approximately one-fourth of participants reported an increase in hot flashes and musculoskeletal symptoms from baseline to day 90. There does not appear to be worsening fatigue, depression scores, cognitive problems, or weight gain. After stratifying by self-perceived sensitivity to medicine, patients with high PSM scores have a greater median change (0.5 and 0.33) in symptoms compared to those with low PSM scores (0 and 0) for hot flashes and musculoskeletal symptoms, respectively (Figure 1). **Conclusions:** When looking at this cohort, there was no change in symptoms or quality of life after the 3-month course of pre-ET. Evaluation of the changes in PROs identified a subset of participants with worsening symptoms after pre-ET. Future analyses, when trial accrual is complete, will examine the relationship between PROs and long-term adherence to adjuvant ET and will elucidate if the

patients who experience worsening BCPT-SCL symptoms during the 90-day period are more likely to opt for RT.

Figure 1 Change in symptoms after pre-ET

Figure 1:



Change in hot flash burden and musculoskeletal symptom burden is greater in patients with high perceived sensitivity to medicine.

PO3-01-11

Clinical Significance of HER2-low Breast Cancer

Presenting Author(s) and Co-Author(s):

F. Zaiem. Wayne State University, United States

A. AbuJamea. Wayne State University, United States

M. Kheil. Wayne State University, United States

A. Numi. Wayne State University, United States

O. Abbas. Wayne State University, United States

S. Awada. School of Medicine and Surgery, Wayne State University, United States

R. Almsaddi. School of Medicine and Surgery, Wayne State University, United States

S. Al-Juburi. School of Medicine and Surgery, Wayne State University, United States

L. Larson. School of Medicine and Surgery, Wayne State University, United States

D. Jain. Departments of Pathology, School of Medicine and Surgery, Wayne State University, United States

M. AISaghir. School of Medicine, Oakland University, United States

H. Jang. Biostatistics and Bioinformatics Core, Karmanos Cancer Institute Department of Oncology, School of Medicine, Wayne State University, United States

S. Kim. Biostatistics and Bioinformatics Core, Karmanos Cancer Institute Department of Oncology, School of Medicine, Wayne State University, United States

S. Bandyopadhyay. Departments of Pathology, School of Medicine and Surgery, Wayne State University, United States

S. Jaiman. Departments of Pathology, School of Medicine and Surgery, Wayne State University, United States

R. Ali-Fehmi. Department of Pathology , University of Michigan, United States

Abstract: Context: Breast cancers with a HER2 immunohistochemistry (IHC) result of 1+ or 2+ and a negative amplification test (FISH), previously treated as HER2 negative, are now termed HER2-low and are being targeted for treatment. We aim to explore the clinical significance of this group. Design: 394 breast cancer cases were included from our institution from 2010. Demographic and clinicopathological data on receptors status, recurrence/metastasis, treatment, and survival was collected. HER2 was re-evaluated according to the 2018 CAP ASCO guidelines and patients were treated according to standardized protocol. HER2 +2 with positive FISH and HER2 +3 were excluded. HER2-low was compared to HER2-0. Appropriate statistical analysis was performed. Results: 394 patients (76% IDC; 8% ILC; 16% others) were included, such that 91 (23%) were HER2-0 and 303 (77%) HER2-low. Median age was 58 years (range: 25-95). Median follow-up was 54 months (range: 0.5-259). Grade 3 tumors were significantly more frequent in HER2-0 than HER-2 low (52% vs. 33%; $p=0.010$). Grade 3 or ILC patients had higher risk of recurrence than Grade 1 (HR 2.55; $p<0.001$) or IDC (HR 2.03; $p=0.033$). After adjusting for grade, HER2-low had a significantly worse RFS than HER2-0 (HR 1.58; $p=0.043$). In the ER negative subgroup, HER2-low had significantly worse RFS than HER2-0 (HR 2.02; $p=0.023$). No differences in overall survival were seen. Conclusions: Our data showed higher recurrence in HER2-low group compared to HER2-0. This suggests that breast cancer patients with HER2- low are a separate entity and might benefit from additional targeted therapy.

Table 1 Hazard regression analysis of risk factors associated with recurrence

	Events	HR (95% CI)	P Value
Diagnosis			
DC	100/293	Ref.	
ILC	11/50	2.03 (1.06-3.90)	0.033
Grade			
Grade 1	16/80	Ref.	
Grade 2	46/159	1.51 (0.85-2.66)	0.158
Grade 3	64/144	2.55 (1.47-4.41)	<0.001
Subgroup			
HER2-0	28/87	Ref.	
HER2-low	90/296	1.58 (1.01-2.47)	0.043

Table 1 Hazard regression analysis of risk factors associated with recurrence

PO3-01-12

Clinicopathologic Factors affecting response in patients with Estrogen receptor-positive and Human Epidermal Growth Factor Receptor-negative breast cancer receiving neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

J. Lee. Seoul St Mary's Hospital, United States

Y. Lee. Seoul St. Mary's Hospital, United States

D. Kim. Seoul St Mary's Hospital, United States

C. Yoon. Seoul St Mary's Hospital, United States

W. Park. Seoul St Mary's Hospital, United States

S. Bae. Seoul St. Mary's Hospital, United States

Background: The evolution of Neoadjuvant chemotherapy(NAC) regimen has enabled the down-staging of locally advanced breast cancer, allowing patients to undergo breast conserving surgery. NAC is known to be effective in triple-negative breast cancer (TNBC) and HER2-positive breast cancer. However, the role of NAC in hormone receptor-positive and HER2-negative (HR+HER2-) breast cancer patients remains unclear. In this study, we aimed to explore the utility of NAC for estrogen receptor-positive and HER2-negative (ER+HER2-) breast cancer patients. **Methods:** Clinical data were collected from 120 patients who were diagnosed with estrogen receptor (ER)-positive and HER2-negative breast cancer and received neoadjuvant chemotherapy between July, 2017 and April, 2023 at Seoul St Mary's Hospital (Seoul, Korea). We analyzed the factors that affect clinical response subgroups, including pathologic complete response (pCR), partial response (PR), stable disease(SD), and progressive disease (PD), following neoadjuvant chemotherapy. The median follow-up period was 17 months. **Results:** Among 120 patients after NAC, 5.8% achieved pCR, while 67.5% had a partial response. The median age at the time of surgery was 55 years at pCR group, 49 years at PR group, 47 years at SD group, and 49 years at PD group. Although the age of patients achieving pathological complete response was higher, this differences was not statistically significant. Patients achieving pCR had a higher incidence of progesterone receptor (PR) negativity (pCR 71.4% vs PR 30.9%, $p=0.011$) and higher levels of Ki-67 expression than those who did not achieve pCR (71.7% vs 35.6%, $p=0.003$). Also, there was no significant difference in Androgen receptor (AR) and HER-2 expression between the groups. Tumor size was also significantly associated with clinical response ($p=0.003$). However, no differences in clinical response was observed between patients with lymph node metastasis ($p=0.221$). Our analysis of 107 patients who were clinically N positive before NAC showed that the Ki-67 index level was the only factor found to affect nodal pCR. In addition, in the non-pCR group, patients with a Ki-67 index of less than 20% after neoadjuvant had a significantly better disease-free survival (5yr DFS, 79.8% vs 65.9%, $p=0.039$) **Conclusion:** Our analysis revealed that patients with higher levels of Ki-67 and lower level of PR expression were more likely to achieve pCR or PR. Also, decrease in Ki-67 index was confirmed to be an important prognostic factor of ER+HER2- breast cancer. A combination of clinical and molecular factors, such as tumor size, progesterone receptor expression, and Ki-67 expression, can be used to optimize treatment plans and improve outcomes for the patient population.

PO3-01-13

A study of the impact of the implementation of the Oncotype Dx 21-gene breast-cancer assay during the SARS-CoV-2 pandemic for 1-3 node positive early breast cancer: The Clatterbridge Cancer Centre Experience

Presenting Author(s) and Co-Author(s):

A. Johnson. The Clatterbridge Cancer Centre Liverpool, United States

S. Bathla. St Helens and Knowsley Hospitals NHS Trust, United States

L. Chagla. St Helens & Knowsley Teaching Hospitals, UK, United States

J. Cliff. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

A. Hall. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

A. Hargreaves. Countess of Chester NHS Trust, United States

C. Hart. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

Z. Malik. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

C. Roshanlall. The Wilmslow Hospital and The Christie Clinic, United States

R. Sripadam. The Clatterbridge Cancer Centre Liverpool, United States

C. Palmieri. The Clatterbridge Cancer Centre NHS Foundation Trust/ University of Liverpool, United Kingdom

H. Innes. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

Background: The 21-gene breast cancer (BC) assay (Oncotype Dx) is used to predict chemotherapy benefit in ER+, HER-2- lymph node (LN) negative BC. The RxPONDER trial demonstrated that post-menopausal patients with ER+, HER2- BC with 1-3 LN and a recurrence score (RS) of < 25 did not benefit from adjuvant chemotherapy. In response to the SARS-CoV-2 pandemic Oncotype Dx was implemented for ER+, HER2- 1-3 LN+ BC patients in Merseyside, UK (population 2.6 million) This study sought to understand the impact of this measure on clinical practice. **Methods:** All patients whose tumours were assessed with Oncotype Dx assay between Mar 20 - Nov 22 were identified through the Exact Sciences portal. Menopausal status, tumour characteristics, RS and chemotherapy regimen were recorded. The impact on cancer care was estimated using the number of infusions and clinic visits specified by our institution chemotherapy protocol for node positive disease. The financial impact was calculated using the test list price, estimated costs of adjuvant chemotherapy in the UK (Annals of Oncology, Volume 32, suppl 2 S46). The number of patients predicted to receive chemotherapy pre-oncotype DX was calculated using data from the UK PONDx trial data. **Results:** A total of 242 patients were tested over the 32 month period. Table 1 summarises the clinico-pathological characteristics including by RS score. The median age was 58.5 and 77.3% (n=187) were post-menopausal. The median tumour size was 25mm and median LNs with macrometastasis was 1. 198 (81.9%) patients had an RS < 25. Overall 73 patients (30%) received chemotherapy of which 34 had an RS < 25. Pre-menopausal patients were more likely to receive chemotherapy with RS < 25 than post-menopausal patients, 47.9% (23/48) vs 7.3% (11/150) respectively. In the absence of Oncotype Dx testing 169 patients would have received adjuvant chemotherapy. Therefore, 96 patients avoided chemotherapy. This equates to 1,620 chemotherapy infusions and 324 clinic attendances. The estimated cost saving was ~£50K. **Conclusions:** This real-world study demonstrates that the use of Oncotype DX assay for ER+,HER2- 1-3 LN+ early BC spared a significant number of patients chemotherapy during the SARS-CoV-2 pandemic, so avoiding the risk of adverse effects. This also resulted in benefits to

the healthcare system with a reduction in scheduled cancer care and achieved financial savings. This, therefore, demonstrates the benefit of using the Oncotype Dx assay.

Table 1: Clinico-pathological information

Demographic	Total n=242	Cohort by Recurrence Score	
		RS high (>25), n= 44	RS low (<25) n= 198
Age	58.5 (20-85)	64 (38-85)	58 (20-82)
Post-menopausal	187 (77.3%)	37 (84.1%)	150 (75.8%)
Pre-menopausal	55 (22.7%)	7 (15.9%)	48 (24.2%)
Tumour size			
0-19 mm	62 (25.6%)	11 (25%)	51 (25.8%)
20-50mm	153 (63.2%)	30 (68.2%)	123 (62.1%)
>50mm	27 (11.2%)	3 (6.8%)	24 (12.1%)
Tumour grade			
1	38 (15.7%)	0 (0%)	38 (19.2%)
2	152 (62.8%)	30 (68.4%)	122 (61.7%)
3	52 (21.5%)	14 (31.6%)	38 (19.1%)
LNs with macrometastasis			
1	182 (75.2%)	36 (81.8%)	146 (73.8%)
2	49 (20.2%)	6 (13.6%)	43 (21.8%)
3	11 (4.6%)	2 (4.6%)	9 (4.6%)

PO3-01-14

Impact of detection mode, tumor characteristics and additional treatment on adherence to adjuvant endocrine therapy after breast cancer in Sweden.

Presenting Author(s) and Co-Author(s):

A. Andersson. Department of Radiation Sciences, Oncology Unit, Umeå University Hospital, Umeå, Sweden, United States

A. Von Wachenfeldt. Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, Stockholm,, United States

L. Nyström. Department of Epidemiology and Global Health, Umeå University,, United States

F. Isaksson. Department of Radiation Sciences, Oncology, Umeå University, United States

P. Ruohonen. Department of Radiation Sciences, Oncology, Umeå University, United States

Impact of detection mode, tumor characteristics and additional treatment on adherence to adjuvant endocrine therapy after breast cancer in Sweden.

Anne Andersson, Frida Isaksson, Pihla Ruohonen, Anna Von Wachenfeldt, Lennarth Nyström **Background:** Adjuvant endocrine therapy (AET) reduces recurrence and mortality in women with estrogen receptor (ER) positive early breast cancer (EBC). Adherence to AET has been shown to be lower than expected with risk of worse longtime prognosis. In a nationwide study in Sweden women with breast cancer diagnosis 2008-2010 adherence to AET at 5-year follow-up was estimated at 82,5% which is considered good related to recent published studies (manuscript is under review). Differences between regions and age-groups were shown. Present study investigates the impact on adherence of detection mode, tumor characteristics and additional treatment.

Methods: Through the Swedish Cancer Registry (SCR) women with a first primary EBC diagnosed 2008-2010 were identified. From the Swedish National Breast Cancer Registry (NKBC) individual tumor and treatment data were collected. Included in the study was patients with ER positive tumors > 10 mm without distant metastasis at diagnosis. Through the Swedish Prescription Registry dispensed treatment from pharmacies was extracted and medication possession rate (MPR) was calculated as number of dispensed doses divided by treatment duration in days. Good adherence to treatment in a patient was set at MPR ≥80%. Adherence at 3- and 5-year follow-up by detection mode, tumor characteristics and additional treatment was estimated. **Results:** Out of 21 016 women with a first primary BC 2008-2010 registered in the NKBC 10 176 met the inclusion criteria for the study. Among screen-detected tumors the 3- and 5-year adherence were 90,2 respectively 85,1% and 85,4 respectively 78,4% in the non-screen-detected group. In the screen-detected group the tumors were smaller and more often node negative. There was a significantly increased 5-year adherence in patients with stage III disease compared to those with stage I disease (84,1 vs 81,3 %) but not significant at 3-year (89,2 vs 87,3). Adjuvant chemotherapy significantly increased 3- (91.0% vs 85.8%) and 5-year (85.7% vs 79.3%) adherence among screen-detected and non-screen-detected respectively.

Conclusions: Adherence to AET in Sweden was good, although there were differences depending on detection mode, tumor stage and additional adjuvant treatment. Stage and additional medical adjuvant treatment depend on each other and should not be seen as independent factors for adherence for AET.

PO3-02-01

Educational Opportunities to Improve Community Healthcare Professionals' Management of High-Risk HR-Positive/HER2-Negative Early Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Becker. Clinical Care Options, LLC, Woodstock, Georgia, United States

T. Quill. Clinical Care Options, LLC, United States

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

Background: The treatment landscape for patients with hormone receptor–positive/HER2-negative early breast cancer (HR+/HER2- EBC) has evolved with the emergence of adjuvant CDK4/6 inhibitor therapy as a new option for patients with a high risk of disease recurrence. Adjuvant abemaciclib plus aromatase inhibitors (AIs) is guideline recommended for high clinical risk HR+ disease and reduces risk of recurrence regardless of Ki-67 expression level. Here, we examine healthcare professionals' (HCPs') awareness and practice regarding the use of adjuvant abemaciclib.

Methods: Between November 2022 and June 2023, we conducted a series of regional educational activities for HCPs focused on management of high-risk HR+/HER2- EBC. Each activity included an interactive lecture led by a clinical investigator with expertise in managing patients with high-risk HR+/HER2- EBC and polling questions designed to assess key aspects of HCP knowledge and practice in the optimal management of high-risk HR+/HER2- EBC. A wider HCP audience was able to view an interactive on-demand webcast with the same content and embedded polling questions.

Results: In total, 701 HCPs participated in one of 20 live (n = 373) activities or the one associated on-demand (n = 328) webcast. The distribution of HCP participation differed between the live and online activities with more physicians participating in the online activity vs the live activity (59% vs 34%, respectively); the converse was true for nurse participation (9% online vs 34% live). Polling result trends were similar between the live and online activities. At baseline, 38% (n/N = 182/405) of HCPs chose adjuvant therapy with an AI plus abemaciclib for a patient with high-risk, node-positive HR+/HER2- EBC consistent with expert and guideline recommendations. Following the education, 92% (n/N = 405/439) of HCPs selected AI plus abemaciclib for appropriate patients. Before education, 32% of HCPs (n/N = 147/454) were aware that adjuvant abemaciclib plus endocrine therapy improved invasive disease-free survival compared with endocrine therapy alone in patients with high-risk, node-positive HR+/HER2- EBC regardless of Ki-67 expression level, which increased to 87% (n/N = 370/425) following the education. Regarding the management of grade 2 neutropenia associated with adjuvant abemaciclib therapy, HCP knowledge was low at baseline (32%, n/N = 141/446) and improved to 80% (n/N = 332/415) after education.

Conclusions: HCPs' knowledge of and practice concerning adjuvant abemaciclib as a newer approved therapy for patients with high-risk HR+/HER2- EBC remain suboptimal. These results suggest an ongoing need for expert guidance and educational activities on the use of adjuvant abemaciclib therapy for appropriate patients with high-risk HR+/HER2- EBC. As the treatment landscape for HR+/HER2- EBC continues to evolve with the potential approval of additional

new therapies, this need will only increase with a clear impact on optimizing and individualizing adjuvant therapy strategies for patients with HR+/HER2- EBC.

PO3-02-02

A prospective, international, observational, real-world evidence database, and collaborative platform for Investigator-Initiated Studies in Early-Stage Breast Cancer tested with MammaPrint and Blueprint– the FLEX Study

Presenting Author(s) and Co-Author(s):

J. Alberty-Oller. Comprehensive Breast Center, Kings County Hospital NYC Health and Hospital System, United States

L. Riley. St. Luke's Cancer Care Associates, United States

L. Samiiian. Baptist MD Anderson Cancer Center, United States

S. Thayer. Ochsner LSU Health, United States

O. Aseyev. Thunderbay Regional Health Science Center, United States

K. Tedesco. NYOH, United States

V. Poillucci. Agendia, Inc., Cary, North Carolina, United States

W. Audeh. Agendia Inc., United States

D. Jelovac. Johns Hopkins University, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

TIPS SABCS 2023 A prospective, international, observational, real-world evidence database, and collaborative platform for Investigator-Initiated Studies in Early-Stage Breast Cancer tested with MammaPrint and Blueprint– the FLEX Study Background: Clinical trials have been an invaluable tool in providing improvements in the discovery, treatment, and quality of life for various diseases and disorders including breast cancer, which impacts millions of people each year. The MammaPrint 70-gene assay along with Blueprint 80-gene subtype analysis are tools to provide such improvements in treatment planning. Historically, patient trial populations have not been racially diverse. Current efforts are focused on improving diversity and inclusion to promote efficacy and health equity across all races/ethnicities. Given recent publications supporting the ability of MammaPrint and Blueprint to identify genomic differences in outcomes of black women with breast cancer, the ongoing multi-center FLEX trial (NCT03053193) has proven to be an unparalleled source for improvement in breast cancer care. With a target of 30,000 enrolled patients, the collaborative research network within FLEX will use MammaPrint, Blueprint, full transcriptome, and clinical data to explore clinical and genomic differences in (sub)populations of interest to promote and advance precision medicine for patients with early-stage breast cancer. Methods: FLEX is the first of its kind to link clinical data with full transcriptome data. It is a prospective, observational trial that enrolls patients who are ≥ 18 years old with histologically proven stage I-III breast cancer with up to 3 positive lymph nodes. Patient eligibility for study enrollment include standard of care MammaPrint testing with or without Blueprint and consent to clinically annotated full transcriptome data collection. The study's infrastructure facilitates the generation of hypotheses for targeted sub-studies that are important for breast cancer management. The FLEX network fosters collaboration with 99 active sites, including Canada, Greece, and Israel. All proposed substudies are vetted and approved by both internal and external research and scientific review committees. Since launching in April 2017, 13,547 patients have been enrolled including those who have been historically underrepresented in trials (Black n = 1032; Latin n = 373; AAPI n = 276), 43 investigator initiated sub-studies have been approved and are in progress on a varied number of approaches like MammaPrint/ Blueprint clinical utilities, racial disparities, neoadjuvant

treatment planning in ER+, and or HER2+ breast cancer with 31 abstracts accepted in national and international congresses. Five ongoing sub-studies within FLEX address differences in underlying biology and treatment response/management among Black, Latina, and Asian American patients with early-stage breast cancer. These studies provide a broader understanding of how differential gene expression patterns, identified with MammaPrint and BluePrint, are unique to racial/ethnic groups and can impact treatment outcomes. Overall, the FLEX study strives to use MammaPrint, BluePrint, and newly developed immune signature, ImPrint, along with full transcriptome data to improve precision medicine in early-stage breast cancer.

PO3-02-03

Ketogenic diet and letrozole to inhibit PI3K signaling in ER+ breast cancer

Presenting Author(s) and Co-Author(s):

B. Rexer. Vanderbilt University Medical Center, Nashville, Tennessee, United States

V. Abramson. Vanderbilt University Medical Center, United States

S. Nunnery. Vanderbilt University Medical Center, United States

S. Reid. Vanderbilt-Ingram Cancer Center, United States

L. Kennedy. Vanderbilt University Medical Center, Nashville, Tennessee, United States

M. Sanders. Vanderbilt University Medical Center, Nashville, Tennessee, United States

J. Bennett. Vanderbilt University Medical Center, United States

P. Gonzalez-Ericsson. Vanderbilt University Medical Center, United States

V. Sanchez. Vanderbilt University Medical Center, United States

Obesity is associated with an increased risk of breast cancer recurrence, similar in magnitude to the reduction in risk seen with the use of adjuvant chemotherapy. However, whether and how obesity causes that increased risk of recurrence remains unknown. Plausible mechanisms include obesity-mediated increases in estrogen signaling, inflammatory conditions resulting from obesity, or effects on insulin or other growth factor signaling pathways resulting from the insulin-resistant state that often accompanies obesity. While phosphatidyl inositol 3-kinase (PI3K) signaling is the normal, biological effector of insulin signaling, abnormal activation of PI3K is of particular concern in breast cancer, where it is associated with resistance to endocrine therapies and HER2-targeted therapies.

We hypothesize that at least part of the adverse outcome associated with obesity results from aberrant activation of PI3K signaling in tumors. This may confer resistance to established therapies, or directly stimulate tumor growth (particularly in tumors with existing PI3K pathway mutations), or both. We tested a dietary intervention designed to alter insulin resistance pathophysiology coupled with endocrine therapy in the well-established neoadjuvant treatment paradigm in breast cancer. This will allow us to study the effects of the dietary intervention directly on tumor biology.

The primary objective of this neoadjuvant study was to assess feasibility and tolerability of 2 weeks of a very low-carbohydrate ketogenic diet in combination with letrozole for patients with early stage operable ER+ disease. Up to 36 patients will be enrolled for this pilot and feasibility study (24 in the treatment group and 12 controls). Baseline metabolic parameters will be measured and the treatment group will begin a dietitian-supervised 2-week diet to induce a ketogenic state, along with letrozole 2.5 mg daily. The control group will receive only letrozole. At the end of 2 weeks, patients will proceed with surgical treatment of their breast cancer. We will report the primary outcome measure of feasibility, assessed by determining 1) the proportion of patients in the diet group achieving ketosis, 2) adherence to the diet and 3) participant-reported measures of stress, fatigue, and emotional health. For both groups, cell proliferation will be measured in a tumor biopsy obtained from the surgical specimen and compared with the pre-treatment diagnostic biopsy. Correlative studies will evaluate tumor markers of insulin/PI3K signaling before and after the intervention and between diet and control.

PO3-02-04

Comparison of OncotypeDX Recurrence Scores (RS) and MammaPrint (MP) scores, and chemotherapy indications in early-stage Estrogen Receptor positive/ HER2 negative (ER+/HER2-) breast cancer

Presenting Author(s) and Co-Author(s):

R. Singh. UTHSC, United States

W. Barlow. SWOG Statistics and Data Management Center, Seattle, Washington, United States

N. Singh. UTHSC, United States

J. Elliott. UTHSC, United States

R. Fine. West Cancer Center, Germantown, Tennessee, United States

M. Berry. West Cancer Center and Research Institute, United States

E. Cobain. University of Michigan Rogel Cancer Center, Ann Arbor, Michigan, United States

L. Pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

G. Vidal. The West Clinic, Germantown, United States, United States

Background: Both RS and MP are endorsed by ASCO and NCCN practice guidelines to estimate prognosis of early-stage ER+/HER2- breast cancers and results guide adjuvant chemotherapy treatment recommendations. Earlier studies reported around 30% discordance in risk assignments by different genomic assays, but these comparisons were complicated by the 3-way (low, intermediate, high) versus 2-way (low, high) risk assignment by RS and MP respectively. More recently, RS thresholds were re-evaluated in the context of the TAILORx and RxPONDER randomized clinical trials and RS >25 is now considered indication for adjuvant chemotherapy. MP results are now also reported as continuous scores similar to RS, and MP high risk patients can be subdivided into MP1 (high) and MP2 (ultra-high) risk groups. The goal of this analysis was to assess correlation between RS and MP scores as continuous variables and examine concordance in chemotherapy eligibility and risk category assignments.

Methods: 168 patients treated at the West Cancer Center and Research Institute had patients with both MP and RS results available for the same patient generated by Agendia as a research activity and Exact Sciences in the context of routine care. Molecular class was assigned by the MammaPrint Blueprint assay. Results and clinical information were retrieved from the medical records. Median age was 64 years (range 25-92), 77% were postmenopausal, 59% White, 37% Black and 4% other. 78% had histologic grade 1 or 2 cancers, 53%, 38%, and 8% were stage I, II, and III, respectively. 84% were invasive ductal carcinoma, 13% invasive lobular carcinoma, the rest mixed or other rare histologies. Patients were considered high-risk and chemotherapy eligible if the RS was >25 or the MP score was < 0 (i.e. any negative value), MP high-risk patients were further categorized into MP1 (MP score between 0 to -0.5699) and MP2 (MPs score -0.57 or less). Correlation between scores were assessed using Pearson correlation.

Results: There was statistically significant correlation between RS and MP scores with a Pearson correlation coefficient of -0.61, ($p < 0.0001$). 51 (30%) cancers were MP low-risk (Luminal A), and 122 (73%) were RS low risk ($RS \leq 25$). Among the MP low-risk cancers, 47 (92%) had concordant low risk assignment by RS. Based on RS, 46 (27%) patients were high-risk chemotherapy eligible and 42 of these (91%) were concordantly classified as MP high-risk.

MP high-risk cancers included 115 Luminal B and 1 Basal-like cancers, and 64% of these (n=74) had low-risk status by RS. When the MP high category was subdivided into MP 1 (n=105) and MP2 (n=11) subgroups, (35/105) 33% and (7/11) 64% of cases were RS >25, respectively. Black patients had a statistically higher mean index MP score of -0.191 compared to -0.082 for White patients (p=0.02). No statistical difference was noted by race for RS.

Conclusions: There was strong concordance (92%) between low-risk MP and low-risk RS. Similar concordance was not identified when comparing chemotherapy eligible high-risk MP (MP1 and MP2) to high-risk (>25) recurrence scores. Only 36% of chemotherapy eligible MP patients (MP1 and MP2) would be chemotherapy eligible by RS. Higher concordance (58%) for chemotherapy eligibility was seen when limited to the ultra-high (MP2) scores. By contrast most (92%) of chemotherapy eligible patients by RS (>25) were considered high risk by MP (MP1 or MP2).

Table1. RS and MP risk categories

	RS ≤25 (n=122)	RS >25 (n=46)
MP low risk (n=51)	47 (92%)	4 (8%)
MP high risk (n=117)	75 (64%)	42 (36%)
Luminal B	74	41
Basal Like	1	1
MP1	70	35
MP2	4	7

PO3-02-05

Racial and Ethnic Differences in Clinical Outcomes among North American Patients with Hormone Receptor-Positive, HER2-negative, Early Breast Cancer in the PALLAS Trial (AFT-05)

Presenting Author(s) and Co-Author(s):

O. Kantor. Brigham and Women's Hospital/Dana-Farber Cancer Institute, United States

O. Fayanju. Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, United States

A. Dueck. Alliance Statistics and Data Center, Scottsdale, Arizona, United States

M. Gnant. Medical University of Vienna, Wien, Austria

H. Burstein. Dana-Farber Cancer Institute, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

C. Isaacs. Georgetown University, United States

L. Shepherd. Canadian Cancer Trials Group, Queen's University, Kingston, Ontario, Canada, United States

O. Hahn. Alliance for Clinical Trials in Oncology Operations Office, Chicago, Illinois, United States

D. Anderson. Metro Minnesota Community Oncology Research Consortium, United States

K. Miller. Indiana University Simons Comprehensive Cancer Center, Indianapolis, IN, USA, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

T. Traina. Memorial Sloan Kettering Cancer Center, United States

Z. Dayao. University of New Mexico, United States

K. Clifton. Washington University in St Louis School of Medicine, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

A. Wolff. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States

N. Wolmark. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

D. Lu. Pfizer, United States

P. O'Brien. Mayo Clinic, United States

S. Scovil. Alliance Foundation Trials, United States

A. DeMichele. University of Pennsylvania, Philadelphia, Pennsylvania, United States

E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

Introduction: Analyses of multiple clinical trials have suggested racial and ethnic disparities in outcomes for early-stage, hormone receptor-positive and HER2-negative (HR+HER2-) breast cancer, however, none of these studies examined the use of adjuvant CDK4/6 inhibitors. The objective of this study was to explore racial and ethnic differences in toxicity, treatment duration, and disease outcomes in patients (pts) with early-stage HR+HER2- breast cancer

treated with or without adjuvant palbociclib on the PALLAS trial. **Methods:** The PALLAS phase III, global, open-label trial randomized 5,796 pts with stage II-III HR+HER2- breast cancer to 2 years of palbociclib plus ongoing provider/patient choice adjuvant endocrine therapy (ET+palbo) vs. ET alone (ET). The analytic cohort was limited to pts enrolled in North America with known self-reported race and ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian or Pacific Islander). Descriptive statistics were used to examine treatment characteristics, early discontinuation, and toxicity by race and ethnicity. Kaplan-Meier curves were used to estimate 3-year locoregional recurrence-free survival (LRFS) and invasive disease-free survival (IDFS) stratified by racial and ethnic group. Cox proportional hazards models were used identify predictors of LRFS and IDFS. **Results:** 2,547 North American pts were randomized and included in the intent-to-treat population with a median follow-up of 59.8 months; 1,996 (78.4%) identified as Non-Hispanic White (NHW), 132 (5.2%) Non-Hispanic Black (NHB), 156 (6.1%) Hispanic, and 134 (5.3%) Asian or Pacific Islander (API). Stage, performance status, type of surgery, and prior radiation were similar across racial and ethnic groups. Age, body mass index, grade, and prior chemotherapy differed by race and ethnicity ($p < 0.05$). Median age was lowest in API pts and highest in NHW pts (47.5 vs 53.0 years, respectively). Median body mass index was lowest in API and highest in NHB pts (24.4 vs 30.9). NHB pts were most likely to have high-grade disease (40.9% vs 26.9-30.5% in other groups). NHW pts were least likely to have received prior chemotherapy (81.0% vs 87.1-91.0%). Palbociclib early discontinuation was lowest in NHB pts (50.7%) and highest in Hispanic pts (65.9%), $p=0.14$. ET early discontinuation was similar across all groups ($p=0.35$). Palbociclib grade 3-4 overall toxicity was variable across groups (NHW 71.6%, NHB 79.1%, Hispanic 69.5%, API 85.2%), but this variation did not reach statistical significance ($p=0.07$). Neutropenia was highest in API pts (90.0% vs 57.3% in NHW, 58.2% in NHB, and 51.2% in Hispanic pts, $p < 0.01$). Overall 3-year LRFS was 98% (95% CI 97-98%) and IDFS was 89% (95% CI 88-90%). LRFS and IDFS were statistically similar by race and ethnicity and within each study arm (Table). No differences in LRFS or IDFS were seen by race or ethnicity in adjusted models ($p=0.95$). **Conclusions:** In this clinical trial population of HR+HER2- breast cancer patients exposed to similar treatments, no racial/ethnic differences were seen in short-term LRFS or IDFS across study arms. Differences in palbociclib toxicity by racial and ethnic group, particularly neutropenia, were seen with the highest toxicity in API patients; however, this difference did not translate into early discontinuation of palbociclib or ET.

Table: 3-year Kaplan-Meier Survival Outcomes Stratified by Race and Ethnicity

Unadjusted KM 3-year Survival	NHW N=1996		NHB N=132		Hispanic N=156		API N=134	
	Events/N	3-year estimate (95% CI)	Events/N	3-year estimate (95% CI)	Events/N	3-year estimate (95% CI)	Events/N	3-year estimate (95% CI)
LRFS overall	60/1996	98.0 (97.2-98.6)	9/132	96.6 (91.1-98.7)	6/156	95.3 (89.8-97.9)	2/134	99.1 (93.7-99.9)
ET arm	34/993	97.4 (96.0-98.3)	6/64	94.7 (84.4-98.3)	4/72	93.5 (83.7-97.5)	1/72	100.0 (100.0-100.0)
ET+palbo arm	26/1003	98.6 (97.6-99.2)	3/68	98.4 (89.4-99.8)	2/84	96.7 (87.5-99.2)	1/62	98.1 (87.4-99.7)
IDFS overall	322/1996	89.1 (87.6-90.5)	24/132	88.5 (81.3-93.0)	22/156	85.9 (78.7-90.7)	19/134	91.6 (84.9-95.4)
ET arm	166/993	88.6 (86.3-90.6)	12/64	88.1 (76.6-94.1)	9/72	89.3 (78.8-94.8)	12/72	89.0 (78.2-94.6)
ET+palbo arm	156/1003	89.6 (87.4-91.4)	12/68	88.9 (78.1-94.6)	13/84	82.7 (71.5-89.8)	7/62	94.5 (84.0-98.2)

PO3-02-06

Predictive Factors for adjuvant radiation use in patients >70 years with pT1N0 HR+ breast cancers

Presenting Author(s) and Co-Author(s):

S. Chennapragada. LSU health shreveport, United States

R. Shi. LSU Health Shreveport, Shreveport, Louisiana, United States

S. Sharma. LSU health Shreveport, United States

G. Burton. LSU Health shreveport, United States

Introduction: In 2004 the CALGB 9343 study reported that women >70 years of age with pT1N0 hormone receptor positive breast cancer received no meaningful benefit from breast irradiation following lumpectomy. Although there was a modest reduction in local recurrence, there was no improvement in rates of mastectomy for local recurrence, distant metastases, 5-year overall survival (OS) and breast cancer specific survival therefore concluding that it was reasonable to omit radiation therapy in this group. An update of the CALGB 9343 study in 2013 with 10-year follow-up came to the same conclusion. Previous analysis of the National Cancer Database (NCDB) and the SEER database showed, however, that the majority of women with these characteristics were still receiving radiation therapy. We conducted this retrospective analysis from NCDB to identify factors associated with the use of radiation in this population.

Methods: We reviewed the NCDB database and collected records of all breast cancer patients aged >70 years, who had hormone positive (HR+), pT1N0 disease between the years of 2004-2019. They were separated into radiation and non-radiation cohorts and then stratified based on ethnicity, age groups, insurance status, income quartiles, education quartiles, areas of residence, tumor size, comorbidities, diagnosis to treatment time, treatment facility type and geographic location. We then compared mortality between the two cohorts and completed a multivariate analysis to determine the demographic and clinical factors associated with the likelihood of receiving radiation. SAS was used for analysis and p-value < 0.05 was deemed as statistically significant. **Results:** 147,611 patients met the criteria of age > 70, pT1N0, HR+ treated with surgical lumpectomy. The majority of them were white, aged 70-75y, had Medicare, were in higher education and income quartiles and lived in metro areas (Table 1). 57.9% of the total study population received radiation. The possibility of receiving radiation decreased as age increased beyond 75 years. Uninsured patients, Medicare patients, those with comorbidities, higher educational status as well as those who lived 20+ miles away from their treatment facility and treated at urban centers in central or south Atlantic areas were less likely to receive radiation. Those treated at Comprehensive community cancer programs and middle Atlantic areas were more likely to receive radiation. The possibility of radiation also progressively increased with tumor size. However, there were no differences observed when stratified by race, income status or chemotherapy use (Table 2). We also noted a small overall survival advantage for the radiation cohort (HR 0.77, p-value < 0.0001) which could be explained by the fact that patients without comorbidities were more likely to receive radiation. **Discussion:** Our results provide a real-world estimate of radiation use in pT1N0 HR+ early-stage breast cancer in women > 70 years. The major predictors of radiation use included younger age, low comorbidities, insurance and institutions providing care. Lack of awareness about recent updates or concern about local recurrence could be contributing to the continued use of radiation. Although there are minor differences when stratified by demographics, it is concerning that the overall trend of radiation use has not significantly decreased over time. Since there is currently no data to support the routine use of radiation in this patient group as evidenced by randomized

controlled trials, it is prudent to avoid radiation. This approach would help reduce healthcare costs, patient inconvenience and associated morbidity.

Table 1

Characteristic	No Radiation	Radiation
Age group		
1. 70-74y	23353 (33.2%)	42971 (64.8%)
2. 75-84y	18780 (42.5%)	25375 (57.5%)
3. 80-84y	11509 (63.3%)	10076 (46.7%)
4. 85y	4956 (67.94%)	2315 (32%)
Race		
1. White	54238 (41.8%)	75620 (58.2%)
2. Black	4206 (45.8%)	4981 (54.2%)
3. Asian	108 (43.3%)	136 (56.7%)
Insurance status		
1. Medicare	51649 (42.53%)	69709 (57.5%)
2. Medicaid	577 (45.54%)	690 (54.46%)
3. Private	5887 (37.45%)	9332 (62.5%)
4. Uninsured	158 (45.5%)	186 (54.5%)
Diagnosis to treatment time		
1. 0-29 days	30796 (60.02%)	46153 (59.08%)
2. 30+ days	27518 (64.43%)	39398 (55.55%)
Median income quartile		
1. <\$30,000	5612 (48.33%)	5999 (51.67%)
2. \$30,000-\$34,999	9156 (46.45%)	10990 (54.55%)
3. \$35,000-\$45,999	14893 (43.34%)	18470 (56.66%)
4. >\$46,000	21210 (58.94%)	33164 (61.06%)
High school education quartiles		
1. >29%	7004 (48.72%)	7372 (51.28%)
2. 20-28.9%	10780 (43.93%)	13754 (60.05%)
3. 14-19.9%	12514 (41.92%)	17391 (58.08%)
4. <14%	20528 (49.68%)	33202 (60.32%)
Residence		
1. Metro	46580 (60.97%)	67101 (59.03%)
2. Urban	10607 (46.88%)	12019 (53.12%)
Distance from treatment facility		
1. 0-19 miles	39945 (60.67%)	58282 (59.33%)
2. 20+ miles	12176 (47.56%)	13423 (52.44%)
High Charleston comorbidity score		
1. No	44195 (60.33%)	65883 (59.67%)
2. Yes	14353 (48.32%)	15354 (51.68%)
Tumor size		
1. pT1A	6951 (45.47%)	8037 (54.53%)
2. pT1B	10097 (60.33%)	28260 (59.67%)
3. pT1C	32509 (62.43%)	44960 (57.57%)
Facility type		
1. Community Cancer Program	4980 (43.47%)	6477 (56.53%)
2. Comprehensive Community Cancer Program	25961 (60.92%)	37488 (59.08%)
3. Academic/Research Program	14559 (43.76%)	18711 (56.24%)
4. Integrated Network Cancer Program	13048 (41.94%)	18061 (58.06%)
Facility location		
1. New England	3464 (37.43%)	5793 (62.57%)
2. Central	24,833 (44.22%)	31317 (55.78%)
3. Atlantic	21614 (61.28%)	30,794 (68.72%)
4. Mountain	2557 (42.34%)	3482 (57.66%)
5. Pacific	6082 (39.22%)	9424 (60.78%)

Baseline characteristics

Table 2

Primary variable	Sub-variables	aOR with 95% CI	P-value
Private insurance	1. Medicaid	0.78 (0.68-0.89)	0.2026
	2. Medicare	0.90 (0.87-0.94)	0.04
	3. Uninsured	0.71 (0.55-0.91)	0.07
Age group 70-74y	1. 75-79y	0.71 (0.69-0.73)	<0.0001
	2. 80-84y	0.45 (0.43-0.46)	<0.0001
	3. 85+	0.24 (0.22-0.25)	<0.0001
White	1. Asian	1.074 (0.79-1.44)	0.53
	2. Black	0.955 (0.90-1.06)	0.30
No comorbidities	Presence of comorbidities	0.73 (0.71-0.76)	<0.0001
Median income quartile of >\$46,000	1. \$30,000-\$34,999	0.92 (0.88-0.96)	0.36
	2. \$35,000-\$45,999	0.91 (0.88-0.94)	0.06
	3. < \$30,000	0.90 (0.85-0.96)	0.09
High school education quartile of <14%	1. 14-19.9%	0.99 (0.95-1.02)	0.036
	2. 20-28.9%	1.003 (0.96-1.046)	0.004
	3. >29%	0.88(0.83-0.93)	<0.0001
Distance of 0-19 miles from treatment facility	20+ miles	0.82 (0.79-0.85)	<0.0001
Urban areas	Metro areas	0.94 (0.90-0.98)	0.005
Academic programs	1. Community cancer program	1.12 (1.06-1.18)	0.50
	2. Comprehensive community cancer program	1.21 (1.17-1.25)	<0.0001
	3. Integrated network cancer program	1.12 (1.08-1.17)	0.37
New England	1. East north central	0.93 (0.88-0.99)	<0.0001
	2. East South central	0.63 (0.59-0.68)	<0.0001
	3. West north central	0.83 (0.78-0.89)	0.03
	4. West south central	0.76 (0.71-0.82)	<0.0001
	5. Middle Atlantic	1.20 (1.13-1.27)	<0.0001
	6. South Atlantic	0.79 (0.74-0.83)	<0.0001
	7. Mountain	0.83 (0.77-0.91)	0.13
	8. Pacific	1.004 (0.94-1.06)	<0.0001
Days to treatment initiation of 30+ days	0-29 days	1.19 (1.16-1.22)	<0.0001
Tumor stage of pT1A	1. pT1B	1.28 (1.23-1.34)	<0.0001
	2. pT1C	1.22 (1.17-1.27)	<0.0001
Chemotherapy	No chemotherapy	0.96 (0.93-1.005)	0.09

Factors affecting radiation use

PO3-02-07

HER2-low status in inflammatory breast cancer (IBC) is associated with hormone receptors positivity but not with pathological response to neoadjuvant chemotherapy or overall survival

Presenting Author(s) and Co-Author(s):

A. de Nonneville. Institut Paoli-Calmettes 3C, France

P. FINETTI. Predictive Oncology Laboratory, Inserm Umr1068, Aix Marseille University, France

L. Boudin. Predictive Oncology Team, Inserm, CNRS, Institut Paoli-Calmettes, Cancer Research Center of Marseille, Aix-Marseille University, Marseille, France, United States

L. Usclade. Predictive Oncology Team, Inserm, CNRS, Institut Paoli-Calmettes, Cancer Research Center of Marseille, Aix-Marseille University, Marseille, France, United States

P. Viens. Aix-Marseille University (France), United States

F. VIRET. Institut Paoli-Calmettes 3C, France

E. Mamessier. Predictive Oncology Team, Inserm, CNRS, Institut Paoli-Calmettes, Cancer Research Center of Marseille, Aix-Marseille University, Marseille, France, United States

A. Gonçalves. Institut Paoli-Calmettes, France

F. BERTUCCI. Predictive Oncology Laboratory, Inserm Umr1068, Aix Marseille University, France

Background:

Half of HER2-negative breast cancers (BC) show HER2-low expression. The strong efficacy of recent anti-HER2 antibody-drug conjugates (ADC) in HER2-low tumors has risen the interest of HER2-low as a proper BC subtype. However, HER2-low non-inflammatory breast cancer (non-IBC) appears to have only marginal clinicopathological differences compared to HER2-0. Little is known about HER2-low clinical significance in IBC.

Methods:

Data from patients diagnosed with HER2-negative IBC between 1990 and 2021 were collected from the Institut Paoli-Calmettes European Comprehensive Cancer Center database. Two tumor groups were defined (HER2-low and HER2-0). HER2-low tumors were defined by HER2 IHC score of 1+ or 2+ with negative FISH, and HER2-0 by IHC score of 0+. Hormone Receptor (HR) status was determined according to the French guidelines (oestrogen and/or progesterone receptors by IHC with a 10% threshold for HR-positivity). Clinicopathological characteristics, pCR (defined as [ypT0/ypTis] and [pN0sn or ypN0]), and OS rates were compared between the two tumor groups.

Results:

The individual data of 256 IBC patients were analyzed. Thirty-seven percent of tumors were HER2-low and 63% were HER2-0. Among patients with stage III (n = 226) and stage IV (n = 30) IBC, 35% and 53% had HER2-low tumors, respectively. HR positivity, age over 50 years, SBR grade, and menopausal status were associated with HER2-low in univariate analysis, but only HR positivity remained significant in a binary logistic regression (OR: 1.95 [1.06-3.58]; p=3.15E-02). In stage III patients, the pCR rate after neoadjuvant chemotherapy was similar in HER2-low (24%) and HER2-0 (29%) patients (p=0.550). No difference was observed by analyzing pCR by HR status. In univariate analysis, overall survival was affected by the clinical axillary lymph node invasion the presence of metastasis, the pathological type and menopausal

status, but not by HER2 status.

Conclusion:

In IBC, HER2-low is associated with HR positivity but has no effect on pathological response to chemotherapy and overall survival in our retrospective cohort, consistently with data available in non-IBC patients. Of 256 IBC patients, 37% were HER2-low. These results may be useful to design future clinical trials testing anti-HER2 ADCs in IBC.

PO3-02-08

Risk factors and a new predictive nomogram for predicting the Non-sentinel Lymph Node Metastasis in 708 early-stage Breast Cancer Patients with Positive Sentinel Nodes in China

Presenting Author(s) and Co-Author(s):

Z. Song. Department of Breast Center, The Fourth Hospital Of Hebei Medical University, Shijiazhuang, Hebei, China (People's Republic)

X. Zhao. Department of Breast Center, Fourth Hospital of Hebei Medical University, United States

L. Yang. Department of Breast Center, Fourth Hospital of Hebei Medical University, United States

Objective: The management of positive sentinel lymph node biopsies (SLNB) in patients with early-stage breast cancer remains a matter of controversy. Some studies have shown that not all breast cancer patients with positive sentinel lymph nodes (SLNs) benefit from further axillary lymph node dissection (ALND). Our study aims to analyse the risk factors and construct a new nomogram to predict non-sentinel lymph node (NSLN) metastasis in Chinese early-stage breast cancer patients with positive sentinel lymph nodes. **Methods:** The clinical data of 708 patients with early-stage breast cancer who attended The Fourth Hospital of Hebei Medical University for surgical treatment from January 2016 to December 2021 was retrospectively analyzed. All of them were female breast cancer patients with positive sentinel lymph nodes and underwent ALND. The patients were divided into modeling group and validation group according to the time of treatment. The patients in the modeling group were divided into a positive NSLN group and a negative NSLN group. The characteristics: age, maximum tumor diameter, the number of positive SLNs, proportion of positive SLNs, vessel carcinoma embolus, nerve invasion, status of ER, PR, HER-2 and Ki-67 were included in the analysis. And the independent risk factors of NSLN metastasis were screened by univariate (chi-square test) and multivariate (logistic regression) analysis. A nomogram model was established according to the screened independent risk factors, and the model was externally validated by the validation group. The ROC curve was plotted to calculate the area under the curve (AUC) and evaluate the predictive power of the nomogram model. A calibration curve and decision curve analysis (DCA) were used to evaluate the performance of the model. **Results:** Among the 708 patients, (modeling group n=410, validation group n=298), the average age, average number of positive SLNs, and NSLN positive rate were 50.9 ± 11.1 , 1.55 ± 0.87 and 25.71%. The univariate analysis revealed statistically significant differences in the number of positive SLNs ($P < 0.001$), the proportion of positive SLNs ($P < 0.001$), vessel carcinoma embolus ($P=0.001$), nerve invasion ($P=0.012$), and ER status ($P=0.029$) in the NSLN-positive group compared with the negative group. The multifactorial logistic regression analysis revealed that the number of positive SLN ($P=0.002$; OR: 1.700; 95% CI: 1.219-2.370), the proportion of positive SLN ($P=0.048$; OR: 3.214; 95% CI: 1.001-10.490), vessel carcinoma embolus ($P=0.010$; OR: 2.076; 95% CI: 1.194-3.612), nerve invasion ($P=0.024$; OR: 2.119; 95% CI: 1.221-3.678), and ER status ($P=0.045$; OR: 2.978; 95% CI: 1.022-8.675) were independent risk factors for NSLN positivity. Furthermore, the nomogram was built using these 5 factors and validated on 298 patients in the validation group. The AUC was 0.728 ($P < 0.001$; 95%CI: 0.673-0.784) in the modeling group and 0.810 ($P < 0.001$; 95%CI: 0.735-0.886) in the validation group. The calibration curves of the modeling and validation groups were close to the ideal curve, and DCA also showed that the model could be applied in clinical practice. **Conclusion:** For early-stage breast cancer with positive SLNs, these factors as the positive number of SLNs > 2 , the ratio of positive SLNs $> 50\%$, vessel carcinoma embolus,

nerve invasion and ER-positive could predict NSLN metastasis well. The proposed nomogram appears to accurately estimate the likelihood of positive NSLNs and may greatly help the surgeon to decide intraoperatively whether to perform further ALND and avoid non-essential ALND as well as postoperative complications.

PO3-02-09

Breast cancer in women under the age of 40 years. A south Wales UK reflection on incidence, tumour biology and outcomes over 10 years.

Presenting Author(s) and Co-Author(s):

S. Khan. Prince Phillip Hospital, Llanelli SA148QF, UK, Llanelli, Wales, United Kingdom

S. Khawaja. Prince Phillip Hospital Llanelli, UK, Llanelli, Wales, United Kingdom

Y. Sharaiha. Prince Philip Hospital / Hywel Dda Health Board, Wales, United Kingdom

A. Munir. Prince Philip Hospital / Hywel Dda Health Board, Wales, United Kingdom

A. Huws. Prince Philip Hospital, Llanelli, United Kingdom

Introduction: The incidence of breast cancer in the under 40-year-old age group is approximately 7% (Anders et al., 2009). Studies suggest that the management of Breast cancer in adolescent and young women is more challenging, with this age group under-represented in clinical trials. We investigated the management and outcomes of a cohort of 98 patients seen between 2013 and 2023 in the Hywel Dda NHS University Health Board, Wales, UK.

Methods: A retrospective review was performed. Demographic, surgical and outcome data for patients under the age of 40 years was collated and analysed.

Results: The cohort size was 98, representing 2.45% of the breast cancer population treated in the Health Board during this timeframe. The age of the cohort ranged from 23 years to 40 years, 12 out of 98 (12.24%) were under 30 years. Mean age was 35.28 years.

Unfortunately, 8.16% (8/98) of the cohort died between 12 months to 96 months. Two patients were lost to follow up. Tumour biology results confirmed that most of the cohort had invasive ductal carcinoma (IDC), with 13.27% Grade 1, 37.76% Grade 2 and 40.82% Grade 3. There were 4 (4.08%) invasive lobular carcinomas (ILC) in the cohort, 2 Grade 2 and 2 Grade 3. The remaining tumour groups were, 1 case of DCIS (Grade-2 intermediate grade), Grade-1 mucinous carcinoma, 1 Grade-1 ductal-lobular breast cancer and 1 medullary carcinoma. 10.20% of the cohort had triple negative cancers (ER, PR, Her-2 negative) and 10.20% were ER, PR, HER2 positive [Triple positive]. 40.82% metastatic axillary lymph nodes involvement on histology either on presentation or following sentinel node biopsy.

Operative details confirmed that the 51.02% (50/98) of the cohort underwent mastectomy. 10 out of those 50 patients underwent contralateral risk reducing mastectomy. 46 patients had breast conservation surgery. One patient is awaiting surgery, the other has been diagnosed with metastatic breast cancer at diagnosis. Patients received both neoadjuvant and adjuvant chemotherapy depending on initial assessment and MDT discussion [ACP, FEC, Taxane and platinum-based chemotherapy, Anti Her-2]. NAC was provided for all HER-2+ patients. Endocrine treatment and ovarian function suppression, and adjuvant Radiotherapy was also given. Some patients had a complete pathological response to NAC; however, some did not respond well. In addition, 10.20% of the cohort underwent bilateral salpingo-oophorectomy during their treatment and follow up.

Genetic assessment confirmed that 3/98 (3.06%) of the cohort were BRCA2 positive, one BRCA1 carrier, 2 patients were BRCA negative, two have been referred for genetics assessment and two still awaiting consultation with genetics. In one patient somatic mutation

was found in PTEN, BIRC3, HRAS, TP53, PMS, (5 gene panel). In one patient, panel was reassuring. PALB-2, TP53 was also reassuring in one patient. One patient who passed away at the age of 34 did not have any alteration in 5 gene panel.

Three patients developed other malignancies during the 10-year period: 1 uterine, 1 cervix, 1 papillary thyroid cancer.

6/98 (6.12%) developed metastatic disease and one developed a local recurrence. One patient developed metastasis while pregnant, and by contrast one patient gave birth to a baby after stopping her endocrine treatment. One patient who passed away had no response to neoadjuvant chemotherapy (NAC).

Discussion: The results from the cohort confirm that the incidence of TNBC and triple positive cancers is like that found in the general breast cancer population (10-15%).

Our engagement with the genetics team has increased since the initial 2013 cohort. There is now an established system for referrals for young women with breast cancer. It is probably not surprising that other primary invasive cancers were found, whilst on follow up.

PO3-02-11

Impact of Tumor Volume on Oncologic Outcomes in Patients with T1 Breast Cancer: A Retrospective Analysis

Presenting Author(s) and Co-Author(s):

H. Koh. Seoul National University Bundang Hospital, United States

E. Kim. Seoul National University Bundang Hospital, Seongnam-si, Kyonggi-do, Republic of Korea

H. Shin. Seoul National University Bundang Hospital, United States

Backgrounds: Measuring the extent of tumor cell accretion in the primary organ typically involves assessing the longest diameter, an important component of the widely employed TNM staging system. The largest tumor diameter is considered indicative of the risk of cancer metastasis and the likelihood of distant recurrences. However, relying solely on the unidimensional diameter to determine the degree of cancer cell accretion can be inadequate since each tumor has a unique three-dimensional shape, thus leading to different tumor volumes.

Purpose: The aim of this study was to investigate the impact of tumor volume on oncologic outcomes in patients with T1-2 breast cancer.

Method: We retrospectively reviewed the medical records of 1,018 patients diagnosed with invasive breast cancer who underwent breast-conserving surgery at Seoul National University Bundang Hospital from 2010 to 2015. Patients with multiple tumors, positive margins leading to mastectomy, or those who received neoadjuvant chemotherapy were excluded. Tumor volume was defined as the product of the length of the three axes to simplify the calculation. Recurrence-free survival (RFS) was estimated by the Kaplan-Meier analysis.

Result: The median value for tumor volume was 7.502 cm³. Out of 1,018 patients, 124 patients exhibited tumor volumes greater than the median value. Higher tumor volume was associated with pathologic T stage ($P < 0.001$), pathologic N stage ($P = 0.004$), histologic grade ($P < 0.001$), and luminal B subtype ($P = 0.008$). In multivariable logistic regression analyses for recurrence, higher tumor volume (OR 3.532, 95% CI 1.708-7.303, $P = 0.001$), CEA elevation (OR 6.129, 95% CI 1.497-25.092, $P = 0.012$), pN stage (OR 2.038, 95% CI 1.005-4.132, $P = 0.048$), and luminal B subtype (OR 2.407, 95% CI 1.060-5.470, $P = 0.036$) were shown to be predictive factors for recurrence, while completion of radiation therapy (OR 0.142, 95% CI 0.050-0.402, $P < 0.001$) and completion of hormone therapy (OR 0.200, 95% CI 0.047-0.849, $P = 0.029$) were identified as protective factors. The 5-year RFS was significantly lower in patients with higher tumor volume compared to those with lower volume (97.4% vs. 91.9%; $p < 0.001$). In multivariable Cox regression analysis, tumor volume (HR 3.056, 95% CI 1.572-5.940, $P = 0.001$), CEA elevation (HR 4.934, 95% CI 1.437-16.935, $P = 0.011$), luminal B subtype (HR 2.336, 95% CI 1.076-5.073, $P = 0.032$), completion of RT (HR 0.131, 95% CI 0.053-0.325, $P < 0.001$), and completion of HTx (HR 0.199, 95% CI 0.060-0.655, $P = 0.008$) were identified as independent prognostic factors for RFS.

Conclusion: In the current study, we showed higher tumor volume results in poorer oncologic outcomes in patients with T1-2 breast cancer. Therefore, the T stage based on tumor volume, which includes all three-dimensional measurements, can better predict the prognosis in breast

cancer patients than the traditional T stage that is solely dependent on the unidimensional longest tumor diameter.

PO3-02-12

Dalpiciclib combination with letrozole as neoadjuvant therapy for HR-positive HER2-negative breast cancer: a single-arm, prospective exploratory clinical study

Presenting Author(s) and Co-Author(s):

J. Li. The First Affiliated Hospital of Zhengzhou University, United States
Y. Gu. The First Affiliated Hospital of Zhengzhou University, United States
C. Du. The First Affiliated Hospital of Zhengzhou University, United States
J. Zhang. The First Affiliated Hospital of Zhengzhou University, United States
Y. Zhang. The First Affiliated Hospital of Zhengzhou University, United States
L. Zhang. The First Affiliated Hospital of Zhengzhou University, United States
N. Wang. The First Affiliated Hospital of Zhengzhou University, United States
L. Li. The First Affiliated Hospital of Zhengzhou University, United States
F. Wang. The First Affiliated Hospital of Zhengzhou University, United States
P. Lv. Department of Breast surgery, The First Affiliated Hospital of Zhengzhou University
Zhengzhou, United States
H. Zong. The First Affiliated Hospital of Zhengzhou University, China (People's Republic)
X. Pei. The First Affiliated Hospital of Zhengzhou University, United States
B. Xue. The First Affiliated Hospital of Zhengzhou University, United States
Y. Wang. The First Affiliated Hospital of Zhengzhou University, United States
D. Gao. The First Affiliated Hospital of Zhengzhou University, United States

Background:

CDK4/6 inhibitors effectively block tumor cells from progressing from the G1 phase to the S phase, thereby interrupting the cell cycle progression and inhibiting tumor cell proliferation. Dalpiciclib is a novel CDK4/6 inhibitor developed independently in China, which has been approved for use in combination with fulvestrant for the treatment of HR-positive/HER2-negative recurrent or metastatic breast cancer in patients who have experienced disease progression after prior endocrine therapy, or in combination with aromatase inhibitors as initial treatment for HR-positive/HER2-negative locally advanced or metastatic breast cancer patients. This study aims to explore the efficacy and safety of dalpiciclib in combination with letrozole as neoadjuvant therapy for HR-positive, HER2-negative breast cancer.

Methods:

This is a single-arm, open-label study that enrolled female breast cancer patients with early or locally advanced HR-positive, HER2-negative tumors and an ECOG performance status of 0 to 1. After enrollment, patients first received 4 cycles of dalpiciclib (150mg po qd, d1-21, q4w) in combination with letrozole as neoadjuvant therapy. Breast MRI was performed every 2 cycles, and treatment response was evaluated according to the RECIST 1.1 criteria. If patients achieved a confirmed complete response (CR) or partial response (PR) after 4 cycles, they would continue to receive an additional 4 cycles of dalpiciclib in combination with letrozole treatment. If the treatment response was stable disease (SD) or disease progression (PD), the investigator might modify other treatment regimens based on the individual circumstances of the subjects. The primary endpoint was residual cancer burden (RCB 0/I), and the secondary study endpoints were objective response rate (ORR), complete cell cycle arrest (CCCA, C1D15 Ki67 \leq 2.7%) rate and safety. This study is registered at the Chinese Clinical Trial Registry

Centre (registration No. ChiCTR2200057104).

Results:

From April 2022 to June 2023, a total of 38 patients were screened and enrolled in the study. All patients had ER \geq 50%, and 84% (32/38) had Ki67 \geq 88%. Among the 21 patients who completed the assessment after 4 cycles, the overall response rate (ORR) was 81% (17/21). Additionally, among the 22 patients who underwent C1D15 biopsy and Ki67 analysis, 55% (12/22) had C1D15 Ki67 \leq 2.7%. After completing 8 cycles of neoadjuvant treatment with the combination of dalpiciclib and letrozole, 12 patients underwent surgery. The postoperative RCB scores were as follows: 1 patient had RCB (0-I), and 11 patients had RCB (II-III). The most common adverse event was decreased neutrophil count (25/38 [66%]). Among the 38 patients, 16 (42%) experienced grade 3 or worse treatment-related adverse events. There were no occurrences of grade 4 or worse adverse events.

Conclusions:

The combination of dalpiciclib and letrozole has shown efficacy in downstaging and shrinking tumors in patients with early or locally advanced HR-positive/HER2-negative breast cancer. Patients who exhibit a positive response in the assessment after 4 cycles may consider it as a viable option for chemo-free neoadjuvant treatment.

PO3-02-13

Breast Cancer in Very Young Adult Women At or Under the Age of 35 Years: Characteristics and Outcomes

Presenting Author(s) and Co-Author(s):

A. Abusanad. Faculty of medicine, King Abdulaziz university, United States

R. Ajabnoor. Faculty of medicine, King Abdulaziz university, United States

A. Al-Awadhi. department of Medical Oncology, Tawam hospital - SEHA, United States

O. abualkhair. Suliman Alhabib hospital, United States

Background: Breast cancer (BC) is the most common malignancy among women in Saudi Arabia. Noticeably, it shows a higher incidence in younger age groups than what is reported from Western countries. Age 35 years and less is an applied cut-off age for clinically defining BC in very young women (BCVY). This study describes characteristics, survival and risk of death associated factors in this rare subset of patients. Methods: A retrospective cohort study included females > 18 and < 35 years with histologically confirmed primary non-metastatic breast cancer from an academic hospital in Jeddah, Saudi Arabia between the years 2009-2019. Demographic data, tumor clinicopathological features, and outcomes were obtained. Survival and potential associated factors were examined. A p-value of less than 0.05 was regarded as statistically significant. Results: 204 female patients with a confirmed breast cancer diagnosis were included. The mean age at diagnosis was 31.43 ± 2.94 years. Fifty-three percent of the patients had a left-sided tumor with the majority being IDC (92%) and one-third with positive axillary lymph nodes (N+) and multifocal disease in 17%. One-quarter of the tumors showed LVI, 45% revealed associated DCIS and 26% showed tumor necrosis on histopathology examination. The presence of tumor-infiltrating lymphocytes (TILs) was reported in 23% of TNBC cases. Tubular differentiation score 3 was reported in 79.4%, nuclear pleomorphism score 3 in 79% and mitosis activity score 3 in 19% while the most reported overall grade was II in 48.5% followed by grade III in 34%. HER2-positive in 33.8 %, HR-positive in 34.3 %, TNBC in 24% and unknown in 8% of the patients. Thirty percent had a distant recurrence and 15% were deceased. The mean survival time was 4.61 years with a maximum of 6.54 years and a minimum of 3.67 years. Table 1 shows the multivariate logistic regression analysis of factors influencing the risk of death in very young patients with breast cancer. Conclusions: The current study describes the clinicopathological characteristic, survival and related factors of breast cancer in very young patients < 35 years, which is considered an uncommon presentation. Large, high-grade tumors and a high frequency of HER2 and TNBC were observed in BCVY patients. Involvement of the regional lymph nodes and the development of distant recurrence were associated significantly with an increased risk of death. The presence or absence of TILs, LVI and tumor necrosis on histopathological examination did not influence the risk of recurrence or death in this cohort.

Table 1. The multivariate logistic regression analysis of factors influencing the risk of death in very young patients with breast cancer.

Variables	Total No. (%)	No. Death 174 (18.9%)	Death 30 (1.5%)	Odds Ratio (CI 95%)	p-value
Tumor size (mm)	4.29 ± 3.17	3.85 ± 2.86	6.98 ± 3.73	1.15 (0.95-1.39)	0.146
Molecular Subtype				0.99 (0.11-1.81)	0.291
HER2	69 (34)	61 (35)	8 (27)		
Luminal	70 (34.5)	61 (35)	9 (30)		
TN	49 (24)	36 (21)	13 (43.3)		
NA	16 (8)	16 (9)	0 (0.0)		
LN				6.17 (1.12-33.77)	0.036
No	145 (71)	132 (80)	13 (43.3)		
Yes	59 (29)	42 (24)	17 (57)		
Distant recurrence				15.1 (2.49-29.45)	0.002
No	143 (70)	139 (80)	4 (13.3)		
Yes	61 (30)	35 (20)	26 (87)		

PO3-02-14

The Safety of Breast Reconstruction: The Impact of Breast Reconstruction Surgery on Postoperative Adjuvant Therapy for Breast Cancer

Presenting Author(s) and Co-Author(s):

N. Nagura. St Luke's International Hospital, United States

A. Ogiya. Cancer Institute Hospital, Japanese Foundation for Cancer Research, United States

H. Nogi. The Jikei University School of Medicine, United States

K. Narui. Yokohama City University Medical Center, United States

H. Mori. Tokyo Medical and Dental University, United States

S. Sasada. Hiroshima University, United States

M. Ishitobi. Mie University Hospital, United States

N. Kondo. Nagoya City University Graduate School of Medical Sciences, United States

C. Yamauchi. Shiga General Hospital, United States

A. Shimo. St. Marianna University School of Medicine, United States

M. Saiga. Okayama University Hospital, United States

H. Seki. Kyorin University School of Medicine, United States

T. Sakurai. Sakurai Breast Clinic, United States

T. Shien. Okayama University Hospital, Okayama-city, Okayama, United States

Background: Postoperative adjuvant therapy is very important in treating breast cancer, and increasing numbers of patients are undergoing immediate breast reconstruction (IBR) at the same time as breast cancer surgery. However, the impact of breast reconstruction surgery on adjuvant therapy is controversial. In this multicenter cohort study led by the Japanese Breast Cancer Society, we examined the impact of reconstructive surgery on postoperative adjuvant therapy in breast cancer patients who underwent IBR. **Methods:** We examined the association between adjuvant therapy and complications of reconstructive surgery in 4726 patients with primary breast cancer who underwent IBR during the period from January 1, 2008 to December 31, 2016. Statistical analysis employed the χ^2 test. **Results:** Of the 995 patients who received adjuvant chemotherapy, the median time from the date of surgery to the start of chemotherapy was 51.0 days, with 63 patients (6.2%) starting more than 90 days after surgery. Eighty-four IBR complications required surgery (8.4%), including infections and tissue expander (TE) removal. Of the 63 patients for whom chemotherapy was initiated 90 days or more after surgery, 10 patients (15.9%) had complications requiring surgery, significantly more than the 74 patients (7.9%) in the < 90 days group ($P = 0.028$). Post-mastectomy radiation therapy (PMRT) was performed after breast cancer surgery in 359 cases: 69 cases received autologous tissue irradiation, 46 TE irradiation, 241 silicone breast implant (SBI) irradiation, and 3 artificial material removal before irradiation. 5 cases given autologous tissue irradiation and 26 receiving artificial material irradiation (22 of whom the artificial material was removed) required surgery within 1 year after the cancer surgery due to complications of IBR. There was no significant difference in the frequency of complications requiring surgery between autologous tissue irradiation and artificial material irradiation ($P=0.632$). There were 33 complications (9.2%) requiring surgery in the irradiated group, significantly more than the 129 cases (3.0%) in the non-irradiated group ($P < 0.001$). **Conclusion:** Adjuvant chemotherapy was generally not delayed, but complications requiring surgery related to IBR were more frequent in those with delay beyond 90 days, suggesting that postoperative complications from breast reconstruction

may have influenced the delay in initiating chemotherapy. Therefore, in cases for whom postoperative chemotherapy is anticipated, complications from breast reconstruction may have impacted outcomes, making preoperative risk assessment even more important. There was no difference in the frequency of reconstructive complication surgery according to whether autologous tissue irradiation or artificial material irradiation had been used, but further investigation is needed.

PO3-03-01

Impact of Environmental Temperature on Clinical Outcomes and Tumor Microenvironment of Early-Stage Breast Cancer

Presenting Author(s) and Co-Author(s):

- A. Roy. Roswell Park Comprehensive Cancer Center, Amherst, New York, United States
- S. Rosario. Roswell Park Comprehensive Cancer Center, United States
- A. George. Roswell Park Comprehensive Cancer Center, United States
- Q. Hu. Roswell Park Comprehensive Cancer Center, United States
- B. Czerniecki. H. Lee Moffitt Cancer Center, United States
- J. Carpten. University of Southern California, United States
- V. Borges. University of Colorado Anschutz Medical Center, United States
- B. Schneider. Indiana University School of Medicine, United States
- J. Kolesar. University of Kentucky, United States
- C. Moskaluk. University of Virginia, United States
- C. Shriver. Uniformed Services University, Bethesda, Maryland, United States
- C. Matsen. University of Utah, Huntsman Cancer Institute, United States
- S. Ganesan. Rutgers Cancer Institute of New Jersey, United States
- S. Phadke. University of Iowa, Iowa city, Iowa, United States
- W. Razaq. Oklahoma university of health Sciences, Oklahoma City, Oklahoma, United States
- K. Attwood. Roswell Park Comprehensive Cancer Center, United States
- S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

Background

Preclinical evidence using mouse model suggests that thermal/cold stress increases tumor growth by modulating the tumor microenvironment (TME); however, the clinical relevance of temperature on breast cancer (BC) outcomes is unknown. Studies show that residing in cold regions is associated with higher incidence of BC. We aim to study the impact of environmental temperature on the pathological complete response (pCR) and survival of early-stage BC patients (pts).

Methodology

A multi-institutional study was conducted within the Oncology Research Information Exchange Network (ORIEN). We analyzed the clinical and genomic data for early-stage BC pts from 12 centers in different environment zones (5 warm and 7 cold) (based on average annual regional temperature obtained from National Centers for Environmental Information). Cox regression was used to measure the association of climate and overall/relapse-free survival (OS/RFS) after adjusting for age, race, body mass index, grade, stage, treatments, comorbidities, and subtype. Raw feature counts were normalized, and differential expression analysis was carried out using DESeq2, while adjusting for all of the covariates. Differential expression rank order was used for subsequent gene set enrichment analysis (GSEA), performed using the cluster profile package in R. Gene sets queried included the Hallmark, Canonical pathways, and GO Biological Processes Ontology collections available through the Molecular Signatures Database (MSigDB).

Results

Out of the 1,304 early-stage BC pts, 271 pts received neoadjuvant chemotherapy (NAC) (186 warm, 85 cold). Higher clinical T- and N-stages were observed in pts from warm compared to cold regions ($p < 0.001$). Pts residing in cold regions had more comorbidities (57.6% vs 4.8%, $p < 0.001$). Pts in warm regions had higher pCR, though not statistically significant (8% vs 2.5%, $p = 0.1$). In the overall population, the OS (univariate (UV) HR= 0.48, 95% CI 0.27-0.64, $p < 0.001$; adjusted HR (aHR)= 0.56, 95% CI 0.32 - 0.96, $p = 0.03$) and RFS (UV HR= 0.51, 95% CI 0.38 - 0.68, $p < 0.001$; aHR= 0.52, 95% CI 0.36 - 0.75, $p = 0.0005$) were higher in pts from warm compared to cold regions (Table 1). Among the patient subgroup treated with NAC, the OS (aHR= 0.35, $p = 0.02$) and RFS (aHR= 0.49, $p = 0.02$) of pts from warmer regions was also higher than cold regions. RNA sequencing was performed on 826 tumors (443 warm, 383 cold) using pre-treatment samples. Naïve B-cells (mean: 0.09 vs 0.08, $p=0.004$), CD4 naïve T cells (0.03 vs 0.02, $p= 0.0008$), CD4+ memory T cells (0.03 vs 0.02, $p= 0.04$), gamma-delta T-cells (0.007 vs 0.004, $p= 0.006$) were higher in pts residing in cold compared to warm regions while CD8 T cells, T regulatory cells, macrophages, dendritic cells, natural killer cells were similar in both regions. Macrophage signaling, cholesterol metabolism and the pathway for negative regulation of cell migration in angiogenesis were upregulated in pts living in warm compared to cold regions.

Conclusion

Early-stage BC pts living in cold have worse OS and RFS compared to warm regions. Our study is the first to report significant differences in the TME among these pts. However, it is important to acknowledge that the limited availability of comprehensive data regarding patients' relocation to different environmental temperature zones during treatments, and individual temperature preferences may be considered a potential limitation of our study. To ensure the validity and robustness of these intriguing findings, larger multi-center studies should be conducted, encompassing detailed information on the duration of exposure to both warm and cold weather conditions.

Table 1: OS and RFS of patients living in warm vs cold environments

Regions (n)	5-yr OS (95% CI)	Median OS (months) (95% CI)	p-value	5-yr RFS (95% CI)	Median RFS (95% CI)	p-value
Cold (782)	83 (76-86) %	157.7 (116.6-NR)	<0.001	69 (62-76) %	108.4 (88.9-147.8)	<0.001
Warm (522)	95 (92-97) %	214.7 (205.3-NR)		83 (79-87) %	250.4 (129.9-250.4)	

PO3-03-02

Effect of Surgery on Breast Cancer-Specific Mortality in Elderly Patients with Hormone Receptor-Positive, HER2-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Yatsuyanagi. Hiraka General Hospital, Japan

T. Shimada. Hiraka General Hospital, Japan

Y. Takeishi. Hiraka General Hospital, Japan

Y. Matsuzaka. Hiraka General Hospital, Japan

C. ohsawa. Hiraka General Hospital, Japan

Background: The number of elderly patients with breast cancer has been increasing in Japan. Although standard treatment including surgery is desirable if the expected life expectancy is sufficient, not all elderly patients with breast cancer are eligible for surgery due to frailty and comorbidities. Endocrine therapy (ET) alone is an alternative option if surgery is not considered adequate in patients with hormone receptor-positive breast cancer. We evaluated whether ET alone was associated with inferior overall and breast cancer-specific survival compared to standard treatment including surgery in elderly patients.

Methods: This study included all patients aged 75 years and over who were diagnosed with non-metastatic primary invasive hormone receptor-positive, HER2-negative breast cancer and treated at Hiraka General Hospital from July 2006 to March 2022. Patients were divided as those who received ET alone (ET alone group) and those who received surgery with other therapies (Surgery group). Survival status as on March 31, 2023 and cause of death were determined. Overall survival and breast cancer-specific survival were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate analysis and multivariate Cox proportional hazards regression model including age, Eastern Cooperative Oncology Group performance status (PS) score, clinical stage, and treatment were used to identify survival-associated factors. Propensity score matching was used to reduce the effect of selection bias on treatment type during survival comparison of the groups.

Results: The study cohort comprised 128 patients, including 33 and 95 patients in the ET alone group and Surgery group, respectively. The median ages were 84.6 and 80.4 years in the ET alone group and Surgery group, respectively ($p < 0.05$). Ten patients (30%) in the ET alone group had poor PS (3 or 4), and no patient in the Surgery group had poor PS ($p < 0.01$). Also, 24.2%, 54.5%, and 21.2% of the patients in the ET alone group and 48.4%, 43.2%, and 8.4% of the patients in the Surgery group had clinical stage I, II, and III disease at diagnosis, respectively ($p < 0.05$). Survival status was confirmed in all patients, and the cause of death was confirmed in 52 of the 53 patients who died (98%) during the study period, including 24 and 29 patients in the ET alone group and Surgery group, respectively. Breast cancer was the cause of death in 3 patients (13%) in the ET alone group and 5 patients (17%) in the Surgery group. By univariate analysis, overall survival was significantly better in the Surgery group than in the ET alone group (median, 12.5 vs. 4.1 years; $p < 0.0001$). Similarly, breast cancer-specific survival was better in the Surgery group than in the ET alone group ($p < 0.05$). By multivariate Cox proportional hazards regression analysis, age was associated with shorter overall survival time (hazard ratio [HR] 1.07, 95% confidence interval [CI] 1.00–1.15; $p = 0.04$) and surgery was associated with longer overall survival (HR 0.24, 95% CI 0.12–0.47; $p < 0.001$). Breast cancer-specific survival was associated with age (HR 1.18, 95% CI 1.03–1.36; $p = 0.02$) and clinical stage (HR 8.89, 95% CI 1.05–75.5; $p < 0.05$) but not with treatment (HR 0.66, 95% CI 0.73–5.85; $p = 0.71$). After propensity score matching, overall survival was significantly better in the Surgery group than in the ET alone group (HR 0.26, 95% CI 0.09–0.73; $p = 0.01$) whereas

breast cancer-specific survival was not significantly different between the two groups (HR 0.82, 95% CI 0.08–8.27; $p = 0.86$).

Conclusion: Even in elderly patients, surgery should be considered if sufficient life expectancy is expected. However, most of the deaths were not related to breast cancer in the present study cohort. Therefore, for elderly patients without sufficient life expectancy, endocrine therapy alone would be an appropriate option.

PO3-03-03

Prospective non-randomized study to compare accuracy of clinical examination under anesthesia, axillary ultrasound and histo-pathological evaluation for axillary nodal staging in women with clinically N0 early breast cancer

Presenting Author(s) and Co-Author(s):

V. Parmar. Tata Memorial Centre, United States
Z. Sanghvi. Tata Memorial Hospital, Mumbai, India
S. Joshi. Tata Memorial Hospital, United States
N. Nair. Tata Memorial Hospital, United States
P. Popat. Tata Memorial Centre, India
S. Kembhavi. Mackay Base Hospital Australia, Australia
S. KN. Tata Memorial Hospital, Mumbai, India
S. Mynalli. Tata Memorial Hospital, Mumbai, India
P. Thakkar. Tata Memorial Hospital, Mumbai, United States
G. Chitkara. Tata Memorial Hospital, Mumbai, Maharashtra, India
S. Desai. Tata Memorial Centre, United States
T. Shet. Tata Memorial Centre, United States
R. Badwe. Tata Memorial Centre, Mumbai, India

Introduction: Accurate assessment of axillary lymph nodes is crucial in the management of early breast cancer (EBC), especially in clinically node negative (cN0) axilla to avoid extensive axillary surgery. Clinical examination alone underestimates nodal disease in nearly 30% women with cN0 axilla. The current study compares, in cN0 axilla, the benefit of axillary ultrasonography (USG) and clinical axillary examination under anesthesia (EUA) to predict involvement of axillary lymph nodes. The gold standard in these patients however remains pathological evaluation after sentinel node biopsy/low axillary sampling (SNB/LAS) and a complete axillary lymph node dissection (ALND) if node positive. **Methodology:** Prospectively, 500 women with cN0 EBC were enrolled from Aug 2015 to April 2023 in a study approved by Institutional Ethics Committee. After informed consenting, a preoperative axillary USG was carried out in addition to standard breast imaging to determine number of axillary node(s) and its architecture. The USG assessment was labeled as suspicious or not and the result was blinded to the surgeons. A USG-guided FNAC was not performed as it would then be difficult to blind the surgeon and pathologist preoperatively. During surgery, an initial axillary EUA was performed before starting and any suspicious node was documented. This was followed by axillary staging by standard dual tracer SNB/LAS. A complete axillary dissection was done (level 1-3) if any node was positive on frozen section evaluation or final histopathology. Axillary node histopathology was the gold standard for comparison of effectiveness of clinical exam, USG, EUA, and SNB/LAS for prediction of axilla. Standard diagnostic tests such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were used. **Results:** Thirty-six patients were excluded in the final analysis (disease progression, chemotherapy first, or had a surgery elsewhere). Of the eligible 464 cN0 patients, 129 were detected to have axillary metastases (27.8%) in final histopathology. The 2 interventions namely USG axilla, EUA were compared to final axillary nodal histopathology. Axillary USG reported suspicious/indeterminate node(s) in 129 (27.8%) patients. USG had a low sensitivity of 46.5% and a low PPV of 46.5% to identify a positive node. However, the specificity and NPV

both were 79.4%. Axillary USG was 70.2% accurate in predicting axillary nodal involvement. EUA also had sensitivity of 60% and low PPV of 14.8%. However, the specificity of EUA was 73.4%, NPV of 95.9%; higher than that of USG. EUA was 72.4% accurate. SNB/LAS had the sensitivity of 93.3%, specificity 79.2%, NPV 82.9%, PPV 91.6% and accuracy rate 89.2% in predicting a positive axilla. **Conclusions:** While the fallacy of clinical exam remains at 27.8%, both USG alone (without FNAC) and EUA failed in predicting a positive axillary node. EUA fared better at predicting a negative axilla. USG guided FNAC would perhaps improve the sensitivity of USG, however additional investigations are difficult in resource constraint and high-volume center, especially, when surgical interventions like SNB or LAS remain standard of care.

Table 1

Intervention N=64	Sensitivity %	Positive predictive value %	Specificity %	Negative predictive value %	Accuracy %
Axillary ultrasound	46.5	46.5	79.4	79.4	70.2
Examination under anesthesia	60	14.8	73.4	95.9	72.4
Sentinel node biopsy/low axillary sampling	93.3	91.6	79.2	82.9	89.2

PO3-03-04

Metaplastic breast cancer: a single center retrospective study

Presenting Author(s) and Co-Author(s):

M. AUPRIH. Division of Medical Oncology, Institute of Of Oncology Ljubljana, Ljubljana, Slovenia

G. Gasljevic. Department of Pathology, Institute of Oncology Ljubljana, United States

E. Setina. Medical Faculty Ljubljana, Ljubljana, Slovenia

A. Zizek. Division of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia

S. Borstnar. Institute of Oncology, Ljubljana, Slovenia

Background: Metaplastic breast cancer (MBC) is a rare malignancy that accounts for up to 1% of all primary invasive breast carcinomas (BC). It is histologically heterogeneous, usually presents with a triple-negative phenotype and comprises low-grade and high-grade (HG) variants. HG variants have a higher risk of recurrence and a shorter disease-free and overall survival compared to other BC subtypes. Our research aimed to estimate the prevalence of HG-MBC among the Slovenian population and determine the characteristics of patients (pts) and tumours and the disease outcome.

Patients and methods: Our retrospective study included pts diagnosed with HG-MBC at the Institute of Oncology Ljubljana from January 1983 until January 2021. Clinicopathologic characteristics such as tumour subtype, size and grade, nodal status, hormonal receptors (HR) and HER-2 status, lymphovascular invasion (LVI), tumour-infiltrating lymphocytes (TIL) and presence of germline BRCA mutation status were determined. The survival analyses were performed using the Kaplan-Meier method. The Cox proportional hazard model examined the association between risk factors and survival outcomes.

Results: We evaluated 113 HG-MBC pts among a total of 27700 pts diagnosed with BC over 38 years (0.41%). The median age was 61.6 years (range 29.7 -93.9), majority of pts were postmenopausal (78.69%). The median follow-up was 15.5 years. The most common tumour subtype in our cohort was mixed MBC (53 cases, 46.9%), followed by MBC with mesenchymal differentiation (24 cases, 21.2%), squamous cell carcinoma (20 cases, 17.7%) and spindle cell carcinoma (16 cases, 14.2%). From the 113 evaluated pts, we obtained data about the stage in 105 pts, pathological tumour size in 100 pts, number of positive lymph nodes in 99 pts, HR status in 95 pts, HER2 status in 76 pts, grade in 97 pts, LVI in 85 pts, MIB-1 in 41 pts and TIL in 77 pts.

At diagnosis, 17/105 pts (16.2%) had stage I disease, 59/105 pts (56.2%) stage II, 25/105 pts (23.8%) stage III and 4/105 pts (3.8%) stage IV. Most tumours were poorly differentiated (90/97, 92.2%) without LVI (60/85, 70.6%). Only 6/95 (6.3%) pts had positive HR, 7/76 (9.2%) pts had positive HER-2 status and 8/77(10.4%) pts intensive TIL. Overall, 13 pts were tested for BRCA germline mutation, among which only 1 (7.7%) had BRCA1 mutation. Modified radical mastectomy was the most frequent type of surgery (63.5%); 49.5% of the patients received radiotherapy. In total, 66/113 pts received CT: from 1983 to 2000, 16/36 (44.4%), and after 2000 50/77 (74.9%). In the first period, most pts received CMF (14/16; 87.5%) and anthracyclines and taxanes (27/50; 54%) in the second period.

The disease progressed at 37 pts. At 19 pts, new malignancies were found. 55 pts died, 37 of them because of BC. Five- and 10-year disease-free survival (DFS) was 61.7% and 54.1%,

while 5-and 10-year overall survival (OS) was 67.1 % and 56.7%, respectively. However, DFS and OS did not differ between the pre-2000 and post-2000 periods. The best outcome was found in pts with squamous cell carcinoma (5- and 10-year DFS 83.5% and 77.0% and 5-and 10- year OS 89.4 % and 83.0%).

A subtype of MBC (squamous cell vs other) was the only predictive factor in multivariate analysis for both DFS (HR 0.21; 95% CI 0.05-0.92; $p = 0.038$ and OS (HR 0.27; 95%CI 0.09-0.78; $p = 0.016$), no association was seen between survival and tumour size, nodal status, stage, HR and HER2 status, grade, LVI and TILs.

Visceral organs were the most common localization of distant metastases (21/37, 56.8%). Metastases in CNS occurred in 9/37 (24.3%) pts. Median OS after the first progression was only 0.9 years.

Conclusions: The proportion of HG-MBC in our cohort of pts is 0.41%. Disease outcomes are poor; the 10-year OS of pts with early HG-MBC is only 56.6% and has not improved during the last decades. Squamous cell differentiation predicts a better outcome and is the only independent predictive factor of DFS and OS among HG-MBC pts.

PO3-03-05

Clinical outcomes in early-stage TNBC according to HER2-low status

Presenting Author(s) and Co-Author(s):

A. Garrido-Castro. Dana-Farber Cancer Institute, and Harvard Medical School, Brookline, Massachusetts, United States

D. Brandes Zakon. University of Texas MD Anderson Cancer Center, United States

Q. Jin. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

M. Grimm. Ohio State University Comprehensive Cancer Center, United States

A. Singareeka Raghavendra. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Hughes. Dana Farber Cancer Institute, United States

M. Cherian. The Ohio State University Comprehensive Cancer Center, Dublin, Ohio, United States

J. Vincuilla. Dana-Farber Cancer Institute, United States

T. Parker. DFCl, Massachusetts, United States

P. Tarantino. Breast Oncology Program, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

E. Mittendorf. Dana Farber Cancer Institute, Boston, Massachusetts, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

V. Valero. Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Bellaire, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

B. Ramaswamy. The Ohio State University Comprehensive Cancer Center, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

C. Barcenas. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background: Clinical outcomes according to HER2 immunohistochemistry (IHC) in patients with early-stage HER2-negative breast cancer have differed across studies. For early-stage TNBC (eTNBC), less representation of this subtype in cohorts studied to date has limited interpretation of results. We sought to evaluate outcomes according to HER2 IHC in a multi-institutional cohort of patients (pts) with eTNBC who received neoadjuvant therapy (NAT). Methods: Pts diagnosed with stage I-III TNBC (including HR-low; ER and PR < 10%) who received NAT and underwent surgery between 1/1/16-6/30/19 were identified across three institutional prospective databases. HER2 was defined as low (1+ or 2+/ISH non-amplified) or HER2-0 according to

local testing at diagnosis. Pathological complete response (pCR) was defined as no residual invasive disease in breast and axilla. Multivariable logistic regression was used to compare pCR rates (HER2-low vs HER2-0) adjusting for age at diagnosis, race, anatomic clinical stage, germline BRCA1/2 (gBRCA), histology, HR status and receipt of anthracycline and taxane NAT. Recurrence-free (RFS), distant recurrence-free (DRFS), and overall survival (OS) were estimated using the Kaplan-Meier method. Multivariable Cox proportional hazards model was used to estimate adjusted hazard ratios. Results: A total of 978 pts were identified of which 388 (39.7%) had HER2-low and 590 (60.3%) had HER2-0 tumors at diagnosis. Median age was 50.3 (range: 21.0-83.4) yrs. 174 (17.8%) pts had HR-low tumors. 142 (14.5%) pts had a known gBRCA mutation. 790 pts (80.8%) received anthracycline- and taxane NAT. No significant differences were observed in age, race, gBRCA, histology, HR status (low vs negative), clinical tumor size, or type of NAT between HER2-low and HER2-0 groups. Clinical nodal positivity was higher in HER2-low (55.2%) vs HER2-0 (46.6%), $p=0.011$. No significant difference in pCR was observed between HER2-low (32.0%) and HER2-0 (32.7%) groups, adjusted $p=0.928$. Among pts with residual disease (RD) post-NAT with HER2 IHC also available in the RD sample, 244/363 (67.2%) had concordant HER2 status. 70/225 (31.1%) of HER2-0 tumors at diagnosis had IHC expression post-NAT (66 HER2-low, 4 HER2-positive); 48/138 (34.8%) of HER2-low tumors at diagnosis were HER2-0 post-NAT. At a median follow-up of 3.1 yrs, RFS did not significantly differ between HER2-low vs HER2-0 pts with pCR ($p=0.368$) or in those with RD post-NAT ($p=0.573$). Similarly, DRFS did not differ according to HER2 category for pts with pCR ($p=0.509$) or RD ($p=0.812$), nor did OS for pts with pCR ($p=0.514$) or RD ($p=0.285$) (Table 1). Conclusion: In a large cohort of pts with eTNBC treated with NAT, HER2-low status was not associated with pCR or survival after adjusting for clinical factors. High rate of discordance in HER2 IHC between diagnostic and RD post-NAT was observed, highlighting the importance of repeat IHC testing in serial samples given the development of antibody drug conjugates for HER2-low breast cancer.

Table 1. RFS, DRFS and OS by HER2 expression

Table 1. RFS, DRFS and OS by HER2 expression

3-year survival	pCR				Non-pCR			
	HER2-low (95% CI) (N=124)	HER2-0 (95% CI) (N=193)	Adjusted Hazard Ratio (HER2-low vs HER2-0)	p value	HER2-low (95% CI) (N=264)	HER2-0 (95% CI) (N=397)	Adjusted Hazard Ratio (HER2-low vs HER2-0)	p value
RFS	90.6% (85.1-96.5%)	88.4% (83.6-93.4%)	0.71 (0.34-1.49)	0.368	48.8% (42.6-55.9%)	55.1% (50.2-60.4%)	1.07 (0.85-1.35)	0.573
DRFS	91.6% (86.4-97.1%)	90.3% (85.7-95.0%)	0.77 (0.35-1.69)	0.509	53.0% (46.8-60.0%)	58.8% (53.9-64.1%)	1.03 (0.81-1.32)	0.812
OS	94.9% (90.9-99.0%)	93.7% (89.9-97.6%)	0.75 (0.32-1.78)	0.514	64.9% (58.7-71.8%)	66.6% (61.7-71.9%)	0.86 (0.65-1.14)	0.285

PO3-03-06

Real-world efficacy and safety of neoadjuvant pembrolizumab plus chemotherapy in Brazilian patients with early-stage triple-negative breast cancer.

Presenting Author(s) and Co-Author(s):

- i. souza. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil
- A. Comini. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil
- I. BORGES. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil
- F. Balint. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil
- L. Martins. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil
- D. Sousa. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil
- S. Sanches. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil
- M. Cesca. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil
- V. Cordeiro de Lima. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil
- M. Tavares. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil

Background: Early-stage triple-negative breast cancer (TNBC) is associated with high risk of early recurrence and disease-specific mortality. Studies suggest a sustained clinical benefit in patients with TNBC who have a pathological complete response (PCR) after neoadjuvant chemotherapy (NACT). In TNBC, the combination of immunotherapy based on immune checkpoint inhibitors (anti-PD-1/PD-L1) combined with chemotherapy has been shown to be effective both in the advanced and early. In the early-stage setting, the addition of pembrolizumab to platinum-containing NACT significantly increased pathological complete response (pCR). Methods: We performed a retrospective observational cohort study of patients diagnosed with TNBC, stage II-III, who received NACT with chemotherapy based on paclitaxel and carboplatin (TC) followed by doxorubicin plus cyclophosphamide (AC) associated with pembrolizumab, treated from June 2022 to July 2023, at AC Camargo Cancer Center, São Paulo, Brazil. Objectives: To investigate the real-world pCR rate and safety profile of early-stage TNBC treated with neoadjuvant chemotherapy (weekly TC, ddAC/AC) associated with pembrolizumab and to describe the clinical-pathological characteristics of this population. Results: Eighty patients received neoadjuvant pembrolizumab plus chemotherapy. Around 50.6% of patients were premenopausal, with a median age of 47 years old at diagnosis. About 18% carried a germline mutation in the BRCA1 (50%). Regarding the pathological characteristics of the tumor, 90.9% were invasive ductal carcinoma (IDC), 80% had histological grade (HG) III, and average Tumor Infiltrating Lymphocytes (TILs) was 18%. In 94.8% of cases, Ki67 was expressed in more 20% of tumor cells. The expression of HER2 was low in 14%, and 5% were ER-low. Regarding the clinical stage of the primary tumor, (64.9%) cT2, (18%) cT3, (10%) cT1c, and (2.5%) cT4. Regarding regional lymph node staging, 48%, 33.7%, 10.3%, and 6.4% were classified as cN0, cN1, cN2a, and cN, respectively. Clinical stage was IIA (42.8%), IIB (24.6%), IIIA (14.2%), IIIB (9%), and IIIC (5%). Regarding chemotherapy, 57.1% received dose dense AC, 54% percent had chemotherapy-related toxicity, 35.7% had neutropenic fever, 32.4% required hospitalization, and 31% used antibiotics. 31% received eight cycles of neoadjuvant pembrolizumab and 53.2% of patients completed all NACT, among these patients, 61% had complete .A cutoff date, about 61% of patients have undergone surgery, and 66.6% achieved a complete pathological response (ypT0ypN0). Patients that received eight cycles of neoadjuvant pembrolizumab had a higher chance of pathological complete response rate (61% vs. 45.2%) p=0.073. Immune-related toxicities (IRT) were observed in 16.8% patients, being the

most common endocrinologic and cutaneous, being G3 or higher in 46%. About 15.5% used corticosteroids. Fifty percent had already started or completed adjuvant therapy, from which 66.6% received only adjuvant pembrolizumab, 28% had adjuvant pembrolizumab plus capecitabine, 1.2% received adjuvant capecitabine, and 1.2% had adjuvant olaparib. Eight percent of our patients have already completed nine cycles of adjuvant pembrolizumab, 12.7% did not receive adjuvant pembrolizumab due to prior toxicity. In our cohort, we observed greater intercurrents related to ddAC versus conventional AC 61.4% versus 52.4%, $p=0.492$, therefore, it did not impact whether or not the chemotherapy was completed. Conclusion: Our cohort is composed mostly of pre-menopausal with stage IIA tumors. Most patients received ddAC, Fifty-four percent had chemotherapy-related toxicity. We observed a high rate of pCR (61%) on our patients have already undergone surgery, 66.6% achieved a complete pathological response. Of those who received 8 cycles of neoadjuvant pembrolizumab had a higher chance of pathological complete response rate (61% vs. 45.2%) $p=0.073$

PO3-03-07

Patterns of Chemotherapy Utilization among Elderly Patients with Early-Stage Triple-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

C. Malinowski. The University of Texas MD Anderson Cancer Center, Houston, TX, USA, United States

X. Lei. The University of Texas MD Anderson Cancer Center, Houston, TX, USA, United States

S. Giordano. Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, USA, United States

M. Chavez. UT MD Anderson Cancer Center, Houston, Texas, United States

Background: Patterns of adjuvant and neoadjuvant chemotherapy use among patients with breast cancer have changed over time. Historically, adjuvant chemotherapy has been the standard treatment approach for patients with triple-negative breast cancer after surgical resection, aiming to eliminate any remaining cancer cells and reduce the risk of recurrence. Advancements in treatment strategies, research findings, and clinical guidelines have contributed to shifts in cancer care approaches, with an increase in the use of neoadjuvant chemotherapy. In this study, we explore chemotherapy utilization in a large cohort of elderly patients diagnosed with early-stage triple-negative breast cancer (TNBC).

Methods: Data were obtained from the SEER- and Texas Cancer Registry (TCR)-linked Medicare databases. We identified female patients aged 66 years or older, diagnosed with early-stage (localized or regional disease) TNBC between 2010 and 2017 with claims until 2019. We identified the use of chemotherapy using HCPCS codes from outpatient and physician's carrier claims. We used descriptive statistics and analyzed overall chemotherapy utilization and time trends of neoadjuvant versus adjuvant use via the Cochran-Armitage trend test, and evaluated factors associated with chemotherapy use via logistic regression models. This study adhered to the STROBE reporting guidelines for cohort studies.

Results: Among 8,848 patients with localized or regional stage TNBC (median age 74) a total of 5,159 (58%) were treated with chemotherapy. The rate of chemotherapy utilization increased yearly from 52% in 2010 to 66% in 2017 ($p < 0.001$). After multivariable adjustment, any chemotherapy use was associated with recent year of diagnosis (OR=1.77; 95%CI 1.54-2.04), regional stage compared to localized (OR=3.78; 95%CI 3.34-4.27), and Northeastern region compared to South (OR=1.2; 95%CI 1.06-1.37). Conversely, decreased chemotherapy use was associated with age ≥ 76 (OR=0.24; 95%CI 0.2-0.27), being single (OR=0.76; 95%CI 0.67-0.86), and higher comorbidity score (OR=0.69; 95%CI 0.61-0.78). Among chemotherapy-treated patients, 3,808 (73.8%) received it in the adjuvant setting, 722 (14.0%) received it in the neoadjuvant setting, and 629 (12.2%) received chemotherapy both preoperatively and postoperatively. Among those who were treated with any chemotherapy, the percentage of patients treated with neoadjuvant chemotherapy increased from 15.2% in 2010 to 37.4% in 2017 ($p < 0.001$). Among patients treated with chemotherapy, neoadjuvant chemotherapy use was associated with recent year of diagnosis (OR=3.38; 95%CI 2.77-4.12), regional stage (OR=3.28; 95%CI 2.86-3.77), and inversely associated with older age (OR=0.77; 95%CI 0.64-0.94), non-White, non-Hispanic, non-Black race or ethnicity (OR=0.64 95%CI 0.45-0.94), non-metro area (OR=0.61; 95%CI 0.5-0.74), and Northeastern region (OR=0.66; 95%CI 0.56-0.78).

Conclusion: Our study highlights the significant changes in patterns of adjuvant and

neoadjuvant chemotherapy use among elderly patients with early-stage TNBC. We observed an increasing trend in chemotherapy utilization, with a notable shift from adjuvant to neoadjuvant treatment. This transition reflects the evolving landscape of cancer care and the adoption of more personalized approaches to treatment, with increased utilization of neoadjuvant chemotherapy offering opportunities for better risk assessments and tailored treatment strategies.

PO3-03-08

Use of adjuvant Capecitabine after neoadjuvant chemotherapy: A Cohort Study among Elderly Patients with Early-Stage Triple-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Sullivan. The University of Texas MD Anderson Cancer Center, Houston, TX, USA, United States

X. Lei. The University of Texas MD Anderson Cancer Center, Houston, TX, USA, United States

C. Malinowski. The University of Texas MD Anderson Cancer Center, Houston, TX, USA, United States

S. Giordano. Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, USA, United States

M. Chavez. UT MD Anderson Cancer Center, Houston, Texas, United States

Background: The use of capecitabine in the adjuvant setting in patients with residual disease after neoadjuvant chemotherapy has been incorporated into practice based on the results of the CREATE-X trial. We evaluate utilization patterns of adjuvant capecitabine use, its association with outcomes, and subsequent hospitalizations and emergency room (ER) visits among elderly patients with early-stage triple-negative breast cancer (TNBC).

Methods: We identified patients aged ≥ 66 , diagnosed with early-stage TNBC between 2010 and 2017 in the SEER and Texas Cancer Registry (TCR)-linked Medicare databases. All patients were treated with neoadjuvant chemotherapy for localized or regional-stage disease. All patients had continuous enrollment in Medicare Parts A & B without a Health Maintenance Organization enrollment 12 months before cancer diagnosis and 12 months after cancer diagnosis. Chemotherapy administration was identified using HCPCS codes from outpatient and physician's carrier claims. We analyzed the patterns of capecitabine use, its association with survival outcomes, and the frequency of ER visits and hospitalizations during treatment (between the first capecitabine claim and 30 days after the last claim for capecitabine). Descriptive statistics were used. Primary analyses included logistic regression, Kaplan-Meier estimates, and Cox regression models with propensity score adjustments. This study adhered to the STROBE guidelines for cohort studies.

Results: 1,239 patients with localized or regional TNBC treated with neoadjuvant chemotherapy were included (median 72 years). Of them, 96 (7.7%) were prescribed adjuvant capecitabine. Treatment with capecitabine was associated with recent year of diagnosis, regional disease, and residing in non-metropolitan areas. Specifically, the use of capecitabine increased from 1% in 2010 to 10% in 2016 and 21% in 2017. The median duration of capecitabine treatment was 4 cycles. In multivariable logistic regression analyses, older age was associated with decreased odds of receiving ≥ 4 cycles of capecitabine (OR=0.25; 95% CI: 0.11–0.60; $p=0.002$). Among capecitabine users, 3-year OS was 46% and 78% for patients who received 1-3 and ≥ 4 cycles of capecitabine, respectively ($p < 0.001$). The 3-year estimate of BCSS was 43% and 85% respectively ($p < 0.001$). After multivariable adjustment for comorbidity score, stage, and propensity score, receiving ≥ 4 cycles of capecitabine was associated with decreased risk of death (HR=0.29; 95%CI 0.13–0.63, $p=0.002$) and breast cancer-specific death (HR=0.15; 95%CI: 0.05–0.51, $p=0.002$) compared to receiving 1-3 cycles. Twenty-seven (28%) patients had ER/hospitalization during capecitabine treatment; median time from initial capecitabine claim to ER/hospitalization was 24 days (IQ 13-39). The median number of capecitabine cycles was 3 (IQR 2-5) and 5 (IQR 3-8) for those with and without ER/hospitalization ($p=0.02$). The

most common diagnosis codes associated with ER/hospitalization included pleural effusion, GI symptoms, pneumonia, and acute kidney failure. A higher comorbidity score at diagnosis was associated with an increased risk of ER/hospitalization (HR=2.76; 95%CI 1.05-7.28, p=0.04).

Conclusion: We demonstrate an increasing trend in capecitabine utilization among elderly patients with early-stage TNBC. Although the limited sample size hindered a conclusive analysis, more cycles of capecitabine were associated with improved survival outcomes. Notably, a significant proportion of patients undergoing capecitabine treatment experienced ER/hospitalizations. These findings contribute valuable information on the risks and benefits of capecitabine treatment, aiding evidence-based decision-making to prevent serious complications.

PO3-03-09

Clinical Significance of Grade in Triple Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Malik. Schulich School of Medicine & Dentistry, Western University, Windsor, Ontario, Canada

N. Ramanan. Schulich School of Medicine & Dentistry, Western University, Windsor, Ontario, Canada

S. Upneja. Schulich School of Medicine & Dentistry, University of Windsor, Ontario, Canada

M. Brackstone. London Health Sciences Centre, London, Ontario, Canada

L. Porter. University of Windsor, United States

B. Fifield. University of Windsor, Windsor Cancer Research Group, Windsor, Ontario, Canada

C. Hamm. Windsor Regional Hospital, United States

Triple negative breast cancer (TNBC) is a heterogeneous cancer type that lacks receptors for estrogen (ER), progesterone (PR), and human epidermal growth factor receptor-2 proteins (HER-2). An important prognostic factor for breast cancer patients is the tumour grade, which is the degree of cell proliferation or differentiation of the tumour cells from normal cells. In our initial study involving 305 TNBC patients from 2004-2017 at Windsor Regional Hospital Cancer Centre, we found a statistically significant difference between grade 2 and grade 3 patients, with grade 2 predicting significantly inferior progression-free and overall survival. In our initial study, the overall survival rates for grade 1, 2, and 3 tumours were 90.12%, 64.4%, and 77.2% respectively ($p = 0.019$) with relapse rates of 70%, 55.6%, and 75.6% respectively ($p = 0.04$). Our current study is an attempt to validate these initial findings by expanding our data set to include data from the London Health Sciences Centre. A literature review on TNBC and grade was conducted, followed by a retrospective chart review for 305 TNBC patients from the Windsor Regional Hospital and 515 TNBC patients from the London Health Sciences Centre. The parameters for data collection included patient demographics, tumour demographics, therapies, and patient outcomes. We calculated all patient stages using both American Joint Committee on Cancer 7th edition (AJCC7) and the updated AJCC8 staging systems. Initial review of the data supports our earlier findings with a relapse rate of 12.5% in patients with grade 3 tumours and 17% in patients with grade 1 and grade 2 tumours. The completed data set will be analyzed and presented at the conference. Validating our previous findings of significantly inferior patient outcomes for grade 2 compared to grade 3 patients may alter the staging system used for TNBC patients.

PO3-03-10

Race and neoadjuvant treatment of triple negative breast cancer (TNBC) in the US community oncology setting

Presenting Author(s) and Co-Author(s):

P. Raska. Ontada, Cleveland Heights, Ohio, United States

J. Dye. Ontada, Irving, Texas, United States

N. Robert. Ontada, United States

A. Kidd. US Oncology Network, United States

M. Danso. Virginia Oncology Associates, Norfolk and Virginia Beach, VA, USA, United States

Background: TNBC is an aggressive subtype of breast cancer with limited targeted therapies. Black women have twice the incidence of TNBC compared to White women and within TNBC, Black women have worse outcomes than White women. Differences in both tumor biology of TNBC and social determinants of health (SDOH) play a role in observed disparities. The focus of this study is to evaluate SDOH factors associated to differences in the use of neoadjuvant chemotherapy (NC) in Black and White women in the US community oncology setting.

Methods: This study was a retrospective, observational, cross-sectional design and used iKnowMedSM EHR data from the The US Oncology Network. Patients diagnosed with TNBC between 03/31/2017 and 09/30/2021 with stages II-III disease of tumor size ≥ 2 cm (T2 or higher) were included. The index date was date of TNBC diagnosis and records were assessed from 6 months pre- to 6 months post-diagnosis for NC initiation. Univariable and multivariable logistic regression was conducted to evaluate impact of self-reported race on NC. Age, stage, BMI, insurance, area deprivation index (ADI), size of practice represented by physician count and geographical region, were studied in their mediating and moderating effects¹ on the relationship between race and NC treatment.

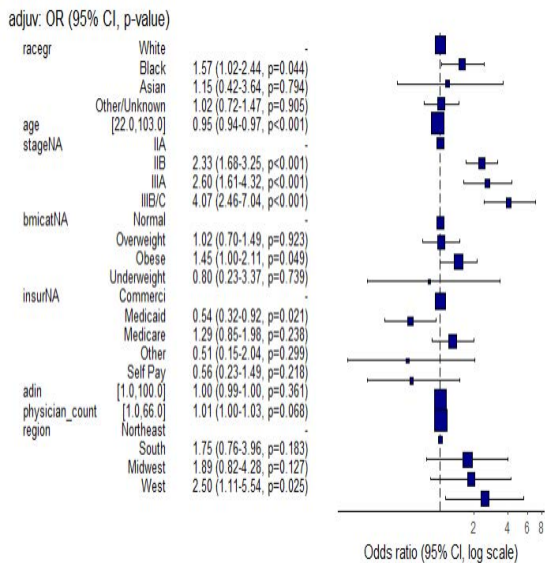
Results: Of the 3321 patients with TNBC identified in this study, 1969 self-reported white and 494 self-reported black (80% and 20% respectively). In multivariable regression accounting for all variables, Black race (OR = 1.57, 95% CI [1.02 , 2.44], $p=0.04$), younger age, more advanced stage, obesity, non-Medicaid insurance, and West region, were all found to be positively associated with use of NC. Higher physician count was nominally associated, ($p = 0.07$). ADI was not found to be associated to NC. Mediator and moderator analysis for the relationship between race and NC showed that only stage and ADI variable inclusion in the model are required for the positive association between black race and NC. This is driven by a significant interaction between ADI and stage ($p = 0.027$) which differed for Black and White women. Mainly, for Black women ADI is positively associated to NC treatment in stage IIA, but negatively associated in all other stages (interaction term, $p = 0.033$). For White women, ADI is negatively associated to NC treatment in all stages. Only Black women with stage IIA tend to be treated more instead of less with NC in areas of greater deprivation (greater ADI). BMI presents nominal interactions with both race and stage, where obesity was more strongly associated with NC treatment in Black women ($p = 0.088$) and in stage IIA ($p = 0.086$). All other variables presented association to NC treatment without mediation or moderation of the race effect and without detectable differences across stages.

Conclusions: Black women with stage IIA appear to be a special subgroup of TNBC patients for whom treatment with NC increases with ADI. Increased ADI generally results in less standard

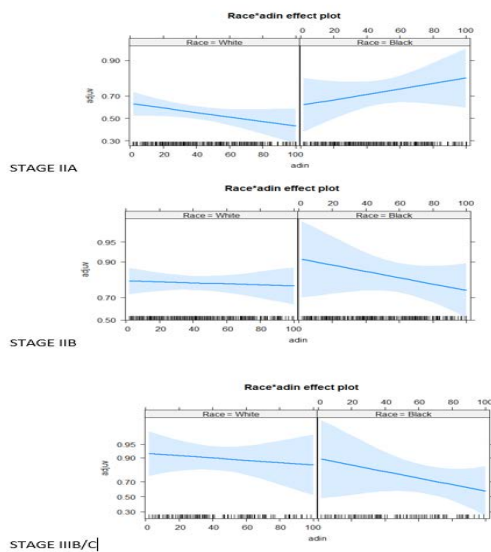
of care treatment; this is observed in this study for White women overall and for Black women in stages > IIA. Black women in areas of greater deprivation with stage IIA disease, may be perceived to be presenting with more aggressive disease and thus offered NC preferentially. This result lends support to the hypothesis that young black women present with a distinct, more aggressive subtype of TNBC in the early stages. Mediator and moderator analyses are important tools in elucidating the relationships between factors underlying racial disparities in both care and outcomes.

1. Hayes AF, Rockwood NJ. Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. Behav Res Ther. 2017 Nov;98:39-57.

Odds ratios for multivariable analysis

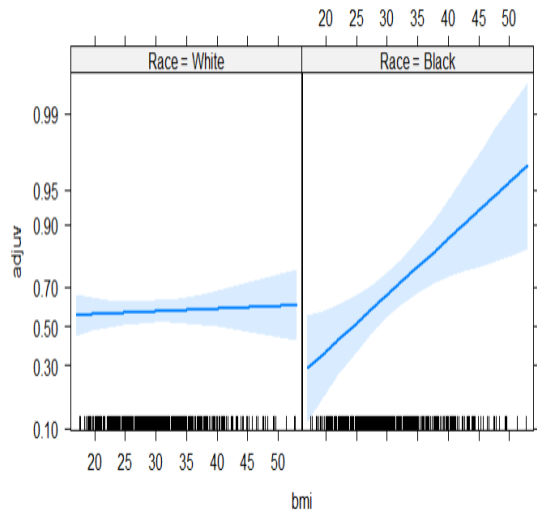


Race, stage and ADI



Race and BMI in stage IIA

Race*bmi effect plot



PO3-03-11

Receptor discordance after neoadjuvant chemotherapy with pembrolizumab in early-stage triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

A. LeVee. City of Hope Comprehensive Cancer Center, United States

M. Wong. City of Hope Comprehensive Cancer Center, United States

S. Flores. City of Hope Comprehensive Cancer Center, United States

N. Ruel. City of Hope Comprehensive Cancer Center, United States

H. McArthur. UT Southwestern, Dallas, Texas, United States

J. Waisman. City of Hope Comprehensive Cancer Center, United States

J. Mortimer. City of Hope, Duarte, California, United States

Background: Discordance in hormone receptor (HR) and/or HER2 status between matched primary tumors and residual specimens following neoadjuvant therapy is a known phenomenon. In the neoadjuvant setting, systemic treatment is primarily informed by the HR and HER2 status from the diagnostic biopsy. Current guidelines recommend additional adjuvant capecitabine and/or pembrolizumab and/or olaparib for patients with triple-negative breast cancer (TNBC) after neoadjuvant systemic therapy if residual disease is present at the time of surgery. Discordance in biomarker status between the initial diagnosis and residual cancer may impact postoperative systemic therapy recommendations. This study aims to investigate the discordance rate in HR and HER2 status after neoadjuvant chemotherapy (NAC) plus pembrolizumab in early-stage TNBC. Furthermore, given the emerging data in support of novel antibody-drug conjugates (ADCs) for HER2-low breast cancer, the prevalence of HER2-low disease following standard-of-care neoadjuvant therapy may have critical clinical importance.

Methods: We performed a single-institution, retrospective study of early-stage TNBC patients diagnosed between February 1st, 2020 and December 1st, 2022 who were treated with neoadjuvant chemotherapy and pembrolizumab. Patients who had not undergone definitive surgery were excluded. Demographic information, clinical and pathologic characteristics, and treatment data were collected from an institutional database. Pathologic complete response (pCR) was defined as ypT0/Tis and ypN0. HR and HER2 status before and after neoadjuvant therapy were collected. This study was approved by an Institutional Review Board.

Results: Among the 94 patients included the median age was 55 years (IQR 47.0-61.8). The majority of patients had invasive ductal carcinomas (90.4%), were clinical T2 stage (68.1%), and node negative (55.3%). On the core tumor biopsy, estrogen receptor (ER) was < 1% in 90 (95.7%) patients and 1-10% in 4 (4.3%) of patients. Progesterone receptor (PR) was < 1% in 91 (96.8%) of patients and 1-10% in 3 (3.2%) of patients. HER2 was 0 by IHC in 49 (52.1%) patients, 1+ in 30 (31.9%) patients, 2+ in 11 (11.7%) patients, and not performed in 4 (4.3%) patients. A pCR (ypT0/Tis ypN0) was achieved in 60 (63.8%) of the 94 patients. In the 34 patients with residual disease, 29 patients had ER status evaluated at the time of surgery. Of these patients, 4 had tumors with ER < 1% at baseline but >5% at surgery. 28 patients with residual disease had PR evaluated at the time of surgery. Of these patients, all had tumors with PR < 1% at the time of surgery. 28 patients had residual tumors with HER2 status evaluated at the time of surgery (table). Of these patients, 18 (64.3%) tumor specimens were HER2-ultra-low, 9 (32.1%) were HER2-low-positive, and 1 (3.6%) was HER2-positive.

Conclusion: Receptor discordance from the time of initial biopsy to residual disease can occur in patients with early-stage TNBC treated with NAC with pembro. As additional systemic therapy is indicated in patients who do not achieve pCR, accurate tumor marker status is critical. This study highlights the potential impact of reassessment of HR and HER2 status on the surgical tumor specimen. Clinical trials that tailor adjuvant therapy recommendations based on residual biomarker analyses may further improve outcomes for women with high risk TNBC.

Table. Discordance in HER2 Status Between Primary Tumor and Residual Specimen

	Residual tumor specimen							
	HER2-0		HER2-low		HER2-positive		Total	
Primary tumor	n	%	n	%	n	%	n	%
HER2-0	13	46.4%	2	7.1%	0	0%	15	53.6%
HER2-low	4	14.3%	6	21.4%	1	3.6%	11	39.3%
HER2 IHC not reported/FISH negative	1	3.6%	1	3.6%	0	0%	2	7.1%
Total	18	64.3%	9	32.1%	1	3.6%	28	100%

PO3-03-12

Factors associated with response to neoadjuvant chemoimmunotherapy in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

A. LeVee. City of Hope Comprehensive Cancer Center, United States

M. Wong. City of Hope Comprehensive Cancer Center, United States

S. Flores. City of Hope Comprehensive Cancer Center, United States

N. Ruel. City of Hope Comprehensive Cancer Center, United States

H. McArthur. UT Southwestern, Dallas, Texas, United States

J. Waisman. City of Hope Comprehensive Cancer Center, United States

J. Mortimer. City of Hope, Duarte, California, United States

Background: The addition of pembrolizumab (pembro) to neoadjuvant chemotherapy (NAC) became a standard-of-care for the treatment of early-stage triple negative breast cancer (TNBC) after the phase III KEYNOTE-522 trial demonstrated improved pathologic complete response (pCR) rates and event free survival with the combination. To date, clinical predictors of response to pembro with NAC are lacking. We sought to identify real-world clinical characteristics and treatment variables associated with response to NAC with pembro.

Methods: We performed a single institution, retrospective study of early-stage TNBC patients diagnosed between February 1st, 2020 and December 1st, 2022 who were treated with NAC and pembro. Patients who had not undergone definitive surgery were excluded. Demographic information, clinical and pathologic characteristics, and treatment data were collected. pCR was defined as ypT0/Tis and ypN0. Univariate and multivariate analysis was performed using logistic regression to identify factors associated with pCR. This study was approved by an Institutional Review Board.

Results: Of the 94 patients analyzed, 93 were female and 1 was male. The median age was 55 years (IQR 47 – 61.8) and median body mass index (BMI) was 30 (24.1-33.6). Self-reported racial/ethnic groups included 37 non-Hispanic White (39.4%), 33 Hispanic (35.1%), 13 Asian (13.8%), 7 Black (7.4%), and 4 other/unknown (4.3%). 8 (8.5%) and 2 (2.1%) of patients had deleterious germline BRCA1+ and BRCA2+ mutations, respectively. The majority of patients had invasive ductal histology (90.4%), clinical T2 stage (68.1%), and node negative (55.3%) disease. 61 (64.9%) patients completed the planned 8 cycles of NAC, while 42 (44.7%) completed the planned 8 cycles of neoadjuvant pembro. A pCR (ypT0/Tis ypN0) was achieved in 60 (63.8%) of the 94 patients. Among those who achieved a pCR, 32 (53.3%) completed the prescribed course of NAC and pembro in combination, whereas 9 (47.1%) of the 34 patients with residual disease did not. In univariate analyses, patients under 55 years at time of diagnosis (vs. age >55 years), higher ki-67, those completing the prescribed course of NAC, those completing the prescribed course of pembro, the months from start of NAC to surgery, and the months from start of pembro to surgery were associated with pCR. The duration from start of NAC or pembro to surgery overlapped considerably with the response explained by completion of NAC or pembro, respectively. Although pCR estimates were lower for Hispanic (60.6%) and non-Hispanic White patients (Black: 57.1%, Asian: 53.8%, and Other: 50%) when compared to non-Hispanic White patients (73.0%), the results were not statistically significant. In multivariate analyses, patients under 55 years at time of diagnosis (OR 3.06, 95% CI:1.18-8.0, p=0.02) and those completing the full course of pembro (OR 2.86, 95%CI: 1.08-7.58,

p=0.034) had improved rates of pCR. BMI, race, BRCA1/2 status, histology, clinical T and N stage, grade, time between start/end of NAC and IO to surgery were not significantly associated with pCR on multivariate analysis.

Conclusion: In our experience, younger TNBC patients were more likely to achieve a pCR with NAC with pembro. Moreover, the completion of the planned course of pembro prior to surgery was also associated with improved pCR rates. These findings suggest that adherence to neoadjuvant pembro prior to surgery may be more important than the completion of the NAC. Further research to identify the optimal exposure of NAC with pembro is needed to refine treatment recommendations in this high-risk population.

PO3-04-01

Population Pharmacokinetics of trastuzumab deruxtecan (T-DXd) in HER2-positive breast cancer subjects: analyses across 12 Phase 1-3 studies

Presenting Author(s) and Co-Author(s):

C. Li. Daiichi Sanyko, Basking Ridge, New Jersey, United States

S. Henning. Certara USA, Inc., United States

K. Patel. Certara USA, Inc., United States

K. Hui. Certara USA, Inc., United States

G. van der Vleuten. Certara USA, Inc., United States

m. Abutarif. Daiichi Sanyko, United States

T. Garimella. Daiichi Sanyko, United States

A. Khatri. Daiichi Sanyko, United States

Population Pharmacokinetics of trastuzumab deruxtecan (T-DXd) in HER2-positive breast cancer subjects: analyses across 12 Phase 1-3 studies

Authors: Claire Li¹, Stefanie Henning², Kashyap Patel², Katrina Hui², Gerly van der Vleuten², Malaz Abutarif¹, Tushar Garimella¹, Amit Khatri¹ ¹Quantitative Clinical Pharmacology, Daiichi Sankyo, Basking Ridge, NJ, USA ²Certara, Inc, NJ, USA **Background:** T-DXd, an antibody-drug conjugate composed of a humanized anti-HER2 monoclonal antibody and a topoisomerase I inhibitor payload, is approved for adult patients with unresectable or metastatic HER2-positive (HER2+) BC administered T-DXd 5.4 mg/kg Q3W with a prior anti-HER2-based therapy either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy. The objective of this analysis was to present pharmacokinetic (PK) characterization of T-DXd and DXd in patients with advanced/metastatic HER2-positive breast cancer from a pooled data source of 12 phase 1 to 3 clinical trials. **Methods:** Data from subjects with HER2-positive breast cancer and other solid tumors enrolled in studies DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, DS8201-A-U201, DS8201-AJ202, DS8201-A-U205, DS8201-A-U204, DS8201-A-U206, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303 were used for this analysis. A population PK (PopPK) analysis was performed using nonlinear mixed effects modeling approach using NONMEM® (version 7.4.3). The effect of significant covariates was evaluated by univariate and multivariate analyses on steady-state exposure of T-DXd and DXd. **Results:** Data across T-DXd doses 0.8 to 8 mg/kg with 2216 subjects were included. The PK of T-DXd and DXd were adequately described by PopPK analysis based on standard model diagnostic techniques. T-DXd elimination clearance and volume of distribution of central and peripheral compartments were estimated at 0.402 L/day, 2.68 L and 5.91 L, respectively. DXd elimination clearance was estimated at 18.4 L/hour. Covariates previously detected to be statistically significant (cancer type, tumor size, albumin, race-country, body weight and sex for T-DXd; age, cancer type, AST, total bilirubin, ritonavir or itraconazole use, race-country, formulation and body weight for DXd) were retained in the PopPK model. No new covariates were identified as statistically significant in the PopPK analysis. All covariates were contained within the 0.8 to 1.25 exposure ratio interval in T-DXd and DXd steady-state area under the concentration-time curve (AUC), indicating no clinically meaningful effect, except for subjects with high body weight (90 kg; 95th percentile) showing a 28% and 26% higher T-DXd and DXd AUC, respectively, relative to a BC subject with median body weight of 60 kg. None of these changes were clinically meaningful based on exposure-response analyses of efficacy and safety endpoints. T-

DXd and DXd post hoc exposure estimates in all BC subjects (HER2-positive and HER2-low) as well as BC subjects with HER2- positive were comparable across hepatic function, renal function, region, race-country and line of therapy. **Conclusions:** Similar T-DXd and DXd exposures were obtained for the recommended dosing of 5.4 mg/kg Q3W T-DXd in BC subjects across categories of hepatic function, renal function, region, race-country, HER2 status, and line of therapy.

PO3-04-02

Exposure-efficacy and safety analysis of trastuzumab deruxtecan (T-DXd) in patients with advanced/metastatic HER2+ breast cancer (BC): Analyses from Phase 3 Studies DESTINY-Breast02 (DB-02) and DESTINY-Breast03 (DB-03)

Presenting Author(s) and Co-Author(s):

C. Li. Daiichi Sanyko, Basking Ridge, New Jersey, United States

R. Wada. QuanTx Consulting, United States

H. Li. QuanTx Consulting, United States

H. kastrissios. QuanTx Consulting, United States

m. Abutarif. Daiichi Sanyko, United States

T. Garimella. Daiichi Sanyko, United States

A. Khatri. Daiichi Sanyko, United States

Exposure-efficacy and exposure-safety analyses of trastuzumab deruxtecan (T-DXd) in patients with advanced/metastatic HER2+ breast cancer (BC): Analyses from Phase 3 Studies DESTINY-Breast02 (DB-02) and DESTINY-Breast03 (DB-03) Authors: Claire Li¹, Russ Wada², Hanbin Li², Helen Kastrissios², Malaz Abutarif¹, Tushar Garimella¹, Amit Khatri¹ ¹Quantitative Clinical Pharmacology, Daiichi Sankyo, Basking Ridge, NJ, USA ²QuanTx Consulting Mountain View, CA, USA Background: T-DXd, an antibody-drug conjugate composed of a humanized anti-HER2 monoclonal antibody and a topoisomerase I inhibitor payload, is approved for adult patients with unresectable or metastatic HER2+ BC with a prior anti-HER2-based therapy either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy. The analysis evaluated the relationship between T-DXd pharmacokinetic (PK) exposure and efficacy/safety endpoints following 5.4 mg/kg Q3W in HER2+ BC subjects. Methods: Exposure-efficacy (E-E) analyses were evaluated from BC subjects in two Phase 3 studies, DB-02 (N=404 for T-DXd; 3L+ BC) and DB-03 (N=257 for T-DXd; 2L+ BC). In studies DB-02 and DB-03, 202 and 263 subjects in control arm were treated with treatment of investigator's/physician's choice (TPC) and T-DM1, respectively. Exposure-safety (E-S) analyses were conducted using 12 clinical studies ranging from Phase 1 to 3 (N=2216, 68.7% BC), including DB-02 and DB-03. Population PK-predicted exposure metrics included T-DXd and DXd peak concentration, trough concentration, and AUC in Cycle 1 and at steady state. Key efficacy endpoints were progression-free survival (PFS) based on blinded independent central review (BICR) and overall survival (OS). Safety endpoints included any Grade and Grade ≥ 3 adjudicated drug-related interstitial lung disease (ILD). Exploratory analyses were conducted for other safety endpoints (i.e., Grade ≥ 3 TEAEs). Results: T-DXd exposure was a significant predictor ($p < 0.01$) of OS in DB-02. In study DB-03, T-DXd exposure was a marginally significant covariate ($p < 0.05$) for OS in univariate Cox regression but was dropped in the multivariate analysis. The relationship between T-DXd exposure and PFS in both studies were not statistically significant ($p > 0.01$), suggesting a flat E-E relationship due to the narrow exposure range resulting from the single-dose level (5.4 mg/kg Q3W) in both studies. Clinically meaningful efficacy in the T-DXd arm relative to the control arm was observed in both studies (PFS: 17.8 months [T-DXd arm] vs. 6.9 months [TPC arm] in study DB-02 and 28.8 months [T-DXd arm] vs. 6.8 months [T-DM- arm] in study DB-03). Therefore, the E-E analyses supports clinically meaningful efficacy across the entire exposure range with the T-DXd 5.4 mg/kg dose in BC subjects.

For E-S, a statistically significant relationship ($p < 0.001$) was observed between increasing T-DXd exposures across all the dose levels (0.8 to 8 mg/kg) and increasing hazard of any Grade and Grade ≥ 3 ILD. The predicted Day 360 incidence rate of any Grade and Grade ≥ 3 ILD at 5.4 mg/kg Q3W T-DXd in BC subjects was 14.8% and 3%, respectively. These findings are consistent with previous safety analyses. Observed rates of the exploratory safety endpoints were also generally consistent with previous model-predicted rates of adverse events in BC¹. Conclusions: The E-E analyses support clinically meaningful efficacy (PFS and OS) relative to control with a flat exposure-response relationship in HER2+ BC subjects at the T-DXd 5.4 mg/kg dose. The E-S analyses showed any Grade and Grade ≥ 3 ILD event rates for this dose are comparable to prior studies¹. Those event rates appeared to increase with increasing T-DXd exposures. Overall, these model-based analyses continue to support T-DXd 5.4 mg/kg Q3W dosing in previously treated HER2+ BC. Reference: Yin O, Iwata H, Lin, C, et al. Exposure-Response Relationships in Patients with HER2-Positive Metastatic Breast Cancer and Other Solid Tumors Treated with Trastuzumab Deruxtecan. *J Clin Pharm Ther.* 2021; 110(4):986-96

PO3-04-03

Drug Holidays in Patients with HER-2 Positive Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Kurtom. University of Pittsburgh, United States

K. Senol. Uludag University, Medical Faculty, General Surgery, Bursa, Turkey

Q. Sabih. University of Pittsburgh, United States

E. Sezgin. Breast Health Working Group International, United States

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

V. Gorantla. University of Pittsburgh Medical Center, United States

S. Puhalla. UPMC Hillman Cancer Center, United States

A. Soran. UPMC Department of Surgery, Breast Health Working Group International, United States

Background

Treatment of HER-2 positive metastatic breast cancer (MBC) involves the use of HER-2-targeted therapy in combination with cytotoxic chemotherapy and/or hormone therapy. Treatment duration for HER2-targeted agents is not standardized, and patients are often kept on these drugs indefinitely. Drug holidays can be initiated due to poor tolerance of drug or can be considered when trying to limit drug toxicity. Our study aims to determine the safety of utilizing drug holidays for patients receiving HER2-targeted therapies and the effect on overall survival and disease progression.

Methods

Study Design

This retrospective study included patients who were diagnosed with metastatic HER2 positive breast cancer and had complete clinical and survival data available within UPMC Magee Women's Hospital. The patients were divided into two groups based on whether they had a drug holiday or not. A drug holiday was defined as the temporary cessation of antiHER2 therapy for a minimum of three months in patients receiving HER2-targeted treatments. This involved the discontinuation of earlier- and later-line medications without considering the cessation of hormone therapy.

Statistical Analysis

The chi-square test or Fisher's exact test was used to compare categorical variables and the Mann-Whitney U test was used to compare continuous variables. The results were reported as proportions for categorical variables and as medians with 25th-75th percentiles for continuous variables. Survival rates and Hazard ratios were estimated using Kaplan-Meier log-rank tests and Cox models, respectively. The significance level was set at $p < 0.05$ for all analyses.

Results

83 patients with HER2+ MBC treated with HER2-targeted therapy were identified, of which 54 patients were in the drug holiday group. Of noted patient variables, there was no significant difference in the tumor histology, distribution of estrogen receptor (ER) status ($p = 0.38$) and progesterone receptor (PR) status ($p = 0.64$). The use of hormonotherapy, immunotherapy, radiotherapy to the primary tumor, and radiotherapy to metastasis did not significantly differ between the two groups ($p > 0.05$ for all comparisons). Subgroup analysis was conducted

within the hormonotherapy subgroup to assess the survival difference in the no drug holiday group and to evaluate the impact of drug holiday on antiHER2 therapy cessation while continuing hormonotherapy. There was a trend towards a higher proportion of patients who were deceased in the no drug holiday group (62%) compared to the drug holiday group (42%), although this difference did not reach statistical significance ($p = 0.16$). The disease status differed significantly between the two groups ($p < 0.0001$). In the no-drug holiday group, 72% of patients had progressive disease, while 20% had stable disease with the anti-HER2 therapy and 7% had no-evidence of disease. In contrast, the drug holiday group had a higher proportion of patients with no-evidence of disease (48%) compared to progressive disease (38%) and stable disease (14%). The drug holiday group demonstrated higher overall survival (61% with median follow-up 1719 days 25th-75th percentile: 963-2222) compared to the no drug holiday group (39% with median follow-up time of 803 days 25th-75th percentile: 216-1510) ($p = 0.04$).

Conclusion

Overall, our findings suggest that utilization of a drug holiday in stable and NED HER2+ MBC is not associated with decreased survival. Analysis within the hormonotherapy subgroup indicated no survival difference in the drug holiday group, highlighting the potential for cessation of antiHER2 therapy while continuing hormonotherapy in this specific subgroup. However further prospective studies with long drug holiday intervals, larger sample size, and control of other potential confounding factors are needed to validate these results.

PO3-04-04

Long term survival of metastatic HER2 positive breast cancer patients with no radiographic evidence of disease (NED) on HER2 antibody therapy.

Presenting Author(s) and Co-Author(s):

A. Bennett. University Hospital Cleveland Medical Center, Cleveland, Ohio, United States

Z. Chen. Case Western Reserve University School of Medicine, Cleveland, Ohio, United States

J. Martin. University Hospitals/Seidman Cancer Center, Cleveland, Ohio, United States

N. Mallat. University Hospital Cleveland Medical Center, Cleveland, Ohio, United States

P. Fu. Case Western Reserve University, Department of Population and Quantitative Health Sciences, United States

A. Montero. UH/Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA, United States

Introduction A small proportion of women with human epidermal growth receptor 2 (HER2) positive metastatic breast cancer (mBC) achieve “no evidence of disease” (NED) status with HER2 monoclonal antibody therapy. Patients who achieve NED status have excellent long term outcomes with overall (OS) and progression free survival (PFS) rates greater than 95%. Presently there are no reliable biologic or clinical factors which are predictive of NED. It is also unclear in NED patients when it would be safe to discontinue therapy. Therefore, even in HER2+ mBC NED patients, HER2 therapy is often continued indefinitely. In this study, we characterize clinical outcomes in HER2+ mBC patients who achieved NED status and received HER2 antibody therapy for 5+ years. **Methods** We conducted a retrospective analysis of patients at a U.S. academic medical center. Patients with HER2+ mBC who had received at least 5 years of either trastuzumab or trastuzumab/pertuzumab (from 2014- 2023) were identified for our NED cohort. For a non-NED comparator group, we identified women with stage IV HER2+ mBC from the tumor registry (from 2012-2021). Descriptive statistics were used to describe the demographic information and clinical characteristics. Kaplan-Meier method with log-rank test was used to analyze OS and PFS between both patient cohorts. **Results** 102 patients were identified that received trastuzumab or trastuzumab/pertuzumab for 5+ years. From this group, 33 patients were identified as NED based on clinical documentation and imaging. From our tumor registry data, there were 58 stage IV HER2+ patients. 34 patients met inclusion criteria for our non-NED cohort. The median follow-up time was 132 (range: 39 - 296) months for the NED cohort and 26 (range: 1-99) months for the non-NED cohort. The average diagnosis age was significantly older for the NED cohort (61 vs. 52 years, $P=0.001$). No other significant differences with respect to hormone receptor expression, race, or the presence of brain metastases were observed between groups. With respect to HER2 therapy, 61% of NED patients had received trastuzumab alone, and 39% trastuzumab/pertuzumab. By contrast in the non-NED cohort most received trastuzumab/pertuzumab (59%). The median time on HER2 therapy for the NED group was 125 months—70% of patients in the NED cohort were still receiving therapy vs, 12% for the non-NED cohort. As expected, the median OS (NR vs. 25.5 months; $P< 0.0001$) and PFS (NR vs. 7.9 months; $P< 0.0001$) were significantly longer in the NED cohort. 5 and 10 year OS rates for the NED cohort were 90.5% (95% confidence interval (CI): 80.8-100%) and 87% (95% CI: 75.9-99.8%), respectively. By contrast, for the non-NED cohort 5 and 10 year OS rates were only 21.3% (95% CI: 11.06-41.1%) and 0% (95% CI: 0-0%), respectively. 5 and 10 year PFS rates were 84.1% (95% CI: 72.2-97.9%) and 76.6% (95% CI: 67.7-93.6%), respectively for the NED cohort, and both were 0% for the non-NED cohort. The presence of brain metastases in the NED cohort was associated with reduced 5 and 10

year OS rates: 60% (95% CI: 29.3-100%) and 40% (95% CI: 13.7-100%), respectively. We observed in the NED cohort was associated with a drop in ejection fraction and clinically significant heart failure in 24% of patients while on HER2 therapy. Conclusions HER2+ mBC patients who achieve NED status have an excellent prognosis with starkly different clinical outcomes compared to HER2+ mBC patients who do not. We observed that 10 year OS rates in HER2+ NED patients was approximately 90%, which did not differ from 5 year OS rates. This suggests that HER2 therapy could be potentially discontinued after 5 years in mBC patients who achieve NED. More studies are needed to develop robust predictive markers for patients likely to achieve NED with HER2 targeted therapy.

PO3-04-05

Efficacy and safety of the recombinant humanized anti-HER2 monoclonal antibody-MMAE conjugate RC48-ADC in patients with HER2-positive or HER2-low expressing, metastatic breast cancer: a single-arm phase II study

Presenting Author(s) and Co-Author(s):

F. Qu. Department of Oncology, First Affiliated Hospital, Nanjing Medical University, United States

W. Li. Department of Oncology, First Affiliated Hospital, Nanjing Medical University, United States

Y. Yin. The First Affiliated Hospital of Nanjing Medical University, United States

Q. Liu. The First Affiliated Hospital of Nanjing Medical University, United States

Background: Current treatment options for HER2-positive (IHC 3+, or IHC 2+/FISH+) advanced or metastatic breast cancer at third-line and above have shown limited clinical benefit. There is no recommended HER2-targeting treatment for HER2-low expressing (IHC 2+/FISH-, or IHC 1+) population. RC48 (Disitamab vedotin), a newly developed antibody-drug conjugate (ADC), is comprised of three well-defined components: hertuzumab against the prominent tumor target-HER2, monomethyl auristatin E (MMAE) and a cleavable linker, with a bystander effect in tumor cell killing. There is a lack of data on the administration of RC48 in the Chinese population. Here, we report the efficacy and safety of RC48-ADC in the advanced or metastatic breast cancer. **Methods:** Patients with HER2-positive or HER2-low expressing, locally advanced or metastatic breast cancer were eligible and received RC48 2.5 mg/kg every two weeks alone or combined with drugs with different anti-tumor mechanisms, such as immune checkpoint inhibitors (ICIs), tyrosine kinase inhibitors (TKIs) and antiangiogenic compounds. The primary endpoint was the objective response rate (ORR) assessed by the primary researcher. Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), time to progression, and safety. **Results:** At the time of data cutoff (June 30, 2023), 120 Chinese female breast cancer patients were enrolled and treated with RC48-ADC. 82 patients (68.3%) were HER2-positive and 38 patients (31.7%) were HER2-low expressing. At baseline, 52 patients (43.3%) had liver metastases, 40 patients (33.3%) had brain metastases, 70 patients (58.3%) had ≥ 3 metastases lesions, and 84 patients (70.0%) had received ≥ 3 prior chemotherapy regimens. In the overall population, the ORR was 38.3% (95% confidence interval [CI]: 30.0%-47.3%). The median PFS was 5.7 months (95% CI: 4.6-6.9 months). The DCR was 64.2% (95% CI: 54.9%-72.6%). In the HER2-positive subgroup, the ORR and mPFS were 42.7% (95% CI: 32.0%-54.1%) and 6.3 months (95% CI: 4.9-7.6 months). In the HER2-low expressing subgroup, the ORR and mPFS were 29.0% (95% CI: 16.0%-46.1%) and 3.6 months (95% CI: 2.0-5.3 months). In addition, the mPFS in the dual drug combination-treated group were longer than those in the single drug treatment group, with mPFS of 7.1 months (95% CI: 5.0-9.2 months) and 4.6 months (95% CI: 3.5-5.8 months), respectively. The most frequently reported treatment-related adverse events (TRAEs) were increased AST (45.8%), increased ALT (41.7%), decreased white blood cell count (25.0%), and fatigue (25%), most were grade 1-2 in severity. **Conclusions:** RC48-ADC showed consistent efficacy in HER2-positive and HER2-low expressing subgroups. No new safety signals were observed. Coadministration with ICIs, TKIs and antiangiogenic compounds demonstrated substantially enhanced efficacy compared to the monotherapies and could be a future direction in development of ADC.

PO3-04-06

A comparison of the efficacy of trastuzumab deruxtecan in advanced HER2-positive breast cancer: active brain metastasis versus progressive extracranial disease alone

Presenting Author(s) and Co-Author(s):

J. Pearson. The Clatterbridge Cancer Centre NHS Foundation Trust/ University of Liverpool, United Kingdom

A. Khan. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

T. Bhogal. The Clatterbridge Cancer Centre NHS Foundation Trust/ University of Liverpool, United Kingdom

H. Wong. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

A. Law. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

S. Mills. The Walton Centre, United Kingdom

N. Santamaria. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

J. Cliff. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

D. Errington. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

A. Hall. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

C. Hart. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

Z. Malik. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

R. Sripadam. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

H. Innes. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

H. Flint. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

G. Langton. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

E. Ahmed. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

J. Bishop. The Clatterbridge Cancer Centre NHS Foundation Trust, United Kingdom

R. Jackson. University of Liverpool, United Kingdom

C. Palmieri. The Clatterbridge Cancer Centre NHS Foundation Trust/ University of Liverpool, United Kingdom

Background Trastuzumab deruxtecan (T-DXd) has demonstrated efficacy in patients with brain metastasis (BM), a group historically with poor outcomes. The prevalence of BMs in patients commencing T-DXd is currently unknown. To date, no direct comparisons have been made of the activity of T-DXd in patients with active BM versus those with extracranial progression alone. This real-world study explored the prevalence of BMs at commencement of T-DXd, the efficacy of T-DXd in active BM versus extracranial progression alone and the safety of T-DXd. Methods Patients with HER2-positive advanced breast cancer treated with T-DXd between June 2021 and February 2023 at our specialist cancer hospital were identified and notes reviewed. Clinico-pathological information, prior treatment, the presence or absence of CNS disease, outcomes and treatment-emergent adverse events (TEAE) were recorded. Data cut-off was 28th February 2023.

Results 29 female patients: 16 extracranial disease alone, 12 BM and 1 LMD were identified. Prevalence of BM at commencement of T-DXd was 41% (12 of 29). Median age was 52 (IQR 44-62), with a median 2 (range 2-6) prior lines of HER2 directed and chemotherapy:86% (25 of 29) had received prior trastuzumab and pertuzumab, 100% (29 of 29) T-DM1 and 3% (1 of 29)

patient trastuzumab duocarmazine. At a median follow-up of 13.8 months, median progression free survival (PFS) for overall population was 13.9 months (95% CI: 12.4-NE), 16.1 months (95% CI: 15.1-NE) for active BMs, and 12.4 months (95% CI: 8.3-NE) for progressive extracranial disease alone (P=0.106). 12-month OS rate was 74% (95% CI: 59-95) in the overall population, 83% (95% CI: 58-100) and 66% (95% CI: 45-96) for active BMs, and extracranial only disease respectively (P=0.678). Objective response rates: overall population was 69% (95% CI: 52-86), active BMs was 60% (95% CI: 30-90), and progressive extracranial disease alone was 69% (95% CI: 46-91). 6% (1 of 16) with extracranial disease alone developed BM during treatment with T-DXd. Reasons for treatment discontinuation: 67% (10 of 15) disease progression or death; 33% (5 of 15) toxicity. 48% (14 of 29) remain on treatment. Most common TEAEs were fatigue (97%; 28 of 29), alopecia (76%; 22 of 29), and constipation (72%; 21 of 29). Pneumonitis occurred in 9 patients (31%, included 2 deaths). 1 pathologically confirmed case of radionecrosis was documented. An updated analysis with an additional 9 patients who commenced T-DXd since February 2023 will be presented.

Conclusion In this real-world study a significant number of patients had BM at the commencement of T-DXd. We demonstrate that in advanced HER2 positive breast cancer that T-DXd is as effective, in terms of PFS and OS, in active BMs as it is in progressive extracranial disease alone. These data provide the first evidence that in contrast to the historical data that active BM may no longer be a detriment to survival as compared to progressive extracranial disease alone when treated with T-DXd. These observations warrant further investigations in larger series. The high rate of pneumonitis warrants further consideration.

PO3-04-07

Characterization of response to first-line chemotherapy, trastuzumab, and pertuzumab among patients with de novo metastatic HER2-positive breast cancer

Presenting Author(s) and Co-Author(s):

E. Ferraro. Memorial Sloan Kettering Cancer Center/Breast Medicine Service, New York City, New York, United States

A. Khan. MSKCC, United States

G. Plitas. Memorial Sloan Kettering Cancer Center, United States

Y. Chen. Memorial Sloan Kettering Cancer Center, United States

M. Ahmed. Memorial Sloan Kettering Cancer Center, United States

J. An. Memorial Sloan Kettering Cancer Center, United States

C. Dang. Breast Medicine Service, Memorial Sloan-Kettering Cancer Center, United States

M. Robson. Memorial Sloan Kettering Cancer Center, New York, United States

S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

S. Modi. Memorial Sloan Cancer Center, New York, New York, United States

P. Razavi. Memorial Sloan Kettering Cancer Center, New York, New York, United States

S. Shen. Memorial Sloan Kettering Cancer Center, United States

Background: With optimization of treatment for early-stage human epidermal growth factor receptor 2-positive (HER2+) breast cancer, the proportion of patients diagnosed with HER2+ metastatic breast cancer (MBC) who have de novo disease is expected to increase. The standard first-line treatment for HER2+ metastatic breast cancer (MBC) is the combination of a taxane, trastuzumab (H), and pertuzumab (P) based on the CLEOPATRA trial. Complete response (CR) rates with this regimen range from 13-18%; previous exposure to anti-HER2 therapies is associated with worse outcomes. However, rates of CR, clinicopathologic characteristics associated with CR, duration of response, and most common sites of relapse among patients with de novo HER2+ MBC are not well described. Methods: Patients with de novo HER2+ MBC who received first line HP-based therapy between 5/2011 and 2/2023 with genomic sequencing data available were included in this retrospective study. Clinicopathologic characteristics were abstracted from medical records. The primary objectives were to define CR rate and progression-free survival (PFS). For response assessment, radiology reports from imaging studies (PET or CT) following initiation of therapy were utilized and response was categorized as CR, defined as interpretation of “no evidence of disease,” or non-CR. Progression of disease (PD) was defined as increase in disease burden that led to treatment change. Factors associated with CR were examined using Wilcoxon rank sum test, Pearson’s Chi-squared test, and multivariable logistic regression. PFS was defined as time from first dose of therapy to PD or death and was calculated and compared using Kaplan Meier estimate and log-rank test. Results: We identified 705 patients with HER2+ MBC treated with first-line chemotherapy and HP, of whom 212 had de novo presentation. After exclusion of 40 patients due to incomplete treatment information, 172 patients were included in this analysis. Median age was 49. 108 patients (62.8%) had hormone receptor-positive disease. 149 (86.6%) patients were treated with paclitaxel or nab-paclitaxel, 20 (11.6%) patients were treated with docetaxel, and 3 patients (1.7%) were treated with vinorelbine. Response assessment was based on PET scans in 144/172 patients (83.7%) and CT scans in 28/172 patients (16.3%). 79 patients (45.9%) had CR while 93 patients (54.1%) had non-CR. Factors associated with CR included younger age at diagnosis (median age 42 among CR vs. 53 among non-CR, $p=0.01$) and HER2

3+ immunohistochemistry ($p=0.007$); hormone receptor-positivity was not associated with CR (65% CR rate among hormone receptor-positive, 63% among hormone receptor-negative, $p=0.9$). Among patients with CR, median time to CR was 5.5 months (interquartile range 3.6-10.2 months). In the total cohort, median follow-up was 50.9 months. 117 patients (68.0%) have progressed or died; 55 patients remain on first-line treatment. 37/79 (46.8%) of patients with CR have progressed or died and 80/93 (86.0%) of patients with non-CR have progressed or died ($p<0.001$). Median PFS was 21.6 months (95% CI 17.9-29.9) but differed by response; median PFS was 67.2 months (95% CI 49.1-not reached) for patients with CR vs. 12.9 months (95% CI 10.2-18.9) for patients with non-CR ($p<0.0001$). PD by site was as follows: breast/axillary nodes (34.2%), bone only or non-visceral site (25.4%), central nervous system (21.9%), and visceral site (18.4%). Conclusions: Nearly half of patients with de novo HER2+ MBC have CR on first-line chemotherapy and HP; patients with CR have significantly longer PFS compared to patients with non-CR. Future studies evaluating treatment discontinuation following durable CR and the utility of circulating tumor DNA in this setting are needed.

PO3-04-09

Prognoses of Patients with Hormone Receptor-Positive and Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer Receiving Neoadjuvant Chemotherapy before Surgery: A Retrospective Analysis

Presenting Author(s) and Co-Author(s):

J. Zhang. The 3rd Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin 300060, China, Tianjin, China (People's Republic)

Y. Liu. The 3rd Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin 300060, China, Tianjin, China (People's Republic)

S. Zhang. The 3rd Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin 300060, China, Tianjin, China (People's Republic)

Abstract: Purpose: To evaluate the clinical characteristics, pathological response, and prognostic significance of hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer (BC) after neoadjuvant chemotherapy (NAC). Methods: A survival analysis was performed to detect the factors related to recurrence and death in 3070 consecutive patients with HR+/HER2- BC who received NAC from 2011 to 2022. All patients received current "standard of care" following neoadjuvant therapy based on guidelines, including surgery and adjuvant endocrine therapy. HER2-low was defined as immunohistochemistry (IHC) 1+ or IHC 2+ and fluorescence in-situ hybridization-negative. Results: The complete pathological response (pCR) (ypT0/is ypN0) rate was 14.5%. The clinical tumor size (cT), ER scores, PR status, and Ki67 levels were related to pCR. The 5-year disease-free survival (DFS) and overall survival (OS) rates were 82.6% and 90.4%, respectively. PR, Ki67 levels, and postmastectomy radiotherapy were independent factors for DFS and OS, and the extranodal extension (ENE) correlated with DFS. However, pCR and HER2 status were related to OS. The pCR rate in PR negativity BC was significantly higher than that in PR positivity BC (21.1% vs. 12.2%, $p = 0.000$), but PR negativity BC had a poorer prognosis than PR positivity BC. HER2-low BC showed high ER scores (over 50%), PR positivity, large ypT, ENE, and lymphovascular invasion but a lower pCR rate than HER2-zero BC. Patients with HER2-low BC had shorter OS than those with HER2-zero BC ($p = 0.037$). However, there was no difference in DFS. Conclusions: Depending on PR status and HER2 status, patients with ER positivity and HER2 negativity exhibit different pathologic complete response rates to neoadjuvant chemotherapy and long-term outcomes, especially patients with PR negativity or HER2-low status. Keywords: breast cancer; neoadjuvant chemotherapy; survival; prognosis; PR; HER2-low

PO3-04-10

Real-world progression-free survival and overall survival of palbociclib plus endocrine therapy in Japanese patients with HR+/HER2- ABC in the first- or second-line setting: A multicenter observational study

Presenting Author(s) and Co-Author(s):

N. Masuda. Nagoya University Graduate School of Medicine, Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

M. Hattori. Aichi Cancer Center, United States

T. Yoshinami. Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, United States

T. Okamura. Department of Breast Oncology, Tokai University School of Medicine, Kanagawa, Japan

K. Watanabe. NHO Hokkaido Cancer Center, Sapporo, Japan

T. Nakayama. Department of Breast and Endocrine Surgery, Osaka International Cancer Institute, United States

H. Masuda. Department of Breast Surgical Oncology, School of Medicine, Showa University, United States

M. Tsuneizumi. Department of Breast Surgery, Shizuoka General Hospital, Japan

D. Takabatake. Department of Breast Oncology, National Hospital Organization Shikoku Cancer Center, United States

M. Harao. Department of Breast Oncology, School of Medicine, Jichi Medical University, United States

H. Yoshino. Breast and Endocrinological Surgery, Ishikawa Prefectural Central Hospital, United States

N. Mori. Department of Breast Surgery, Seirei Hamamatsu General Hospital, United States

H. Yasojima. Department of Surgery, Breast Oncology NHO Osaka National Hospital, United States

C. Oshiro. Kaizuka City Hospital, United States

M. Iwase. Department of Breast and Endocrine Surgery, Nagoya University Graduate School of Medicine, United States

M. Yamaguchi. Department of Breast Surgery, JCHO Kurume General Hospital, United States

T. Sangai. Department of Breast and Thyroid Surgery, Kitasato University School of Medicine, United States

S. Sasada. Hiroshima University, United States

T. Ishida. Division of Breast and Endocrine Surgical Oncology, Tohoku University Graduate School of Medicine, Miyagi, United States

M. Futamura. Department of Breast Surgery, Gifu University Hospital, Japan

N. Kosaka. Oncology Medical Affairs, Pfizer Japan Inc., United States

Y. Shibasaki. Oncology Medical Affairs, Pfizer Japan Inc., United States

S. Nagai. Division of Breast Oncology, Saitama Prefecture Cancer Center, United States

Introduction

Palbociclib (PAL), a selective, oral inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6), plus (+) endocrine therapy (ET) is standard therapy for the treatment of hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) and was launched in December 2017 in Japan. Efficacy and safety of PAL + ET was shown by randomized clinical studies, PALOMA-2 and PALOMA-3. Further, recent large real-world studies, P-REALITY/P-REALITY X, confirmed effectiveness of PAL+ aromatase inhibitor (AI) for HR+/HER2- ABC in routine United States clinical practice. However, there is limited real-world evidence (RWE) for PAL in Japan. To strengthen the RWE of PAL+ET for HR+/HER2- ABC treatment under different clinical practice and healthcare system, we examine the real-world effectiveness of PAL + ET as 1st line (1L) and 2nd line (2L) treatment for HR+/HER2- ABC in Japan.

Methods

In this multicenter, observational study, patients with HR+/HER2- ABC, who initiated PAL + ET from 15 December 2017 to 31 December 2020 were enrolled. To reduce selection bias, all patients who started PAL during the above period were listed and their eligibility confirmed. Eligible patients had 1) diagnosis of HR+/HER2- ABC; 2) received PAL + ET as 1L or 2L treatment; 3) at least 6 months of follow up from start of PAL or died within that period. The 1L treatment was defined as the first systemic therapy received for ABC regardless of recurrence timing if receiving adjuvant treatment. The subsequent treatment after 1L treatment was defined as a 2L treatment. The primary endpoint was real-world progression-free survival (rwPFS) defined as the time from PAL+ET start to physician-documented disease progression or death due to any cause, whichever occurs first. Secondary endpoints included overall survival (OS), and chemotherapy-free survival (CFS). Results were stratified by treatment line (ie. 1L or 2L). rwPFS, OS, and CFS were analyzed with the Kaplan-Meier method (NCT05399329).

Results

In this study, 677 patients were enrolled. Among them, 419 (62%) patients and 258 (38%) patients received PAL + ET as 1L and 2L, respectively. The median age was 59.0 (range 29-87) and 470 patients (69.8%) were postmenopausal. 49.0% patients had visceral involvement and 63.8% had a disease-free interval >24 months, defined as date of breast cancer surgery to the diagnosis date of recurrence, and 26.9% had de novo metastatic disease. The starting dose of PAL was 125 mg (89%), 100mg (9%), and 75mg (2%); dose reductions during the treatment period were required for 72% of patients. The most common ET combined with PAL was fulvestrant (FUL; 56.3% in 1L, 76.7% in 2L) followed by letrozole (LET; 37.9% in 1L, 16.3% in 2L). After a median follow-up of 36.2 months, the median rwPFS (95% CI) was 24.5 months (19.9-29.4) for 1L treatment and 14.5 months (10.2-18.3) for 2L treatment. Among the 604 patients initiating at 125 mg/day, the median rwPFS was 25.6 months (21.3-30.4) for 1L treatment and 14.3 months (9.7-18.3) for 2L treatment. Although median OS was not reached (NR) in 1L, median OS of 2L was 44.1 months (39.2 -NR). The 48-months OS rates for 1L and 2L treatment were 62.0% (55.4-67.9) and 48.4 % (40.4-55.9), respectively. The median CFS was 36.7 months (31.8-43.9) for 1L treatment and 23.8 months (20.5-27.3) for 2L treatment.

Conclusions

Our real-world data are consistent with findings from the PALOMA-2 and PALOMA-3 studies and those from RWE in routine United States clinical practice. FUL was the most commonly endocrine partner with PAL regardless of treatment lines. These observations add to the body of evidence supporting PAL effectiveness in clinical practice for Japanese ABC patients.

PO3-04-11

Unmet clinical need in patients with pre-treated hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer in routine care: a targeted literature review

Presenting Author(s) and Co-Author(s):

L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

S. Collin. AstraZeneca Pharmaceuticals, Cambridge, England, United Kingdom

I. Dhillon. AstraZeneca Pharmaceuticals, Cambridge, England, United Kingdom

G. Long. AstraZeneca Pharmaceuticals, Cambridge, England, United Kingdom

E. Bertranou. AstraZeneca Pharmaceuticals, Cambridge, England, United Kingdom

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background Treatment options remain limited to chemotherapy (CT) for patients with HR+/HER2- metastatic breast cancer (MBC) who have progressed on endocrine therapy (ET) with/without CDK4/6 or PI3K pathway inhibitors (i). We aimed to review the current unmet need in patients who had received ≥ 1 prior systemic therapy in terms of ET resistance as well as CT survival outcomes, tolerability and discontinuation. **Methods** MEDLINE, Embase and the Cochrane Library were searched via Ovid for observational studies (≥ 50 patients who had received ≥ 1 prior systemic therapy, January 2018 – January 2023). Abstracts from relevant congresses (January 2021 – February 2023) were reviewed. All screening was performed in a single-blind manner by one reviewer and any uncertainties were resolved by a senior reviewer. **Results** We included 72 full-text publications and 48 congress abstracts (US based 39%, European 28%, Asian 23%).

Median treatment duration was 1.9–16.2 months (m) for ET (7 studies) and 2.0–24.5 m for ET-based therapy (5 studies). Exceptional responders (10% of patients treated for the longest time) received ET for ≥ 43.6 m (1 study, N = 4195).

The proportion of patients with ET-resistant disease ranged widely (3–100%; 22 studies) and increased by line (L) of therapy: 14–19% of patients treated in 1L had primary resistance, 14–49% in ≥ 2 L and 27–68% in ≥ 3 L; acquired resistance was reported for 26–38% of patients in 1L, 51–57% in ≥ 2 L, 32–60% in ≥ 3 L (2 studies).

One or more prior lines of CT had a negative impact on median overall survival (mOS; 5 studies) and median progression-free survival (mPFS; 11 studies) in subsequent therapy lines regardless of the chosen treatment; prior CT had no effect on mOS in 3 studies, no effect on mPFS in 4 studies.

Consecutive CT cycles (primarily after ET + CDK4/6i) steadily lost clinical benefit (Table), with mPFS with 2 to 5 lines of CT: 7.6 m, 4.8 m, 4.2 m and 3.2 m, and mOS: 13.5 m, 9.1 m, 6.8 m and 7.2 m, respectively (1 study, N = 266). Paclitaxel + bevacizumab as second CT had a mPFS and a mOS of 8.6 m and 19.8 m, respectively (1 study, N = 538). Eribulin use in ≥ 2 L had a mPFS of 4.6–10.0 m (2 studies) and a mOS of 10.1–11.2 m (2 studies). Patients who progressed on CDK4/6i as best response and those with a mPFS of < 6 m on ET benefited

more from CT than ET in $\geq 2L$ with a mPFS of 7.1–8.1 m compared with 1.7–3.9 m, respectively (2 studies).

Discontinuation due to toxicity was 2–36% (3 studies) for CT in 2L and dose reduction was required in 19–37% of patients (2 studies). Common grade 3/4 adverse events in patients receiving CT were leukopenia (17%), neutropenia (7%), thrombocytopenia (3%) and pneumonitis (1–3%) (3 studies). Conclusions Our review of real-world evidence highlights the limitations of repeated CT for patients with ET-resistant HR+/HER2– MBC, characterized by diminishing clinical benefit and significant toxicity burden. Results are limited by treatment and study population heterogeneity. Clinical outcomes are expected to improve with the use of new therapies, for which real-world evidence has yet to accrue.

Table Real-world clinical outcomes with chemotherapy from observational studies

Treatment	Line of therapy	mOS (95% CI), months	mPFS (95% CI), months
CT (1 study, N = 266)	Second CT	13.5 (10.7–16.3)	7.6 (6.4–9.4)
	Third CT	9.1 (7.6–11.0)	4.8 (4.1–6.1)
	Fourth CT	6.8 (4.6–11.0)	4.2 (2.3–5.8)
	Fifth CT	7.2 (2.9–13.0)	3.2 (2.0–3.9)
Paclitaxel + bevacizumab (1 study, N = 538)	As second CT	19.8 (17.0–22.8)	8.6 (7.2–9.7)
Eribulin (2 studies)	$\geq 2L$ (prior CDK4/6i + ET; 1 study, N = 54)	NR	10.0
	$\geq 3L$ (2 prior lines of CT; 1 study, N = 233)	10.1 (9.2–11.3)	4.6 (4.0–6.0)
	$\geq 3L$ (prior CDK4/6i and 2 lines of CT; 1 study, N = 72)	11.2 (10.0–12.3)	6.1 (5.7–6.9)

CI, confidence interval; CT, chemotherapy; L, line; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported

PO3-04-12

SUMIT-BC: Phase 2 randomized study of fulvestrant with or without the cyclin-dependent kinase 7 inhibitor (CDK7i) samuraciclib in advanced hormone receptor positive (HR+) breast cancer after CDK4/6i

Presenting Author(s) and Co-Author(s):

- G. Clack. Carrick Therapeutics Ltd, Dublin, Ireland
- S. Aksoy. Hacettepe University Medical School, Ankara, Turkey, Turkey
- M. Bellet- Ezquerro. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain
- B. Bermejo. Hospital Clínico Universitario de Valencia, Valencia, Spain, United States
- C. Arslan. Izmir Ekonomi University Medical Park Izmir Hospital, Medical Oncology Unit, Izmir, Turkey, Izmir, Turkey
- M. Castro-Henriques. Hospital del Mar Passeig Marítim 25, 08003 Barcelona, United States
- I. Cicin. Trakya University Faculty of Medicine, Edirne, Turkey., United States
- M. Gumus. Istanbul Medeniyet Universitesi, Turkey, United States
- C. Hinojo-González. Hospital Universitario Marqués de Valdecilla, Instituto de Investigación Valdecilla (IDIVAL). GEICAM Spanish Breast Cancer Group, Spain
- N. Karadurmus. University of Health Sciences Gulhane Training and Research Hospital, Medical Oncology Clinic, Ankara, Turkey, Ankara, Ankara, Turkey
- D. Lee Cervantes. Hospital Angeles Clinic London, CDMX, Mexico, United States
- R. Lozano Mejorada. IBSAL - Hospital Universitario de Salamanca, Spain, United States
- E. de la Mora Jimenez. Av. Manuel Acuña 2543, Guadalajara, Mexico, United States
- F. Moreno Antón. Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISSC), CIBERONC, Madrid, Spain
- S. Pernas. SOLTI Cancer Research Group, Barcelona, Spain Institut Catala d'Oncologia; IDIBELL, L'Hospitalet, Barcelona, Spain
- T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States
- C. Zuloaga Fernandez del Valle. Juan Palomar y Arias 530 (Esquina Manuel Acuña), Guadalajara, Mexico, United States
- O. yazıcı. Gazi University Turkey, United States
- S. McIntosh. Carrick Therapeutics Ltd, Ireland

Background: CDK7 has 3 critical roles in cancer: enhanced transcription of oncogenes and upregulation of anti-apoptotic genes, acceleration of the cell cycle through phosphorylation of other CDKs and driving estrogen receptor (ER) resistance to hormonal therapy. Inhibition of CDK7 is therefore a potential novel anti-cancer therapeutic strategy. In an initial single-arm evaluation samuraciclib (CT7001), a once daily (QD) oral CDK7 inhibitor has demonstrated a favourable safety profile and clinical activity in combination with fulvestrant, a selective estrogen receptor degrader (SERD), in patients with HR+/HER2- advanced breast cancer who have previously been treated with a CDK4/6 inhibitor. There was evidence of enhanced benefit in patients with no detectable TP53 mutation from baseline circulating tumor DNA (ctDNA) analysis and in patients without baseline liver metastases [1]. Samuraciclib is associated with

low grade gastrointestinal (GI) adverse events such as nausea, vomiting and diarrhea managed with simple prophylaxis and patient counselling. An instant release capsule formulation was used in the initial clinical evaluation of samuraciclib requiring patients to take multiple capsules designed to rapidly release a large amount of material high in the GI tract. In this study a novel single tablet formulation will be administered which may enhance GI tolerability (2). This Phase 2 open-label randomised study will evaluate the efficacy, safety, pharmacokinetics and Quality of Life (QoL) impact of samuraciclib in combination with fulvestrant in comparison to a fulvestrant monotherapy control arm. Consistent with the principles of the current Project OPTIMUS initiative, 2 dose levels of samuraciclib will be evaluated [3]. All patients will undergo baseline ctDNA evaluation of TP53 mutation status to permit a prospective evaluation of its patient selection biomarker potential. Trial Design: Eligible patients will provide written informed consent, be aged 18 years or older, have histologically or cytologically confirmed ER+/HER2-advanced or metastatic breast cancer not amenable to resection or radiotherapy of curative intent, have received an aromatase inhibitor in combination with a CDK4/6 inhibitor in either the adjuvant or advanced setting, be receiving a luteinizing hormone-releasing hormone agonist if pre/perimenopausal and have RECIST v1.1 evaluable disease. Prior SERD, mammalian target of rapamycin inhibitor (mTORi) or chemotherapy for advanced breast cancer are not permitted. All patients will undergo baseline Guardant360 ctDNA analysis to establish their TP53 mutation status among others. 60 patients will be enrolled and will all receive fulvestrant 500mg IM administered on days 1, 15 and 29 and then monthly thereafter. Patients will be randomized 1:1:1 to fulvestrant alone, fulvestrant and samuraciclib 240mg QD or fulvestrant and samuraciclib 360mg QD. Patients will undergo RECIST v1.1 evaluation at baseline every 8-weeks until week 48, followed by every 12-weeks thereafter. The pharmacokinetics of samuraciclib and fulvestrant will be studied though the first 6 months of the study, with highest intensity during month 1. To evaluate Quality of Life (QoL) The Functional Assessment of Cancer Therapy -Breast questionnaire (FACT-B) will be completed. The primary endpoint is clinical benefit response at 24 weeks. Secondary endpoints are tolerability, progression free survival, overall response rate, duration of response, and the pharmacokinetics of fulvestrant and samuraciclib. QoL and correlations between ctDNA detectable TP53 mutations and efficacy/safety finding in this patient population will be reported. The study opened for recruitment in June 2023. References: 1. Coombes et al., SABCS 2021, 2. Bardia et al., JCO 2021, 3. www.fda.gov

PO3-04-13

SUMIT-ELA: Phase 1b/2 combination of cyclin-dependent kinase 7 inhibitor (CDK7i) samuraciclib and selective estrogen receptor degrader (SERD) elacestrant in advanced hormone receptor positive (HR+) breast cancer after CDK4/6i

Presenting Author(s) and Co-Author(s):

- A. Patnaik. START San Antonio, United States
- S. Antolin Novoa. Complejo Hospitalario Universitario A Coruña (CHUAC). GEICAM Spanish Breast Cancer Group., Spain
- M. Bellet- Ezquerria. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain
- F. Bidard. Institut Curie, Paris, France
- V. Boni. NEXT Madrid, University Hospital Quironsalud, Madrid, Spain, United States
- M. Brunet. Institut Bergonié, Nouvelle-Aquitaine, France, United States
- M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France
- C. Garay. Stemline Therapeutics, Inc, United States
- R. Gómez-Bravo. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain, United States
- S. Howell. The University of Manchester, Manchester, England, United Kingdom
- R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
- S. Lord. University of Oxford, Oxford, United Kingdom
- P. Mazzei. MENARINI Group, United States
- M. De Miguel. START-CIOCC HM Sanchinarro, Madrid, Spain
- E. Roesch. Cleveland Clinic, Ohio, United States
- A. Stradella. Institut Català d'Oncologia, Oncology Department, Barcelona, Spain
- H. Vanacker. Léon Bérard Center, Lyon, France, United States
- C. Vicier. Institut Paoli-Calmette, United States
- S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States
- G. Clack. Carrick Therapeutics Ltd, Dublin, Ireland
- S. McIntosh. Carrick Therapeutics Ltd, Ireland

Background: CDK7 has 3 critical roles in cancer: enhanced transcription of oncogenes and upregulation of anti-apoptotic genes, acceleration of the cell cycle through phosphorylation of other CDKs and driving estrogen receptor (ER) resistance to hormonal therapy. Inhibition of CDK7 is therefore a potential novel anti-cancer therapeutic strategy. Samuraciclib (CT7001), a once daily oral CDK7 inhibitor has demonstrated a favorable safety profile and clinical activity in combination with fulvestrant (SERD) in patients with HR+/HER2- advanced breast cancer who have previously been treated with a CDK4/6 inhibitor [1]. Extended benefit was observed in patients with no TP53-mutation per circulating tumor DNA (ctDNA) analysis detectable at baseline. Limitations in the pharmacokinetic (PK) properties and route of administration (intramuscular only) of fulvestrant mean that oral alternatives are desirable. Recently, the EMERALD phase 3 study of the oral SERD elacestrant demonstrated a significant PFS benefit over standard of care endocrine treatment in the ER+/HER2- advanced or metastatic breast cancer population previously treated with a CDK4/6 inhibitor. [2]. Non-clinical data indicate that

the underlying biology driving samuraciclib combination with endocrine therapy translates from fulvestrant to elacestrant, clinical evaluation is warranted [3]. This open-label Phase 1b dose escalation and Phase 2 dose expansion study will evaluate the safety, efficacy and pharmacokinetics of samuraciclib in combination with elacestrant. ctDNA analysis is informative for both elacestrant and samuraciclib, via ESR1-mutation status and TP53-mutation status respectively, and is an integral part of the study design. Trial Design: Eligible patients will provide written informed consent, be aged 18 years or older, have histologically or cytologically confirmed ER+/HER2- advanced or metastatic breast cancer not amenable to resection or radiotherapy of curative intent, have received an aromatase inhibitor in combination with a CDK4/6 inhibitor in either the adjuvant or advanced setting, be receiving a luteinizing hormone-releasing hormone agonist if pre/perimenopausal and have RECIST v1.1 evaluable disease. Prior SERD, mammalian target of rapamycin inhibitor (mTORi) or chemotherapy for advanced breast cancer are not permitted. The study will enrol ~48 patients. All patients will undergo baseline Guardant360 ctDNA analysis to establish their ESR-1 and TP53-mutation status. Patients will undergo RECIST v1.1 evaluation at baseline every 8-weeks until week 48, followed by every 12-weeks thereafter. Initially both samuraciclib and elacestrant will be administered once daily in a dose escalation/de-escalation approach under supervision of the study Safety Review Committee. The primary endpoint in Phase 1b is the identification of tolerable combination dose levels for both samuraciclib and elacestrant and in Phase 2 expansion to quantify the progression free survival benefit of the combination. Secondary endpoints are tolerability, clinical benefit response at 24 weeks, overall response rate, duration of response, best percent change in tumor size, pharmacokinetics and correlations between ctDNA detectable ESR1 and TP53 mutations and efficacy/safety finding in this patient population. The study opened for recruitment in June 2023. References: 1. Coombes et al., SABCS 2021, 2. Bidard et al., JCO 2022, 3. Data on file

PO3-05-01

Locoregional Management Based on Mode of Progression for HR+/HER2- metastatic breast cancer Treated with Combined CDK4/6 inhibitor with Aromatase inhibitor.

Presenting Author(s) and Co-Author(s):

A. Redfern. University of Western Australia, Perth, Western Australia, Australia

N. Law. Fiona Stanley Hospital, Perth, Western Australia, Australia

I. Weerasena. St John of God Hospital Bunbury, Bunbury, Western Australia, Australia

L. Spalding. Harry Perkins institute for Medical Research, Perth, Western Australia, Australia

H. Martin. Fiona Stanley Hospital, Perth, Western Australia, Australia

Background - Standard management for HR+/HER2- metastatic breast cancer (MBC) comprises concurrent aromatase inhibitor (AI) and cyclin-dependent kinase 4/6 inhibitor (CDK4/6i), providing improved progression-free (PFS) and overall survival over anti-estrogen alone. Eventual resistance mechanisms potentially include phenotypic changes, clonal selection, and new mutations. We theorized that limited progressive disease (LPD) would be more common on combination therapy due to eventual new mutations or clonal selection, in comparison to generalized progressive disease (GPD) occurring more frequently on AI alone due to phenotypic cellular changes across all disease sites. Potentially loco-regional treatment (LRT) options could significantly extend disease control in selected patients on combined therapy. Methods - Patterns of progressive disease (PD) for 55 historical AI-only treated controls (group A) were compared to those for 60 patients on combined treatment with an AI and a CDK4/6 inhibitor (group B) for first-line management of HR+/HER2- MBC. Mode of progression was classified as general (GPD - PD in the majority of lesions) or limited (LPD - PD in up to three lesions in a single organ). All LPDs were assessed for suitability for LRT at time of progression. PFS was assessed for those with LPD who continued present treatment after locoregional therapy. Results - LPD occurred in 13 of 55 patients (23.6%) in group A compared to 26 of 60 (43%) in group B ($p = 0.026$). For LPD patients, all 13 cases in group A were considered appropriate for LRT but only 3 (23.1%) received it and all patients also switched systemic therapy. In group B, 23 of 26 LPD patients were considered suitable for LRT and 16 (57.7%) received it, of whom 11 then continued first line systemic treatment. For these 11 group B patients median PFS was 12+ months (range 3 to 36+ months). LRT consisted of RT in 14 cases (bone in 13 cases, lymph node in one case) and resection in one (isolated brain metastasis). Conclusion - Patients treated with combined CDK4/6i and AI for first line HR+/HER2- MBC were significantly more likely to develop LPD than those on single agent anti-estrogen, where local therapy could often be delivered with no change to systemic therapy. This strategy, applied to 11 of 60 combination treated patients (18%), delivered a median PFS in excess of a year. In contrast more general PD was more commonly observed in patients treated with AI alone, warranting change in systemic therapy.

PO3-05-02

Impact of hormone receptor expression level in HR+/HER2- metastatic breast cancer in the large French ESME cohort.

Presenting Author(s) and Co-Author(s):

M. Alexandre. Medical oncology department, Regional Cancer Institute, Montpellier, montpellier, France

F. Castan. Biostatistics Unit, Regional Cancer Institute, Montpellier, United States

t. DE LA MOTTE ROUGE. CENTRE EUGENE MARQUIS, Rennes, Bretagne, France

A. Mailliez. Oscar LAMBRET Centre, LILLE, France

E. Brain. European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium, United States

T. Bachelot. Medical Oncology, Centre Léon Bérard, Lyon, France

M. Arnedos. Department of Medical Oncology, Institute Bergonié, Bordeaux, France, United States

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

J. Ferrero. Centre Antoine Laccassagne, Nice, France

V. Massard. Department of medical oncology, Lorraine Cancer Institute, United States

I. Desmoulins. Centre Georges-François Leclerc, Dijon, France

M. Mouret-Reynier. Centre Jean Perrin, United States

C. Levy. Centre François Baclesse, Caen, Basse-Normandie, France

A. Gonçalves. Institut Paoli-Calmettes, France

A. Berghian. Anatomical Pathology Unit, Department of Biopathology, Centre Henri Becquerel, France

A. Savoye. /, United States

J. frenel. Health Data and Partnership department, Unicancer, United States

L. Bosquet. Department of Medical Oncology, ICO Cancer Center, United States

S. Delaloge. Institut Gustave Roussy, Villejuif, Ile-de-France, France

W. Jacot. Institut du Cancer de Montpellier, Université de Montpellier, INSERM U1194, Paris, Montpellier, Languedoc-Roussillon, France

Background: In patients (pts) with early breast cancer (BC), the level of expression of estrogen receptor (ER) evaluated by immunohistochemistry is prognostic and predictive while progesterone receptor (PR) expression has an additional prognostic value. Allred scoring combines the percentage of positive cells and the intensity of staining. It is widely used for treatment choice for early BC. In metastatic setting, its role is less defined.

Methods: The ESME database is a French National cohort of all consecutive pts who initiated a first-line treatment for metastatic BC (MBC) between January 2008 and December 2020 in one of the 18 French Comprehensive Cancer Centers (NCT03275311). For this study, we selected pts with HER2- MBC, known ER expression and intensity percentages, known PR status and who received endocrine-based therapy as first-line metastatic treatment.

Primary objective was to evaluate the overall survival (OS) and first line progression-free

survival (PFS1) under endocrine therapy according to ER and PR expression level. ER expression was defined using Allred score on the last available tumor sample. PR status was defined using a positive ($\geq 10\%$) vs negative ($< 10\%$) threshold.

Secondary objective was to evaluate clinical PFS1 whether de novo or recurrent MBC and according to type of first line therapy (mono- vs combined endocrine therapy).

Results: In the ER+ \pm PR+/HER2- population, 8269 pts had information on ER percentage and staining intensity. Median follow-up was 53.4 months (95%CI [51.9; 54.7]). Allred score distribution, OS and PFS1 are described in table 1.

Median OS was 43.1 months [41.1; 45.0] for the PR- group compared with 52.3 months [50.5; 54.4] for the PR+ group. After adjustments, patients with a PR- tumour had still a worse prognosis (HR=1.20, 95%CI [1.12-1.28], $p < 0.001$). Median PFS1 was 10.2 months [9.6; 10.8] and 14.8 months [14.2; 15.4] for pts with PR- vs PR+ tumour (HR=1.36 (1.29-1.43), $p < 0.001$) and PR status remained significant prognostic factor independently of de novo or recurrent status and association or not with a targeted therapy.

Conclusion: ER expression evaluated using the Allred scoring, as well as PR positivity, retain prognostic value in first-line MBC patients.

Table 1 : OS and PFS according to Allred status, de novo status and type of endocrine therapy.

	Allred group				P value
	1-5 n=389	6 N=430	7 N=1273	8 N=6177	
OS (months), [95% CI]	38.8 [35.1 ; 43.3]	44.3 [40.7 ; 52.7]	47.7 [44.5 ; 50.0]	50.8 [49.0 ; 52.6]	P<0.001
Multivariate analysis* for OS HR, [95% CI]	1.42 [1.23 ; 1.63]	1.34 [1.17 ; 1.54]	1.15 [1.06 ; 1.26]	1.00 (ref.)	P<0.001
PFS1 (months), [95% CI]	8.5 [7.3 ; 9.5]	10.3 [8.9 ; 11.7]	11.9 [10.8 ; 12.9]	14.1 [13.6 ; 14.7]	P<0.001
Multivariate analysis* for PFS1 HR, [95% CI]	1.32 [1.17 ; 1.48]	1.18 [1.05 ; 1.32]	1.08 [1.01 ; 1.16]	1.00 (ref.)	P<0.001
PFS1 (months), [95% CI]	8.9 [8.3 ; 13.9] N=53	12.1 [7.6 ; 15.6] N=95	14.2 [12.1 ; 16.2] N=273	17.3 [16.4 ; 18.1] N=2097	P=0.057
PFS1 (months), [95% CI]	8.4 [7.3 ; 9.5] N=336	9.9 [7.5 ; 11.2] N=355	11.2 [10.1 ; 12.4] N=1000	12.5 [11.8 ; 13.0] N=4080	P<0.001
PFS1 (months), [95% CI]	8.6 [7.3 ; 9.7] N=6071	10.1 [7.8 ; 11.7] N=353	10.9 [9.9 ; 12.0] N=1049	13.5 [12.9 ; 14.0] N=4945	P<0.001
PFS1 (months), [95% CI]	8.3 [4.8 ; 10.8] N=1598	11.0 [6.7 ; 19.7] N=77	16.4 [14.0 ; 19.6] N=24	17.9 [16.3 ; 19.1] N=1236	P<0.001

* Selected variables on multivariate model include PR status, age, SBR grade, histological subtype, number of metastatic site, type of metastasis (non visceral, visceral, brain visceral), HER 2 (0 vs 1-2), metastatic-free interval, mono- vs combined endocrine therapy.

PO3-05-03

Real-World Data on First-line Treatment of Hormone Receptor-positive, HER2-negative, Metastatic Breast Cancer in Brazil (BRAVE study - LACOG 0221)

Presenting Author(s) and Co-Author(s):

G. Werutsky. Hospital São Lucas, PUCRS University, Porto Alegre, Rio Grande do Sul, Brazil

D. Rosa. Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul, Brazil

T. Reinert. Oncoclinicas, Porto Alegre, Brazil

R. Barroso-Sousa. Dasa Oncology, United States

H. Resende. Centro Universitário UNIFOA, Volta Redonda, Brazil; Instituto Projeto Cura, São Paulo, Brazil; Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil, United States

P. Signorini. Centro Integrado de Pesquisa da Amazônia (CINPAM), Manaus, Amazonas, Brazil

E. Cronenberger. CRIO, Fortaleza, Brazil, United States

J. Góes Martins Fagundes. Oncoclínicas Paraíba, João Pessoa, Brasil, United States

J. Santos Leal. Oncoclínicas, Salvador, Brazil

M. Dutra Giffoni. Hospital Monte Sinai, Juiz de Fora, Brasil, United States

A. Vieira. Oncoclínicas, Parana, Brazil

L. Nardin Weis. Hospital de Base do Distrito Federal, Brasília, Distrito Federal, Brazil

J. Figueiredo. Instituto do Câncer Brasil, Taubaté, Sao Paulo, Brazil

T. Correa. Hospital Sirio-Libanês, United States

F. Castilho Venero. Hospital Moinhos de Vento, Porto Alegre, Brazil, United States

L. Mostardeiro Tabajara Franche. Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil, United States

M. Musse Bernardes. Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil, United States

R. Jesus. Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Rio Grande do Sul, Brazil

G. Gössling. Latin American Cooperative Oncology Group (LACOG), United States

J. Bines. Instituto Nacional de Câncer (INCA), Brazil

Introduction: Endocrine therapy (ET) plus CDK 4/6 inhibitors is considered the standard of care as first-line therapy in hormone receptor positive (HR+)/HER2 negative (HER2-) metastatic breast cancer (mBC). Nonetheless, the use of chemotherapy (CT) is frequent in clinical practice, and access to CDK 4/6 inhibitors is limited in some countries. We used real-world data to describe treatment patterns, the impact of health insurance type, and outcomes among Brazilian patients with HR+/HER2- mBC treated in the first-line setting. Methods: In this observational retrospective study, female patients ≥ 18 years old diagnosed with de novo or recurrent HR+/HER2- mBC between January 2018 and December 2020 were included. Patients' data were extracted from medical charts or electronic health records (EHR). The primary endpoint was first-line treatment patterns in public and private health system cohorts. Key secondary endpoints were progression-free survival (PFS), defined as time from 1L treatment to progression or death, and overall survival (OS), defined as time from diagnosis of

mBC until death or censoring. No formal statistical assumption was performed for sample size, the study recruited 2 cohorts of 150 patients from the public and 150 patients from the private health insurance system. Results: A total of 307 patients were included, 156 from public and 151 from private health insurance system, from 13 sites in Brazil. Median age was 56.8 (range 19.9-94.1), and 32.2% (N=99) had de novo MBC. Treatment patterns are described in Table 1. The most frequent treatment received in 1L was ET alone 42.4%, followed by CT (alone or CT followed by ET +/- CDK4/6i) 31.6% and ET + CDK4/6i 25.1%. There was a significant difference between the 1L treatment with ET + CDK4/6i in the private and public systems, 48.3% vs 2.6%, $p < .0001$, respectively. The most frequently used CDK4/6i in 1L setting was Ribociclib (65.0%), followed by Palbociclib (36.9%) and Abemaciclib (7.1%). There was an increase in the use of CDK4/6i over time, 17% in 2018, 30.0% in 2019, and 27.9% in 2020. With a median follow-up of 32.2 months (95% CI: 29.4 - 34.4), the median 1L PFS was 22.9 months (95% CI: 16.9 - 25.2) in the public and 21.8 months (95% CI: 17.7 - 31.1) in the private health system, $p=0.92$. Median 1L PFS by treatment received was 13.6 months (95% CI: 6.1-39.0) with CT, 18.4 months (95% CI: 12.1-22.1) with CT followed by ET +/-CDK4/6i, 21.9 months (95% CI: 17.3-25.5) with ET and 31.1 months with ET plus CDK 4/6i (95% CI: 15.8-42.8). Overall, median OS was 52.8 months (95%CI 49.4-NR). The 4-year OS rate per 1L treatment received were 50.3% (95% CI: 28.7-68.5) with CT, 39.0% (95% CI: 13.9-63.8) CT followed by ET +/- CDK4/6i, 74.4% (95% CI: 58.0-85.1) with ET alone, 71.3% (95% CI: 49.6-85.0) ET + CDK4/6i, 50.3% (95% CI: 28.7-68.5) with CT and 39.0% (95% CI: 13.9-63.8) CT followed by ET +/- CDK4/6i. Conclusion: ET is the most commonly used 1L treatment in clinical practice in Brazil, followed by ET + CDK4/6i and CT. A large difference in CDK4/6i use was observed between private and public health systems, reflecting the current limited access to CDK4/6i in Brazil. This study highlights treatment disparities within a nation with a fragmented health insurance system.

Table 1. Treatment Patterns in Public and Private Healthcare Systems

Treatment	Public (n=156)	Private (n=151)	Both (N=307)
Chemotherapy	32 (20.5)	23 (15.2)	55 (17.9)
Chemotherapy followed by ET	27 (17.3)	8 (5.3)	35 (11.4)
Chemotherapy followed by ET + CDK 4/6 inhibitor	1 (0.6)	6 (4.0)	7 (2.3)
Endocrine therapy	90 (57.7)	40 (26.5)	130 (42.4)
Endocrine therapy + CDK 4/6 inhibitor	4 (2.6)	73 (48.3)	77 (25.1)
None*	2 (1.3)	1 (0.7)	3 (1.0)

*Patients died before being treated; $P<0.001$

PO3-05-04

Characteristics and clinical outcome of patients with HR positive HER2 low metastatic breast cancer treated with CDK 4/6 inhibitors

Presenting Author(s) and Co-Author(s):

- K. Čular. Department of Oncology, University Hospital Center Zagreb, United States
K. Kanceljak. Department of Oncology, University Hospital Center Zagreb, United States
A. Glas. Department of Urology, University Hospital Sveti Duh, United States
D. Gudelj. Department of Oncology, University Hospital Centre Zagreb, United States
M. Križić. Department of Oncology, University Hospital Center Zagreb, United States
M. Popović. Department of Oncology, University Hospital Center Zagreb, United States
N. Dedić Plavetić. University Hospital Centre Zagreb, United States
M. Sirotković-Skerlev. Department of Oncology, Division of Pathophysiology and Experimental Oncology, University Hospital Center Zagreb, United States
S. Pleština. Department of Oncology, University Hospital Center Zagreb, United States
T. Silovski. Department of Oncology, University Hospital Center Zagreb, United States

Introduction Breast cancer (BC) is a disease characterized by significant intra- and intertumoral heterogeneity. Hence, it is not surprising that new subtypes with distinct biological features are being discovered, even among previously well-defined BC groups. Recently, HER2-low BC emerged as a new entity with specific clinical behavior, response to treatment and prognosis. HER2-low is a subset of HER2-negative BC, with HER2 immunohistochemical (IHC) score of 1+ or 2+, without HER2 gene amplification measured by in situ hybridization (ISH). As new therapeutic options become available for HER2-low patients, the best treatment sequence is yet to be determined. Furthermore, it is important to distinguish whether there is a difference in the response to standard treatment lines, such as CDK 4/6 inhibitors in metastatic HR positive BC patients, depending on HER2-low status. **Methods** A retrospective study of 369 metastatic BC (mBC) cases who started CDK 4/6 inhibitor therapy from January 2018 through December 2022 at University Hospital Centre Zagreb was conducted, with prior Ethics Committee approval. All patients with HR positive HER2 negative mBC, determined by standard IHC and ISH, were included in the research. Patient demographics and clinical presentation, tumor characteristics and treatment information were collected. Progression-free survival (PFS) analysis was done with the final data cut-off date being June 1st, 2023. Type 1 right censoring was performed. The data was analyzed using the Kaplan-Meier method and Cox proportional-hazards regression for clinically relevant covariates (age, line of treatment, de novo metastatic disease, endocrine resistance, liver metastases, and detected PIK3CA mutation). **Results** Median follow-up was 23 months. Of the 283 patients included, 146 (51.59%) had HER2-low disease. A change in HER2 expression between primary tumor and metastasis was found in 16.96% (N=48) patients. Of them, 10.25% (N=29) who were initially HER2-low, were found to be HER2-0 in metastatic disease. Meanwhile, 6.71% (N=19) of patients had a change in HER2 expression from 0 to low upon becoming metastatic. In the HER2-low group, 47.06% (N=45) patients had a PIK3CA mutation as opposed to 33.33% (N=30) in the HER2-0 group. Odds ratio for a PIK3CA mutation in HER2-low patients was 1.86 (95% confidence interval (CI): 1.01-3.43, p-value 0.046). Median PFS in the HER2-low group was 18 months (95% confidence interval (CI): 14-24) versus 23 (95% CI: 18-30) in the HER2-0 group. Using multivariable analysis an adjusted hazard ratio of 1.15 (95% CI: 0.84-1.57; p-value 0.389) was calculated. Covariates associated with a statistically significant increased risk of disease progression were

a higher line of therapy (HR 1.39, 95% CI 1.36-1.71, p-value 0.002) and the presence of liver metastases (HR 2.17, 95% CI 1.42-3.32, p-value 0.0004). A covariate associated with a statistically significant longer PFS was de novo metastatic disease (HR 0.63, 95% CI 0.41-0.97, p-value 0.034). Conclusion There was a trend toward worse PFS in HER2-low mBC that did not reach statistical significance. HER2-low patients were more likely to harbor PIK3CA mutations than HER2-0 patient group. Longer follow-up and a larger cohort are needed in order to make definitive conclusions.

PO3-05-05

The effect of histological breast cancer subtype on progression free survival in patients with CDK4/6 inhibitors

Presenting Author(s) and Co-Author(s):

C. Bauters. KU Leuven, United States

K. Van Baelen. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, Leuven, Vlaams-Brabant, Belgium

H. Wildiers. University Hospitals Leuven, United States

G. Floris. University Hospitals Leuven, United States

S. Han. University Hospitals Leuven, Leuven, Vlaams-Brabant, Belgium

P. Berteloot. University Hospitals Leuven, United States

T. Baert. UZ Leuven, United States

A. Smeets. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, United States

I. Nevelsteen. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, Leuven, Belgium

Y. Van Herck. UZ Leuven, United States

A. Deblander. University Hospitals Leuven, United States

C. Remmerie. Multidisciplinary Breast cancer Center (MBC), University Hospitals Leuven, Leuven, Belgium, United States

L. Dullens. KU Leuven, United States

M. Van Houdt. UZ Leuven, United States

A. Laenen. KU Leuven, United States

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

Background: Multiple trials have proven that adding CDK4/6 inhibitors to endocrine treatment increases progression free (PFS) and overall survival (OS) of patients with metastatic estrogen receptor (ER)-positive HER2 negative breast cancer. However, only limited evidence is available of treatment efficacy of CDK4/6 inhibitors for invasive lobular carcinoma (ILC). This retrospective study aims to compare treatment duration of the three FDA/EMA approved CDK4/6 inhibitors in patients with no special type (NST) breast cancer versus patients with ILC. **Methods:** All patients with metastatic ER-positive HER2-negative breast cancer who were treated with a CDK4/6 inhibitor (1st, 2nd, 3rd line) in University Hospitals Leuven between December 2014 and February 2023, were included. A comparison of PFS and OS was made between patients with NST and ILC by use of the Kaplan Meier method. Other histological subtypes as well as mixed subtypes were excluded. Uni- and multivariable cox regression models were performed to quantify the association of histological subtype with PFS and OS. **Results:** A total of 418 patients were included of which 119 (28.5%) patients with ILC (median age at primary diagnosis 59 years, range 36 – 89 years) and 299 (71.5%) patients with NST (median age at primary diagnosis 55 years, range 23 – 90 years). Median follow-up was 26.8 months (range 1.1 – 88.1 months). Median PFS was 15.2 months (range 1.0 – 74.6 months) and 14.7 months (range 1.0 – 89.3 months) for patients with ILC and NST respectively. The OS

rate after 60 months follow up was 39.2 % (CI 26.8 – 51.4) for ILC and 40.1% (CI 32.2 – 47.8) for NST. As shown in table 1, clear differences were observed in PFS rates after 12, 24 and 60 months between patients with NST that received CDK4/6 inhibitors in first line versus second or third line. These differences were less apparent for patients with ILC. For both NST and ILC, endocrine resistance at start of CDK4/6 inhibition impacted PFS rates negatively (table 2). In multivariable analyses, histological subtype was not predictive for CDK4/6 inhibition outcome (PFS: hazard ratio (HR) 0.996, CI 0.728 – 1.364, p-value 0.981; OS: HR 0.872, CI 0.602 – 1.263, p-value 0.468). Endocrine sensitivity vs. resistance at the time CDK4/6 inhibitor was started, was proven to be predictive for both PFS (HR 0.478, CI 0.337 – 0.678, p-value < 0.001) and OS (HR 0.528, CI 0.347 – 0.804, p-value 0.003). Conclusion: In our center, the histological subtype of breast cancer did not seem to impact PFS and OS significantly after treatment with CDK4/6 inhibition. Patients with NST seemed to have an increased benefit in PFS from treatment with CDK4/6 inhibition in first line as compared to later lines. While for patients with ILC, no difference between treatment lines were observed. Therefore, clinicians might be able to safely postpone CDK4/6 inhibitors to second- or third-line treatment in patients with metastatic ILC.

Table 1: PFS rates by histological subtype and line of CDK4/6 treatment

Months	% PFS (95% CI)			
	NST		ILC	
	Line 1	Line 2/3	Line 1	Line 2/3
12	73.76 (67.20;79.21)	47.53 (35.76;58.39)	69.17 (57.28;78.36)	67.23 (49.53;79.90)
24	55.00 (47.49;61.87)	31.62 (21.24;42.51)	42.30 (30.07;54.01)	46.96 (30.01;62.21)
60	32.02 (23.45;40.90)	9.52 (3.06;20.46)	20.38 (9.81;33.62)	11.18 (2.32;27.95)

CI: confidence interval; ILC: invasive lobular carcinoma, NST: no special type; PFS: progression free survival

Table 2: PFS rates by histological subtype and endocrine sensitivity at start of CDK4/6 inhibition

% PFS (95% CI)				
Months	NST		ILC	
	Sensitive	Resistant	Sensitive	Resistant
12	80.92 (73.69;86.34)	51.28 (42.41;59.45)	77.60 (63.12;86.96)	61.62 (48.40;72.40)
24	65.46 (56.72;72.86)	30.58 (22.62;38.90)	54.32 (38.15;67.95)	36.47 (24.26;48.74)
60	38.36 (26.97;49.63)	11.67 (5.80;19.77)	22.41 (8.46;40.41)	12.77 (4.76;24.88)

CI: confidence interval; ILC: invasive lobular carcinoma, NST: no special type; PFS: progression free survival

PO3-05-06

Targeting PAM50 HER2-Enriched intrinsic subtype with enzalutamide in hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer: results of the SOLTI-1502 ARIANNA trial.

Presenting Author(s) and Co-Author(s):

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

T. Pascual. SOLTI Cancer Research Group, Barcelona, Spain /Department of Medical Oncology, Hospital Clínic de Barcelona, Spain / Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

S. Pernas. SOLTI Cancer Research Group, Barcelona, Spain Institut Catala d'Oncologia; IDIBELL, L'Hospitalet, Barcelona, Spain

M. Margelí. SOLTI Cancer Research Group. Medical Oncology Department, ICO Badalona, B-ARGO Group. GEICAM Spanish Breast Cancer Group., Catalonia, Spain

S. Blanch. Medical Oncology Department, IVO Instituto Valenciano de Oncología, Barcelona, Spain, United States

B. Adamo. Medical Oncology Department, Hospital Clínic de Barcelona ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain, Catalonia, Spain

F. Salvador Bofill. Hospital Universitario Virgen del Rocío, Seville, Spain, Andalucia, Spain

X. Gonzalez-Farré. Instituto Oncológico Dr. Rosell, Hospital General de Catalunya, Catalonia, Spain

S. Chillara. SOLTI Breast Cancer Research Group, Spain

P. Galván. Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

E. Sanfeliu. August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Spain

P. Blasco. August Pi i Sunyer Biomedical Research Institute (IDIBAPS), United States

V. Sirenko. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, United States

A. Espinosa. SOLTI Cancer Research Group, Catalonia, Spain

C. Perou. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA, United States

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

L. Manso. Hospital Universitario 12 de Octubre, Madrid, Spain

Background Pre-clinical evidence and retrospective studies suggest that PAM50 HER2-Enriched (HER2-E), HR+/HER2- tumors have estrogen receptor (ER) independence and poor prognosis but seem to have androgen receptor (AR)-addiction. Enzalutamide (ENZ) is a potent inhibitor of AR signaling. We hypothesized that ENZ may induce a significant proliferative arrest in PAM50 HER2-E, HR+/HER2-negative advanced breast cancer (ABC), leading to clinical benefit in this poor prognosis population. Methods Eligible patients (pts), males or pre/post-menopausal women with advanced HR+/HER2- ABC resistant to endocrine therapy, received ENZ 160 mg/day until disease progression. Pts were assigned to different cohorts according to

PAM50 intrinsic subtypes identified in the pre-treatment tumor biopsy: Cohort A included pts with HER2-E and Cohort B pts with Luminal A/B tumors. Centralized molecular assessment of pre-treatment and C1D15 tumor biopsies were required for the primary endpoint evaluation. After C1D15 biopsy, exemestane 50mg QD could be added to ENZ at physician's discretion. Tumor assessments were performed every 8 weeks. Primary efficacy endpoint was the relative change in the PAM50 11-gene proliferation-related signature in Cohort A. Secondary objectives included anti-proliferative effect of ENZ in Cohort B, overall response rate (ORR), Clinical benefit rate (CBR; partial response [PR] + stable disease \geq 24 weeks) progression-free survival (PFS), and safety. Results From June 2020 to October 2022, 47 tumors were screened, and 6 PAM50 HER2-E tumors were identified (13%). A total of 34 pts were enrolled: 6 pts in Cohort A and 28 pts in Cohort B. Among them, 4 pts from Cohort A received ENZ plus exemestane and 23 pts in Cohort B. Mean age was 59 (range 39-76), 89% of pts were postmenopausal, 74% had liver disease, and 59% received (neo)adjuvant treatment. The median number of lines for ABC was 4 (1-8). Mean Ki67 (central assessment) in Cohort A was 37% (5%-70%), while in Cohort B it was 30% (3%-90%). Mean central AR in Cohort A was 66% (30-100), while in Cohort B it was 55% (1-100). The mean suppression of PAM50 11-gene proliferation-signature after 2 weeks of treatment with ENZ was 3.7% ($p=0.848$) in Cohort A and 1.2% ($p=0.909$) in Cohort B. The median change in Ki67 levels in Cohort A was -0.43% ($p=0.812$), while in Cohort B it was +3.86% ($p=0.081$). No statistically significant differentially expressed genes or changes in intrinsic subtypes were observed. Overall, the median PFS was 1.8 months (95% CI 1.6-1.8). In Cohort A, median PFS was 1.6 months (95% CI 1.0-1.9), and in Cohort B, it was 1.8 months (95% CI 1.6-1.8). CBR was 0% and 11% ($n=3$, 95% CI 2.8-25.9%) in Cohorts A and B, respectively. A PR with 16 months duration in cohort B was observed in a patient with an AR-mutated tumor (AR c. 689C >T). Regarding safety, grade 1-2 and 3-4 toxicities occurred in 94.1% and 35.3% of patients, respectively. ENZ dose reduction and discontinuation occurred in 2 (5.9%) and 3 (8.8%) pts, respectively. The most common toxicities related to ENZ were nausea ($n=8$, 24%), decreased appetite ($n=8$, 24%), AST increase ($n=6$, 18%) and vomiting ($n=6$, 18%).

Conclusions The hypothesis that ENZ could induce proliferation arrest in HR+/HER2-, PAM50 HER2-E tumors was not confirmed, and ARIANNA was prematurely closed due to the lack of efficacy. Additional research is needed to explore if ENZ may benefit specific populations of pts with breast cancer (e.g. AR-mut tumors) and whether alternative AR modulators are more effective in blocking AR signaling in HR+/HER2-, PAM50 HER2-E tumors

PO3-05-07

SOLTI-1718 NEREA Trial: Neratinib in hormone receptor (HR)-positive/HER2-negative HER2-enriched (HER2-E) advanced breast cancer (BC)

Presenting Author(s) and Co-Author(s):

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

X. Gonzalez-Farré. Instituto Oncológico Dr. Rosell, Hospital General de Catalunya, Catalonia, Spain

F. Salvador Bofill. Hospital Universitario Virgen del Rocío, Seville, Spain, Andalucia, Spain

M. Vidal. Medical Oncology Department, Hospital Clínic of Barcelona ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; SOLTI Breast Cancer Research Group ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Catalonia, Spain

I. Blancas. Medical Oncology Dept, University Hospital San Cecilio, Granada, Spain

E. López-Miranda. Medical Oncology Department, Hospital Ramon y Cajal, Spain

M. Iglesias. Medical Oncology Department, Hospital Son Llatzer, Spain

M. Arumí. Vall d'Hebron University Hospital, Barcelona, Spain, United States

M. Margelí. SOLTI Cancer Research Group. Medical Oncology Department, ICO Badalona, B-ARGO Group. GEICAM Spanish Breast Cancer Group., Catalonia, Spain

C. Pulido. Medical Oncology Department, Hospital da Luz Lisboa, Portugal

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

F. Henaó. Medical Oncology Hospital Virgen de la Macarena, Sevilla, United States

P. Sanchez. Hospital Universitario Virgen de la Arrixaca, Spain

S. Alves. 1Medical Oncology Department, Instituto Português de Oncologia do Porto FG, EPE (IPO-Porto), Portugal

A. Godoy Ortiz. UGCI Oncología Medica, Hospitales Universitarios Regional y Virgen de la Victoria de Málaga, Spain. Universidad de Málaga (UMA). Centro de Investigación Biomédica en Red de Oncología, CIBERONC-ISCIII. GEICAM Breast Cancer Group, Spain

J. Passos Coelho. Hospital da Luz, Lisboa, Portugal, Lisboa, Portugal

S. Escrivá-de-Romaní. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

A. Espinosa. SOLTI Cancer Research Group, Catalonia, Spain

T. Pascual. SOLTI Cancer Research Group, Barcelona, Spain /Department of Medical Oncology, Hospital Clínic de Barcelona, Spain / Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

Background Breast cancer (BC) is a clinically and biologically heterogenous disease where intrinsic subtypes play a role. Non-luminal subtypes within HR+/HER2-negative disease do not benefit to the same extent from standard of care treatments as the luminal subtypes. Thus,

other strategies are needed. HER2-E subtype represents approximately 15.0% of HR+/HER2-negative tumors in metastatic setting. According to an exploratory analysis of EGF30008 trial, HER2-E advanced BC patients, despite presenting poor outcomes across treatments, showed benefit from anti-HER2 therapy with lapatinib. Here, we report the efficacy and safety of the NEREA trial, the first study designed to evaluate neratinib and endocrine therapy in HR+/HER2-negative, PAM50 HER2-E ABC. Methods SOLT1-1718 NEREA (NCT04460430) is a single-arm, multicenter phase II study evaluating neratinib in combination with endocrine therapy (ET) in patients with HR+/HER2-, PAM50 HER2-E ABC. Key inclusion criteria include progression to prior endocrine therapy, ≤ 1 line of chemotherapy for advanced breast cancer (ABC), ECOG 0-1, and HER2-E disease by PAM50 on a metastatic tumor biopsy. The availability of a metastatic tumor sample was mandatory in the pre-screening phase to assess PAM50 subtype. Included patients received neratinib 240 mg daily in combination with ET, with either exemestane, fulvestrant or tamoxifen (as per investigator's decision). All patients received prophylactic loperamide with an established dosing scheme during the first cycle and on-demand in subsequent cycles. The primary endpoint was progression-free survival rate at 6 months (PFS6). Secondary endpoints include other efficacy endpoints and safety.

The study was based on a Simon two-stage design. Stage I of the trial would be considered successful if at least 14 of 33 patients achieved PFS > 6m. In that case, the trial would recruit up to 56 patients for a target PFS6 $\geq 50\%$. Results. Between July 2020 and June 2022, molecular subtyping was performed on tumors from 136 patients, and 18 HER2-E tumors were identified (7.6%). 12 evaluable patients were enrolled. Baseline characteristics were as follows: median age 60 years, 91.7% of pts were postmenopausal, 75% had visceral disease and 59% received (neo)adjuvant treatment. The median number of lines for ABC was 3 (1-5). Neratinib was combined with exemestane (41.7%), fulvestrant (33.8%) and tamoxifen (25%).

At the time of data cut-off (June 2023), 9 patients (75%) had stopped their treatment because of PD and 2 (16.7%) due to toxicity. The PFS6 months occurred in one patient (8.3%, CI: 0.2% - 38.5%). Median PFS was 1.7 months (95% CI 1.6-1.9) with a patient still on treatment after 27.1 months.

The incidence of treatment-related adverse events (trAEs) was 25%; diarrhea (25%), asthenia (16.7%), nausea (8.3%), vomiting (8.3%) and rash (8.3%) were most common and were predominantly grade 1/2. 25% of patients experienced grade 3 trAEs. Conclusions. Due to slow enrollment, the study was stopped early. At the time of study close, the hypothesis that neratinib has efficacy in HR+/HER2-, PAM50 HER2-E tumors was not confirmed.

We thank PUMA BIOTECHNOLOGY, INC for their provision of Neratinib and financial contribution to the study.

PO3-05-08

Updated results from VERITAC evaluating vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, in ER-positive/human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer

Presenting Author(s) and Co-Author(s):

S. Hurvitz. Fred Hutchinson Cancer Center, Seattle, Washington, United States
A. Schott. Rogel Cancer Center, University of Michigan Health, Ann Arbor, Michigan, United States
C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States
R. Nanda. University of Chicago Medicine, Chicago, Illinois, United States
G. Zahrah. Whittingham Cancer Center, Norwalk, Connecticut, United States
N. Hunter. Fred Hutchinson Cancer Center, Seattle, Washington, United States
A. Tan. Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, United States
M. Telli. Stanford University School of Medicine, San Francisco, California, United States
J. Anampa Mesias. Albert Einstein College of Medicine, Bronx, NY, United States
R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
P. Munster. University of California San Francisco, San Francisco, California, United States
E. Zhi. Arvinas Operations, Inc., New Haven, Connecticut, United States
E. Duperret. Arvinas Operations, Inc., New Haven, Connecticut, United States
C. Mather. Arvinas, Inc, New Haven, Connecticut, United States
E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States
H. Han. H. Lee Moffitt Cancer Center, Tampa, Florida, United States

Background: Vepdegestrant (ARV-471) is an oral PROTAC ER degrader with activity toward wild-type and mutant ER. The phase 2 expansion (VERITAC) of a phase 1/2 study (NCT04072952) tested 2 vepdegestrant doses (200 mg once daily [QD] and 500 mg QD) in heavily pretreated patients with ER+/HER2- advanced breast cancer. Vepdegestrant 200 mg QD was selected as the phase 3 monotherapy dose based on comparable efficacy and favorable tolerability vs 500 mg QD and robust ER degradation (data cutoff: Jun 6, 2022). We present updated data for the vepdegestrant 200 mg QD cohort after 12 additional months of follow-up.

Methods: Vepdegestrant was administered to patients with ER+/HER2- locally advanced/metastatic breast cancer who had received ≥ 1 prior endocrine therapy for ≥ 6 months, ≥ 1 cyclin-dependent kinase (CDK)4/6 inhibitor, and ≤ 1 chemotherapy regimen. The primary endpoint was clinical benefit rate (CBR; rate of confirmed complete response, partial response, or stable disease ≥ 24 weeks).

Results: As of Jun 6, 2023, 35 patients received vepdegestrant 200 mg QD; 34 (97.1%) were female and median age was 63 y (range: 42–79). Patients had received a median of 4 prior regimens (range: 1–9) in all settings and 3 prior regimens (range: 0–7) in the metastatic setting; 100% had prior CDK4/6 inhibitors, 88.6% had prior aromatase inhibitors, 74.3% had prior fulvestrant, and 74.3% had prior chemotherapy (45.7% in metastatic setting). CBR with vepdegestrant 200 mg QD was 37.1% (95% CI: 21.5–55.1) in all evaluable patients (n=35) and

the objective response rate was 8.3% (95% CI: 1.0–27.0) among 24 patients with measurable disease at baseline. Median progression-free survival in all evaluable patients was 3.5 months (95% CI: 1.8–8.2). As of the data cutoff date, 14 patients in the 200 mg QD cohort received treatment for ≥ 24 weeks (4 for ≥ 48 weeks) with 1 patient ongoing. No patients required a dose reduction due to a treatment-emergent adverse event (TEAE); 2 (5.7%) patients had a TEAE that led to vepdegestrant discontinuation (grade 3 QT prolongation and grade 3 anemia). The most common treatment-related adverse events ($\geq 10\%$) were fatigue (43%), hot flush (20%), nausea (17%), arthralgia (11%), increased aspartate aminotransferase (11%), and increased blood alkaline phosphatase (11%); all were grade 1/2. Substantial on-treatment decreases in mutant ESR1 circulating tumor DNA levels were observed with vepdegestrant 200 mg QD and sustained for multiple treatment cycles.

Conclusions: With 12 months of additional follow-up from the first data report, durable clinical activity with vepdegestrant 200 mg QD was seen in heavily pretreated patients with ER+/HER2- advanced breast cancer, in addition to sustained reduction in circulating mutant ESR1 tumor DNA levels. Vepdegestrant 200 mg QD continued to show a favorable safety profile. The ongoing global, randomized phase 3 VERITAC-2 study (NCT05654623) is evaluating vepdegestrant 200 mg QD vs intramuscular fulvestrant in patients with ER+/HER2- advanced breast cancer after prior combination CDK4/6 inhibitor therapy and endocrine therapy.

PO3-05-09

The impact of body mass index on CDK4/6 inhibitor treatment survival outcomes in metastatic breast cancer

Presenting Author(s) and Co-Author(s):

F. Zhang. Montefiore Medical Center, United States

J. Anampa Mesias. Albert Einstein College of Medicine, Bronx, NY, United States

Introduction: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6is) are important in the treatment of hormone receptor-positive (HR+)/HER2-negative metastatic breast cancer (MBC). Previous studies have shown that CDK4/6is affect metabolic processes and cell metabolism, including adipogenesis, lipid synthesis, and glucose regulation. Obesity has been associated with worse survival in breast cancer. We aimed to assess the effect of body mass index (BMI) on survival outcomes in patients treated with CDK4/6is for MBC.

Methods: Patients diagnosed with metastatic HR+/HER2-negative BC and who were treated with palbociclib, ribociclib, or abemaciclib from 6/10/2015 to 12/28/2022 were selected from the Montefiore Health system database and followed until 3/24/2023. The patients were divided into three groups according to BMI level as follows; normal: 18.5-24.9 kg/m², overweight: 25-29.9 kg/m² and obese: ≥ 30 kg/m². Patients were also stratified by BMI measured after 3 months of therapy. Characteristics of the patients and tumors in the subgroups were compared using chi-squared/Fisher's exact test for categorical data and Kruskal-Wallis/Wilcoxon signed rank tests for continuous data. Kaplan-Meier and Cox proportional hazards analysis were used to compare overall survival (OS) and progression free survival (PFS).

Results: Among 221 patients, 66 were normal weight, 78 were overweight, and 77 were obese. There was no statistically significant difference in clinicopathological characteristics among the cohorts. Neither BMI measured at baseline nor after 3 months of therapy had any association with OS (P = 0.8 at baseline and P = 0.1 after 3 months) or PFS (P = 0.4 at baseline and P = 0.6 after 3 months). Multivariable analysis showed no statistically significant association between BMI and worse OS (HR: 1.1 for overweight, P = 0.7; and 0.96 for obese, P = 0.9) or worse PFS (HR: 0.9 for overweight, P = 0.8; and 0.76 for obese, P = 0.5). Multivariate analysis revealed a significant effect of obese BMI after 3 months of treatment on OS (HR: 0.48, P = 0.035) but not on PFS (HR: 0.88, P = 0.8). Overweight BMI after 3 months of treatment was not found to have a significant effect on OS (HR: 0.49, P = 0.063) or PFS (HR: 0.89, P = 0.9).

Conclusion: The clinical effectiveness of CDK4/6is was not found to be influenced by BMI measured prior to therapy; however, there may be an association between improved OS and obese BMI after 3 months of treatment.

Table 1

Characteristic	BMI at Baseline			p-value ¹	BMI after 3 Months			p-value ¹
	Normal, N (%)	Overweight, N (%)	Obese, N (%)		Normal, N (%)	Overweight, N (%)	Obese, N (%)	
Demographics								
Age (years)	58.5 (39%)	58.5 (39%)	58.5 (39%)	0.9	58.5 (39%)	58.5 (39%)	58.5 (39%)	0.8
Male	5	5	5	0.9	5	5	5	0.8
Race								
White	32 (24%)	34 (24%)	33 (24%)	0.9	32 (24%)	33 (24%)	33 (24%)	0.8
Black	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
Asian	1 (1%)	1 (1%)	1 (1%)	0.9	1 (1%)	1 (1%)	1 (1%)	0.8
Other	1 (1%)	1 (1%)	1 (1%)	0.9	1 (1%)	1 (1%)	1 (1%)	0.8
Unknown	0	0	0	0.9	0	0	0	0.8
Stage								
Female	63 (46%)	77 (54%)	77 (54%)	0.9	63 (46%)	63 (46%)	63 (46%)	0.8
Stage	1.1 (2%)	1.1 (2%)	1.1 (2%)	0.9	1.1 (2%)	1.1 (2%)	1.1 (2%)	0.8
Age Category								
Age < 60	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Age ≥ 60	37 (27%)	46 (32%)	46 (32%)	0.9	37 (27%)	37 (27%)	37 (27%)	0.8
Performance Status								
ECOG	43 (31%)	53 (37%)	54 (38%)	0.9	43 (31%)	43 (31%)	43 (31%)	0.8
WHO	24 (17%)	33 (23%)	33 (23%)	0.9	24 (17%)	24 (17%)	24 (17%)	0.8
Unknown	0	0	0	0.9	0	0	0	0.8
Comorbidities								
Diabetes Mellitus	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Cardiovascular	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Other	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Unknown	0	0	0	0.9	0	0	0	0.8
Chemotherapy System								
System	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Unknown	0	0	0	0.9	0	0	0	0.8
Number of Lines of Chemotherapy								
1	32 (24%)	32 (24%)	32 (24%)	0.9	32 (24%)	32 (24%)	32 (24%)	0.8
2	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
3	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
4	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
5	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
Unknown	0	0	0	0.9	0	0	0	0.8
Time to Progression (TTP)								
Median	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Range	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Unknown	0	0	0	0.9	0	0	0	0.8
Number of Lines of PFS								
1	32 (24%)	32 (24%)	32 (24%)	0.9	32 (24%)	32 (24%)	32 (24%)	0.8
2	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
3	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
4	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
5	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
6	16 (11%)	16 (11%)	16 (11%)	0.9	16 (11%)	16 (11%)	16 (11%)	0.8
Unknown	0	0	0	0.9	0	0	0	0.8
OS								
Median	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Range	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Unknown	0	0	0	0.9	0	0	0	0.8
PFS								
Median	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Range	10 (7%)	10 (7%)	10 (7%)	0.9	10 (7%)	10 (7%)	10 (7%)	0.8
Unknown	0	0	0	0.9	0	0	0	0.8

Baseline characteristics of patients with MBC comparing different BMI groups (normal, overweight, and obese) at baseline prior to therapy and after 3 months of therapy.

Table 2

Characteristic	OS		PFS	
	50% Percentile	p-value ¹	50% Percentile	p-value ¹
BMI at Baseline		0.8		0.4
Normal	35 (24, 45)		42 (24, -)	
Overweight	35 (27, 44)		37 (35, -)	
Obese	32 (23, 43)		38 (35, 50)	
BMI3.Category		0.10		0.6
Normal	35 (21, 45)		35 (24, -)	
Overweight	45 (40, 56)		44 (37, -)	
Obese	35 (24, 50)		38 (32, -)	

¹p<0.05; **p<0.01; ***p<0.001

Median OS and PFS in patients with MBC comparing different BMI groups (normal, overweight, and obese) at baseline prior to therapy and after 3 months of therapy.

Table 3

Characteristic	BMI at Baseline OS			BMI at Baseline PFS			BMI after 3 Months OS			BMI after 3 Months PFS		
	N	HR	p-value ^a	N	HR	p-value ^a	N	HR	p-value ^a	N	HR	p-value ^a
BMI at Baseline	169			169								
Normal	51	—		51	—							
Overweight	55	1.10	0.7	55	0.90	0.8						
Obese	63	0.96	0.9	63	0.76	0.5						
BMI after 3 Months							111			111		
Normal							34	—		34	—	
Overweight							33	0.49	0.063	33	0.89	0.9
Obese							44	0.48	0.035*	44	0.88	0.8
Ethnicity	169			169			111			111		
Hispanic	60	—		60	—		42	—		42	—	
non-Hispanic	109	0.99	>0.9	109	1.50	0.5	69	0.63	0.3	69	0.99	>0.9
Race	169			169			111			111		
White	29	—		29	—		19	—		19	—	
Black	83	1.19	0.6	83	0.94	0.9	52	1.27	0.5	52	0.55	0.4
Asian	8	1.30	0.6	8	1.69	0.5	6	0.98	>0.9	4	1.95	0.8
Other	49	1.35	0.5	49	1.56	0.5	34	0.92	0.9	34	0.39	0.3
Age Category	169			169			111			111		
Age < 50	31	—		31	—		22	—		22	—	
Age >= 50	138	0.62	0.14	138	1.39	0.6	89	0.16	<0.001***	89	0.44	0.3
Visceral Metastases	169			169			111			111		
FALSE	62	—		62	—		43	—		43	—	
TRUE	107	0.84	0.4	107	0.71	0.3	68	1.08	0.8	68	0.69	0.4
Hormone Status	169			169			111			111		
ER+ PR+	119	—		119	—		84	—		84	—	
ER+ PR-	50	0.91	0.7	50	1.23	0.6	27	0.70	0.3	27	0.34	0.2
ER- PR+	0	—		0	—		0	—		0	—	
Grade Category	169			169			111			111		
1-2	102	—		102	—		74	—		74	—	
3	67	0.71	0.2	67	0.76	0.5	37	0.32	0.001**	37	0.33	0.30
Charlson Comorbidity Index	169	1.16	0.031*	169	1.11	0.4	111	1.41	<0.001***	111	1.46	0.013*
Prior Chemotherapy	169			169			111			111		
FALSE	143	—		143	—		95	—		95	—	
TRUE	26	0.98	>0.9	26	0.54	0.4	16	1.11	0.8	16	0.00	>0.9
Prior ET	169			169			111			111		
FALSE	113	—		113	—		77	—		77	—	
TRUE	56	0.57	0.026*	56	0.57	0.2	34	0.35	0.009**	34	0.21	0.008

^ap<0.05. **p<0.01. ***p<0.001.

Multivariable analysis of OS and PFS for patients with MBC comparing different BMI groups (normal, overweight, and obese) at baseline prior to therapy and after 3 months of therapy.

PO3-05-10

Efficacy and safety of eribulin plus gemcitabine in second-line or beyond for patients with HER2-negative metastatic breast cancer (MBC): A multi-center, open-label, single-arm, phase II study

Presenting Author(s) and Co-Author(s):

P. Peng. The Fifth Affiliated Hospital of Sun Yat-sen University, United States

X. Xu. Department of Breast diseases, The Cancer Center of the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, Guangdong, People's Republic of China, United States

J. Zhong. The First Affiliated Hospital Of Guangxi Medical University, No.6 Shuangyong Road Nanning Guangxi, People's Republic of China, United States

J. Ye. The First People's Hospital of Zhaoqing · NO.9 Donggang East Road, Duanzhou District, Zhaoqing City, Guangdong Province, United States

Z. Wang. Jiangmen Central Hospital, 23 Haibian Street, Pengjiang District, Jiangmen City, Guangdong Province, United States

H. Wang. Department of Breast Surgery, Zhuhai Maternity and Child Health Hospital, Zhuhai, Guangdong Province, People's Republic of China, United States

H. Lin. Department of Breast Disease · Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine. Zhuhai City · 519015 · Guangdong Province, People's Republic of China, United States

C. Du. Cancer Hospital Chinese Academy Of Medical Sciences, Shenzhen Center, United States

G. Zou. Department of Medical Oncology, Guangzhou Panyu Central Hospital, United States

J. Ouyang. Dongguan People's Hospital, No. 3, South Wan Road, Xinguyong, Dongguan City, United States

Y. Shi. Department of Breast Disease · Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine. Zhuhai City · 519015 · Guangdong Province. · People's Republic of China, United States

F. Xu. Sun yat-sen university cancer center, United States

G. Yu. Jiangmen Central Hospital, 23 Haibian Street, Pengjiang District, Jiangmen City, Guangdong Province, 529000, United States

Y. Lu. Guangxi Medical University Cancer Center, United States

Y. Wang. Dongguan People's Hospital, No. 3, South Wan Road, Xinguyong, Dongguan City, United States

S. Cui. Breast Center, Department of General Surgery, Zhongshan City People's Hospital, Zhongshan, Guangdong, People's Republic of China, United States

L. Li. Zhongshan Hospital of Traditional Chinese Medicine Affiliated to Guangzhou University of Traditional Chinese Medicine, People's Republic of China, United States

Background: Eribulin is a halichondrin non-taxane inhibitor of microtubule dynamics approved in China for advanced breast cancer patients who have received at least two prior chemotherapy treatments. The combination of eribulin and gemcitabine has demonstrated a similar progression-free survival (PFS) benefit as paclitaxel plus gemcitabine, with less neurotoxicity, for patients with MBC who have not received prior cytotoxic chemotherapy.

However, the effect of eribulin plus gemcitabine on PFS in second line or beyond remains unclear. Methods: This open-label, single-arm, phase II study (NCT05263882) was conducted at 13 institutions in China. Eligible patients had histologically confirmed HER2-negative MBC and had received at least one prior taxane-containing chemotherapy regimen for advanced disease, and anthracycline-containing regimens in the adjuvant setting. Patients received intravenous infusions of eribulin (1.4 mg/m²) and gemcitabine (1.0 g/m²) on days 1 and 8 of a 21-day cycle. Efficacy outcomes, including PFS, objective response rate (ORR), and disease control rate (DCR), were assessed using RECIST v1.1. Adverse events (AEs) were graded according to NCI-CTC version 5.0. Results: A total of 65 patients were enrolled from November 2021 to May 2023; 47 (72.3%) had HR+/HER2- and 18 (27.7%) had triple-negative MBC. The median patient age was 50 years (range: 31-68), and the sites of metastasis were the bone (70.8%), liver (58.5%), lymph nodes (50.8%), lung (43.1%) and brain (10.8%). Patients had received a median of 3 prior lines of systemic treatment, 2 lines of chemotherapy, and 1 line of endocrine treatment. Among all patients, the ORR was 52.3%, the DCR was 92.3% and the median PFS was 7.6 months (Table). For the HR-positive subgroup, the median PFS was 8.4 months, while for the triple-negative subgroup, it was 7.6 months. Among patients who had received prior CDK4/6 inhibitor treatment, the median PFS was 7.2 months. In the subgroup of patients who had not received CDK4/6 inhibitor treatment, the median PFS had not been reached. The most common grade 3-4 AEs were hematological, including neutropenia (41.6%), leukopenia (33.9%), anemia (23.1%), and thrombocytopenia (15.4%). No grade ≥3 perceived AEs were reported. Conclusion: Eribulin plus gemcitabine was effective in heavily pretreated patients with HER2- MBC, while maintaining a predictable and manageable safety profile.

Table. Summary of efficacy outcomes

	Total (N=65)	HR+/HER2- (n=47)	TNBC (n=18)	Post-CDK4/6i (n=27)	CDK4/6i naive (n=20)
ORR, n (%)	34 (52.3)	25 (53.2)	9 (50.0)	14 (51.9)	11 (55.0)
DCR, n (%)	60 (92.3)	45 (95.7)	15 (83.3)	26 (96.3)	19 (95.0)
Median PFS, months (95% CI)	7.6 (6.5, 15.8)	8.4 (6.5, 16.5)	7.6 (3.2, NR)	7.2 (5.0, 15.8)	NR
NR, not reached; TNBC, triple-negative breast cancer.					

PO3-05-11

Enhancing the interpretation of real-world quality of life (QoL) in patients (pts) with hormone receptor positive human epidermal growth factor 2 negative (HR+/HER2-) advanced breast cancer (ABC) enrolled in the POLARIS trial.

Presenting Author(s) and Co-Author(s):

G. Rocque. University of Alabama at Birmingham, Birmingham, Alabama, United States

J. Blum. Texas Oncology, Baylor-Sammons Cancer Center, US Oncology, Dallas, TX, Dallas, Texas, United States

Y. Ji. HealthPartners Cancer Center at Regions Hospital, United States

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

J. Migas. Mid-Illinois Hematology & Oncology Associates, Ltd., United States

S. Lakhanpal. Alabama Oncology, Saint Vincent's Birmingham, Birmingham, Alabama, United States

E. Jepsen. Novant Health, United States

E. Gauthier. Pfizer Inc, San Francisco, California, United States

Y. Wang. Pfizer Inc., New York, New York, United States

M. Montelongo. ICONplc, Blue Bell, Pennsylvania, United States

J. Cappelleri. Pfizer Inc., United States

C. Chen. Pfizer Inc, United States

M. Karuturi. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background POLARIS is a prospective, observational real-world study of pts with HR+/HER2-ABC receiving palbociclib in routine clinical practice. We have previously shown that palbociclib treatment did not have any significant adverse impact on pt QoL when assessed by the EORTC-QLQ-C30 questionnaire,¹ consistent with published clinical trial findings. Now, to enhance interpretation, we sought to characterize EORTC scores (using updated POLARIS data) into terms that are meaningful to pts, physicians, and other stakeholders, using a similar approach to established clinical problem threshold methodology.² Methods EORTC data were collected at baseline (BL), monthly for the first 3 months, and every 3 months thereafter until palbociclib discontinuation. Response options for each EORTC question (ordinal scale from 1=very poor to 7=excellent) were grouped into "favorable" (taking a conservative approach of using only responses 5, 6 or 7) and "less favorable" (response of ≤4) for the two items on global health status/QoL. The proportion of pts with favorable or less favorable response was compared between subgroups (line of therapy, age, race, bone metastases, visceral metastases, and dose modification) at timepoints BL, month 6, 12, and 18 using Fisher's exact test. Results Between January 2017 and December 2018, 1285 pts were enrolled, of whom 1250 received at least one dose of palbociclib and subsequently analyzed as part of the final data cut of 09 Jan 2023. EORTC Q29 – Overall Health completion rates were 1167/1250 (93.4%) at baseline, 732/1250 (58.6%) at month 6, 484/1250 (38.7%) at month 12, and 353/1250 (28.2%) at month 18 (Table). The proportion of pts with a favorable response for

EORTC Q29 was consistently higher than with a not favorable response (BL, 56.1% vs 43.9%; month 6, 69.3% vs 30.7%; month 12, 68.6% vs 31.4%; and month 18, 70.0% vs 30.0%; Table). When analyzed by subgroup, no significant differences were observed in the proportion of pts with a favorable (to less favorable) response for any subgroup covariate, except for age at BL; however, this significance was not observed at month 6, 12 or 18 (Table). Similar results were observed for EORTC Q30 – Overall QoL (data not shown). Conclusions The proportion of pts indicating a favorable response in the EORTC questionnaire Overall Health and Overall QoL questions increased or were maintained in pts with HR+/HER2- ABC treated with palbociclib from BL through to month 18 across overall and all subgroups. It is important to note that these data are conditional on the pts who responded to the questions, whose numbers diminished over time.

Table. Item-level analysis of EORTC Overall Health

Subgroup		Number of patients with a favorable response, n (%) ^a			
		Baseline (n=1167)	Month 6 (n=732)	Month 12 (n=484)	Month 18 (n=353)
Full population		655 (56.1)	507 (69.3)	332 (68.6)	247 (70.0)
Subgroups					
LOT	1L	464 (54.7)	385 (69.9)	256 (69.4)	198 (71.7)
	≥2	191 (59.9)	122 (67.4)	76 (66.1)	49 (63.6)
BL Age, years	<70	248 (62.2)	170 (68.8)	118 (72.4)	87 (70.7)
	≥70	407 (53.1)	337 (69.5)	214 (66.7)	160 (69.6)
Race ^b (BIPOC)	Yes	134 (62.1)	101 (68.7)	59 (62.8)	54 (77.1)
	No	492 (56.7)	387 (69.4)	259 (70.0)	186 (68.9)
BL bone metastases	Bone only	249 (55.1)	181 (65.3)	109 (64.9)	78 (63.9)
	Bone + other	195 (50.9)	172 (69.1)	122 (72.2)	88 (70.4)
BL visceral disease	Yes	245 (53.3)	189 (70.5)	119 (66.5)	83 (67.5)
	No	410 (58.0)	318 (68.5)	213 (69.8)	164 (71.3)
Dose modification	Yes	266 (59.2)	237 (71.8)	169 (69.3)	129 (67.2)
	No	389 (54.2)	270 (67.2)	163 (67.9)	118 (73.3)

Note: Comparative statistical p-values were derived using Fisher's exact test on the association of EORTC domains (favorable/less favorable) with each subgroup at timepoint. All Fisher's exact test subgroup comparisons were not considered to be significant (i.e., $p > 0.10$), except age at baseline ($p=0.003$).

^a Remainder (to 100%) are less favorable.

^b Totals differ from overall totals owing to missing ethnicities.

BL, baseline; BIPOC, black, indigenous, and people of color; EORTC, European Organization for Research and Treatment of Cancer; LOT, line of therapy.

PO3-05-12

Randomized Phase 2 of Bria-IMT, an Allogenic Human Cell Line with Antigen Presenting Activity, in Heavily Pretreated Metastatic Breast Cancer.

Presenting Author(s) and Co-Author(s):

C. Calfa. University of Miami Miller School of Medicine, United States

C. Nangia. Hoag Hospital Newport Beach, United States

M. Barve. Mary Crowley Cancer Research, Dallas, TX, USA, United States

J. Knecht. Tranquil Clinical Research, United States

J. Holmes. St. Joseph Hospital, United States

K. Roland. Carle Clinic, United States

R. Boccia. The Center for Cancer and Blood Disorders, United States

F. Valdes-Albini. University of Miami, United States

Z. Gostout. BriaCell Therapeutics, United States

M. Chang. BriaCell Therapeutics, Pennsylvania, United States

W. Williams. BriaCell Therapeutics, Havertown, Pennsylvania, United States

C. Wiseman. Briacell Therapeutics, Jerusalem, Israel

B. Guerin. Atlantic Health, United States

S. Dakhil. Cancer Center of Kansas, United States

G. Del Priore. BriaCell Therapeutics, Philadelphia, Pennsylvania, United States

S. Chumsri. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

Introduction Despite progress in MBC, too many continue to succumb due to treatment resistance or intolerance. SV-BR-1-GM is an allogenic human breast cancer cell line with antigen presenting cell activity designed to overcome the immune-suppressive tumor microenvironment while being acceptable to extensively pretreated contemporary MBC patients. We report interim exploratory analysis of the ongoing RCT of the Bria-IMT regimens. **Methods** An interim exploratory analysis using preliminary partially available evaluable data of the ongoing prospective, randomized phase 2 (NCT03328026; 2018-present) of Bria-IMT (irradiated SV-BR-1-GM) with a PD-1 check point inhibitor (CPI) every 3 weeks (25 patients dosed to date). Both regimens include cyclophosphamide 300 mg/m² 48-72 hours prior to intradermal Bria-IMT (~20 x 10⁶ cells) followed by interferon-alpha at the inoculation sites 2 days later. The control arm used the original sequence with simultaneous start of Bria-IMT and CPI in cycle 1. The experimental arm started CPI in cycle 2 after the 2nd inoculation. Candida skin test was performed before cycle 1 to determine anergy status while delayed-type hypersensitivity skin test (DTH), defined as >5mm erythema & induration, was done at every cycle by intradermal injection of a small test dose of Bria-IMT prior to full dose inoculation. **Results** Median age: 58 (range 37-81); median prior therapies: 8 lines (range 4-18); 89% were grade 2/3 (n=18); 68% hormone receptor positive; 61% HER2 negative, 33% HER2 low, and 6% HER2 high; 33% triple negative. Overall, 53% of subjects had a clinical benefit as best response by BICR, PI or target lesion measurement. The two treatment arms were similar with a trend showing longer median durations on therapy (mDOT) of 3.7 mo in the experimental delayed CPI arm compared with mDOT = 2.9 for original sequence control arm. 47% of patients were anergic to candida. Among all anergic subjects, the mDOT was 3.5 compared to 2.5 mo for non-anergic patients. However, among anergic subjects, the alternative treatment arm had a

lower risk of treatment discontinuation (improved HR) with mDOT of 3.7 compared to the 3.3 mo mDOT of the original treatment. 50% of anergic subjects eventually developed DTH to SV-BR-1-GM. mDOT was 4.0 mo for DTH+ pts vs 3.0 mo for those who did not mount DTH. Median OS was not yet reached; mean OS was higher in non-anergic vs anergic pts. Among those who developed an inoculation site reaction to Bria-IMT, OS was greater than for those who did not. Time on the Bria-IMT regimen exceeded the time on penultimate treatment in 22% of subjects while 33% of subjects with prior CPI use exceeded last therapy. AEs were mild with 28% of subjects (n=7) having > grade 3 events. The most common grade 3+ AE was lipase increase (n=3). One subject with encouraging changes in peripheral blood tumor markers and CTCs completed a PET study using Zr-89 crefmirlimab berdoxam, a zirconium-89 labelled truncated antibody specific to human CD8 α (CD8 Immuno-PET) and demonstrated increased uptake in some metastatic lesions and draining lymph nodes. Updated results will be provided at the meeting. Conclusion Sequencing of CPI with Bria-IMT is associated with differential clinical outcome trends but not statistically significant in this interim preliminary exploratory analysis regardless of prior CPI use. Bria-IMT is immunogenic with clinical benefit demonstrated for both treatment schedules among patients with inducible DTH reactions. Patients who develop an immune response to Bria-IMT had an increase in OS compared to those who did not. The nodal localization of CD8+ cells on PET may indicate a systemic activation of CD8 positive lymphoid cells. It also provides support that the Bria-IMT + CPI combination immune-based therapy can result in an increase of CD8+ tumor infiltrating lymphocytes in breast cancer metastatic sites. These preliminary results will be evaluated in the ongoing randomized phase 3 pivotal registrational trial.

PO3-05-13

A Multi-Institutional Review of Contralateral Axillary Metastases: Time for Reclassification as Local-Regional Event?

Presenting Author(s) and Co-Author(s):

M. Flanagan. University of Washington / Fred Hutchinson Cancer Center, Seattle, Washington, United States

S. Downs-Canner. Memorial Sloan Kettering Cancer Center, United States

S. Thomas. Duke University School of Medicine, Durham, North Carolina, United States

A. Botty van de bruele. Duke University School of Medicine, North Carolina, United States

M. Lillie. University of North Carolina, United States

K. Gallagher. UNC-CH, Chapel Hill, North Carolina, United States

T. Gibson. Mayo Clinic, United States

J. Jakub. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

A. Verosky. University of Colorado Anschutz, United States

S. Tevis. University of Colorado School of Medicine, Department of Surgery, United States

M. Brennan. Department of Surgery, University of Washington, Seattle, WA, United States

F. Verdial. Massachusetts General Hospital, United States

J. Zhang. Department of Surgery, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, Pennsylvania, United States

L. Elmore. Department of Surgery, Perelman School of Medicine, The University of Pennsylvania, United States

J. Plichta. Duke University School of Medicine, Durham, North Carolina, United States

L. Rosenberger. Department of Surgery, Duke University Medical Center, Durham, NC, USA, Durham, North Carolina, United States

Background Current American Joint Committee on Cancer (AJCC) breast cancer staging considers contralateral axillary metastasis (CAM) stage IV disease (M1). Retrospective studies suggest that women with CAM have improved overall survival (OS) compared to those with distant metastasis (M1) and/or comparable OS to locally advanced breast cancer (LABC). These studies support consideration of curative intent treatment; however, they contain heterogeneous cohorts with highly variable treatment strategies. We sought to evaluate treatment and outcomes in a well-defined CAM cohort treated with contemporary systemic and locoregional therapy. Methods We performed a retrospective multi-institution cohort study to compare OS of patients with CAM matched 1:3 on age +/- 5 years to LABC (defined as cN2-3 and/or pN2-3), and to non-CAM M1. CAM patients classified as type 1) de novo CAM, synchronous with the contralateral primary, 2) metachronous isolated CAM in the setting of prior surgical and/or radiation treatment to primary index cancer, 3) synchronous with, or 4) metachronous after an in-breast or axillary nodal recurrence of the primary index cancer. The M1 cohort included de novo and recurrent metastasis with varied sites and number of metastasis. OS was defined as time from CAM diagnosis to death or last follow-up for CAM patients; time from primary diagnosis to death or last follow-up for LABC; and time from metastatic diagnosis to death or last follow-up for M1. Unadjusted OS was estimated with the Kaplan-Meier method, and Cox proportional hazards models were used to estimate the association of group with OS after adjustment for covariates Results We identified 57 CAM and

155 LABC from 8 institutions (2016-2022), and 632 M1 from a single institution. The median age was similar between groups (CAM=59 years, LABC=58, M1=57, $p=0.44$), and there were no statistically significant differences in hormone receptor status ($p=0.25$). There were more Non-Hispanic Black patients in the M1 cohort compared to CAM or LABC ($p < 0.001$). The majority of CAM cases were delayed metachronous from the index cancer (type 2, 35.1%), or synchronous with a recurrence (type 3, 33.3%). Type 1 (de novo, 14%) and type 4 (delayed metachronous after breast cancer recurrence, 17.5%) were less frequent. Among CAM patients, 49.1% were hormone receptor positive (HR+) / HER2-negative (HER2-), 22.8% HR-/HER2-, 10.5% HR+/HER2+, and 5.3% HR-/HER2+. Comparing CAM versus LABC, invasive ductal carcinoma (IDC) was more commonly seen in CAM (82.5% vs 66.5%), as was grade 3 (45.6% vs 35.5%), and triple negative (22.8% vs 13.5%). Conversely, in LABC, treatment of the primary index cancer more frequently included chemotherapy (CAM=71.9%, LABC=92.3%), mastectomy (CAM=54.4%, LABC 74.2%), and adjuvant radiation (CAM=73.7%, LABC=90.3%). On multivariable analysis adjusting for age, race/ethnicity, and hormone receptor status, both CAM and M1 had inferior survival to LABC (Table 1), but with a 2.4-fold difference for CAM (95% CI 1.42-4.07, $p=0.001$) versus a 6.3-fold difference for M1 (95% CI 4.29-9.23, $p < 0.001$). Discussion In this contemporary, multi-institution study, we demonstrated that CAM patients selected for presumed curative intent treatment experienced improved OS when compared to stage IV (M1) patients. Our data adds additional support for re-evaluating the current stage IV designation, in favor of N3, and consideration of curative intent treatment in this disease.

Table. Adjusted* Overall Survival Comparing Patients with Breast Cancer Contralateral Axillary Metastasis (CAM) to those with Locally Advanced Breast Cancer (LABC) and Metastatic Disease (M1)

Cohort	Hazard Ratio (95% CI)	p-Value
Locally advanced breast cancer (LABC)	REF	
Contralateral axillary metastasis (CAM)	2.4 (1.42-4.07)	0.001
Distant metastasis (M1)	6.3 (4.29-9.23)	<0.001

*Adjusted for age, race/ethnicity, hormone receptors.

PO3-05-14

Practice patterns for sequential use of antibody-drug conjugate after antibody-drug conjugate in metastatic breast cancer: results from a physician survey

Presenting Author(s) and Co-Author(s):

Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States

P. Bhardwaj. University of Massachusetts Chan School of Medicine – Baystate, United States

R. Abelman. Mass General Cancer Center/Dana-Farber Cancer Institute, Boston, Massachusetts, United States

L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

L. Carey. UNC-Lindberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

P. Sharma. University of Kansas Medical Center Westwood, Westwood, Kansas City, Kansas, United States

Introduction: Antibody-drug conjugates (ADCs) have become a key part of metastatic breast cancer (MBC) treatment. Trastuzumab deruxtecan (T-DXd), and Sacituzumab Govitecan (SG) are approved ADCs available for the treatment of MBC. Completed trials that led to the approval of these ADCs did not include patients who had received the other ADC as prior therapy. Little is known about the optimal sequencing of these agents and how clinicians are incorporating ADC sequencing decisions at bedside. **Methods:** An online survey regarding the use of sequential ADCs was distributed electronically from April 2023 to July 2023 among US clinicians who treat patients with breast cancer. The survey included eight questions assessing clinician practice settings and the use of ADC sequencing and five case-based scenarios (table 1). Descriptive statistics were used to assess survey responses. **Results:** 107 survey responses were received, out of which 72% were female responders and 93% were medical oncologists. The majority of responders practiced in an academic setting (83%) and reported being involved in clinical research (82%). 58% of responders have been in practice for >10 years and 68% treat >20 breast cancer patients per week. 87% had prescribed an ADC post-ADC for MBC. 46% of responders thought that the degree of benefit for an ADC post-ADC would be similar to the benefit noted in the pivotal ADC trials, and 54% thought that the degree of benefit with sequencing would be lower than in the pivotal trials. Regarding the case-based questions for patients with triple-negative breast cancer and HER2 low disease who had disease progression on first-line metastatic therapy, 64-71% of clinicians opted to give SG as the first ADC followed by T-DXd as the second ADC in sequence, regardless of age, PDL1 status and prior metastatic therapies. For a patient with hormone-positive (HR+), HER2 low MBC, who had received capecitabine as the first metastatic chemotherapy, 50% opted to give T-DXd as the first ADC followed by SG as the second ADC, and 40% opted to give weekly paclitaxel followed by SG as the first ADC. For a patient with HR+, HER2 low MBC who had received two prior chemotherapies for metastatic disease, 77% opted for T-DXd as the first ADC, followed by SG as the second sequential ADC. When grade 1 pneumonitis was added as a comorbidity to the case, only 16% opted to give T-DXd as the first ADC choice. **Conclusion:** Almost 90% of clinicians report prescribing sequential ADCs for MBC, yet there is little uniformity in how these ADCs are sequenced. More than 50% felt that the benefit of the second ADC in the sequence will be lower than the registration trials that led to the approval of the ADC

in a setting of no prior ADC treatment. The optimal sequencing of ADCs remains an area of unmet need and further studies are needed to guide optimal medical decisions regarding sequential ADC-based treatment algorithms for patients with MBC.

Table 1. Case-based scenarios for ADC sequencing

Table 1. Case-based scenarios

Case 1.	A 38-year-old female with metastatic PD-L1+ TNBC (HER2 IHC = 1+). First-line therapy with abraxane + pembrolizumab. Now with symptomatic disease progression, mainly in the lungs. Which treatments would you consider for the next two lines of therapy?
Case 2.	A 58-year-old female with metastatic PD-L1- TNBC (HER2 IHC = 1+). First-line therapy with abraxane, followed by second-line therapy with capecitabine. Now with disease progression. Which treatments would you consider for the next two lines of therapy?
Case 3.	A 63-year-old female with metastatic HR+ breast cancer (HER2 IHC = 1+). Disease progression on endocrine-based therapy and capecitabine. No organ dysfunction. Which treatments would you consider for the next two lines of therapy?
Case 4.	63-year-old female with metastatic HR+ breast cancer (HER2 IHC = 1+). Disease progression on endocrine-based therapy, capecitabine and paclitaxel. No organ dysfunction. Which treatments would you consider for the next two lines of therapy?
Case 5.	35-year-old female with metastatic HR+ breast cancer (HER2 IHC = 1+). Disease progression on endocrine-based therapy and capecitabine. History of grade 1 pneumonitis from CDK 4/6 inhibitor therapy. Which treatments would you consider for the next two lines of therapy?

PO3-06-01

Factors associated with first- and second- line attrition among metastatic breast cancer patients

Presenting Author(s) and Co-Author(s):

- E. Blondeaux. IRCCS Ospedale Policlinico San Martino, Genoa, Italy, United States
L. Boni. IRCCS Ospedale Policlinico San Martino, Genoa, Genova, Italy
G. Chilà. Candiolo Cancer Institute, FPO-IRCCS, Candiolo Italy, United States
A. Dri. Santa Maria della Misericordia University Hospital, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, United States
R. Caputo. Fondazione Pascale IRCCS, United States
F. Poggio. IRCCS Ospedale Policlinico San Martino, United States
A. Fabi. Precision Medicine in Breast Cancer, Fondazione Policlinico Universitario A. Gemelli, IRCCS Rome - Italy, Rome, Italy
G. Arpino. Federico II University Naples - Italy, United States
F. Pravisano. Azienda Sanitaria Universitaria Friuli Centrale (ASUFC) Udine, Italy, United States
E. Geuna. Candiolo Cancer Institute, FPO-IRCCS, Candiolo Italy, United States
T. Ruelle. Department of Medical Oncology 2, IRCCS Ospedale Policlinico San Martino, 16132 Genoa, Italy, United States
I. Giannubilo. Department of Medical Oncology 2, IRCCS Ospedale Policlinico San Martino, 16132 Genoa, Italy, United States
M. de Laurentiis. Istituto Nazionale Tumori "Fondazione Pascale", Italy
F. Puglisi. Department of Medicine (DAME), University of Udine, Udine, Italy and Department of Medical Oncology - CRO Aviano, National Cancer Institute, IRCCS, Aviano, Friuli-Venezia Giulia, Italy
C. Bighin. University of Genova, Genova, United States
M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy
F. Montemurro. Breast Surgery Strategic Program, Candiolo Cancer Institute, Fondazione del Piemonte per l'Oncologia - IRCCS, Torino, Italy, United States
L. Del Mastro. University of Genova - IRCCS Ospedale Policlinico San Martino, United States

Background: Estimating patient attrition across lines of treatment, i.e., the probability that upon failing one treatment the patient will be able to receive a subsequent treatment, may be a valuable tool for treatment sequencing. We sought to describe first-to-second line (1to2-line) and second-to third line (2to3-line) attrition rate and factors associated with attrition.

Methods: The GIM14/BIO-META is an ongoing, ambispective observational multicenter study enrolling breast cancer patients receiving first-line therapy. In progressing patients, attrition was defined as no further anticancer treatment and death within 6 months from the end of the previous line. Attrition from 1to2-line and from 2to3-line was studied by descriptive analyses, factors associated with attrition by univariate and multivariable logistic models.

Results: From January 2000 to December 2021, 3,109 patients with metastatic breast cancer were enrolled in the GIM14/BIO-META study. After the exclusion of 611 patients with ongoing

first-line treatment, we included 2,498 patients in the analysis of 1to2-line attrition. Considering tumor subtype, 1,650 (66.0%) patients were diagnosed with metastatic luminal-like, 622 (24.9%) with HER2-positive and 177 (7.1%) with triple negative (TN) tumors. At the time of diagnosis of advanced disease, almost half of the patients (52.0%) had only one involved metastatic site and 45.9% of the patients were diagnosed with visceral involvement. Overall, 1to2-line attrition was 9.0% (224/2,498) with similar attrition for patients with luminal-like (8.5%) and HER2-positive (7.1%) breast cancer. Patients with TN disease experience the highest 1to2-line attrition (13.0%). Age, disease-free interval from primary tumor diagnosis, and type of metastatic spread independently predicted 1to2-line attrition. Univariate analyses of factors associated with 1to2-line attrition among patients with luminal-like breast cancer were similar to those of the entire cohort. Overall, 2to3-line attrition was 14.0% (260/1,861) with higher attrition rates among patients with TN disease (22.7%) compared to patients with luminal-like (13.4%) and HER2-positive (13.0%) breast cancer. Age, tumor subtype, pattern of visceral spread and shorter time-to treatment discontinuation during first-line therapy were independent factors associated with 2to3-line attrition.

Conclusions: Pending confirmation in independent series and integration with biomarkers of treatment failure, these results, may provide a valuable support for treatment decisions and clinical research on treatment sequencing.

PO3-06-02

Ten years axillary recurrence and survival after omission of axillary lymph node dissection in breast cancer patients with micrometastases or isolated tumor cells in the sentinel node: A Danish national register study.

Presenting Author(s) and Co-Author(s):

R. Hawaz-ali. Department of Breast Surgery - Herlev and Gentofte Hospital, Taastrup, Hovedstaden, Denmark

F. Munck. Herlev-Gentofte Hospital, Hovedstaden, Denmark

T. Tvedskov. Herlev-Gentofte Hospital, Hovedstaden, Denmark

N. Kroman. Department of Breast Surgery - Herlev and Gentofte Hospital, United States

Background: Until 2012, breast cancer patients with micrometastases (pN1mi) or isolated tumor cells (pN0(i)) in the sentinel node (SN) received axillary lymph node dissection (ALND). ALND is associated with lymphedema, paresthesia, functional impairment, and pain. In 2012, national Danish guidelines for patients with pN1mi and pN0(i) were changed reflecting several randomized clinical trials showing non-inferior prognosis when ALND was omitted. Since 2012, approx. 450 Danish breast cancer patients have been spared ALND each year. Development of axillary recurrence (AR) from minimal metastatic disease left in the axilla may take longer than experienced after macrometastatic disease. Hence, long-term follow-up is needed to evaluate the safety of omitting ALND for patients with pN1mi and pN0(i). Therefore, we aimed to investigate these outcomes with 10 years of follow-up. **Methods:** In this national register-based study, we included all women with primary breast cancer surgery between 01.01.2008 and 31.12.2021, who had pN1mi and pN0(i) in the SN. Women treated between 01.01.2008-31.12.2011 had received ALND, while in women treated between 01.01.2012 and 31.12.2021 ALND was omitted. The two groups were compared with SN-negative patients (pN0) without ALND.

The primary outcome was AR, and the secondary outcome was overall survival (OS). Information on surgery, nodal status, and recurrence were retrieved from the national Danish breast cancer group (DBCG) database. The definitions of pN1mi, pN0(i) and pN0 were according to AJCC, 8TH edition.

We analyzed patient- and tumor characteristics with descriptive statistics, χ^2 and Fisher exact test. The cumulative incidence of AR was calculated. OS was estimated using the Kaplan-Meier method and compared with a log-rank test. The effect of ALND was estimated with a Cox proportional hazards model, adjusting for age at operation, histology, malignancy grade, hormone receptor, HER2 status, and whether they received adjuvant systemic treatment or radiation therapy. With all statistical analysis, a two-tailed α -level of 0.05 was used. **Results:** 22,790 patients were included in the study. Overall, 14.3% had pN1mi, 8.6% had pN0(i) and 77.1% had pN0. Of pN1mi or pN0(i) patients, 1490 had an ALND; 1227 patients with pN1mi and 263 patients with pN0(i). In 3737 patients ALND was omitted: 2036 with pN1mi and 1701 with pN0(i).

Regarding the primary outcome, 1.1% of patients with pN1mi or pN0(i) had an AR, while 0.5% of the pN0 patients had AR. Analyzing patients with pN1mi or pN0(i) with or without ALND, 0.2% and 1.5%, respectively, had an AR. In subanalysis of patients with pN1mi with or without ALND, 0.2% and 1.8%, respectively, had an AR. In a subanalysis of patients with pN0(i), no patients with pN0(i) and ALND had an AR, while 1.1% of patients with pN0(i) had an AR when ALND was omitted.

OS after 10 years of follow-up for the group of patients with pN1mi or pN0(i) was 81.5%; 83.7%

for patients with and 79.12% for patients without ALND. For pN0 patients without ALND OS was 82%. This difference between the three groups was statistically significant ($p < 0,01$). However, when adjusting for risk factors, there was no statistically significant difference in OS between the patients with pN1mi or pN0(i) with and without ALND ($p=0.6$). Likewise, no statistically significant difference was found in OS, when looking at the subgroups of pN1mi with or without ALND ($p=0.5$) and pN0(i) with and without ALND ($p=0.41$). Conclusion: In this large register-based nationwide study we found a slightly higher rate of AR after 10 years of follow-up in breast cancer patients with micrometastases or isolated tumor cells in the SN if ALND was omitted. However, the axillary recurrence rate was low ($< 2\%$), and after adjusting for other risk factors the increased recurrence rate did not affect OS. These results confirm the safety of omitting ALND in these patients.

PO3-06-03

Overall Survival and Disease Interval Among Breast Cancer Subtypes in Patients with Brain Metastasis

Presenting Author(s) and Co-Author(s):

A. Shrestha. University of Arkansas for Medical Sciences, Little Rock, AR, USA, United States

S. Gouli. Rochester Regional Health, Rochester, NY, USA, United States

S. Niraula. Vassar Brother Medical Center/Nuvance Health, Poughkeepsie, NY, USA, United States

R. Babbra. Wilmot Cancer Institute/University of Rochester Medical Center, Rochester, NY, USA, United States

N. Neupane. Rochester Regional Health, Rochester, NY, USA, United States

S. Stanford. University of Rochester Medical Center, Rochester, NY, USA, United States

M. Strawderman. University of Rochester Medical Center, Rochester, NY, USA, United States

Z. Kharel. Rochester Regional Health, Rochester, NY, USA, United States

H. Zhang. University of Rochester Medical Center, Rochester, NY, USA, United States

S. Hardy. University of Rochester Medical Center, Rochester, NY, USA, United States

N. Mohile. University of Rochester Medical Center, United States

C. Anders. Duke Cancer Institute, Durham, North Carolina, United States

D. Hicks. University of Rochester Medical Center, United States

R. O'Regan. University of Rochester Medical Center, Rochester, New York, United States

A. Dhakal. University of Rochester Medical Center, Rochester, New York, United States

Background:

Breast cancer brain metastasis (bcm) is associated with limited survival. There is a paucity of clinical trials and real-world data on the survival and disease interval [primary breast cancer (pbc) to metastatic breast cancer (mbc) or bcm] of bcm patients. We performed a retrospective study comparing the overall survival (OS) and disease intervals (INT) between the date of pbc surgery, diagnoses of mbc, and bcm among 3 subtypes of bc in patients with bcm.

Methods:

The informatics team generated a preliminary list of patients with a history of breast cancer and brain metastasis who were treated at the Wilmot Cancer Institute (WCI) of the University of Rochester. Key inclusion criteria were evidence of bcm, bcm diagnosed between Jan 1st, 2010 and June 1st, 2021, and adequate medical records available. Patients with de novo mbc were excluded. Final eligible patients were registered for the study. Median OS in bc subtypes was assessed with the Kaplan-Meier method and compared using the log-rank test. Median INTs among bc subtypes were compared using the Kruskal-Wallis test. Registered patients were divided into triple-negative (TNBC), estrogen receptor-positive/HER2 negative (ER+/HER2-), and HER2+ subtypes.

Results:

Out of 191 patients screened, 83 patients were eligible for the study. The total number of patients enrolled by subtype was 26 (TNBC), 35 (ER+/HER2-), and 22 (HER2+). Disease and patient characteristics are shown in Table 1. Median OS from pbc, mbc, and bcm among 3

subtypes are shown in Table 2. The differences in the median OS from these 3 different time points were not statistically significant among 3 subtypes. After adjusting for important variables (age, race, tumor grade, stage, and presence of perioperative therapy) in a Cox regression model, there was still no statistical evidence that these 3 subtypes differed in OS. Three different INTs (pbc-mbc, pbc-bcbm, mbc-bcbm) among 3 subtypes are shown in Table 3. INTpbc-mbc and INTpbc-bcbm were significantly different among 3 subtypes of bc. After adjusting for the factors in the model, the subtypes didn't differ significantly with respect to INTpbc-mbc and INTpbc-bcbm. Stage 3 at pbc was significantly associated with shorter INTpbc-mbc and INTpbc-bcbm. The distribution of INTmbc-bcbm was highly non-normal due to the high % of patients with concurrent diagnoses of mbc and bcbm. Thus an exploratory logistic regression model assessed the association of subtypes and important variables with the odds of having mbc and bcbm concurrently (INTmbc-bcbm < 1 month). It showed that the ER+/HER2- subtype had 4 times lower odds of concurrent mbc and bcbm diagnosis than the HER2+ subtype (p=0.03). In an unadjusted pairwise comparison between the subtypes (Table 3), the ER+/HER2- group had statistically longer INTpbc-mbc and INTpbc-bcbm than TNBC. However, when the subtypes were adjusted for Stage 3 vs 1 or 2, these subtypes were not significantly different for these INT. In our study, a higher proportion of Stage 3 tumors in TNBC subtype is likely associated with the shorter INTs seen with TNBC in unadjusted analysis.

Conclusion:

Adjusted comparison of OS and disease intervals from pbc between TNBC, ER+/HER2-, and HER2+ subtypes were not statistically different in this cohort of bcbm patients. Interestingly, median OS from mbc were numerically very similar (3.6-3.7 years) among these subtypes. Median OS from pbc and bcbm were numerically longer in HER2+ bc than the other 2 subtypes. Intervals between pbc to mbc and to bcbm and between mbc to bcbm were numerically longer in ER+/HER2- subtypes than the other 2 subtypes. ER+/HER2- subtype was 4 times less likely to have concurrent bcbm at the time of mbc diagnosis than the HER2+ subtype. These results are exploratory and hypotheses generating.

Table 1: Disease and Patients Characteristics

	TNBC	ER+/HER2-	HER2+	P-value (Exact Chi Square for categorical, Kruskal-Wallis for continuous variables)
Number	26	35	22	N/A
Age at PBC median (range)	53 (30, 79)	53 (26, 83)	52 (36, 79)	0.99
Age at BM median (range)	59 (28, 90)	57 (28, 90)	60 (39, 83)	0.80
Race				0.38
White	19 (73.1)	26 (76.5)	21 (95.5)	
Black	6 (23.1)	7 (20.6)	1 (4.6)	
Other	1 (3.9)	1 (2.9)	0	
Unknown	0	1	0	
Ethnicity				>0.99
Non-Hispanic	25 (96.2)	33 (94.3)	22 (100)	
Hispanic	1 (3.9)	2 (5.7)	0	
ER Status				N/A
Positive	0	35 (100)	10 (45.5)	
Negative	26 (100)	0	12 (54.6)	
Grade at PBC				0.90
1	0	1 (3.3)	1 (7.1)	
2	7 (36.8)	12 (40.0)	5 (35.7)	
3	11 (57.9)	17 (56.7)	8 (57.1)	
Unknown	7	5	8	
TNM Staging at PBC				0.27
1	4 (15.4)	12 (36.4)	8 (38.1)	
2	11 (42.3)	11 (33.3)	9 (42.9)	
3	11 (42.3)	10 (30.3)	4 (19.1)	
Unknown	0	2	1	
Perioperative systemic therapy				0.05
Yes	20 (80.0)	34 (97.1)	20 (95.2)	
No	5 (20.0)	1 (2.9)	1 (4.8)	
Unknown	1	0	1	

Table 2: Overall Survival Unadjusted

Overall Survival (95% CI) in years	TNBC	ER+/HER2-	HER2+	P-value (Log-rank)
From PBC	8.0 (5.4-NE)	8.4 (7.2-11.4)	12.1 (5.0-16.6)	0.9318
From MBC	3.6 (2.8-NE)	3.6 (2.2-6.1)	3.7 (2.8-7.5)	0.8219
From BCBM	0.6 (0.2-NE)	1.5 (1.0-3.3)	2.8 (1.5-7.5)	0.6267

Table 3: Disease Intervals Unadjusted

Disease Interval (INT) Median (Range) in months	TNBC	ER+/HER2-	HER2+	P-value (Kruskal Wallis)
PBC-MBC	24 (6, 196)	58 (1, 157)	48 (1, 212)	0.04
PBC-BCBM	40 (6, 196)	81 (1, 175)	53 (7, 257)	0.02
MBC-BCBM	1 (0, 94)	14 (0, 76)	0 (0, 76)	0.20
Pairwise Unadjusted Comparison of Disease Intervals				
PBC-MBC	TNBC vs ER+/HER2-			0.009
	TNBC vs HER2+			0.26
	ER+/HER2- vs HER2+			0.34
PBC-BCBM	TNBC vs ER+/HER2-			0.007
	TNBC vs HER2+			0.42
	ER+/HER2- vs HER2+			0.10
MBC-BCBM	TNBC vs ER+/HER2-			0.13
	TNBC vs HER2+			0.95
	ER+/HER2- vs HER2+			0.15

PO3-06-04

Clinical Features and Survival Outcomes of Oligometastatic Breast Cancer Patients: The Mayo Clinic Experience

Presenting Author(s) and Co-Author(s):

T. Pai. Mayo Clinic, United States

R. Zarrar. Baptist Hospital of Southeast Texas, United States

Z. Peng. Mayo Clinic, United States

Z. Li. Mayo Clinic, Jacksonville, United States

L. Cornell. Mayo Clinic Florida, Jacksonville, Florida, United States

K. Sideras. Mayo Clinic, Jacksonville, Florida, United States

R. Rao. Mayo Clinic, Jacksonville, United States

A. Moreno-Aspitia. Mayo Clinic, Jacksonville, Florida, United States

S. Chumsri. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

S. McLaughlin. Mayo Clinic, Jacksonville, United States

J. Jakub. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

E. gabriel. Mayo Clinic, Jacksonville, United States

S. Bagaria. Mayo Clinic, Jacksonville, United States

L. Vallow. Mayo Clinic, Jacksonville, United States

S. Maimone. Mayo Clinic, Jacksonville, United States

P. Advani. Mayo Clinic, United States

Background

The current definition, prognosis, and optimal treatment (tx) for oligometastatic breast cancer (OMBC) are not fully known. With advances in multimodality breast cancer (BC) tx and overall improvement in patient (pt) outcomes, it is important to identify baseline pt factors that confer better prognosis in OMBC and assess the impact of local/regional tx and metastasis (mets)-directed tx on survival outcomes.

Methods

We reviewed 105 Mayo Clinic pts with OMBC (up to 5 mets) from 2003 to 2021. Pts were excluded from analysis if they were misidentified as having OMBC (n=6), did not have a primary breast mass (n=1), developed de novo BC during tx (n=1), or were lost to follow up (n=2). Categorical variables were summarized as counts. Continuous variables were reported as medians. Kaplan-Meier method was used to estimate survival and the time from diagnosis to next tx at 1, 3, and 5 years. Log-rank test was used to compare survival rates between baseline factors. Univariate Cox proportional hazards models were performed on both baseline and time-dependent factors. All tests were two-sided with p-value < 0.05 considered statistically significant.

Results

Total pts included were 95. Median age was 49 (range, 26-86), most (93.6%) pts were White, and 46.8% were postmenopausal. Invasive ductal carcinoma (89.5%) was the most common BC type. Median survival was 10.8 years; 1-, 3-, and 5-year survival rates were 98.9%, 87.7%, and 81%, respectively. 58 pts (61.1%) required a change in tx due to disease progression. No

significant survival difference was observed in pre- vs. postmenopausal pts ($p=0.71$) or in groups based on hormone receptor and/or human epidermal growth factor receptor 2 status. 47 pts (49.5%) received local/regional tx; no significant difference in survival (HR 0.57, 95% CI 0.23-1.40; $p=0.217$) or time to next tx (HR 0.67, 95% CI 0.39-1.15; $p=0.144$) was seen in this subgroup. Of these pts, 36 (76.6%) received neoadjuvant chemotherapy and/or immunotherapy, 5 of whom (10.6%) also started endocrine tx preoperatively. Overall, 11/47 pts (23.4%) received neoadjuvant endocrine tx. 20 pts received systemic tx without eventual surgery, and 5 pts got palliative radiation (RT). Biopsy-confirmed mets were noted in 76 pts (80%), with bone-only mets in 50%, 30 pts (31.6%) with viscera-only mets and 7 pts (7.4%) with both bone and visceral mets. 18 pts had suspected mets on imaging but did not undergo biopsy. The hazard of death was 6.34 times higher in pts with both bone and visceral mets than those with bone-only mets ($p=0.008$). Pts with viscera-only mets had higher survival at 2 and 3 years than pts with bone-only or both bone and visceral mets ($p=0.093$). Pts with 3 mets (7/76, 7.4%) had decreased survival at 1, 2, and 3 years compared to pts with 1-2 (65/76, 85.5%) mets ($p=0.6$). 67 pts (70.5%) received mets-directed tx; RT alone was the most common modality (52/67, 77.6%), followed by surgery (6/67, 9%), RT plus surgery (5/67, 7.5%), and ablation alone (3/67, 4.5%). There was no significant difference in survival (HR 1.27, 95% CI (0.53, 3.07), $p=0.589$) or time to next tx (HR 0.95, 95% CI (0.56, 1.63), $p=0.856$) in pts who received mets-directed tx. Multivariate analysis was not performed because most findings were not statistically significant in univariate analysis.

Conclusions

We did not find any significant differences in survival based on characteristics like menopausal status or site or number of mets in pts with OMBC. There was a trend toward improved survival in pts with viscera-only mets, but this finding requires validation. Local/regional and mets-directed tx did not improve survival; however, survival at 1, 3, and 5 years was excellent in this OMBC pt population. Our study was limited by low pt numbers and heterogeneity in the pt population. Findings need validation in larger studies.

PO3-06-05

Association of tumor-derived extracellular vesicles with circulating tumor DNA alterations in metastatic breast cancer patients: exploring differences in inflammatory breast cancer

Presenting Author(s) and Co-Author(s):

E. Nicolò. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

L. Foffano. Department of Medicine, University of Udine, United States

L. Munoz Arcos. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, New York, United States

M. Serafini. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA; United States

M. MANAI. Weill Cornell Medicine, NY, New York, United States

L. Pontolillo. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, United States

N. Bayou. Faculty of Medicine-University of Tunis El Manar, Department of Human Genetics/Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

E. Molteni. Department of Medicine, University of Udine, Italy/Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

A. Strickland. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA; United States

Y. Zhang. Northwestern Medicine Northwestern University, Chicago, Illinois, United States

P. D'Amico. Northwestern University, United States

A. Davis. Washington University in St Louis School of Medicine, United States

J. Donahue. Weill-Cornell, New York, New York, United States

H. Iiu. Robert H. Lurie Comprehensive Cancer Center, Departments of Pharmacology and Medicine-Hematology and Oncology, Feinberg School of Medicine, Northwestern University, United States

W. Gradishar. Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, United States

A. Shah. Northwestern University - Feinberg School of Medicine, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

C. REDUZZI. Weill Cornell Medicine, United States

M. Cristofanilli. Weill Cornell Medicine, United States

Background: Liquid biopsy provides a real-time assessment of metastatic breast cancer (MBC). Recently, the complementary prognostic value of tumor-derived extracellular vesicles (tdEVs) and circulating tumor cells (CTCs) has been reported. We have previously confirmed the strong prognostic significance of CTCs and tdEVs in inflammatory breast cancer (IBC). While previous

studies have reported the association of CTCs with circulating tumor DNA (ctDNA) alterations in MBC, no evidence is available for tdEVs. This study aimed to analyze the association of tdEVs with ctDNA alterations, to investigate the molecular pathways underlying their presence. Moreover, we explored potential differences of this association in patients (pts) with IBC to provide a comprehensive liquid biopsy-based portrait of this aggressive subtype of BC.

Methods: Blood samples were collected from 355 pts with MBC before starting a new line of therapy at Northwestern University (Chicago, IL) between 2016 and 2021 (NU16B06 trial). For CTCs and tdEVs analysis, 7.5 mL of blood was processed with the CellSearch® system. The ACCEPT software was applied to CellSearch® images to automatically enumerate CTCs and tdEVs. Positivity cutoff was ≥ 5 for CTCs, while tdEV cutoff points were < 20 (low), 20-79 (intermediate), and ≥ 80 (high). For ctDNA analysis, matched plasma samples (± 1 month) were analyzed with the Guardant360™ NGS platform for the detection of somatic single nucleotide variants (SNVs) and copy number variations (CNVs), which were classified into oncogenic pathways based on defined profiles generated on the Cancer Genome Atlas database (p53, PI3K, ER, RTK, RAS, RAF, WNT, MYC, cell cycle, notch). Associations between ctDNA pathways alterations and tdEVs were tested in the overall population by multinomial logistic regression and corrected for significant clinical characteristics. Differences in liquid biopsy features between IBC and non-IBC subgroups were analyzed through Fisher's exact test.

Results: Of the 355 MBC pts, 210 (62%) had HR+ BC, 61 (17%) had HER2+ BC, and 68 (20%) had triple-negative BC. Eighty-three (23%) had a diagnosis of IBC and had a numerically lower tdEV count. Also, lower tdEVs were detected in HER2+ BC as compared with HR+. Significantly higher tdEVs were observed among pts with lobular histology, liver, and bone metastases. CTC count was significantly associated with tdEV number. A matched plasma sample for ctDNA analysis was available for 175 pts (62 IBC and 113 non-IBC). In the overall population, SNVs in ER pathway were associated with intermediated/high levels of tdEVs ($p=0.004$ and 0.008). A similar association was observed for CNVs in the cell cycle pathway ($p=0.008$ and 0.007). Moreover, associations with ≥ 80 tdEVs were observed for PI3K SNVs and CNVs ($p=0.039$ and 0.004 , respectively), RTK CNVs ($p=0.023$), and MYC CNVs ($p=0.001$). In multivariable analysis, clinical characteristics associated with higher tdEVs were lobular histology ($p=0.014$ for 20-79 and < 0.001 for ≥ 80) and bone metastases ($p=0.019$ for 20-79 and 0.002 for ≥ 80). When considering clinical variables of interest, only ER SNVs and MYC CNVs were significantly associated with intermediate ($p=0.031$) and high ($p=0.022$) tdEV counts, respectively. While the association with ER SNVs and cell cycle CNVs was significant both in the IBC and non-IBC subgroups, others were specific for a certain subgroup: higher tdEVs were significantly associated with PI3K SNVs only in non-IBC pts whereas the significant association with CNVs in PI3K and MYC pathways was observed only in pts with IBC.

Conclusion: Detection of tdEVs was associated with particular genomic profiles. These alterations seem to be different in IBC further underlying a different biology of this BC subtype. Additional studies are needed to explore how to integrate different liquid-biopsy based biomarkers in the management of pts with MBC.

PO3-06-07

Efficacy and safety of sintilimab in combination with anlotinib plus metronomic chemotherapy in advanced triple negative breast cancer (SPACE): preliminary results of a single-arm, multicenter phase II trial

Presenting Author(s) and Co-Author(s):

h. Li. Department of Breast Medical Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, China (People's Republic)

D. Zhou. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

Z. Yv. The First School of Clinical Medicine of Binzhou Medical University, China (People's Republic)

Y. Liao. The First Affiliated Hospital of Nanchang University, United States

J. Huang. Shandong Cancer Hospital and Institute, United States

S. Sun. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

f. zheng. Department of Breast Medical Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, United States

B. Li. Taian City Central Hospital, United States

S. Fang. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

L. Qiang. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

G. Ren. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

B. Bu. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

P. Qiu. Shandong Cancer Hospital & Institute, Jinan, Shandong, China, United States

X. Wang. Department of Breast Surgery, Shandong Cancer Hospital and Institute, China (People's Republic)

C. Li. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

F. Cao. Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University,, United States

Q. Shao. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

D. Han. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

L. Song. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

B. Zhang. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

B. Fan. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

L. Xu. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

X. Xie. The University of Texas MD Anderson Cancer Center, United States

X. Zhao. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

L. Liu. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

W. Li. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, China (People's Republic)

Z. Wang. The First School of Clinical Medicine of Binzhou Medical University, China (People's Republic)

C. Liu. The First School of Clinical Medicine of Binzhou Medical University, China (People's Republic)

H. Fu. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, China (People's Republic)

X. Sun. Shandong Cancer Hospital & Institute, Jinan, Shandong, China, United States

Z. Shi. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, China (People's Republic)

F. Li. Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, China (People's Republic)

Background: Antiangiogenic drugs have demonstrated synergistic effect with anti-PD-1 antibody in advanced triple negative breast cancer (TNBC). Anlotinib is an oral multi-target tyrosine kinase inhibitor (TKI) that strongly inhibits VEGFR, PDGFR, FGFR, and c-kit. Preclinical studies showed that metronomic chemotherapy inhibited angiogenesis and enhanced the efficacy of immunotherapy in TNBC via modulation of the tumor immune microenvironment. We hereby conducted a single-arm, multicenter, phase II trial to investigate the efficacy and safety of sintilimab (anti-PD-1 antibody) plus anlotinib and metronomic chemotherapy as a potential novel therapeutic strategy in advanced TNBC and explore potential biomarkers. **Methods:** Forty-four cases were planning to be included in this trial. The eligible patients who had received no more than two lines of chemotherapy for metastatic disease were enrolled and received sintilimab (200 mg iv q3w) and anlotinib (12 mg po d1-14 q3w) plus capecitabine (500 mg po, tid) or vinorelbine (40 mg po, tiw) until disease progression or intolerable toxicity. The primary endpoint is objective response rate (ORR) and secondary endpoints are disease control rate (DCR), progression free survival (PFS), and overall survival (OS). The safety profile has also been assessed. **Results:** As of April 2023, a total of 44 patients were enrolled, and 42 patients were evaluable for efficacy. 3 patients (7.1%) achieved complete response (CR). 6 patients (14.3%) achieved partial response (PR). 25 patients (59.5%) achieved stable disease (SD). The ORR is 21.4% (95%CI 0.103-0.368) and DCR is 81.0% (95%CI 0.810-0.659). The median PFS was 5.06 months (95%CI 2.051-8.069). The most common grade 1 or 2 adverse events (AEs) include elevated thyroid stimulating hormone (52.38%, 22/42), elevated bilirubin (23.81%, 10/42), hand-foot syndrome (22.22%, 8/42), leukopenia (16.67%, 7/42), nausea (14.29%, 6/42). Grade 3 AEs include elevated bilirubin (2.38%, 1/42), hypertension (2.38%, 1/42) and herpes zoster (2.38%, 1/42). No grade 4 or 5 AEs occurred. **Conclusions:** Our data showed that sintilimab in combination with anlotinib plus

metronomic chemotherapy have shown favorable efficacy and acceptable safety profile in patients with advanced TNBC. Clinical trial information: ChiCTR2100044725

PO3-06-08

Epithelial to Mesenchymal Transition Confers Sensitivity to Cytotoxic Agent Ophiobolin A via Alterations in Mitochondrial Function and Metabolic Pathways

Presenting Author(s) and Co-Author(s):

H. Parker. Baylor University, United States

K. Haberman. Baylor University, United States

J. Taube. Baylor University, United States

A. Kornienko. Texas State University, United States

A. Evidente. University of Naples Federico II, United States

D. Romo. Baylor University, United States

B. Kaiparettu. Baylor College of Medicine, United States

Epithelial to Mesenchymal Transition Confers Sensitivity to Cytotoxic Agent Ophiobolin A via Alterations in Mitochondrial Function and Metabolic Pathways Haleigh Parker¹, Kayla Haberman¹, Alexander Kornienko², Antonio Evidente³, Daniel Romo⁴, Benny Abraham Kaiparettu^{5,6}, Joseph Taube^{1,6} 1 Department of Biology, Baylor University, Waco, TX, USA 2 Department of Chemistry and Biochemistry, Texas State University, San Marcos, TX, USA 3 Department of Chemical Sciences, University of Naples Federico II, Complesso Universitario Monte Sant'Angelo, Naples, Italy 4 Department of Chemistry and Biochemistry, Baylor University, Waco, TX, USA 5 Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA 6 Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA Background Metastatic progression in patients with triple negative breast cancer (TNBC) occurs in approximately half of all patients, reducing median overall survival. Metastasis may be facilitated through the epithelial to mesenchymal transition (EMT), which generates cancer cells with enhanced metastatic capacity and resistance to chemotherapeutics, features which are partially mediated by alterations in metabolic pathways and mitochondrial function. Here, we show a drug-like small molecule possesses EMT-specific cytotoxic activity via EMT-imparted variations in metabolic and mitochondrial functions. The fungus-derived sesquiterpenoid, Ophiobolin A (OpA), possesses nanomolar cytotoxic activity and a high therapeutic index, though its target and mechanism of action remain unknown. Objectives The objectives of this study are to characterize alterations in metabolic pathways and mitochondrial function in the context of EMT, determine OpA induced alterations in specific metabolic pathways involved in metastasis and identify metabolic targets for the treatment of chemotherapeutic-resistant, metastatic triple negative breast cancer. Methods This study identifies distinct, novel metabolic alterations associated with EMT status and specific changes in mitochondrial and metabolic function associated with OpA treatment via analysis of intermediate metabolites, rates of oxidative phosphorylation and glycolysis, metabolic pathway capacity and dependency, protein expression, iron localization, reactive oxygen species accumulation and transmission electron microscopy. Results Our analysis indicates that OpA acts in a mitochondria-specific manner to cause a loss of membrane potential in EMT-positive, but not EMT-negative, cells with specific effects on complex III of the electron transport chain and oxidative phosphorylation as a whole. Furthermore, distinct shifts in glycolysis not only support previous data, but also provides insight as to mitochondrial functionality. Cells were also found to have distinct metabolic pathway capacities/dependencies and ROS and iron accumulation, depending on EMT status and OpA treatment. Finally, specific morphological alterations were uncovered via TEM image analysis. Therefore, we conclude that EMT imparts

alterations in mitochondrial function and metabolic pathways, conferring sensitivity to the cytotoxic effects of OpA.

PO3-06-09

A phase II study of nivolumab plus ipilimumab and androgen receptor antagonist bicalutamide to stimulate thymic T cell generation in HER2-negative metastatic breast cancer

Presenting Author(s) and Co-Author(s):

D. Page. Robert W. Franz Cancer Research Center and Alliance, Portland, Oregon, United States

A. Hall. Earle A. Chiles Research Institute, United States

K. Collins. Earle A. Chiles Research Institute, United States

N. Moxon. Providence Cancer Institute, Portland, Oregon, United States

S. Mellinger. Providence Cancer Institute, Portland, Oregon, United States

T. Kelly. Providence Cancer Institute, Portland, Oregon, United States

A. Kelley. Earle A. Chiles Research Institute, United States

N. Fredrich. Providence, United States

A. Seino. Earle A. Chiles Research Institute, United States

G. Liberatore. Memorial Sloan Kettering Cancer Center, United States

A. Conlin. Providence Cancer Institute, United States

Z. Topp. Earle A. Chiles Research Institute, United States

K. Perlewitz. Earle A. Chiles Research Institute, United States

S. Stanton. Earle Chiles Research Institute, Portland, Oregon, United States

W. Urba. Earle A. Chiles Research Institute, United States

Y. Wu. Earle A. Chiles Research Institute, United States

M. Martel. Earle A. Chiles Research Institute, United States

Z. Sun. Earle A. Chiles Research Institute, United States

Y. Kogushi. Earle A. Chiles Research Institute, United States

W. Redmond. Earle A. Chiles Research Institute, United States

T. Traina. Memorial Sloan Kettering Cancer Center, United States

A. Guculp. Memorial Sloan Kettering Cancer Center, United States

Background: Systemic chemotherapy is used commonly in breast cancer and is associated with lymphopenia, potentially limiting efficacy of immune checkpoint blockade. The androgen receptor (AR) serves as a negative regulator of thymic function. AR antagonists, such as bicalutamide, may stimulate thymic production of naïve T-cells, which may help to restore lymphocyte diversity and augment immunotherapy response. The AR is expressed in 50% of hormone receptor negative (HR-) metastatic breast cancer (MBC) and >75% of HR+ MBC, and bicalutamide is clinically active with stable disease as best response. We hypothesize that bicalutamide could be combined with dual immune checkpoint blockade (anti-programmed death 1, nivolumab; plus anti-cytotoxic T-lymphocyte antigen 4, ipilimumab), stimulating T-cell production and resulting in durable clinical response. Methods: This is a phase II Simon 2-stage trial of nivolumab (240 mg IV q2w), ipilimumab (1 mg/kg IV q6w), and bicalutamide (150mg oral daily) for first- or second-line treatment of HER2-negative MBC (NCT03650894). The primary endpoint is iRECIST 24-week clinical benefit rate (CBR), evaluated separately for HR+ MBC

(n=15) and AR+/HR- MBC (n=15). An optimum Simon 2-stage design (80% power, 5% one-sided alpha) is employed to evaluate an alternative hypothesis of >50% CBR compared to historical control of < 30% CBR for conventional chemotherapy, with expansion of each cohort planned if ≥6/15 responses are observed. Secondary outcomes include best overall objective response rate (ORR), progression-free and overall survival (PFS,OS), and safety. Exploratory endpoints include assessment of peripheral T-cell counts and T cell receptor excision circles (TREC PCR, Mayo Laboratories, a surrogate of thymic T-cell production) over time. Results: Durable responses were observed, with an ongoing complete response at 41+ months in a patient who discontinued due to toxicity (AR+/HR- cohort, PD-L1 CPS score 3%). Therapy was tolerated with a toxicity profile consistent with prior studies of ipilimumab & nivolumab, with five subjects (19%) requiring treatment discontinuation related to toxicity. Outcomes by cohort and PDL1 are summarized in Table 1. Using mixed effects linear models, therapy was associated with a significant expansion of CD8+ T cells (23/mcL/month, p< .01) but not CD3+ T cells (7/mcL/month, p=.59) or CD4+ T cells (4/mcL/month, p=.65). Baseline TREC counts were higher in younger participants (mean: < 50y 2156/mcL; 50-65y 961/mcL; >65y 311/mcL). TRECs did not increase globally, however TREC expansions were observed in several younger participants. Conclusions: The regimen of ipilimumab, nivolumab, plus bicalutamide is safe and clinically active in 1st/2nd-line HER2-negative MBC. Neither cohort crossed the Simon futility barrier for cohort expansion, however durable responses were observed including in PD-L1-negative patients, highlighting the unmet need for biomarkers to identify candidates for chemotherapy-sparing checkpoint blockade. Further research is indicated to evaluate the impact of AR antagonists on T-cell function and thymic stimulation in MBC. Acknowledgements: Drug and study support was provided by Bristol-Myers Squibb and The BMS International Immuno-Oncology Network (II-ON).

Clinical outcomes

Table 1	HR+	AR+/HR-	CPS≥10	CPS<10
Clinical Benefit Rate				
12 weeks	21% (3/14)	58% (7/12)	50% (2/4)	30% (6/20)
18 weeks	14% (2/14)	33% (4/12)	25% (1/4)	15% (3/20)
24 weeks	8% (1/13)	33% (4/12)	25% (1/4)	15% (3/20)
Objective Response Rate				
12 weeks	14% (2/14)	17% (2/12)	50% (2/4)	10% (2/20)
18 weeks	14% (2/14)	8% (1/12)	25% (1/4)	5% (1/20)
24 weeks	8% (1/13)	17% (2/12)	25% (1/4)	5% (1/20)
Progression-free survival	72d (range 15-252d)	119d (range 32-1248+d)	81d (range 27-252d)	76d (range 15-1248+d)
Overall Survival	809d (range 103-1248+d)	506d (range 51-1248+d)	886d (range 51-1120d)	531d (range 103-1248+d)

HR: hormone receptor; AR: androgen receptor; CPS: PD-L1 combined positive score

PO3-06-10

Real World Outcomes with Sacituzumab Govitecan in Metastatic Triple Negative Breast Cancer Patients: A Multi-Institution Study

Presenting Author(s) and Co-Author(s):

S. Alaklabi. King Faisal Specialist Hospital & Research Center, RIYADH, Saudi Arabia

A. ROY. Dept of Oncology, Roswell Park Comprehensive Cancer Center, Buffalo NY, USA, BUFFALO, New York, United States

P. Zagami. 1 Lineberger Comprehensive Center, University of North Carolina, Chapel Hill, NC, USA. 5 University of Milan, Milan, Italy., North Carolina, United States

N. Held. MCW, Wisconsin, United States

S. Shaikh. FOX CHASE CANCER CENTER, Pennsylvania, United States

L. Chaudhary. Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

Background Sacituzumab govitecan (SG) is approved for treatment of metastatic triple negative breast cancer (mTNBC) in the second line and beyond. Little is known about the real-world outcomes of SG. We aim to evaluate the real-world effectiveness and toxicity outcomes of SG in heterogenous heavily pretreated mTNBC patients (pts) to investigate the consistency of the outcomes in comparison to the clinical trial population. **Methods** A multi-center retrospective study of pts with mTNBC treated with SG in the US from January 2021 until May 2023 was conducted. Demographics and clinicopathological variables including site of metastases, prior lines of therapy, relative dose intensity (RDI), adverse events (AEs), HER2 immunohistochemistry (IHC) score at time of metastasis, clinical response, clinical benefit rate (CBR) defined as (complete response, partial response (PR) or stable disease (SD) > 6 months) and last follow-up were collected. For continuous variables, Mann-U Whitney and Kruskal Wallis tests were used to compare mean, median, standard deviation, and range. For categorical variables, Fisher's exact tests and Pearson Chi-square tests were used. Univariate and multivariate cox regression models examined RDI and survival outcomes. SAS v9.4 was used to perform statistical analysis at a significance level of 0.05. **Results** A total of 111 pts were analyzed. The median age was 58 years (range 29-84). The majority of pts were heavily pretreated: 59.1% received >3 prior lines of treatment (Tx) in the metastatic setting, 54.1% received prior immune checkpoint inhibitor (ICI), 8.1% received prior olaparib. 55% of pts had significant disease burden defined by >=3 organs involved by metastatic disease, with 22.5% having brain metastasis at the time of initiation of SG. Of note, 51% had primary refractory disease defined as relapse within 12 months of completion of adjuvant chemotherapy. 98.1% experienced any grade AEs, with the most common being anemia 63.1%. Grade 3 AEs occurred in 51.4% pts with neutropenia being the highest 32.4% followed by anemia 14.4%, diarrhea 7.2% and fatigue 7.2%. Tx interruptions and dose reductions due to AEs occurred in 52.3% of patients and Tx discontinuation rate due to AEs was 11.8%. Elderly pts (defined as >65 years) did not have higher rates of dose reductions due to AEs compared to young pts (<= 65 years) (37.8% vs 59.7 %), p=0.043). The median RDI is 92% (interquartile range (IQR) 33%-100%). The median RDI in elderly pts was 94% (IQR 50%-100%). Among pts in which response was assessed, objective response rate (ORR) was 26.6% (25 pts had PR), and 38.3% had SD. Interestingly, the rate of alopecia was higher in pts who had PR as the best response (28%), compared to 5.6% in pts who had SD, and 3% in progressive disease (PD) p=0.004. The median prior line of therapy in pts who had PR and SD as best response was 2

(IQR 1, 5) (IQR1, 12), respectively, compared to a median of 3 (IQR 1, 7) in pts with PD, $p < 0.001$.

The CBR was 49% (46/94). The median duration of clinical benefit was 7 months IQR (2, 16) with median overall survival of 13 months IQR (2.5, 39) compared to 5.7 months IQR (0.03, 27) in pts without clinical benefit ($p < 0.001$). 56.9% (62/109) of pts had HER2 low disease and the clinical benefit rate in this subgroup was 14.3% (23/62). Conclusion: In a heavily pretreated cohort, SG retains clinical activity and tolerability in mTNBC. This is reassuring given pts on clinical trials tend to be healthier compared to real-world clinical practice.

PO3-06-11

Undated analyses from a Phase Ib open-label study of Pucotenlimab (HX008) in combination with gemcitabine and cisplatin as first-line treatment of metastatic triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

X. Hu. Shanghai Cancer Center, Fudan University, Shanghai, China

j. Cao. Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

B. wang. Department of Oncology, Fudan University Shanghai Cancer Center, Shanghai, China, United States

J. Zhang. Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

L. Wang. Fudan University Shanghai Cancer Center, United States

Z. Tao. Fudan University Shanghai Cancer Center, Shanghai, China (People's Republic)

Background: Gemcitabine plus cisplatin (GP) therapy was preferred in China as the first-line therapy for metastatic triple-negative breast cancer (mTNBC), with a median progression-free survival (PFS) of 7.73 months, and a median overall survival (OS) of 19.37 months [1]. Pucotenlimab (HX008) is a novel humanized IgG4 anti-PD-1 monoclonal antibody with an engineered Fc domain. Preliminary results from the phase 1b trial [2] have shown that HX008 combined with GP has a manageable safety profile and demonstrates promising antitumor activity in patients (pts) with mTNBC. Here, we present the updated results from the long-term survival analysis.

Methods: Eligible subjects were those who were treatment-naïve mTNBC patients and had measurable lesion. Participants received HX008 at a dose of 3 mg/kg every 3 weeks in combination with chemotherapy (gemcitabine + cisplatin) for 6 cycles and maintained with HX008 until disease progression or unacceptable toxicity occurred. The primary endpoints included overall response rate (ORR) and safety, and the secondary endpoints included duration of response (DoR), PFS, and OS.

Results: Between July 2019 and March 2020, a total of 31 pts were enrolled in this study. The median age of patients was 50 years (range 29–69). By the cut-off date (April 24th, 2023), the median follow-up period was 20.7 m (IQR: 12.2, 25.6). The confirmed ORR was consistent with the previously reported data and remains at 74.2% (95% CI: 55.4%, 88.1%). The median PFS was 9.0 months (95% CI, 7.3, 9.3). The median DoR was 7.3 months (95% CI, 5.0, 9.8). The OS was immature, with the result of 23.1 months (95% CI, 13.4, NE), while the 12-m, 24-m and 36-m OS rate was 77.4% (95%CI: 64.0%, 93.6%), 42.7% (95%CI: 28.0%, 65.3%), and 24.4% (95%CI: 11.3%, 52.7%), respectively. The most common grade 3 or 4 treatment-related adverse events included neutropenia (71.0%), leukopenia (45.2%), anemia (38.7%), and thrombocytopenia (32.3%). There was no treatment-related death and no new safety signals were identified.

Conclusion: The combination therapy of HX008 plus GP demonstrates favorable clinical efficacy with a manageable safety profile in pts with mTNBC. The combination therapy led to a longer PFS and OS than GP therapy reported previously, regardless of PD-L1 status. The safety profile was consistent with the known toxic effects of each agent. In this updated

analysis, no new safety signals were identified.

Clinical trial information: NCT04750382

References:

[1]. Zhang J, et al. *Ann Oncol.* (2018). PMID: 29905759

[2]. Cao J, et al. *Front Oncol.* (2022). PMID: 35982961

PO3-06-12

Targeting Fatty Acid Synthase in Brain Metastatic Triple-negative Breast Cancer

Presenting Author(s) and Co-Author(s):

H. Serhan. University of Michigan, United States

L. Bao. University of Michigan, United States

X. Cheng. University of Michigan, United States

M. Soellner. University of Michigan, United States

S. Merajver. University of Michigan, United States

A. Morikawa. University of Michigan School of Medicine, Ann Arbor, Michigan, United States

N. Merrill. University of Michigan, United States

Introduction: Treating triple-negative breast cancer (TNBC) is challenging due to the lack of clearly defined and targetable biomarkers, and treatment options become increasingly limited with TNBC brain metastases (BM). Since the brain microenvironment has relatively low lipid availability, breast cancer cells that colonize the brain increase their reliance on the endogenous biosynthesis of fatty acids. This reveals a potential metabolic vulnerability that can be targeted, and fatty acid synthase (FASN) inhibition has been shown to decrease breast cancer cell invasion in preclinical models.

Methods: In our study, we utilized the TNBC cell line MDA-MB-231-Luc/GFP, its brain-seeking subclone, MDA-MB-231-BR-GFP, and two novel cell lines generated from patient-derived organoids obtained from serial collection of brain-metastatic TNBC resections from the same patient, denoted PDO-BC25 and PDO-BC25-2. Cell lines were screened with FASN inhibitors as single agents vs. combined with SN-38 (topoisomerase I inhibitor) and synergy was assessed by the Chou-Talalay method. To characterize signaling changes with FASN inhibition and identify any off-target signaling, we used a Nanostring metabolic pathways nCounter panel to perform differential expression analysis on cells treated with the FASN inhibitor, TVB-2640, vs. vehicle control across the four cell lines. This panel detects the expression of 768 metabolism-related genes. We used 4 biological replicates per sample and the Benjamini-Hochberg statistical method to control for the false discovery rate after performing a t-test to calculate P-values. In addition, we performed spheroid outgrowth assays to identify any phenotypic impacts of FASN inhibition on spheroid outgrowth.

Results: Combinatory drug screening between FASN inhibitors and SN-38 revealed synergy in MDA-MB-231-BR-GFP, PDO-BC25, and PDO-BC25-2, but not in the parental MDA-MB-231-Luc/GFP. The Nanostring nCounter metabolic pathways panel identified direct target engagement where FASN, SCD, and the transcription factor SREBP1 were significantly upregulated in the cells treated with TVB-2640 compared to vehicle control (P-adjusted < 0.05). Other upregulated genes were related to the pentose phosphate pathway, nucleotide salvage and synthesis, reactive oxygen species response, amino acid synthesis and transport, and autophagy. Genes that were down-regulated are involved in cell cycle progression, deoxynucleotide synthesis, DNA damage repair, fatty acid oxidation, and cytokine and chemokine signaling. Moreover, despite no decrease in cell viability, TVB-2640 alone was able to slow the outgrowth and invasion of Matrigel-embedded spheroids in a spheroid outgrowth assay.

Conclusions: In our study, we have shown that the combination of SN-38 and FASN inhibitors

is synergistic in the TNBC brain-seeking cell lines, and that FASN inhibition alone causes on-target transcriptome-level changes and a decrease in spheroid invasion. Next, we plan on testing the brain-metastatic potential of these cell lines in the presence and absence of a FASN inhibitor using an organ-on-chip microfluidic device developed by our lab that mimics the blood-brain barrier, to identify if this strategy has a potential role in prevention of brain metastases. Further studies to refine the molecular basis of the mechanism of action of the combination are underway.

PO3-06-13

A novel stable 6-aryl-2-benzoyl-pyridine colchicine-binding site inhibitor targeting microtubules (60c) is effective against taxane-resistant, metastatic breast cancer

Presenting Author(s) and Co-Author(s):

D. Oluwalana. University of Tennessee Health Science Center, Memphis, Tennessee, United States

K. Hartman. University of Tennessee Health Science Center, United States

R. Krutilina. University of Tennessee Health Science Center, United States

H. Chen. University of Tennessee Health Science Center, United States

H. Playa. University of Tennessee Health Science Center, United States

S. Deng. BridGene Biosciences, United States

D. Parke. University of Tennessee Health Science Center, United States

D. Miller. University of Tennessee Health Science Center, United States

T. Seagroves. University of Tennessee Health Science Center, Memphis, Tennessee, United States

W. Li. University of Tennessee Health Science Center, United States

Background: Improving survival for patients diagnosed with metastatic disease and treating spontaneous chemoresistance remain major clinical challenges in treating breast cancer. Triple negative breast cancer (TNBC), characterized by a lack of therapeutically targetable receptors (ER/PR/HER2), is an aggressive subtype of breast cancer. TNBC therapy relies on a combination of systemically administered chemotherapies, including microtubule-targeting agents (MTAs) like paclitaxel (taxane class) or eribulin (vinca class); however, there are currently no FDA approved MTAs that bind to the colchicine-binding site. Approximately 70% of patients who initially respond to paclitaxel, a first-line MTA, will develop taxane resistance (TxR) within 6 months. We have previously reported that an orally bioavailable colchicine-binding site inhibitor (CBSI), sabizabulin (formerly known as Veru-111), not only inhibits TNBC tumor progression but also treats pre-established metastatic disease in a taxane-refractory PDX model, HCI-10-Luc2. Sabizabulin is currently in phase II/III trials for advanced prostate cancer. To further improve potency and metabolic stability, we created next-generation derivatives of the sabizabulin scaffold, including 60c. Results: 60c shows improved potency compared to sabizabulin against taxane-sensitive and TxR TNBC models, inhibiting proliferation and clonogenicity at low nanomolar concentrations, and inducing apoptosis in a dose-dependent manner. In vivo, 60c therapy significantly suppressed primary tumor growth and lung metastasis in an orthotopic MDA-MB-231-TxR xenograft model without gross toxicity, and with equivalent efficacy to combrestatin A4 phosphate (CA-4P), another CBSI in clinical trials. In the taxane-refractory HCI-10-Luc2 PDX model, 60c significantly suppressed both the growth of the primary tumor (by ~3.5 fold) and the expansion of pre-established axillary metastases (by ~26 fold) whereas paclitaxel had no effect. Analysis of total photon flux of organs excised at study endpoint showed that 60c had distinct anti-metastatic tropism as compared to sabizabulin. Whereas 60c completely suppressed metastases to the spleen (0/9 mice had signal), and significantly reduced metastatic burden in the leg bones (only 3/9 mice had signal) and in the kidney (only 2/9 mice had signal), 60c had no statistically significant effect on liver metastases. In contrast, we had previously reported that sabizabulin strongly repressed liver metastases in the same PDX model (0 mice with detectable liver metastases), with less potent effects on bone. Unlike 60c, sabizabulin showed no improvement relative to the vehicle control for spleen

and kidney metastases. Together, our data positions 60c as a promising candidate for TNBC therapy, particularly for patients with TxR disease. Our results also suggest that different CBSI scaffolds may preferentially inhibit metastasis to specific organs, which requires further investigation.

PO3-06-14

Phase I/II study of pembrolizumab in combination with oral binimetinib in patients with unresectable locally advanced or metastatic triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

S. Chumsri. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

J. Larson. Mayo Clinic, United States

D. Adams. Creatv Microtech, Inc., Monmouth Junction, New Jersey, United States

K. Tenner. Mayo Clinic, United States

C. Tang. Creatv MicroTech, Inc., United States

M. weidner. Mayo Clinic, United States

A. Arnold. Mayo Clinic, United States

D. Haley. Mayo Clinic, United States

P. Advani. Mayo Clinic, United States

K. Sideras. Mayo Clinic, Jacksonville, Florida, United States

A. Moreno-Aspitia. Mayo Clinic, Jacksonville, Florida, United States

E. Perez. Mayo, United States

K. Knutson. Mayo Clinic, United States

Background: Activation of the RAS/MAPK pathway is associated with reduced tumor-infiltrating lymphocytes and poor outcomes in triple-negative breast cancer (TNBC). This trial evaluated the efficacy of pembrolizumab in combination with binimetinib, a MEK inhibitor.

Methods: Patients with unresectable locally advanced or metastatic TNBC with ≤ 3 prior lines of therapy were enrolled. Treatment includes a 2-week run-in with binimetinib followed by pembrolizumab. There were 2 dose levels (DL) with binimetinib at 45 mg at DL 0 and 30 mg at DL -1. A standard 3+3 design was used in Phase I, and Simon's two-stage Optimal design was used in Phase II. PD-L1 22C3 was performed in archival samples with CPS ≥ 10 considered as positive (PD-L1+). Tumor-infiltrating lymphocytes (TILs) were quantified into 0, 1, 2, and 3+. Circulating tumor cells (CTC) and circulating cancer-associated macrophage-like cells (CAML) were isolated using CellSieve microfilters and immunofluorescently labeled with PD-L1 and p-ERK. Wilcoxon rank sum test, Chi-square test, Cox regression model, and Spearman correlation were used for analysis.

Results: 22 patients were enrolled with a median age of 58 years old. Dose-limiting toxicity (DLT) was observed in 2 out of 4 patients in DL 0, with grade 3 ALT abnormality, flank pain, and nausea. In the next 6 patients in DL -1, there was 1 DLT with grade 3 AST/ALT abnormality. There were 17 patients treated with DL -1 and were evaluable for response. The objective response rate (ORR) was 29.41% (95% CI: 10.31-55.9) with 1 complete response (CR) and 4 partial responses (PR). The clinical benefit rate (CBR ≥ 24 weeks) was 35.29% (95% CI: 14.21-61.67). ORR in patients without liver metastases was 55.56% (95% CI: 21.20 - 86.30) and CBR was 66.67% (95% CI: 29.93-92.51). No response was observed in all 5 patients with liver metastases. There were 40.9% of patients with PD-L1 CPS ≥ 10 . ORR in patients with PD-L1+ was 80%. However, 11.1% of patients with PD-L1 negative tumors also had an objective response and 44.4% of patients had clinical benefit ≥ 24 weeks. PD-L1 expression in archival tissue was associated with ORR (p 0.032) but not CBR (p 0.198),

progression-free survival (PFS, p 0.373), and overall survival (p 0.348). TILs in archival tissue were also not associated with CBR (p 0.155) and PFS (p 0.157). One patient with TILs 0 had a stable disease \geq 24 weeks and 2 patients TILs 1+ also had an objective response. We further evaluated blood-based biomarkers with CTC and CAML. Baseline PD-L1 in CAML (p 0.04) and decline in CAML size (p 0.02) after 1 cycle was significantly associated with CBR. However, baseline CTC count, CAML count (p 0.64), CAML size (p 0.46), p-ERK in CAML (p 0.23), and changes in CTC count, CAML count (p 0.83), p-ERK (p 0.07), and PD-L1 (p 0.08) in CAML were not significantly associated with responses. Using Cox regression analysis, a reduction in CAML count (p 0.02), CAML size (p 0.01), and PD-L1 in CAML (p 0.03) were associated with significant improvement in overall survival but not the reduction in p-ERK (p 0.6). However, PD-L1 expression in CAML is not associated with PD-L1 expression in archival tissue (Spearman correlation 0.13).

Conclusions: Pembrolizumab and binimetinib at 30 mg are safe with manageable toxicities. Consistent with the preclinical data that MEKi can restore T cell function, promising activity was observed even in patients with low TILs and PD-L1 negative, particularly in patients without liver metastases. PD-L1 expression in peripheral blood CAML rather than archival tumor tissue may serve as a better biomarker to predict the clinical benefit of this combination. Early reductions in CAML count and size, were also significantly associated with responses. Future larger clinical trials are warranted to further evaluate the efficacy of this chemotherapy-free combination.

PO3-07-01

Multiscale Computational Analysis of Patient-Matched Multi-Modal Imaging of Breast Tissue Microenvironment

Presenting Author(s) and Co-Author(s):

J. Hamilton. University of Maine, Alton, Maine, United States

M. Olzinski. University of Maine, United States

K. Batchelder. University of Maine, United States

K. Tilbury. University of Maine, United States

A. Khalil. University of Maine, United States

Introduction: Mammographic breast density is a strong quantitative cancer risk factor, but its link to underlying tissue and cellular level changes are weakly understood. Understanding the complex restructuring changes in the breast tumor microenvironment and its impact on breast density is integral to improving risk assessment and treatment strategies. A novel approach was developed to stratify mammographic dense breast tissue into areas of active dense tissue and passive dense tissue. Active dense tissue is structurally reorganizing and links to cancer dynamics, whereas passive dense mammographic tissue remains organized.^{1,2} A complementary wavelet-based analysis technique to measure the multiscale anisotropy of collagen fibers from Second-Harmonic Generation (SHG) imaging demonstrated clinical cancer diagnostic potential in mouse carcinoma and human pancreatic cancer.^{3,4} This tool is now leveraged for a multi-modal study in which patient-matched H&E tissue biopsies are imaged using both bright-field microscopy and SHG imaging to compare with the patient's corresponding mammograms. Stratifying the mammographic density into active and passive dense areas, a correlation between biopsy tissue anisotropy and mammographic density subtypes can be calculated to help understand how tumor microenvironment changes affect a patient's mammographic breast tissue composition. **Methods:** SHG and brightfield-imaged biopsy slides from 10 patients (five malignant, five benign) collected from Maine Medical Center (Maine, US) were analyzed using the 2D Wavelet Transform Modulus Maxima (WTMM) Anisotropy Method generating a large-scale and a small-scale anisotropy factor as well as a scale-combined anisotropy calculated from their large- and small-scale anisotropy separation. A multi-modal anisotropy score was calculated by adding the imaged area's H&E combined anisotropy score with its respective SHG combined anisotropy score. This analysis was done on eight randomly selected ductal areas for each imaging modality on a slide and correlated with the measured areas of density subtypes from the whole mammographic view. Linear regression was used for determining correlation between H&E and SHG anisotropy factors as well as with active and passive mammographic density subtype measurements. **Results:** The malignant patients' small-scale H&E anisotropy factor positively correlated with their small scale SHG anisotropy factor ($R^2=0.571$). No correlation was found for the benign patients ($R^2=0.011$). The strongest correlations were found between benign patients' mammographic passive (positive correlation) and active (negative correlation) dense tissues vs the H&E anisotropy scale-combined factor ($R^2=0.858$ and $R^2=0.961$, respectively). The largest malignant patient correlation was a negative relationship between SHG anisotropy scale-combined factor and overall mammographic density (inclusive of both active and passive dense tissue) ($R^2=0.891$). The multi-modal anisotropy score correlated with overall mammographic density for both benign (positive correlation, $R^2=0.698$) and malignant patients (negative correlation, $R^2=0.773$). Combining the multi-modal anisotropy factor from SHG and H&E with the active dense tissue

measurement using K-Means clustering, 5/5 malignant and 4/5 benign patients were correctly classified. **Conclusion:** Density in mammograms correlates with underlying quantitative changes in a patient's tissue and collagen anisotropy. Combining both H&E and SHG analysis on tissue biopsy with active and passive density metrics from computational mammography leads to the best predictive potential than any one method on their own. References: 1. Marin et al. *Med Phys*, 2017. 44(4): p. 1324-36. 2. Gerasimova-Chechkina et al. *Front. in Physiol*, 2021. 12(595). 3. Tilbury et al (2021) *JBO*. 26(6), 065002. 4. Hamilton et al. (2022) *Front. in Oncol*, 12, 991850.

PO3-07-02

Radiomics Models for B-mode Breast Ultrasound and Strain Elastography to improve Breast Cancer Diagnosis (INSPIRED 005): An International, Multicenter Analysis

Presenting Author(s) and Co-Author(s):

A. Pfob. Department of Obstetrics & Gynecology, Heidelberg University Hospital (Heidelberg, Germany), United States

T. He. University Breast Unit, Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany | Medical Faculty of the University of Heidelberg, United States

L. Cai. University Breast Unit, Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany, United States

R. Barr. Department of Radiology, Northeast Ohio Medical University, Ravenna, USA, United States

V. Duda. Department of Gynecology and Obstetrics, University of Marburg, Marburg, Germany, United States

Z. Alwafai. Department of Gynecology and Obstetrics, University of Greifswald, Greifswald, Germany, United States

C. Balleyguier. Gustave Roussy, Université Paris-Saclay, Department of Radiology, Villejuif, F-94805, France, United States

D. Clevert. Department of Radiology, University Hospital Munich-Grosshadern, Munich, Germany, United States

S. Fastner. University Breast Unit, Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany, United States

C. Gomez. University Breast Unit, Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany, United States

M. Goncalo. Department of Radiology, University of Coimbra, Coimbra, Portugal, United States

I. Gruber. Department of Gynecology and Obstetrics, University of Tuebingen, Tuebingen, Germany, United States

M. Hahn. Universitätsklinikum Tübingen, United States

A. Hennigs. University Breast Unit, Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany, United States

P. Kapetas. Department of Biomedical Imaging and Image-guided Therapy Medical University of Vienna, United States

S. Lu. MD Anderson Center for INSPIRED Cancer Care (Integrated Systems for Patient-Reported Data), The University of Texas MD Anderson Cancer Center, Houston, USA, United States

J. Nees. University Breast Unit, Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany, United States

R. Ohlinger. Department of Gynecology and Obstetrics, University of Greifswald, Greifswald, Germany, United States

F. Riedel. Department of Gynecology and Obstetrics, Breast Unit, Heidelberg University Hospital, Heidelberg, Germany, United States

M. Rutten. Department of Radiology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands. Radboud University Medical Center, Nijmegen, The Netherlands, United States

B. Schaeffgen. University Breast Unit, Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany, United States

A. Stieber. University Breast Unit, Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany, United States

R. Togawa. University Breast Unit, Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany, United States

M. Tozaki. Department of Radiology, Sagara Hospital, Kagoshima, Japan, United States

S. Wojcinski. Department of Gynecology and Obstetrics, Breast Cancer Center, Klinikum Bielefeld Mitte GmbH, Bielefeld, Germany, United States

C. Xu. MD Anderson Center for INSPIRED Cancer Care (Integrated Systems for Patient-Reported Data), The University of Texas MD Anderson Cancer Center, Houston, USA
Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, USA, United States

G. Rauch. Institute of Biometry and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, United States

J. Heil. Department of Gynecology and Obstetrics, Breast Unit, Heidelberg University Hospital, Heidelberg, Germany, United States

C. Sidey-Gibbons. Anderson Center for INSPIRED Cancer Care (Integrated Systems for Patient-Reported Data), The University of Texas MD Anderson Cancer Center, Houston, USA
Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, USA, United States

M. Golatta. Universitätsklinikum Heidelberg, Germany, United States

Background: Breast Elastography, a technique that quantifies tissue stiffness, has been evaluated to objectify and improve the performance of B-mode breast ultrasound. However, large prospective trials showed benefits in BI-RADS 4a breast masses only and a high operator dependency. Modern Artificial Intelligence techniques for automated image processing like radiomics, a technique where quantified features are extracted from images, may overcome these limitations. We aimed to develop and validate radiomics models based on B-mode and Strain Elastography (SE) images for patients with BI-RADS 3 or 4 breast masses and compare their performance to the respective human experts. **Methods:** This is a secondary analysis of an international, multicenter trial (NCT02638935), evaluating the performance of SE in women with BI-RADS 3 or 4 breast masses. Women were recruited at 12 institutions in 7 countries and underwent B-mode breast ultrasound as well as SE. B-mode images were saved and re-assessed by three ultrasound readers (>10 years of experience), resulting in three independent assessments and a final consensus assessment. SE was interpreted using the E-/B ratio. B-mode and strain images were manually segmented and quantitative radiomics features were extracted using pyradiomics. We used 10-fold cross-validation to build machine learning models (XGBoostTree, MARS) based on data of 11 of 12 study sites. The data of the 12th (largest) study site was used as external validation set. Performance metrics included sensitivity, specificity and area under the receiver operator characteristic curve (AUROC). **Results:** The study included a total of 1288 patients, 1206 with evaluable B-mode images and 1190 with evaluable Strain images. Mean age was 46.6 years (SD 16.02) and a total number of 29.0% (350 of 1206) and 28.9% (344 of 1190) breast masses were malignant in the B-mode and Strain cohort, respectively. Distribution of BI-RADS categories was 33.0%, 34.5%, 14.5%, and 18.0% for BI-RADS 3, 4a, 4b, and 4c, respectively. In the external validation set (n = 342), the B-mode radiomics model (XGBoostTree) achieved an AUROC of 0.86 (95% CI 0.82 to 0.90), with a sensitivity of 97.4% (95% CI 0.93 to 1.00, 113 of 116) and a specificity of 27.0%

(95% CI 0.21 to 0.33, 61 of 226). The model showed equivalent performance compared to the three ultrasound readers ($P = 0.133$); see also Table 1. In the external validation set ($n = 333$), the Strain radiomics model (MARS) achieved an AUROC of 0.84 (95% CI 0.79 to 0.88), with a sensitivity of 100% (95% CI 47.0 to 58.0, 115 of 115) and a specificity of 25.5% (95% CI 0.22 to 0.34, 60 of 218). The model showed equivalent performance compared to the three ultrasound readers ($P = 0.696$) and performed significantly better compared to SE ($P = 0.002$); see also Table 1. Sensitivity of the strain model was descriptively higher (100% vs. 97.4%, see Table 1). Both models were well-calibrated. Conclusion: This is the largest development and validation study for radiomics models based on B-mode breast ultrasound and SE, to date. The radiomics models performed on par with human readers, with the strain radiomics model showing potential to identify initially missed carcinomas in BI-RADS 3 breast masses. Future implementation studies may evaluate the performance of these image analysis algorithms in clinical routine and their integration into the multi-modal breast cancer diagnostics process, including mammography and MRI.

Table 1. Diagnostic performance metrics

	B-mode ultrasound readers (n = 1206)	Strain Elastography (n = 1190)	B mode radiomics (n = 342)	Strain radiomics (n = 333)
AUROC – value (95% CI)	0.83 (0.80 to 0.86)	0.73 (0.67 to 0.78)	0.86 (0.82 to 0.90)	0.84 (0.79 to 0.88)
Sensitivity – % (95% CI); no.	93.7% (0.91 to 0.96) 328 of 350	74.1% (0.69 to 0.79) 255 of 344	97.4% (0.93 to 1.00) 113 of 116	100% (0.97 to 1.00) 115 of 115
Specificity – % (95% CI); no.	25.9% (0.23 to 0.29) 222 of 856	61.6% (0.58 to 0.65) 521 of 846	27.0% (0.21 to 0.33) 61 of 226	25.5% (0.22 to 0.34) 60 of 218
Positive predictive value – % (95% CI); no.	34.1% (0.31 to 0.37) 328 of 962	44.0% (0.40 to 0.48) 255 of 580	40.6% (0.35 to 0.47) 113 of 278	42.1% (0.36 to 0.48) 115 of 273
Negative predictive value – % (95% CI); no.	91.0% (0.87 to 0.94) 222 of 244	85.4% (0.82 to 0.88) 521 of 610	95.3% (0.87 to 0.95) 61 of 64	100% (0.94 to 1.00) 60 of 60

PO3-07-03

Development & Validation of an AI-supported Workflow for Clinical Scoring of HER2, ER, PR & Ki67 Immunohistochemistry in Breast Cancer Tissue

Presenting Author(s) and Co-Author(s):

M. Lodge. Indica Labs, United States

A. Ironside. NHS Lothian, United States

A. Graham. NHS Lothian, United States

A. Polonia. Institute of Molecular Pathology and Immunology of the University of Porto, United States

S. Reinhard. Institute of Tissue Medicine and Pathology, University of Bern, United States

W. Solass. Institute of Tissue Medicine and Pathology, University of Bern, United States

I. Zlobec. Institute of Tissue Medicine and Pathology, University of Bern, United States

P. Caie. Indica Labs, United States

Background: Immunohistochemical evaluation of HER2 status, the hormone receptors ER and PR, and the proliferation marker Ki67 forms part of the routine clinical diagnostic pathway for invasive breast carcinomas, and is the cornerstone of treatment stratification, informing both prognosis and patient management. Pathologist scoring of immunohistochemistry (IHC) at the microscope is time-consuming and prone to significant inter- and intra-observer variability. We developed HALO Breast AI, a decision-support system designed to improve efficiency and diagnostic accuracy through automating whole slide image (WSI) scoring. Here, we present preliminary results of a validation study of HALO Breast AI. Methods: HALO Breast AI was developed with routine diagnostic cases sourced from three institutes. The algorithm was trained using 107,755 pathologist-reviewed annotations to identify and threshold DAB-positive tumor cells within automatically segmented tumor regions. Internal validation was conducted on 80 unseen WSI, using 60,012 pathologist-reviewed annotations to assess analytical performance. Comparison of the algorithm scores to the mode of 3 expert pathologists (where at least 2 out of 3 agreed) was used to assess consensus agreement. Clinical performance and generalizability were assessed by comparing the algorithm scores to clinical data from two independent external institutes across 200 unseen WSI (n=50 per marker) from institute one and 300 unseen WSI (n=100 per marker [ER, PR & HER2, only]) from institute 2. Results: The median image F1-score for tumor classification was 0.91, while the median image F1-score for cell level validation was 0.96. Internal validation showed agreement between HALO Breast AI and the mode of 3 expert pathologists of 100% for ER, 90% for PR, 95% for Ki67 and 90% for HER2. High concordance was measured between the algorithm and the pathologists' scores, with Light's kappa of 0.91 for ER, 0.85 for PR, 0.79 for HER2 and 0.82 for Ki67.

Performance on WSI obtained from external institute one, showed agreement between the clinical score obtained from HALO Breast AI and the clinical data of 96% for ER, 94% for PR, 84% for HER2 and 84% for Ki67. External institute two showed agreement of 90% for ER, 90% for PR and 83% for HER2. Of the ER & PR cases that were in disagreement at the 1% clinical cut-off, the algorithm percent-positive scores were within a 1-3% range in 5 out of the 5 from institute 1 and 14 out of the 20 from institute 2. So, although on a categorical scale the AI assigned category disagreed with the clinical category, the results were close on a continuous scale. Conclusions:

HALO Breast AI accurately detects tumor regions and tumor cells within breast cancer tissue and demonstrates high clinical agreement when scoring routine diagnostic IHC. Additionally,

HALO Breast AI shows good generalisability, with a consistently strong performance across inherent variability that exists between external, independent data sets. Computer-aided diagnostic tools such as HALO Breast AI have the potential to support pathologists in the diagnostic setting by improving workflow efficiency and standardising results.

PO3-07-04

Prediction of PAM50 molecular subtypes from H&E-stained breast cancer specimens using tumor microenvironment features and additive multiple instance learning models

Presenting Author(s) and Co-Author(s):

M. Guramare. PathAI, Boston, Massachusetts, United States

S. Javed. PathAI, Boston, Massachusetts, United States

C. Kirkup. PathAI, Boston, Massachusetts, United States

D. Juyal. PathAI, Boston, Massachusetts, United States

J. Brosnan-Cashman. PathAI, Boston, Massachusetts, United States

V. Mountain. PathAI, Boston, Massachusetts, United States

R. Leung. PathAI, Boston, Massachusetts, United States

B. Rahsepar. PathAI, Boston, Massachusetts, United States

J. Abel. PathAI, Boston, Massachusetts, United States

A. Taylor-Weiner. PathAI, Boston, Massachusetts, United States

J. Conway. PathAI, Boston, Massachusetts, United States

Background: PAM50, a 50-gene signature, classifies breast cancers into one of five subtypes (basal, luminal A, luminal B, HER2-enriched, and normal-like), revealing information about underlying tumor biology, and has emerged as a key prognostic indicator influencing treatment decisions. There is growing interest in bridging the gap between expression-based metrics and histopathology, where immunohistochemistry (IHC) and sequencing-based approaches have been proposed for this purpose. However, hematoxylin and eosin (H&E)-stained slides are ubiquitously utilized by pathologists for cancer diagnosis, while IHC and sequencing-based approaches require additional tissue and specialized processing and/or analysis. Here, we describe a computer vision-based approach to predict PAM50 classification using H&E-stained whole slide images (WSIs).

Methods: We obtained expression-based PAM50 subtype labels and corresponding H&E-stained WSIs for 961 breast carcinomas from the TCGA BRCA cohort. We used two separate machine learning (ML) approaches to predict PAM50 subtypes from WSIs. In the first approach, we deployed previously trained PathExplore models to extract quantitative human-interpretable features (HIFs) that summarize the TME. We subsequently trained random forest classification models on these HIFs to predict PAM50 subtypes. For the second approach, we developed additive multiple instance learning (aMIL) models. Additionally, we explored the effects of PAM50 subtype labeling and aggregation strategies beyond the 5-class approach. Our 3-class approach combines Luminal A and B, as seen in IHC efforts to increase agreement with PAM50 assays, while excluding Normal, a category containing few and heterogeneous samples. We also performed binary classification for each subtype in the 3-class model (e.g. luminal vs. other). Slides were split into training (60%), validation (20%), and test (20%) sets, stratified by PAM50 labels, and model performance was assessed using the area under the receiver operator curve (AUROC) metric on the held-out test set, using a one vs. rest approach for multi-class models. To establish a baseline for PAM50 prediction, we developed random forest classification models using only clinical covariates (tumor stage, histologic grade, histological subtype, and BRCA1/2 status).

Results: We compared the performance of our two ML models (HIF and aMIL) to that of the

baseline model, and we report the AUROC values in Table 1. These models both performed well in predicting Basal, Luminal A, Luminal B, and Luminal (A+B), while the model performance was less strong for predictions of the HER2 and Normal classifications. The three-class model showed improved performance of predicting Luminal classifications relative to the five-class model that separates Luminal A and B. Although simplifying classification problems to a binary use case typically provides improved performance, this phenomenon was not observed for any of the PAM50 subtypes.

Conclusions: These results demonstrate that AI-powered digital pathology can accurately and reproducibly perform molecular-based classification tasks, such as predicting PAM50 classifications, using WSIs, suggesting a more efficient path toward clinically relevant breast cancer characterization.

Table 1. Performance of all models in predicting PAM50 molecular subtypes.

	Five-class predictions			Three-class predictions			Binary predictions		
	aMIL model	HIF model	Baseline model	aMIL model	HIF model	Baseline model	aMIL model	HIF model	Baseline model
Basal	0.93	0.9	0.81	0.93	0.83	0.78	0.85	0.84	0.71
HER2	0.76	0.82	0.41	0.75	0.61	0.65	0.76	0.68	0.56
Luminal (A+B)	0.88	0.87	0.73	0.91	0.79	0.81	0.88	0.84	0.79
Luminal A	0.86	0.87	0.76	-	-	-	-	-	-
Luminal B	0.73	0.72	0.56	-	-	-	-	-	-
Normal	0.54	0.59	0.48	-	-	-	-	-	-

AUROC values are shown. Shaded cells represent the best test-set performance for each class (row).

PO3-07-05

Multi-site validation of a deep learning solution for ER/PR profiling of breast cancer from H&E-stained pathology slides

Presenting Author(s) and Co-Author(s):

S. Arslan. panakeia.ai, United States

A. Bazaga. panakeia.ai, United States

G. Bryson. NHS Greater Glasgow and Clyde, United States

O. Carlos. panakeia.ai, United States

A. Gerald. panakeia.ai, United States

D. Harrison. University of St Andrews, United States

A. Ironside. NHS Lothian, United States

J. Kather. Technical University Dresden, United States

A. Khurram. University of Sheffield, United States

D. Leff. Sheffield Teaching Hospitals NHS Foundation Trust, United States

D. Mehrotra. panakeia.ai, United States

F. Ntelemis. panakeia.ai, United States

J. Nyonyintono. panakeia.ai, United States

J. Schmidt. panakeia.ai, United States

S. Singhal. panakeia.ai, United States

I. Um. University of St Andrews, United States

S. Wolf. panakeia.ai, United States

P. Pandya. Panakeia.ai, United States

Background: Molecular profiling of estrogen and progesterone receptors (ER/PR/Her2) is performed for all malignant breast cancers to inform the choice of targeted therapy. Though existing scoring systems are widely used and well-validated, they can involve costly preparation and variable interpretation. Additionally, discordances between histology and expected biomarker findings can prompt repeat testing to address biological, interpretative, or technical reasons for unexpected results. We evaluate PANProfiler Breast (PPB), a UKCA/CE-IVDD marked deep learning (DL)-based image analysis software, on multiple sites to determine if the majority of ER/PR assays can be replaced, relying only on routinely-used H&E-stained whole slide images. **Methods:** PPB was trained and validated on 5126/4619 WSIs from 5 sites to identify the ER/PR status defined by IHC assays graded in alignment with ASCO/RCPATH guidelines from five different sites in the UK were used for training and validation. The performance is evaluated separately for each site with 3-fold cross-validation, mimicking real-world distribution. **Results:** For ER, with a class ratio (CR) of approximately 4:1, we measure a sensitivity, specificity, and accuracy of 95.5% ($\pm 1.5\%$), 47.5% ($\pm 15.1\%$) and 88.3% ($\pm 0.6\%$) averaged over all sites, reaching up to 97.40%, 67.20%, and 89.30% respectively. For PR (CR approx. 3:1), the averaged sensitivity, specificity, and accuracy are 92.2% ($\pm 8.4\%$), 53.10% ($\pm 20.8\%$), and 86.6% ($\pm 2.4\%$), reaching up to 99.1%, 81.7%, and 88.8%, respectively. The software's performance is comparable to current SoC antibody performance in common ER/PR CDx Assays from Dako, Leica, and Roche, which have sensitivities of 98.5% ($\pm 1.3\%$) and specificities of 38.6% ($\pm 6.3\%$) for ER and sensitivities of 96.9% ($\pm 0.6\%$) and specificities of 23.4% ($\pm 1.4\%$) for PR. Performance was robust to specimen and scanner types, with

accuracies of 87.6% (ER, only biopsies), 88.2% (ER, only resections), 88.5% (ER mixed types), 83.9% (PR, only resections) and 87.3% (mixed types). Accuracy across scanners varied by a standard deviation of 0.3%/1.0% for ER/PR respectively. **Conclusions:** We demonstrate the robustness of a DL-based ER/PR profiling method in breast cancer using only H&E-stained WSIs. This multi-site validation study is the first-of-its-kind for such an approach using real-world clinical data. Our solution could facilitate fast, accurate, and systemic screening of patients for targeted treatments if integrated into routine pathological workflows.

PO3-07-06

Correlation between residual microcalcification and in-breast pathologic response in relation to MRI response and the subtypes after neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

S. Baek. Gangnam Severance Hospital, South Korea

S. Lee. Gangnam Severance Hospital, South Korea

M. Kim. Gangnam Severance Hospital, Seoul, Seoul-t'ukpyolsi, Republic of Korea

S. Moon. Gangnam Severance Hospital, South Korea

J. Kim. Gangnam Severance Hospital, South Korea

Y. Kook. Gangnam Severance Hospital, South Korea

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Background

The significance of residual microcalcifications after neoadjuvant chemotherapy (NAC) in determining the extent of surgical intervention in breast cancer remains unclear. This study aimed to assess whether residual microcalcifications after NAC correlate with the residual disease in patients with breast cancer stratified by subtypes, particularly in excellent radiologic responders.

Methods

We conducted a retrospective study of patients with breast cancer who underwent NAC followed by curative surgery between January 2007 and December 2022. We evaluated the presence of suspicious microcalcifications on pre-NAC mammography and residual microcalcifications on post-NAC mammography. In the patients who had residual microcalcifications on post-NAC mammography, the rates of breast pathologic complete response (pCR), defined as the absence of invasive cancer (ypT0/is) or complete breast pCR defined as the absence of invasive cancer and in-situ cancer in the breast (ypT0), was assessed according to the MRI response and subtypes. We defined complete MRI response as the resolution of suspicious enhancement in the breast and axilla after NAC.

Results

Of the 1078 patients, 554 (51.4%) had suspicious microcalcifications at baseline, of which 518 (93.5%) had residual microcalcifications after NAC. Among the 518 patients with residual microcalcifications, 93 (18.0%) achieved a complete MRI response. We observed a difference in breast pCR rates depending on MRI response and hormone-receptor (HR) status. In the patients without complete MRI response, about one-third of patients (139 of 425 [32.7%]) achieved a breast pCR, irrespective of HR status (19.3% [47 of 244] in HR-positive breast cancer and 50.8% [92 of 181] in HR-negative breast cancer). Of the 93 patients who achieved a complete MRI response, the breast pCR rates were 64.3% (27 of 42) in HR-positive breast cancer and 96.1% (49 of 51) in HR-negative breast cancer, respectively. Moreover, the breast complete pCR rate was 54.8% (23 of 51) in HR-positive breast cancer and 88.2% (45 of 51) in

HR-negative breast cancer, including 87.2% (34 of 39) in HR-HER2+ breast cancer and 91.7% (11 of 12) in triple-negative breast cancer.

Conclusion

Our results suggest that the clinical relevance of the residual microcalcifications differs according to the breast cancer subtypes. For patients with HR-positive breast cancer, removal of the residual microcalcifications should be considered to ensure complete cancer removal, regardless of MRI response. In contrast, de-escalating surgery may be considered in patients with HR-negative breast cancer who achieve complete MRI response after NAC.

PO3-07-07

Predictive Modeling for Identifying Breast Cancer Patients Eligible for Axillary Lymph Node Dissection Exemption Following Neoadjuvant Therapy: A Longitudinal MRI-based Radiomics and Deep Learning Features Analysis

Presenting Author(s) and Co-Author(s):

Y. Yu. Fujian Cancer Hospital, United States

J. Yi. Fujian Medical University Union Hospital, United States

R. Chen. Fujian Medical University Union Hospital, United States

K. Huang. Fujian Cancer Hospital, United States

J. Zhang. Fujian Medical University Union Hospital, United States

C. Song. Fujian Provincial Cancer Hospital, United States

Objective: Neoadjuvant therapy (NAC) has emerged as a pivotal treatment modality for breast cancer. However, accurately identifying patients who can safely avoid axillary lymph node dissection (ALND) following NAC remains challenging. In this study, our aim was to develop a predictive model using longitudinal MRI-based radiomics and deep learning features to identify breast cancer patients suitable for exemption from ALND.

Methods: A total of 140 patients with cN1-2 breast cancer who underwent NAC were included in this study between January 2021 and October 2022. MRI images were collected before and after two cycles of NAC. The dataset was randomly divided into training and validation sets using a 7:3 ratio. Logistic regression (LR), K-nearest neighbors (KNN), LightGBM, and multilayer perceptron (MLP) machine learning models were utilized to predict axillary lymph node pathological complete response (ypN0) in patients following NAC. Finally, a prediction model with a single modality feature was trained by integrating all the extracted data.

Results: Among the 140 patients included, 55 achieved ypN0 following NAC, while 85 did not achieve ypN0. Modeling the features extracted from pre- and post-chemotherapy evaluations revealed that the LR model achieved the highest area under the curve (AUC) values, reaching 0.842 and 0.841, respectively. Moreover, by integrating the evaluation of pre- and post-chemotherapy images and the net change of features between the two time points, the novel developed Amalgamation model demonstrated the highest AUC value of 0.958. The Amalgamation model exhibited an accuracy of 0.9, sensitivity of 0.833, and specificity of 1.

Conclusion: Our study developed a predictive model using MRI images obtained before and after two cycles of NAC to identify breast cancer patients with ypN0 at an early stage. This model has the potential to avoid unnecessary ALND, significantly reducing complications.
Keywords: breast cancer, neoadjuvant chemotherapy, axillary lymph node dissection, MRI, radiomics, deep learning, predictive modeling

Figure 1: The ROC curves of Amalgamation model, Delta-model, Two-cycle reassessment-model and Baseline-model based on Logistic regression.

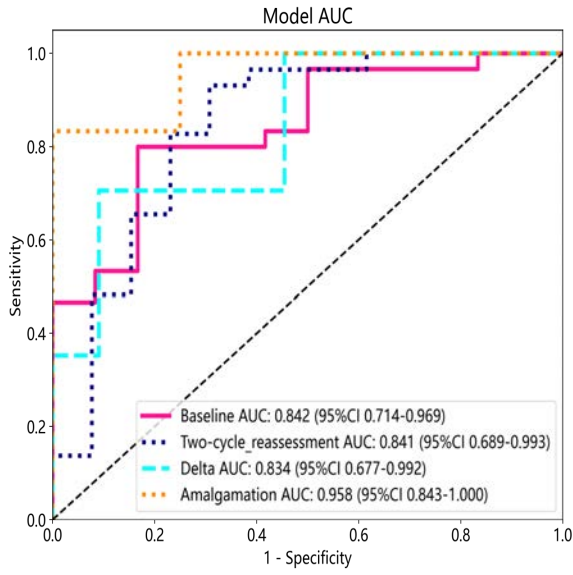


Table 1: Performances of combining different machine learning models for predicting axillary lymph node pathological complete response to neoadjuvant therapy in pre- and post-neoadjuvant therapy MRI images.

Table 1: Performances of combining different machine learning models for predicting axillary lymph node pathological complete response to neoadjuvant therapy in pre- and post-neoadjuvant therapy MRI images.

Model name	Sequence	Accuracy	AUC 95% CI	Sensitivity	Specificity	Precision	PPV	NPV	F1
LR	Baseline	0.810	0.842 (0.714-0.969)	0.800	0.833	0.923	0.923	0.625	0.857
	Two-cycle NAC reassessment	0.857	0.841 (0.689-0.993)	0.931	0.692	0.871	0.871	0.818	0.900
KNN	Baseline	0.786	0.703 (0.523-0.882)	0.933	0.417	0.800	0.800	0.714	0.862
	Two-cycle NAC reassessment	0.595	0.775 (0.643-0.906)	0.414	1.000	1.000	1.000	0.433	0.585
LightGBM	Baseline	0.643	0.764 (0.619-0.909)	0.500	1.000	1.000	1.000	0.444	0.667
	Two-cycle NAC reassessment	0.786	0.643 (0.450-0.836)	1.000	0.308	0.763	0.763	1.000	0.866
MLP	Baseline	0.786	0.806 (0.664-0.947)	0.833	0.667	0.862	0.862	0.615	0.847
	Two-cycle NAC reassessment	0.857	0.833 (0.694-0.972)	1.000	0.538	0.829	0.829	1.000	0.906

PO3-07-08

Breast density estimation with a microwave-frequency imaging system

Presenting Author(s) and Co-Author(s):

E. Fear. University of Calgary, United States

J. Bourqui. Wave View Imaging/University of Calgary, United States

P. Mojabi. University of Calgary, United States

B. Docktor. University of Calgary, United States

A. Garland. University of Calgary, United States

D. Deutscher. University of Calgary, United States

Z. Lasemiimani. University of Calgary, United States

K. McMahon. University of British Columbia, United States

B. Besler. University of Calgary, United States

R. Tsang. University of Calgary, United States

Background: Microwave imaging has been proposed as an alternative method of breast imaging that is low-cost and comfortable for women as it avoids excessive compression. Microwave properties of tissues relate to water content and behavior (Gabriel et al, 1996); specifically, fatty tissues have lower properties and glandular tissues have greater properties (Lazebnik et al, 2007). These differences in microwave signatures of fatty and glandular tissues provide the opportunity to map the composition of the breast and create a density score without a mammogram. This density score may find utility in risk stratification or monitoring interventions aimed at decreasing breast density (Salazar et al, 2020).

Purpose: We examine the feasibility of developing a density score based on microwave images that correlates to mammographic breast density (VOLPARA score) in a pilot study with healthy volunteers.

Imaging System: We have developed a microwave imaging system that facilitates scanning of large groups of patients, as well as comparison to x-ray mammography (Mojabi et al, 2023). The system consists of two plates which are placed in contact with the breast. Microwave transmitters and receivers are embedded in the plates; signals transmitted through the breast are used to estimate microwave frequency properties of tissues, and maps of these estimates form a 2D image.

Methods: 50 patients provided informed consent (study approved by Health Ethics Research Board of Alberta CC-21-0082). Both breasts of each volunteer were scanned. Previously performed mammograms were available for 21 of the volunteers. The number of volunteers with VOLPARA scores A, B, C, and D is 2, 8, 6, and 5, respectively. The percent density reported with the VOLPARA score is also available for these volunteers. Microwave images were formed for each scan and analyzed to predict density with three approaches: (1) average permittivity, (2) segmented regions, and (3) pixel-based intensities. The results demonstrate that the average permittivity of the breast typically increases from VOLPARA A to D, with some overlap in average values observed between the density categories. A correlation between average permittivity and percent breast density was observed. Regions representing glandular tissues are segmented from microwave images; the average values of these regions clearly differentiate between VOLPARA A and D, however do not show consistent ranges for

VOLPARA scores B and C. Finally, the microwave breast density estimated using pixel-based intensities shows good correlation with the percentage density calculations from mammograms.

Conclusions: Microwave images contain features related to the glandular tissues embedded in fat. By analyzing the composition of the breast in these images, density scores are created. While average permittivity appears to correlate to percent density calculated from mammograms, area or pixel-based approaches appear to have greater potential for categorizing into density classes. Expanding the number of participants, identifying biomarkers, and exploring deep learning techniques for density prediction are considered for future work

PO3-07-09

B3 breast lesions in Asian Centers: malignant upgrade rates and risk factors

Presenting Author(s) and Co-Author(s):

W. ANG. Department of Breast Surgery, Tan Tock Seng Hospital, Singapore, United States

J. Jung. Seoul National Univ. Hospital, Surgery, Korea, United States

B3 breast lesions in Asian Centers: malignant upgrade rates and risk factors

Wei-Wen Ang^{1,*}, Ji-Jung Jung^{2,*}, Eunhye Kang², E Jan Sim¹, Hong-Kyu Kim², Hyeong-Gon Moon², Wonshik Han², Ern Yu Tan¹, Han-Byoel Lee¹

¹Tan Tock Seng Hospital, Singapore

²Seoul National Univ. Hospital, Surgery, Korea

*These authors contributed equally to this work and share first authorship

Background Lesions of uncertain malignant potential in the breast (B3 lesions) are composed of a wide spectrum of pathologies with differing risks of breast cancer. With the widespread implementation of screening programs globally, the incidence of these lesions has increased substantially. Asian women tend to have smaller and denser breasts than Western women, making identifying and treating these lesions more challenging. Previous papers quote an upgrade of B3 lesions to malignancy such as ductal carcinoma in situ (DCIS) or cancer at rates of 9.9% to 35.1%. Malignant upgrade on final histology increases patient anxiety and healthcare costs as a second surgical intervention is often required for pathological clearance or lymph node staging. This study aimed to assess the malignant upgrade rate of B3 lesions in Asian women and to evaluate any key factors that may predict the risk of a malignant upgrade.

Materials and Methods A retrospective multicentre international study was done on patients at Seoul National University Hospital (SNUH), South Korea, from April 2021 to 2023, and Tan Tock Seng Hospital (TTSH), Singapore, between March 2006 and 2023. Patients who were diagnosed with a B3 lesion on initial breast core needle biopsy and underwent surgical open excision were included in the study. Results A total of 1049 patients were diagnosed with B3 lesions, with 154 (14.7%) upgrading to malignancy. The most common malignancy was DCIS, 118 (76.6%), followed by invasive ductal carcinoma (IDC), 20 (13.0%) and papillary carcinoma, 4 (2.6%). Within the types of B3 lesions, the malignant upgrade rates were found: atypical ductal hyperplasia (ADH), 88/252 (35%); intraductal papilloma (IDP) with atypia, 16/55 (29%); lobular neoplasia (LN), 9/34 (26%); and radial scar (RS), 5/21 (24%). Most patients had both ultrasound and mammographic evaluation, and all lesions in the study were graded BIRADS 4A and above. Univariate analysis showed that age >50 (OR 2.30 [1.61-3.31], p< 0.001), BMI >23 (OR 2.21 [1.20-4.12], p=0.01), post-menopausal status (OR 2.43 [1.34-4.34], p< 0.001), lesion being identified on mammography (OR 3.00 [2.04-4.51], p< 0.001) and presence of microcalcifications on mammography (OR 0.63 [0.41-0.98], p=0.04) were risk factors for malignant upgrade.

Conclusion Based on our analysis of Asian women, post-menopausal patients with microcalcifications on mammography and a B3 biopsy result should be treated with a higher degree of suspicion for underlying malignancy. Surgical excision with adequate margins should be routinely considered for B3 lesions such as ADH, IDP with atypia, LN and RS. Avoidance of surgery or vacuum-assisted removal can be considered for younger patients with only ultrasound findings and diagnosis of FEA and IDP.

Malignant upgrade after excision

MALIGNANT UPGRADE (Y/N)	All patients (n=1049)
Y	154 (14.7%)
N	895 (85.3%)
BREAST CANCER TYPES	
Ductal carcinoma in situ	118 (11.2%)
Invasive ductal carcinoma	20 (1.9%)
Invasive lobular carcinoma	3 (0.3%)
Tubular carcinoma	2 (0.2%)
Mucinous carcinoma	3 (0.3%)
Papillary carcinoma	4 (0.4%)
Adenomyoepithelioma with carcinoma	1 (0.1%)
Phyllodes tumour, borderline	3 (0.3%)

Clinical characteristics of all patients according to malignant upgrade

Characteristics	All patients (n=1049)	Benign (n=895)	Malignant (n=154)	p-value
Age	49.2 ± 10.6	49.0 ± 10.7	50.7 ± 10.0	0.07
Age				<0.001
≤50	626 (59.7%)	566 (63.2%)	60 (39.0%)	
>50	423 (40.3%)	329 (36.8%)	94 (61.0%)	
Mammo detection (Y/N), is lesion seen on MMG?				<0.001
N	456 (43.5%)	418 (46.7%)	38 (24.7%)	
Y	513 (48.9%)	400 (44.7%)	113 (73.4%)	
Not available	80 (7.6%)	77 (8.6%)	3 (1.9%)	
If Yes, Presence of Microcals (Y/N) (n = 513)				0.310
N	208 (40.5%)	157 (39.2%)	51 (45.1%)	
Y	305 (59.5%)	243 (60.8%)	62 (54.9%)	
Biopsy Pathology				<0.001
Benign lesions with no greater risk	155 (14.8%)	148 (16.5%)	7 (4.5%)	
Flat epithelial atypia	57 (5.4%)	54 (6.0%)	3 (1.9%)	
Lobular neoplasia	30 (2.9%)	21 (2.3%)	9 (5.8%)	
Papillary lesion				
IDP	280 (26.7%)	260 (29.1%)	20 (13.0%)	
IDP with atypia	55 (5.2%)	39 (4.4%)	16 (10.4%)	
Radial scar	15 (1.4%)	10 (1.1%)	5 (3.2%)	
Atypical ductal hyperplasia	171 (16.3%)	96 (10.7%)	75 (48.7%)	
Phyllodes tumour	136 (13.0%)	133 (14.9%)	3 (1.9%)	
Multiple B3 lesions	92 (8.8%)	79 (8.8%)	13 (8.4%)	
Lesions other than B3-lesions				
Complex fibroadenoma	18 (1.7%)	18 (2.0%)	0 (0.0%)	
Sclerosing adenosis	24 (2.3%)	23 (2.6%)	1 (0.6%)	
Mucocoele-like tumor	6 (0.6%)	4 (0.4%)	2 (1.3%)	
Adenomyoepithelioma	10 (1.0%)	10 (1.1%)	0 (0.0%)	

Univariate and multivariate analysis for malignant upgrade

Table 3. Univariate and multivariate analyses for malignant upgrade (except for phyllodes tumor)

Characteristics	No. of women	No. of cancer	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age (>50)			2.3 (1.61-3.31)	<0.001	1.82 (0.58-5.92)	0.30
BMI (>23)			2.21 (1.2-4.12)	0.01	3.25 (1.07-10.9)	0.04
Personal Breast/Ovarian cancer History			2.14 (0.69-5.58)	0.15	5.15 (0.64-43.8)	0.11
Family Breast/Ovarian Cancer History			0.44 (0.11-1.27)	0.20	0.77 (0.04-5.89)	0.80
Menopause			2.43 (1.34-4.34)	<0.001		
Palpable Lesion			0.7 (0.17-2.06)	0.60	1.72 (0.14-17.2)	0.70
Mammo detection (Y)			3 (2.04-4.51)	<0.001		
If Yes, Presence of Microcalc (Y)			0.63 (0.41-0.98)	0.04	5.71 (1.32-27.6)	0.02
USG detection			1.33 (0.87-2.09)	0.20		
Biopsy Pathology						
Benign lesions with no greater risk (4-51%)	155	7	1 [Reference]		1 [Reference]	
Flat epithelial atypia	58	3	1.15 (0.24-4.31)	0.80	3.26 (0.11-95.9)	0.40
Lobular neoplasia	34	9	7.61 (2.61-23.1)	<0.001	NA	NA
Papillary lesion						
IDP	280	20	1.63 (0.7-4.23)	0.30	2.15 (0.39-14.5)	0.40
IDP with atypia	55	16	8.67 (3.45-24)	<0.001	18.6 (2.43-207)	0.01
Radial scar	21	5	6.61 (1.78-23.2)	<0.001	NA	NA
Atypical ductal hyperplasia	252	88	11.3 (5.45-27.7)	<0.001	12.5 (2.76-76.8)	<0.001
Others	58	3	1.15 (0.24-4.31)	0.80	2.38 (0.09-31.1)	0.50
Biopsy Method (MMG, compared to US)			1.78 (0.77-3.74)	0.15	0.21 (0.04-0.83)	0.03

OR = Odds Ratio, CI = Confidence Interval

PO3-07-10

Advanced CD8 ImmunoPET imaging predicts radiation response in primary TNBC

Presenting Author(s) and Co-Author(s):

P. Song. University of Alabama at Birmingham, United States

S. Lynch. University of Alabama at Birmingham, United States

C. DeMellier. University of Alabama at Birmingham, United States

A. Mascioni. Imaginab, United States

F. Jia. Imaginab, United States

A. Sorace. University of Alabama at Birmingham, Birmingham, Alabama, United States

Title: Advanced CD8 ImmunoPET imaging predicts radiation response in primary TNBC

Patrick N. Song^{1,2}, Shannon E. Lynch^{1,2}, Chloe T. DeMellier³, Alessandro Mascioni⁴, Fang Jia⁴, Anna G. Sorace^{1,3,5}

¹Department of Radiology. The University of Alabama at Birmingham, Birmingham, USA

²Graduate Biomedical Sciences. The University of Alabama at Birmingham, Birmingham, USA

³Department of Biomedical Engineering. The University of Alabama at Birmingham, Birmingham, USA

⁴Imaginab, Inc.

⁵O'Neal Comprehensive Cancer Center. The University of Alabama at Birmingham, Birmingham, USA
Background: Tumor immunology and immunosuppression has been observed to drive changes in intratumoral response to cytotoxic and immunotherapy in triple negative breast cancer (TNBC). While radiation therapy is standard of care for TNBC, there is a lack of research into the relationship between long term treatment response and CD8 immune infiltration in the context of a radiation resistant model. Positron emission tomography (PET) imaging allows for noninvasive monitoring of the tumor microenvironment that can precede changes in tumor volume, including approaches that allow for immune imaging of CD8 T-cell trafficking. Noninvasive PET imaging of radiation response has the potential to identify windows of enhanced response to secondary therapy and can guide interventional therapy. The goal of this study is to understand how radiation can prime the tumor microenvironment to be combined with other therapeutics in TNBC through changes in CD8 immune infiltration with [⁸⁹Zr]-CD8 ImmunoPET imaging. Methods: Syngeneic parental 4T1 (radiation sensitive) and a developed radiation-resistant 4T1 sub-cell line were orthotopically injected into BALB/c mice (N = 5 control, N = 9-10 radiation treated for each model). After reaching a tumor volume of ~100 mm³, mice began treatment with 2 Gy fractionated radiation daily from day 0-5. On day 6, mice were injected with ~50 μCi of [⁸⁹Zr]-CD8 minibody (IAB42) and imaged 24 hours post injection. The mean standardized uptake value (SUV) was quantified and normalized to heart SUV to extract out a tumor:heart SUV_{ratio} that describe the CD8 infiltration within tumors. Following imaging, tumors were either excised immediately for immunofluorescence against CD8 or monitored for longitudinal changes in tumor volume. A non-parametric T-test was used to assess for significance between groups. Results: In radiation sensitive 4T1 tumors, [⁸⁹Zr]-CD8 ImmunoPET imaging indicated a 23% increase in CD8 immune infiltration, in radiation-treated tumors compared to control tumors on day 7 (p = 0.02). These immune alterations occurred prior to any changes in tumor volume (p = 0.63). Longitudinally, radiation treated tumors exhibited significant changes in tumor volume beginning on day 20 (p = 0.02), which is

sustained until study endpoint on day 41 ($p < 0.01$). In radiation resistant 4T1 tumors, no significant change was observed in short term CD8 immune infiltration ($p = 0.43$) or in longitudinal tumor volume ($p = 0.31$) in response to radiation therapy, when compared to untreated tumors. Conclusions: [^{89}Zr]-CD8 ImmunoPET imaging reveals significant increases in CD8 immune infiltration that is predictive of eventual response to radiation therapy in radiation sensitive models of TNBC. [^{89}Zr]-CD8 PET imaging of radiation therapy response has the potential to increase the efficacy of precision medicine and prime the tumor microenvironment for secondary therapeutics, thereby improving tumor kill and reducing patient toxicity.

PO3-07-11

Concordance between abbreviated and complete magnetic resonance protocols for screening woman at moderate and high risk for breast cancer

Presenting Author(s) and Co-Author(s):

- M. Mitraud Ottoni Guedes. Mater Dei Health Network, Brazil
- A. Lopes da Silva Filho. Federal University of Minas Gerais, Brazil
- T. Paiva Moraes. Mater Dei Health Network, Brazil
- A. Moraes Campos. CONRAD clinic, Brazil
- I. Braga de Paula. CONRAD clinic, Brazil
- F. Marcondes de Oliveira Coelho. Mater Dei Health Network, Brazil
- B. Silveira Santana. Mater Dei Health Network, Brazil
- B. Andrade Coelho. FIPMoc University Centre, Brazil
- M. Fernanda Sperotto Valadares Gontijo. Mater Dei Health Network, Brazil
- L. Martins De Araujo Campos Linhares. Mater Dei Health Network, Brazil
- A. Dias Salvador. Mater Dei Health Network, Brazil
- W. José de Almeida Junior. Mater Dei Health Network, Brazil
- J. Campos de Avelar. Mater Dei Health Network, Brazil

Introduction: Patients at high risk for developing breast cancer are potential beneficiaries of personalized screening strategies. Breast magnetic resonance imaging (MRI) has shown high sensitivity, but its broader use remains constrained by issues such as high cost and long examination time. The abbreviated magnetic resonance protocol is presented as an alternative to overcome these challenges. Our primary outcome was to evaluate the concordance of the final report between full and abbreviated protocols. Secondary outcomes included the acquisition and reading time of images from the abbreviated protocol.

Methods: A cross-sectional study was conducted on asymptomatic women at moderate and high risk for breast cancer who underwent the full MRI screening protocol in private health institutions in the city of Belo Horizonte, Brazil. The abbreviated protocol was derived from the full protocol by the computer through selection of specific sequences. Each image was independently blind read, and assigned a category from the Breast Imaging - Reporting and Data System (BI-RADS) by at least two examiners. The results were then compared using the Cohen's kappa and Intraclass Correlation Coefficients.

Results: The study included 170 women, and a concordance rate of 96,9% was found for the reported BI-RADS category between protocols in this population. A 21-minute reduction was observed in examination time for the abbreviated protocol.

Conclusion: The significant concordance between protocols indicates that despite the reduction in acquisition time, number of acquired images, and method's complexity, the abbreviated MRI protocol meets most screening demands. It is, therefore, a viable alternative for cost reduction and improving patients tolerability for the studied population.

Table 1. Clinical characteristics of the study population

Table 1: Clinical characteristics of the study population	
Characteristics	Number of subjects (N=170)
Median age	42
Personal risk of breast cancer	
Yes	9 (5,2%)
No	161 (94,71%)
Family history of breast cancer	
Yes	107 (62,94%)
No	63 (37,06%)
Previous genetic testing	
Yes	10 (5,88%)
No	160 (94,12%)

Absolute and percentage data about age, personal risk for breast cancer, family history, and previous genetic testing in the study population.

Table 2. Concordance analysis between abbreviated and complete MRI protocols based on the ACR-BIRADS classification - Coen Kappa and Intraclass Correlation Coefficient

	Full Protocol				Kappa Weight*	Intraclass Correlation Coefficient (ICC)*	
	Birads 1	Birads 2	Birads 3	Birads 4			
Abbreviated Protocol	Birads 1	50 (100%)	0	0	0,9687 (0,9426 - 0,9949) p-value < 0,01	0,982 (0,97 - 0,987) p-value < 0,01	
	Birads 2	0	83 (100%)	0			
	Birads 3	0	0	17 (80,95%)			1 (6,25%)
	Birads 4	0	0	4 (19,05%)			15 (93,75%)

*Coefficient values, Confidence interval 95% and p-value

The Kappa value of 0.9687 (95% CI 0.9426 - 0.9949, $p < 0.01$) indicates almost perfect concordance between the two protocols. The intraclass correlation coefficient of 0.982 (95% CI 0.97 - 0.987, $p < 0.01$), also indicates excellent concordance using the two-way random effect models criteria.

PO3-07-12

Effect of neoadjuvant chemotherapy on peritumoral edema in early stage breast cancer and its prognostic value

Presenting Author(s) and Co-Author(s):

H. Shigematsu. Department of Breast Surgery and Oncology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Hiroshima, Japan, Kure, Hiroshima, Japan

M. Fujimoto. Department of Breast Surgery and Oncology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Hiroshima, Japan, Hiroshima, Japan

Y. Kobayashi. Department of Breast Surgery and Oncology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Hiroshima, Japan, Hiroshima, Japan

T. Yoshiyama. Department of Breast Surgery, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Japan

N. Matsuura. Department of Radiology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, United States

D. Komoto. Department of Radiology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, United States

k. kuraoka. Department of Pathology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, United States

Objectives: We aimed to evaluate the effect of neoadjuvant chemotherapy (NAC) on peritumoral edema (PE) and its prognostic value in operable breast cancer.

Materials & Methods: This retrospective study included 128 cT1-4N0-3M0 breast cancer patients who underwent contrast-enhanced magnetic resonance imaging (MRI) of the breast before and after anthracycline- and/or taxane-based NAC, followed by curative surgery at our hospital, between 2006 and 2016. T2-weighted MRI revealed PE, and PE before NAC (pre-PE) and PE after NAC (residual PE) were evaluated. The correlation between the presence or absence of PE and relapse-free survival was evaluated using a log-rank test and multivariable Cox regression analysis. The risk of recurrence was stratified according to the residual cancer burden (RCB).

Results: Pre-PE was observed in 64 out of 128 patients (50%). Among 64 patients with pre-PE-positive breast cancer, residual PE was observed in 21 (32.8%). In the log-rank test, breast cancer with residual PE had a poorer prognosis than breast cancer with PE that had disappeared ($p < 0.0001$). In the multivariable Cox regression analysis, residual PE was a significant factor of poor prognosis (RR, 20.5; 95% confidence interval, 5.3–108.2; $p < 0.0001$). Regarding RCB stratification, compared to patients with breast cancer with disappeared PE, those with breast cancer with residual PE exhibited significantly poor prognosis in class II and class III ($p = 0.006, 0.02$).

Conclusion: In breast cancer with PE, residual PE after NAC is a significant factor related to poor prognosis.

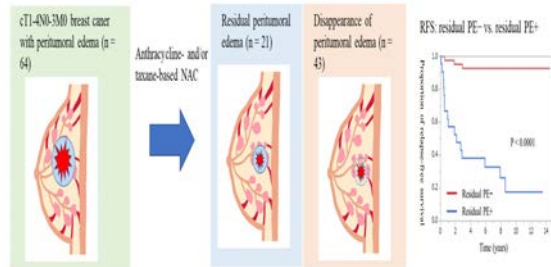
Effect of neoadjuvant chemotherapy on peritumoral edema in patients with breast cancer and its clinical significance

Effect of neoadjuvant chemotherapy on peritumoral edema in patients with breast cancer and its clinical significance

Objectives: We aimed to evaluate the effect of neoadjuvant chemotherapy (NAC) on peritumoral edema (PE) and its prognostic value for residual PE in operable breast cancer.

Materials & Methods: cT1-4N0-3M0 breast cancer patients who underwent contrast-enhanced magnetic resonance imaging of the breast before and after NAC, followed by a curative surgery, were retrospectively evaluated.

Results: Residual PE was observed in 21 (32.8%) out of 64 pre-PE positive patients. In the multivariable Cox regression analysis, residual PE was identified as a significant factor of poor prognosis (RR, 20.5; 95% confidence interval, 5.3-108.2; $p < 0.0001$).



Conclusions: In breast cancer with PE, residual PE after NAC is a significant factor related to poor prognosis.

PO3-08-01

Decision curve analysis to compare breast cancer risk predictions for a polygenic integrated clinical risk model with those of a gold standard

Presenting Author(s) and Co-Author(s):

E. Spaeth. Phenogen Sciences, Charlotte, North Carolina, United States

B. Rosner. Brigham and Women's Hospital and Harvard Medical School, United States

G. Dite. Genetic Technologies, Fitzroy, Victoria, Australia

Risk-based guidelines have been developed to provide advice on options that are available to women who are at increased risk of breast cancer. We and others are focused on improving risk prediction models for general population use. For breast cancer, polygenic risk has been identified as important for risk prediction, especially when combined with clinical risk factors such as family history, anthropometric measures, breast imaging measures, and hormonal and reproductive risk factors.

When comparing the performance of risk prediction models, the AUC is most often used but it focuses on performance in terms of distinguishing between affected and unaffected individuals and does not take into account differences in the specificity (true negative rate) and sensitivity (true positive rate) of the models being compared. In contrast, decision curve analysis takes sensitivity and specificity into account and enables the comparison of the net benefit of risk prediction tools at the clinical risk thresholds that are used to guide clinical management decisions.

Herein, we use decision curve analysis to compare breast cancer risk prediction guidelines for BRISK and the Breast Cancer Risk Assessment Tool (BCRAT) in the UK Biobank, and for BRISK and IBIS version 7 in the Nurses' Health Study. We evaluated the net benefit at the 5-year risk thresholds (1.67% and 3%) that are used to guide clinical management decisions around risk-reducing medication and at the remaining lifetime risk of 20% that is used to guide supplemental MRI surveillance.

In the UK Biobank, BRISK showed a net benefit over BCRAT at the 5-year risk thresholds of 1.67% and 3.0%. The AUCs were 0.649 (95% CI = 0.640, 0.695) for BRISK and 0.567 (95% CI = 0.556, 0.577) for BCRAT and showed that, overall, BRISK discriminated between affected and unaffected women better than BCRAT ($P < 0.001$). In the Nurses' Health Study, BRISK showed a net benefit over IBIS at the remaining lifetime risk threshold of 20%. The AUCs were 0.647; 95% CI = 0.627, 0.668 for BRISK and 0.571; 95% CI = 0.546, 0.595 for IBIS, a statistically significant improvement for BRISK over IBIS ($P < 0.0001$). We also looked at sensitivity, specificity, positive predictive value and negative predictive value even though these risk models are one-step removed from breast cancer diagnosis by screening/risk-reduction options. The positive predictive values are higher for the BRISK (27.1%) model compared to BCRAT (5.5%) in the UK Biobank dataset and higher for BRISK (15.4%) compared to IBISv7 (14.0%) in the Nurses' dataset.

We have shown the application of a statistical tool that can be used to directly compare risk models at clinically relevant thresholds. We have shown that BRISK, which comprises polygenic risk and clinical risk factors, shows higher net benefit at both 1.67% and 3% thresholds compared to BCRAT and at 20% remaining lifetime risk for IBIS version 7.

In breast cancer risk prediction, a tool with high specificity (and therefore a necessary trade-off for low sensitivity) is preferred because we do not want to incorrectly classify women as not being at high risk and deny them the opportunity for intervention in the form of more frequent screening, alternative modes of screening or risk-reducing medication. This improvement in general population risk stratification that BRISK can provide has the potential to have a clinically significant effect on women's health.

PO3-08-03

Comparing prognosis for BRCA1, BRCA2 and non-BRCA breast cancer.

Presenting Author(s) and Co-Author(s):

P. Antunes Meireles. Instituto Português de Oncologia de Lisboa Francisco Gentil, United States

C. Bexiga. Hospital Beatriz Ângelo, United States

S. Fragoso. Instituto Português de Oncologia de Lisboa Francisco Gentil, United States

S. Santos. Instituto Português de Oncologia de Lisboa Francisco Gentil, United States

T. Duarte. Instituto Português de Oncologia de Lisboa Francisco Gentil, United States

F. Vaz. Instituto Português de Oncologia de Lisboa Francisco Gentil, United States

BACKGROUND Breast Cancer (BC) is the most diagnosed malignancy and the leading cause of cancer death in women worldwide. Approximately 10% of BC cases are hereditary, and up to 25% have been linked to germline variants of specific genes. Germline pathogenic variants (PV) in BRCA1 and BRCA2 genes, which account for 20% of familial BC cases, are highly penetrant and are associated with Hereditary Breast/Ovarian Cancer Syndrome.

BRCA1 e BRCA2 are tumor suppressor genes, which interact with recombination/DNA repair proteins in pathways that participate in preserving intact chromosome structure, particularly on the DNA double chain. So far, more than 7000 PV were identified on these genes, including the Portuguese founder mutation (BRCA2 c.156_157insAlu), which accounts for a great proportion of BC cases in our country.

BRCA1 and BRCA2 associated BC have distinct clinicopathological characteristics. Long-term follow-up data related to prognosis and survival of either BRCA1 or BRCA2 BC patients is conflicting. Two large meta-analysis report worse overall survival for both, when compared to sporadic BC, whereas two other large meta-analysis concluded on worse overall survival only for BRCA1 patients, with similar overall survival for BRCA2 patients. One meta-analysis reports similar survival for both groups.

We report the analysis of our cohort of BRCA1/2 BC patients included in our multidisciplinary program. Our goal is to compare clinicopathological characteristics and prognosis between BRCA1 and BRCA2 BC and with a control group without germline PV (non-BRCA). **METHODS** Prospective follow-up was proposed to patients with a diagnosed BRCA1/2 PV. This study included BRCA1/2 patients with BC as first cancer diagnosis, observed between January 2000-May 2023. A control group, with similar phenotype and histological characteristics, without germline PV was used. Statistical analysis was performed to compare characteristics and prognosis between BRCA1 and BRCA2 and non-BRCA BC. ANOVA test was used to compare the age at diagnosis; chi-square was used to compare categorical variables, such as histological subtype and clinical staging at diagnosis; log rank was used to compare the primary and secondary endpoints – overall survival (OS) and invasive disease-free survival (iDFS), respectively. **RESULTS** From 1077 individuals who tested positive for BRCA1/2 PV, 345 patients had BC, mostly with a BRCA2 PV (66.4%). A control group of 339 individuals was assembled. BRCA2 BC was mostly luminal, as non-BRCA patients, compared with BRCA1 (73.8% vs. 65.8% vs. 25.9%, $p < 0.001$) and BRCA1 was mostly triple negative, compared with non-BRCA and BRCA2 (65.5% vs. 16.5% vs. 13.3%, $p < 0.001$). For a mean follow-up time of 10.6 years (± 5.6), recurrence was similar, with central nervous system (CNS) metastases being

more frequent for BRCA1 (66.7% vs. 23.7% in non-BRCA, and vs. 9.1% in BRCA2, $p < 0.001$), and bone metastases were predominant for BRCA2 BC (57.5% vs 33.3% in non-BRCA, and vs. 9.1% in BRCA1, $p = 0.003$). Non-BRCA BC showed longer time to recurrence (99.3 months vs. 76.5 months in BRCA2 BC, and vs. 61.2 months in BRCA1 BC, $p = 0.010$), although longer OS was observed in BRCA2 BC (136.2 months vs. 121.7 months in BRCA1 BC, and vs. 113.2 months in non-BRCA, $p < 0.001$). Development of second primary tumors was more frequent in BRCA2 patients, compared with BRCA1 (20.9% vs 9.2%, $p = 0.002$). DISCUSSION In the Portuguese population, BRCA2 BC is more frequent than BRCA1 BC. Relapses occurred later for BRCA2 BC, affecting mostly the bone, whereas BRCA1 BC relapsed in CNS. As it is stated in the literature, BRCA1 BC is consistent with triple negative, as BRCA2 BC is more associated with luminal subtype. Differences in iDFS favored non-BRCA patients, whereas OS was significantly improved in BRCA2 BC patients. This is the biggest cohort presented in the Portuguese population and one of the biggest presenting BRCA2 BC patients.

Table 1

	All (n=684)	BRCA1 (n=156)	BRCA2 (n=229)	Non-BRCA (n=339)	p value
Age - median (IQR)	42 (15)	40.5 (14)	42 (17)	44 (15)	
Molecular Subtype - n (%)					<0.001
Luminal A	422 (61.7)	30 (25.9)	169 (73.8)	223 (65.8)	
Luminal B	62 (9.1)	6 (5.2)	17 (7.4)	39 (11.5)	
HER-2 enriched	28 (4.1)	3 (2.6)	4 (1.7)	21 (3.1)	
Triple negative	167 (24.4)	76 (65.5)	35 (15.3)	56 (16.5)	
Clinical Stage IV at diagnosis - n (%)					<0.001
IV	16 (2.3)	4 (3.4)	6 (2.6)	6 (1.8)	
Recurrence - n (%)					0.270
all	169 (24.7)	25 (21.6)	63 (27.5)	81 (23.9)	
Ipsilateral	15 (2.2)	1 (0.8)	2 (0.9)	12 (3.5)	
Contralateral	57 (8.3)	10 (8.4)	19 (4.4)	28 (8.3)	
Metastatic	86 (12.6)	13 (11.2)	39 (17.0)	37 (10.9)	
Vital Status					<0.001
Alive	585 (85.5)	96 (82.8)	174 (76.0)	315 (92.9)	
Dead	99 (14.5)	20 (17.2)	55 (24.0)	24 (7.1)	
iDFS - mean (SD)	85.2 (62.4)	61.2 (54.9)	76.5 (55.2)	99.3 (66.7)	0.010
OS - mean (SD)	122.4 (67.9)	121.7 (59.4)	136.2 (85.0)	113.2 (71.1)	<0.001

IQR - Interquartile Range. iDFS - Invasive Disease-Free Survival. SD - Standard deviation. OS - Overall Survival. *9 missing values in Molecular Subtype. *12 missing values in Recurrence.

Characteristics of patients according to BRCA1/2 mutation status (n = 684)

PO3-08-04

Prevalence of BRCA1/2 mutations in an underrepresented population of women with breast cancer: Observations from the City of Hope INSPIRE study

Presenting Author(s) and Co-Author(s):

J. Mortimer. City of Hope, Duarte, California, United States

S. Lindsey. City of Hope, United States

I. Solomon. City of Hope, United States

W. Park. City of Hope, United States

D. Sturgeon. City of Hope National Medical Center, Duarte, CA, United States

K. Blazer. City of Hope, United States

S. Gray. City of Hope, United States

J. Bonner. City of Hope National Medical Center, Duarte, CA, United States

X. Xia. City of Hope, United States

S. Gruber. City of Hope National Medical Center, Duarte, CA, United States

Background: Because African American and Latina women have been less likely to undergo germline testing, it has been difficult to determine the prevalence of hereditary breast and ovarian cancer predisposition in these populations. Here we report the prevalence of BRCA1/2 mutation in patients with a breast cancer diagnosis from City of Hope's (COH) INSPIRE (Implementing Next-generation Sequencing for Precision Intervention and Risk Evaluation) study.

Methods: Patients with a history of any stage breast cancer (stage 0-IV), who were seen by a City of Hope physician at the Duarte or Upland campuses, were approached by a clinical research coordinator for participation in an institutional tissue biorepository project. Demographic information included age, race and ethnicity. Patients consent for this IRB-approved study to store tumor specimens for future research use and Invitae germline testing for 155 predisposition genes which is performed at no cost to the patient.

Results: From 7/9/20 until 4/2023, 2413 women consented for participation and underwent germline testing. Mutations in BRCA1 were identified in 53 and BRCA2 in 65. Table 1 summarizes the prevalence of BRCA1/2 mutations according to race and ethnicity. Pathogenic variants in BRCA1 were identified in 22/742 (3.0%) of Hispanic women compared to 16/1552 (1.7%) non-Hispanics ($p=0.046$). BRCA2 mutations were comparable 16/742 (2.2%) Hispanics and 47/1505 (3%) non-Hispanics. Hispanic women with breast cancer were 2.49 times as likely as non-Hispanics to carry a pathogenic germline BRCA1 mutations than BRCA2 ($p=0.026$)

Prevalence of BRCA 1 and 2 mutations by Self-Reported Race and Ethnicity					
	# Tested	BRCA1	BRCA2	BRCA1 or 2	VUS/Negative
Race					
Native American	15	0	1 (6.7%)	1 (6.7%)	14 (93.3%)
Pacific Islander	8	0	0	0	8 (100%)
Asian	367	5 (1.4%)	11 (3%)	16 (4.4%)	351 (95.6%)
Black	136	7 (5.1%)	4 (2.9%)	11 (8.1%)	125 (91.9%)

White	1675	37 (2.2%)	44 (2.6%)	81 (4.8%)	1594 (95.2%)
Other	86	1 (1.2%)	4 (4.7%)	4* (4.7%)	82 (95.3%)
Unknown	126	3 (2.4%)	1 (0.8%)	5 (3.2%)	122 (96.8%)
TOTAL	2413	53 (2.2%)	65 (2.7%)	117 (4.8%)	2296 (95.2%)
Ethnicity					
Hispanic	742	22(3%)	16 (2.2%)	37* (5%)	705(95%)
Non-Hispanic	1552	26(1.7%)	47(3%)	73(4.7%)	1479 (95.3%)
Unknown	119	53(2.2%)	2(1.7%)	7(5.9%)	112(94.1%)
TOTAL	2413	53(2.2%)	65(2.7%)	7(5.9%)	112(94.2%)
* Patient had both BRCA1 and BRCA2 mutations					

Conclusion: The prevalence of BRCA1/2 mutations in the African American and Latina population is higher than what was observed in White women. These data provide additional support for the recommendation to perform germline testing in all women with breast cancer, regardless of race or ethnicity

PO3-08-05

Prognostic value of multigene test to the patients with Hormone receptor-positive, HER2-negative breast cancer based on special histologic subtypes

Presenting Author(s) and Co-Author(s):

S. Yang. Yonsei University College of Medicine, United States

J. Ahn. Yonsei University college of medicine, United States

S. Lee. Yonsei University college of Medicine, United States

J. Kim. Yonsei University college of medicine, United States

H. Park. Department of Surgery, Yonsei University College of Medicine, United States

S. Kim. Yonsei University college of medicine, United States

B. Park. Yonsei University college of medicine, United States

S. Park. Yonsei University college of medicine, United States

Background: Special histologic subtypes of breast cancer, including mucinous and tubular, account for 25% of all invasive breast cancers. Multigene tests (MGT) play a crucial role in guiding adjuvant chemotherapy and predicting prognosis for the patients with Hormone receptor-positive HER2-negative breast cancer. This research aims to examine the results of multigene tests for special histologic subtype patients and review the prognosis of each group.

Methods: A retrospective analysis was conducted on data from 133 patients with special histologic subtypes of breast cancer who underwent surgery at Severance Hospital between November 2013 and December 2022. Each patient underwent one type of MGT, including Oncotype Dx, MammaPrint, or EndoPredict. Patients were grouped in two groups according to histologic types, based on WHO classification. Favorable types consist of type A mucinous carcinoma, pure tubular carcinoma, invasive solid papillary carcinoma, encapsulated papillary carcinoma with invasion, invasive cribriform carcinoma, secretory carcinoma, and invasive carcinoma with apocrine differentiation. Unfavorable types included type B mucinous carcinoma, mucinous carcinoma with micropapillary feature or neuroendocrine differentiation, mixed IDC, ILC or invasive micropapillary carcinoma, mixed invasive solid papillary carcinoma, mixed invasive papillary carcinoma, and mixed invasive cribriform carcinoma with IDC.

Results: Patients with favorable types accounted for 42.86% (57 patients), while patients with unfavorable types accounted for 57.14% (76 patients). Patients with unfavorable histologic subtypes of breast cancer tended to have a higher incidence of high-risk results in MGT, as well as a greater prevalence of multiple (multifocal, multicentric) cancer and higher histologic grade. In multivariate analysis using logistic regression, unfavorable types showed a significantly high ratio of having high risk on MGT compared to the favorable type (OR = 4.327, 95% CI 1.210 – 15.475, p-value = 0.024). Moreover, overall survival in unfavorable histologic types showed a statistically significant difference between high-risk and low-risk in Kaplan-Meier survival analysis (p-value = 0.001).

Conclusions: Unfavorable subtypes have shown a significantly higher-risk result of MGT, and patients with unfavorable types of breast cancer and high-risk MGT results have exhibited the worst prognosis. Consequently, we can suggest that MGT can be used as a prognosis evaluation tool for certain special subtypes of breast cancer and further utilized to aid in treatment decisions.

PO3-08-06

Challenges in Implementing Genetic Counseling and Genetic Testing for Breast Cancer: Insights from the First 1000 Families Assessed in a Public University Hospital in Argentina

Presenting Author(s) and Co-Author(s):

D. Mansilla. Instituto de Oncología Angel H. Roffo, United States

D. Bequelman. Roffo institute, United States

J. Cavallero. Roffo Institute, United States

H. Ursino. Roffo Institute, United States

B. Gaston. Roffo Institute, United States

I. Martin. Roffo Institute, United States

E. Armanasco. Roffo Institute, United States

A. Aguilar. Instituto de Oncología Ángel H. Roffo, United States

V. Caceres. Roffo Institute, United States

E. Azar. Instituto de Oncología Angel H. Roffo, United States

Introduction: Integrating genetic testing into breast cancer patients care is crucial for personalized treatment recommendations, risk reduction strategies, and family members evaluation. However, Argentina faces several concerns in implementing these services.

Objective: This study aims to explore the challenges encountered in implementing genetic testing for breast cancer, drawing insights from the assessment of the first 1000 patients at a public university hospital in Argentina.

Methods: We conducted a retrospective analysis of patients who underwent genetic counseling in our institution from January 2015 to June 2023. We also analyzed patients who underwent surgery from June 2022 to May 2023.

Results: 1032 patients were evaluated in our unit. 836 patients (81%) met the National Comprehensive Cancer Network (NCCN) criteria for genetic testing. Genetic testing was requested for 575 patients (68.7%) Only 44% of patients were able to access the test, with 60% receiving only the BRCA1/2 test (see Table 1 and 2 for details).

In the analysis of breast cancer surgeries (n=246), 62% (n=154) met the NCCN criteria for genetic testing. However, only 56% of these patients underwent genetic counseling prior to their surgery and only 15 (9.86%) received their results before primary treatment.

Discussion

Unfortunately, only 9.8% of patients have the results of genetic testing prior to their primary treatment, indicating a critical need for timely referrals and mainstream genetic testing. To counteract, our university hospital's breast cancer unit has taken proactive measures since January 2015. Genetic counseling has been established as a standard of care for all patients, and a streamlined workflow has been implemented to optimize referrals. Trained professionals, including a genetic counselor, psycho-oncologist, and geneticist, have been integrated into core teams.

Additionally, healthcare professional continued education has played a pivotal role in improving referrals. Additionally, we have introduced an easy workflow to optimize referrals to genetic counseling.

Completion rate of requested genetic tests is concerning, with 56% of tests not being completed, and 60% of the completed tests limited to BRCA1/2.

Improving access to genetic testing is imperative. Currently, comprehensive genetic testing is inaccessible to patients without medical coverage, and even those with coverage face difficulties in testing access.

Moreover, patient education plays a vital role in promoting the importance of genetic testing and its impact on patient care and their families. In collaboration with the Argentinean Breast Pathology Society, we have developed two informative videos that reinforce knowledge provided by primary care physicians and breast surgeons.

Conclusion,

Our study is the first in Argentina to analyze the numerous challenges faced in conducting genetic testing for breast cancer in a public hospital. By addressing these challenges collectively, we can facilitate the effective integration of genetic counseling and testing into routine practice for breast cancer patients in Argentina.

Table 1: Breast Cancer Genetic Counseling Unit Patients (2015-2023)

Table 1: Breast Cancer Genetic Counseling Unit Patients (2015-2023)	n	%
Evaluated patients	1032	100,00
Patients meeting NCCN testing criteria	836	81,01
<i>Patients meeting testing criteria who were requested for study</i>	575	68,78
<i>Patients meeting testing criteria who were NOT requested for study</i>	261	31,22
No health insurance	133	50,96
More information requested	66	25,29
Psychological distress	31	11,88
Contact with genetic counseling too close to surgery	23	8,81
Does not want testing	8	3,07
Patients without criteria for study request	196	18,99
No NCCN criteria	41	20,92
Inadequate index case	55	28,06
Lack of information for testing decision-making	100	51,02

Table 2: Breast Cancer Genetic Counseling Unit Patients studies (2015-2023)

Table 2: Breast Cancer Genetic Counseling Unit Patients studies (2015-2023)	n	%	n	n	n
Requested studies	575	100,00			
Performed studies	253	44,00	Positive	Negative	VUS
BRCA1 and BRCA 2 sequencing	152	60,08	31	119	2
Ashkenazi Panel	1	0,40	0	1	0
Multigene Panel	82	32,41	20	40	22
Exoma	2	0,79	0	0	2
Not performed	322	56,00			
Denied by health insurance / Lack of financial access	56	17,39			
Deceased	1	0,31			
Does not wish to undergo testing	3	0,93			
Lost follow-up	262	81,37			

PO3-08-07

Licochalcone A as a risk reducing agent against luminal and non-luminal breast cancers.

Presenting Author(s) and Co-Author(s):

A. Hajirahimkhan. Northwestern University, Lisle, Illinois, United States

E. Bartom. Northwestern University, Illinois, United States

s. Chandrasekaran. University of Michigan, United States

S. Clare. Surgery, Breast Surgery Division, Feinberg School of Medicine, United States

S. Khan. Northwestern University, Chicago, Illinois, United States

Background: Breast cancer risk reducing drugs with proven efficacy have adverse side effects, significantly minimizing their uptake and impact. Further, they do not prevent ER- breast cancer. Effective alternative strategies with lower toxicity are needed. Previously, we have shown that licochalcone A (LicA) suppresses aromatase expression and activity, enhances the activity of detoxifying enzymes, and reduces estrogen genotoxic metabolism in cell lines and animal models. These data led us to hypothesize that LicA creates a tumor preventive environment in the breast by reprogramming metabolism and antioxidant/anti-inflammatory responses in the breast leading to decreased proliferation and tumor suppression. We now report on the breast tumor preventive effects of LicA in xenograft models, its oral bioavailability, and its biologic effects on human breast microstructures from women at increased risk of breast cancer.

Methods: We prepared microstructures from the fresh tissue of contralateral unaffected mastectomy specimens of 6 postmenopausal women with incident unilateral breast cancer. After exposing them to DMSO (control) or LicA (5 μ M), we performed total RNA sequencing. Differentially expressed genes were identified and analyzed by gene ontology and pathway membership. The RNA-seq data was also utilized to conduct metabolism flux analysis. Combined enrichment scores > 4 and FDR < 0.05 was considered significant. The NanoString metabolism panel was employed in 6 additional subjects. We performed live cell imaging to monitor proliferation of pre-malignant DCIS.COM, DCIS.COM/ER+ PR+; and malignant MDA-MB-231 (ER- PR-), MCF-7 (ER+ PR+), MCF-7aro, and BRCA1 defective HCC-1937, and HCC3153 cells. Xenograft models of MCF-7aro and MDA-MB-231 tumors were established in female nude mice and the animals treated for 28 days with vehicle or LicA (80 mg/kg.day, s.c.). We measured the rate of tumor growth. We also conducted a PK/PD study with oral LicA (100 mg/kg) in intact BALB/c female mice.

Results: We observed significant (FDR < 0.05) upregulation of antioxidant genes (up to 8-fold), consistent with upregulation of NRF2 and the thioredoxin system, the major regulators of antioxidant pathways. This was accompanied by significant downregulation of RELA- and NF- κ B1-dependent inflammatory pathways. In addition, we observed decreased expression of PI3K-AKT genes and the pro-adipogenic transcription factors SREBF1 and SREBF2, which may explain the downregulation (4 to 32-fold) of cholesterol biosynthesis and transport, and lipid metabolism genes. Metabolism studies confirmed these data and demonstrated a robust increase in the pentose phosphate shunt and NAD(P)H generation without enhancing ribose 5 phosphate formation, suggesting an antioxidant and anti-proliferative environment. LicA also suppressed proliferation of pre-malignant and malignant cells, with sustained effects on aggressive cells at doses $< 10 \mu$ M. LicA significantly reduced tumor growth in luminal (P = 0.008) and triple negative (P = 0.001) in vivo models (unpaired t-test with Welch's correction for unequal variances). Promising serum and breast bioavailability, equivalent to low micromolar

concentrations sufficient to show efficacy was demonstrated as well.

Conclusion: Our data suggest that LicA is a good candidate for breast cancer prevention in both ER+ and ER- breast cancers through reprogramming metabolism and antioxidant pathways leading to decreased proliferation. We will study LicA in intraductal models of ER+ and ER- precancer lesions in immunocompetent mice and will monitor their progression to invasive breast cancer to further establish its preventive efficacy.

PO3-08-08

Basal-Luminal (BL) Cells in Histologically Normal and Malignant Breast Tissue from BRCA1 and BRCA2 Carriers

Presenting Author(s) and Co-Author(s):

R. Fonseca Abreu. Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA, United States

T. Domingos. Department of Pathology, Brigham and Women's Hospital, United States

R. Bonfim Pimenta Peixoto. Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA, United States

A. Patel. Department of Pathology, Brigham and Women's Hospital, United States

K. Taneja. Department of Pathology, Brigham and Women's Hospital, United States

M. Moore. Dana-Farber Cancer Institute, United States

A. Pollaci. Dana-Farber Cancer Institute, United States

J. Garber. Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Division of Cancer Genetics and Prevention, Dana-Farber Cancer Institute, United States

N. Girnius. Harvard Medical School, United States

D. Dillon. Brigham and Women's Hospital, Breast Oncology Program, Susan F. Smith Center for Women's Cancers, Dana-Farber Brigham Cancer Center; Harvard Medical School, United States

Background Single-cell studies of normal breast tissue in BRCA mutation carriers have led to the identification of a candidate cancer precursor cell, the basal-luminal (BL) cell. The localization of BL cells within normal, pre-malignant and malignant breast tissue architecture is not well characterized. Here, using cyclic immunofluorescence (CyCIF), we quantify and localize BL cells within normal and malignant breast tissues from BRCA1 and BRCA2 carriers. **Methods** Formalin-fixed paraffin-embedded breast tissue sections from 9 BRCA1 and 9 BRCA2 consented patients treated at Dana Farber Cancer Institute (2001-2019) were retrieved from the clinical archives and subjected to CyCIF for luminal and basal markers including CK5, CK14 and CK19. Using one section/case, cells co-expressing basal and luminal cytokeratins (CK14/CK19 and/or CK5/CK19) were visually identified in invasive carcinoma, ductal carcinoma in situ (DCIS) and in adjacent normal breast tissue. In histologically normal tissue, regions of interest (ROIs) with co-expressing cells were classified as terminal duct lobular units (TDLUs) or isolated ducts. Within each ROI, the quantity of BL cells was scored as low (1-5 cells), moderate (6-10 cells), or high (>10 cells). **Results** The 9 BRCA1 tumors included 8 invasive ductal carcinomas/no special type and 1 tubular carcinoma. The 9 BRCA2 tumors included 4 invasive ductal carcinomas/no special type and 5 invasive carcinomas with ductal and lobular features. 496 ROIs were evaluated in histologically normal tissue: 297 from BRCA1 cases and 199 from BRCA2 cases. BL cells co-expressing CK14/CK19 and/or CK5/CK19 were identified in normal TDLUs and isolated ducts in both BRCA1 and BRCA2 cases. BL cells were more frequently identified in BRCA2 cases, with at least one BL cell present in 97/297 ROIs (33%) in BRCA1 cases and in 133/199 ROIs (67%) in BRCA2 cases ($p < 0.01$). 55% of BRCA2 ROIs had >10 BL cells each versus 42% of BRCA1 ROIs; however, this difference was not significant. Four BRCA1 cases showed a diffuse BL cell phenotype within the invasive carcinoma with either a diffuse or scattered BL cell phenotype within the DCIS. The BL cell phenotype was not seen diffusely in invasive carcinoma or DCIS in the other 14 cases; however individual tumor

cells or small cell clusters with the BL cell phenotype were occasionally found. Conclusions BL cells are found in histologically normal TDLUs and isolated ducts in breast tissue from BRCA1 and BRCA2 carriers, with greater prevalence in BRCA2 carriers. The BL cell phenotype is present diffusely within tumor cells in almost half of BRCA1-associated cancers and none of the BRCA2-associated cancers in this small cohort. Further study of this interesting cell population is warranted in efforts to understand early changes in epithelium at high risk for the development of cancer.

PO3-08-09

Unique molecular signatures of germline mutations in low expression of human epidermal growth factor receptor 2 (HER2) breast cancer

Presenting Author(s) and Co-Author(s):

N. Liao. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

W. Zhang. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

L. Liu. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

J. Wu. Berry Oncology Corporation, Beijing, China, United States

S. Wang. Berry Oncology Corporation, Beijing, China, United States

L. Cao. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., Guangdong, United States

J. Lai. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

X. Zhang. Berry Oncology Corporation, Beijing, China, United States

A. Yang. Berry Oncology Corporation, Beijing, China, United States

Y. Wang. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

Z. Li. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

G. Zhang. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

C. Ren. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

L. Wen. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

Background: Overexpression of human epidermal growth factor receptor 2 (HER2) in breast cancer (BC) is associated with lower survival and higher risk of disease recurrence. A new subtype of HER2-low BC which has been proposed from several studies demonstrates that HER2-low patients have distinct somatically genetic alterations and clinical outcomes. We have previously reported that HER2-low BC had distinct clinical and somatic mutational feature compared with HER2-zero and HER2-high tumors. We have therefore extended studies by

comparing germline mutation expression among these HER2 subgroups. Methods: 530 Chinese women with BC were enrolled in a prospective protocol between May 2021 to March 2023 at Guangdong Provincial People's Hospital. Genomics data was generated from a gene panel that surveys 102 tumor mutations. Germline variants were classified into pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign (LB) and benign (B) groups according to the ACMG/AMP Standards and Guidelines. The cohort was divided into three groups based on HER2 status as HER2-zero (n = 107), HER2-low (n = 259), and HER2-high (n = 127) according to immunohistochemistry and/or fluorescence in situ hybridization results. Results: The most common mutated genes were ATM, FANCD2, ATR, BRCA2, RECQL4 and APC. A total of 71 pathogenic or likely pathogenic (P/LP) mutations were identified in 25 cancer susceptibility genes from 64 patients (12.16%). The most frequent mutated P/LP genes are BRCA2, BRCA1, PALB2, PMS2, MUTYH and PTEN in the HER2-low group; BRCA2, BRCA1 and PALB2 in the HER2-zero cohort; Interestingly, among the nine HER2-high patients, we detected unique P/LP genes in each sample including MRE11, FANCM, ATM, FLCN, NTRK1, TP53, BRCA1, CHEKE2 and FANCA. In addition to P/LP mutations, 751 variants of uncertain significance (VUS) in 95 cancer susceptibility genes were also detected in 361 patients (68.11%). The most frequent mutated VUS mutations occurred genes are FANCD2, ATM, RECQL4, RAD54B and ATR in HER2-low group; ATM, FANCA, POLE, MSH2 and FANCD2 in HER2-zero cohort; and ATM, BRCA2, RECQL4, POLE, FANCI and FANCM for HER2-high patients. Most of mutated genes were homologous recombination repair (HRR) or DNA damage repair (DDR) pathway related genes. Several genes were differentially altered across HER2 subgroups, including the mutation frequency of the BMPR1A (p=0.0344), MSH2 (p=0.0103), and RAD51C (p=0.0336) genes that were significantly higher in HER2-zero group. It's worth noting that RAD51C was only mutated in HER2-zero subgroup. BMPR1A and MSH2 were also mutated in HER2-low patients. Differentially mutated genes in specific HER2 subgroups may contribute to better research and choice of future therapeutic approaches. In 115 patients who received neoadjuvant therapy and 84 of them were evaluable for pathological response data, HER2-low patients had lower pathological complete response (pCR) rates than HER2-zero and HER2-high subgroups (p=0.0008). In particular, DDR pathway gene ERCC1 have significantly higher mutation frequency in pCR patients (p=0.0115). Conclusion: HER2-low BC patients have distinct germline mutational signatures and differential clinical outcomes under neoadjuvant systemic therapy. These results have provided additional evidence that HER2-low patients comprise a fourth subtype of BC that needs to be accounted for separately in terms of clinical treatment and outcome reporting. Keywords: breast cancer, germline mutations, human epidermal growth factor receptor 2 (HER2), HER2-low, targeted therapy, next-generation sequencing

Table 1. List of most frequent mutated genes in HER2-zero, HER2-low and HER2-high groups

	HER2-zero	HER2-low	HER2-high
# BC patients	107	259	127
P/LP mutations	BRAC1/2 PALB2	BRAC1/2 PALB2 PMS2 MUTYH PTEN	BRAC1 MRE11 FANCM ATM FLCN NTRK1 TP53 CHEKE2 FANCA
VUS	FANCD2 ATM FANCA POLE MSH2	FANCD2 ATM RECQL4 RAD54B ATR	FANCM ATM FANCI POLE BRCA2 FANCM

PO3-08-10

Somatic mutations of a multigene panel in Chinese HER2-positive patients undergoing neoadjuvant therapy and impact on prognosis based on TP53 status : a single-institution retrospective cohort

Presenting Author(s) and Co-Author(s):

M. Xiong. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

L. Wangxu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, 200032 China, United States

J. Xue. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

B. Yang. Fudan University Shanghai Cancer Center, Shanghai, China, Shanghai, China (People's Republic)

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Background: Gene mutations and copy number variations (CNVs) are associated with the occurrence and development of tumors. Neoadjuvant therapy (NAT) has shown greater clinical benefit in the treatment of HER2-positive breast cancer (BC). The impact of genetic mutations on NAT efficacy in BC has been frequently reported, but the relationship between genetic mutations and NAT efficacy and the long-term prognosis in HER2-positive BC patients still requires more high-quality studies. **Methods:** This retrospective cohort study was conducted patients receiving NAT between September 2017 and March 2021 in the Department of Breast Surgery of Fudan University Shanghai Cancer Center (FUSCC). The genomic characteristics of 513 cancer-related genes from the archived tumour blocks were assessed by next-generation sequencing (NGS). The relationship between tumour mutated gene and the postoperative pathological complete response (pCR) as well as prognosis of the disease-free survival (DFS) were further explored. Statistical methods included Chi-square test, fisher's exact test, Kaplan-Meier survival analysis, all of which were completed by SPSS 20.0. **Results:** 208(47.8%) patients achieved pCR after HER2-targeted NAT and 40(9.2%) patients encountered DFS events. The frequency of somatic alterations in TP53(60%), PIK3CA (15%) and ERBB2(11%) was highest in women with HER2-positive breast cancer. KMT2C (P= 0.036) and TP53(P=0.037) mutations were significantly increased in patients with DFS events. In the HER2+/HR- cohort, patients who achieved pCR had significantly benefit in prognosis (HR=3.605, P=0.002), and CCND1 amplifications(p=0.014), ATM(p=0.016) and GATA3(p=0.016) mutations were more frequent. ERBB2 mutations were significantly associated with younger ages of diagnosis(p=0.018). TP53 mutations were associated with worse DFS (HR=3.242, P=0.0110) as well as more DFS events(p=0.048). Furthermore, TP53 mutations had significant prognostic importance in HER2-positive BC patients with HR-negative (HR=3.712, P=0.0266), pCR (HR=6.253, P=0.0268) and who received trastuzumab-only targeted therapy (HR=4.145, P=0.0105). **Conclusions:** Regard to diverse hormone receptor status or neoadjuvant efficacy, the genetic mutation maps of Chinese HER2+ patients receiving NAT are disparate. Our study found that TP53 mutations have significant prognostic value in

patients with NAT for HER2-positive BC and patients benefit differently depending on HR status, neoadjuvant regimens and response.

PO3-08-11

Association between Histologic Variants and the Results of Multigene Testing in Patients with Hormone Receptor-positive, HER2-negative Invasive Lobular Cancer

Presenting Author(s) and Co-Author(s):

J. Ahn. Yonsei University college of medicine, United States

S. Lee. Yonsei University college of Medicine, United States

S. Yang. Yonsei University College of Medicine, United States

J. Kim. Yonsei University college of medicine, United States

H. Park. Department of Surgery, Yonsei University College of Medicine, United States

S. Kim. Yonsei University college of medicine, United States

B. Park. Yonsei University college of medicine, United States

S. Park. Yonsei University college of medicine, United States

Invasive lobular carcinoma (ILC), which accounts for approximately 5-15% of all breast cancers, can be divided into classic type and various other variants. Multigene testing (MGT) has prognostic value in hormone receptor (HR)-positive, HER2-negative breast cancer. We aimed to investigate the association between the results of MGT and histological variation of ILC.

1582 HR-positive, HER2-negative breast cancer patients treated between January 2014 and December 2022 were reviewed. Patients were divided into three groups; ILC-favorable group, ILC-unfavorable group and invasive ductal carcinoma (IDC) group. The ILC-favorable group consisted of classic and tubulolobular types, while the ILC-unfavorable group included pleomorphic, solid, signet ring cell, florid, and alveolar types according to the reported prognosis of each ILC variant. Among the various types of MGT, the 21-gene assay (OncotypeDX), the 70-gene assay (MammaPrint), and the 12-gene assay (Endopredict) assay were used in clinical setting.

The median age of patients was 50 years (range 20-85 years). 75.5% of patients received the 21-gene assay, 12.8% received the 70-gene assay, and 11.6% received the 12-gene assay. The high-risk results in MGT were showed in 7.7% of 155 patients in ILC-favorable group, 26.1% of 23 patients in ILC-unfavorable group, and 20.9% of 1404 patients in IDC group (p-value < 0.001). In the multivariate logistic regression analysis, ILC-favorable group showed significantly lower odds of high-risk results compared to IDC group (OR=0.284, 95% CI; 0.147-0.548), while ILC-unfavorable group did not show any significant difference compared to IDC group (OR=0.797, 95% CI; 0.263-2.411).

In comparison to IDC, the variants of ILC with favorable prognosis show lower rates of high-risk results in MGT, while the variants of ILC with poor prognosis do not differ significantly from IDC. For patients who diagnosed the variants of ILC with poor prognosis, MGT could be useful for prognosis prediction or treatment decision-making.

PO3-08-12

Oncologic Safety and Preventive Impact of Nipple-Sparing Mastectomy in BRCA1/2 Mutation Carriers: A Multicenter Retrospective Study of the Korea Robot-Endoscopy Minimal Access Breast Surgery Study Group (KoREa-BSG)

Presenting Author(s) and Co-Author(s):

H. Kim. Seoul National Univ. Hospital, Surgery, Korea, United States

S. Jang. Samsung Medical Center, United States

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

E. Kim. Kangbuk Samsung Hospital, United States

C. Cha. Hanyang University Seoul Hospital, United States

H. Park. Department of Surgery, Yonsei University College of Medicine, United States

J. Lee. Kyungpook National University Chilgok Hospital, United States

J. Lee. Soonchunhyang University Seoul Hospital, United States

E. Lee. Korea University Anam Hospital, United States

J. Choi. Yeungnam University Hospital, United States

S. Bae. Seoul St. Mary's Hospital, United States

H. Shin. Seoul National University Bundang Hospital, United States

D. Kim. Daerim St. Mary's Hospital, United States

M. Lee. Keimyung University Dongsan Hospital, United States

Y. Kim. Korea University Guro Hospital, United States

S. Han. Kyung Hee University Hospital at Gangdong, United States

J. Lee. Sacred Heart Hospital, Hallym University, Dongtan, United States

Y. CHANG. Korea University College of Medicine, United States

J. Min. Dankook University Hospital, United States

S. Kim. Hallym University Sacred Heart Hospital, United States

H. Choi. Samsung Changwon Hospital, United States

Y. Kang. Incheon St. Mary's Hospital, United States

S. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

J. Ryu. Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam, Ulsan-gwangyoksi, Republic of Korea

Purpose:

Nipple-sparing mastectomy (NSM) is known for its excellent cosmetic results and acceptable oncologic safety. However, evidence supporting NSM in breast cancer (BC) patients carrying pathogenic variant (PV) or likely pathogenic variant (LPV) in BRCA1/2 genes is still limited. This study aims to evaluate the oncologic safety of NSM in BC patients and examine its preventive effect in unaffected individuals with BRCA1/2 PV/LPV.

Methods:

In this multicenter, retrospective study was conducted by the Korea Robot-Endoscopic minimal

access Breast Surgery study Group (KoREa-BSG). We evaluated data from women who underwent NSM and BRCA1/2 genetic testing across 19 South Korean institutions. This study included BC patients aged between 20 and 80 years who had NSM and BRCA1/2 genetic testing between January 2008 and December 2018. Patients with distant metastasis at the initial diagnosis were excluded.

Results:

A total of 786 women, encompassing 906 NSM cases, were included. This population comprised 120 patients who underwent bilateral NSM, 666 with unilateral NSM for unilateral BC. Among them, 214 who received neoadjuvant chemotherapy. The median follow-up period was 62 months, with an age range of 26-74 years (median 44). Sentinel lymph node biopsy was carried out in 74.7% of cases. In the bilateral NSM cohort (n=120), 36 were bilateral BC patients, 41 were unaffected carriers of BRCA1/2 PV/LPV who underwent bilateral risk-reducing NSM (RRNSM), and 33 presented with unilateral BC with BRCA1/2 PV/LPV. In the subset of 33 patients who underwent contralateral RRNSM for unilateral BC, incidental ductal carcinoma in situ (DCIS) was discovered in two cases. In comparing NSM outcomes according to BRCA status, we found no significant difference in local recurrence (LR) between BC patients with BRCA1/2 PV/LPV (n=172) and those without BRCA1/2 PV/LPV (n=592) (LR rates: 11 in BRCA1/2 PV/LPV vs. 45 in non-carriers; $p = 0.7965$). Of the 172 BRCA1/2 PV/LPV carriers who did not undergo RRNSM, contralateral BC occurred in 11 patients (6.4%), while no recurrence was recorded in the RRNSM group.

Conclusions:

NSM appears to be a feasible option in BC patients with BRCA1/2 PV/LPV. While the long-term impact of NSM on breast cancer prevention in BRCA1/2 PV/LPV carriers requires further investigation, current evidence suggests that NSM could serve as an effective risk-reducing strategy.

PO3-09-01

Integrating pathomic and radiomic images to classify risk of subsequent events among women with DCIS

Presenting Author(s) and Co-Author(s):

S. Huang. Washington University School of Medicine, United States

D. Bennett. Washington University School of Medicine, Saint Louis, Missouri, United States

R. West. Stanford University Medical Center, Stanford, California, United States

G. Colditz. Washington University School of Medicine, Saint Louis, Missouri, United States

S. Jiang. Washington University School of Medicine, Saint Louis, Missouri, United States

Background Multiple sources of -omic data can be generated from women at different stages of developing breast cancer, the leading cancer diagnosed in women worldwide. Traditionally interrogation of risk factors to study associations and develop prediction models for future breast events has been limited to one or few risk factors, or summary scores of clinical and tumor characteristics. Methods to bring mammography images and breast biopsies of precancer lesions together to summarize risk of cancer developing in the breast are urgently needed. Integration of these two sources has not been performed to date, but has potential to increase accuracy of risk prediction. **Approach** The Repository of Archival Human Breast Tissue (RAHBT) was established in 2007 at Washington University School of Medicine (WUSM) and maintains biospecimens and medical record data of women treated with breast-conserving surgery (BCS) or mastectomy for breast cancer at WUSM and six other St Louis metropolitan hospitals between 1981-2016. Prospective follow-up of cases is achieved through health records and Siteman tumor registry. Among 1831 patients with pathologically confirmed DCIS who had no prior cancer, 174 developed breast events at least six months after initial DCIS diagnosis. For each case diagnosed between January 1998 and March 2016 with subsequent breast events, two DCIS controls were matched on race, year of diagnosis (± 5 years), age (± 5 years), and type of surgery. Tissue micro arrays (TMAs) are constructed after breast pathology review and processed for H&E and imaged. Breast cancer risk factor data are uniformly retrieved from the medical records at time of processing cases of DCIS. Mammogram images are retrieved for all women. Full-field digital mammograms (FFDM) are all using the same technology (Hologic). Risk factors and outcome variables: ipsilateral breast events (IBE) was defined as the development of invasive cancer or DCIS in the treated breast at least 6 months post-diagnosis. Follow-up time was calculated from the date of DCIS diagnosis to the date of first IBE, death, or last follow-up, whichever occurred first. The predictors included commonly used clinicopathological factors: age, tumor grade (high vs. low/intermediate), comedonecrosis, surgical margins (close (≤ 2 mm) vs. negative (> 2 mm)), local treatment (BCS only and mastectomy vs. BCS+radiation), and endocrine therapy. BMI, menopausal status, and ER were also available for evaluation as predictors. We limited this analysis to women with digital mammograms immediately prior to diagnosis and include 128 cases and controls. Validation cohort As the RAHBT cohort continues to be followed additional second breast events have been documented after the cut off for events identified through March 2016, and the identical procedures used to review / confirm DCIS and subsequent breast events, construct TMAs, process H&E and images, and assemble risk factor data, and the associated digital mammograms. We have 13 additional ipsilateral breast events with complete data and their controls for independently testing the model performance. **Statistical methods** Propose novel supervised learning approach to integrate image data from mammograms and TMA slides that accommodates agreement between multi-omics. **Results** 128 (cases and controls, 21.9% ipsilateral subsequent events) identified for development and internal cross validation.

Median age at diagnosis was 52 and median time to subsequent breast event was 63 mo. Controlling for the clinical/pathologic risk factors (age, BMI, BI-RADs density, treatment, tumor grade, parous, menopausal status, ER status, and race) and integrating the whole mammogram and TMA pathology images, we observe a 5-yr ipsilateral AUC = 0.74; 10-yr AUC 0.75. The independent validation is ongoing. **Conclusions** Integrating heterogeneous multiomic data sources can generate significant improvement in long term risk prediction after initial DCIS diagnosis.

PO3-09-02

Identifying risk factors for trastuzumab-induced cardiotoxicity among multi-ethnic women with HER2-positive early-stage breast cancer

Presenting Author(s) and Co-Author(s):

L. Mishalani. Columbia University Mailman School of Public Health, United States

A. Vaynrub. Columbia University Irving Medical Center, United States

K. Crew. Columbia University Irving Medical Center, United States

Introduction: While trastuzumab, a HER2-targeted therapy for patients with HER2-positive breast cancer, has been shown to improve disease-free and overall survival rates, it also confers the risk of significant morbidity in the way of trastuzumab-induced cardiotoxicity (TIC). TIC may present as asymptomatic decline in left ventricular ejection fraction (LVEF) or as symptomatic heart failure. Given that racial/ethnic minorities are at higher risk for cardiovascular disease (CVD) compared to non-Hispanic Whites, our objective was to assess racial/ethnic differences in TIC and LVEF recovery among multi-ethnic patients with HER2-positive early-stage breast cancer. **Methods:** We conducted a retrospective cohort study including patients diagnosed with stage I-III HER2-positive breast cancer between 2007-2022 who had received adjuvant trastuzumab therapy at Columbia University Irving Medical Center (CUIMC) in New York, NY. TIC was defined as >10% decrease in LVEF to an overall LVEF < 50% and was confirmed by a minimum of two serial echocardiograms, whereas LVEF recovery was defined as a return to a LVEF >50%. Descriptive statistics, univariate and multivariate logistic regression analyses were conducted to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between sociodemographic factors, tumor characteristics, treatment regimens, and CVD risk factors with the main outcome of TIC. **Results:** In the final cohort (N=500), median age was 53 years (IQR: 45.0-62.0) with 36.6% non-Hispanic White (NHW), 15.8% non-Hispanic Black (NHB), 27.8% Hispanic, and 19.8% Asian/Pacific Islander/Other. About 68.2% of patients received adjuvant radiation therapy, 30.2% were treated with anthracyclines, 37.8% with pertuzumab, 4.6% with T-DM1 and 69.0% with endocrine therapy. Fifty-three (10.6%) patients developed TIC, half of which experienced LVEF recovery. Compared to NHW, NHB patients had a higher rate of TIC (9.3% vs. 17.7%, respectively) and lower rate of LVEF recovery (70.6% vs. 21.4 % in those with TIC, respectively). On multivariable analysis, increasing age, lower LVEF at baseline, anthracycline exposure, and coronary artery disease (CAD) were associated with TIC (see Table). We found no association between TIC and use of pertuzumab or T-DM1. **Discussion:** In our racially/ethnically diverse study population, we found an incidence of TIC comparable to previous clinical studies. NHB patients had double the incidence of TIC and a lower incidence of LVEF recovery when compared to NHW patients. Given the observed racial disparities in TIC and LVEF recovery, NHB patients may require closer cardiac monitoring and restricted use of anthracyclines with adjuvant trastuzumab treatment. More research on cardiotoxicity associated with newer forms of HER2-targeted therapies is necessary.

Table: Multivariable logistic regression model with outcome of TIC

Covariate	Odds Ratio (OR)	95% Confidence Interval	P-value
Age	1.03	1.00, 1.06	0.02
CAD	<u>3.32</u>	0.95, 11.0	0.05
LVEF (baseline)	0.86	0.80, 0.91	<.01
Anthracycline use	3.02	1.40, 6.66	<.01

PO3-09-03

Dysbiosis of gut microbiota in patients with breast cancer

Presenting Author(s) and Co-Author(s):

M. Yamada. Kyushu University graduate school of Medecal Sciences, Fukuoka, Fukuoka, Japan

T. Morisaki. Japan / Kyushu University Hospital / Department of Breast Surgery, United States

Y. Sato. Kyushu University graduate school of Medecal Sciences, United States

K. Mizoguchi. Dept. Surgery and Oncology, Kyushu Universty, Japan

Y. Takao. Kyushu University graduate school of Medecal Sciences, United States

Y. Ochiai. Department of Breast Surgery1 of Kyushu University Hospital, United States

Y. Ootubo. Department of Breast Surgery1 of Kyushu University Hospital, United States

S. Hayashi. Department of Breast Surgery1 of Kyushu University Hospital, United States

M. Nakamura. Dept. Surgery and Oncology, Kyushu University, Japan

M. Kubo. Kyushu University graduate school of Medecal Sciences, Kyushu University Hospital, Fukuoka, Fukuoka, Japan

[Background]

The effects of gut microbiome on various diseases have become widely known, and many studies reported that there was a correlation between the change of gut microbiota, that is dysbiosis, and the progression of digestive tract cancer. In addition, it is well-known that gut microbiota was correlated to the efficacy of immune checkpoint inhibitors for multiple types of cancer. However, the significance of gut microbiota in patients with breast cancer still remains unclear. The aim of this study is to analyze the gut microbiota in patients with breast cancer, compared with healthy women.

[Subjects and Methods]

We used the pre-treatment feces of 79 patients with primary breast cancer who received treatment at our facility and performed metagenome analysis of the V3-4 region of 16S rDNA. We also analyzed the breast cancer patients' microbiota with QIIME2 analysis method, compared to randomly selected 100 women aged 30-77 years from NIBIOHN's public data . We also assessed the characteristics of the gut microbiota of breast cancer patients by subtypes and its relationship with clinical and pathological factors.

[Results]

In Japanese gut microbiota, the Firmicutes and Bacteroidetes phyla make up the majority, but Firmicutes was the most common bacterial phylum in 52% of the public cohort, whereas 96.2% (76/79) of the breast cancer patients' group (BC) showed a significantly higher proportion ($p < 0.0001$). In addition, ANCOM analysis revealed that the relative bacterial amounts of the Firmicutes, Bacteroidetes, and Proteobacteria phyla were significantly decreased in BC compared to the public cohort (PC), and at the bacterial genus level, the Feacalibacterium genus was significantly decreased in BC. Furthermore, the percentage of Fusobacteria phylum, which is a well-known oral bacteria that exacerbates digestive tract cancer, was 49.3% in BC, compared to 35% in PC ($p=0.04$). Among BC, the relative frequency of Fusobacteria phylum was significantly higher in the HER2-negative group than in the HER2-positive group ($p < 0.0001$). In BC, both alpha diversity ($p < 0.0001$) and beta diversity ($p=0.001$) were significantly lower than in PC.

[Conclusion]

An increase in the Firmicutes phylum is known to be associated with obesity, and also likely to affect the incidence risk of breast cancer. The results suggest that the Fusobacteria phylum and Feacalibacterium genus may be risk or preventive factors for breast cancer. Dysbiosis of gut microbiota is suggested to be associated with various diseases, and in this study the decrease in bacterial amount and diversity was observed in BC compared to PC, which may affect the onset and progression of breast cancer.

PO3-09-04

Identification of germline pathogenic variants to guide systemic therapy: Prevalence and spectrum of PVs among Mexican patients with metastatic breast cancer

Presenting Author(s) and Co-Author(s):

J. Rodriguez-Olivares. Instituto Nacional de Ciencias Medicas y Nutricion "Salvador Zubiran", Mexico City, Distrito Federal, Mexico

M. Esparza-Orozco. Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, Mexico City, United States

J. Ramirez-Gonzalez. National Institute of Rehabilitation INR-UNAM, Mexico City, United States

R. Sanchez-Reyes. Centro Médico Nacional La Raza, IMSS, Mexico City, United States

E. Talamantes-Gamez. Centro Médico Nacional La Raza, IMSS, Mexico City, United States

G. Quintero-Beulo. Hospital General de Mexico "Eduardo Liceaga", Mexico City, Distrito Federal, Mexico

G. Lopez-Rosas. Centro Oncológico Internacional, Guadalajara, Jalisco, México, United States

K. Centelles-López. Centro Médico Nacional 20 de Noviembre, ISSSTE, Mexico City, United States

B. Moreno-Jaime. Hospital Regional ISSSTE León, Guanajuato, México, United States

D. Vazquez-Juarez. Breast Cancer Center, Hospital Zambrano Hellion TecSalud, Tecnológico de Monterrey, Nuevo Leon, Mexico., United States

A. Hernandez-Murillo. Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, United States

I. de la Puente Tawil. Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, United States

J. Weitzel. Latin American School of Medicine, United States

C. Villarreal Garza. Tecnológico de Monterrey, Monterrey, Mexico

Y. Chavarri-Guerra. Instituto Nacional de Ciencias Medicas y Nutricion "Salvador Zubiran", Distrito Federal, Mexico

BACKGROUND

Currently, international genetic cancer risk assessment (GCRA) guidelines recommend genetic testing for the identification of germline pathogenic variants (PVs) in patients with metastatic breast cancer (MBC) to guide systemic therapy. Patients with PVs in BRCA genes are candidates to receive poly(adenosine diphosphate–ribose) polymerase inhibitors (PARPi). The prevalence of PVs in patients with HER2-negative MBC has been reported to be 10%. The proportion of MBC in low- and middle-income countries (LMIC) is higher. However, access to genetic testing in LMIC is limited and contributes to the gap in genetic epidemiology knowledge. We aimed to describe the frequency of germline PVs in breast cancer associated genes and clinic-pathologic characteristics of Mexican women with MBC.

METHODS

This retrospective study included Mexican women from 7 centers in Mexico, who were diagnosed with MBC and had genetic testing. Pathogenic and likely pathogenic variants were reported. Demographic, histopathological characteristics, family history and access to treatment with PARPi, were obtained from chart review.

RESULTS

From August 2017 to May 2023, 114 Mexican women with MBC were included, median age at diagnosis was 47 years (range 24-80 y), 42% had de novo metastatic, and 58% recurrent disease. 86.8% had infiltrating ductal carcinoma, 51.3% had HR+HER2- (n=58), 4.4% HR+HER+ (n=5), 5.3% HR-HER2+ (n=6), and 38.6% triple negative tumors (n=44). Sites of metastatic disease were as follows: 61.4% non-regional nodes (n=70), 57% bone (n=65), 40.3% lung (n=46), 30.7% liver (n=35), 15.8% central nervous system (n=18) and 7% peritoneal carcinomatosis (n=8). The frequency of PVs was 22% (25/114); 84% of the PVs were heterozygous, mainly identified in BRCA genes (BRCA1 n=12, BRCA2 n=9), and in 4 patients in other genes (PALB2 n=2, PTEN n=1, MUTYH n=1). Among PARPi candidates, 40% (10/25) received Olaparib, the majority received it on the second or subsequent lines of treatment (7/10) with a median progression free survival of 6 months (3-13 m). BRCA carriers were younger at BC diagnosis (38.5 vs. 49 years, $p=0.00694$) and had a significant higher proportion of family history of ovarian cancer ($p=0.00039$), but not for breast ($p=0.06$), prostate ($p=0.71$) or pancreatic cancer ($p=0.098$), compared to non-carriers.

CONCLUSION

We found a high frequency of PVs in BRCA genes in Mexican women with MBC. Access to the genetic testing and targeted therapy should be improve in the Mexican population in order to decrease disparities in cancer care in the Mexican Population. In addition, genetic testing allows to identify other family members at risk with cascade testing and to recommend them risk reduction strategies.

PO3-09-05

Potential novel treatments for high-risk subsets of breast cancer in postpartum and African American women

Presenting Author(s) and Co-Author(s):

T. Lyons. CU Anschutz Medical Campus, United States

L. Crump. CU Anschutz Medical Campus, United States

R. Steinmetz. CU Anschutz Medical Campus, United States

K. Kines. University of Colorado Anschutz Medical Campus, United States

H. Fairchild. University of Colorado Anschutz Medical Campus, United States

A. Elder. University of Colorado Anschutz Medical Campus, United States

Semaphorin 7a (SEMA7A) is a neuroimmune molecule first recognized for its roles in axonal guidance and inflammation. More recently, SEMA7A has emerged as a driver of tumor progression in multiple types of cancer including lung, glioblastoma and breast. Our studies have focused on the roles of SEMA7A in promoting tumor cell growth and survival as well as invasion and metastasis in mouse models including xenograft and syngeneic. Using patient samples and datamining we have shown that SEMA7A can predict for recurrence in women with postpartum breast cancer (PPBC), or breast cancers diagnosed within 10 years of recent childbirth, and SEMA7A mRNA expression in TCGA is highest in young and African American (AA) women with BC, who typically have poor prognosis. Additionally, our analysis of the Cancer Genome Atlas (TCGA) breast cancer (n=593) and METABRIC cohorts (n=2,136) revealed that SEMA7A is increased in invasive disease and in the top 9% and 27% of upregulated genes ($p=1.09E^{-19}$ & $p=0.009$), respectively. Additionally, ~1.2 (TCGA) and ~1.1 (METABRIC) fold increases in SEMA7A mRNA conferred significantly decreased 5-year survival rates ($p=0.009$ & $p=0.002$) and SEMA7A was in the top 4% of mRNAs upregulated in patients who died within 5 years of diagnosis^{20,24-26}. Cumulatively, these results suggest that identifying therapeutic vulnerabilities of SEMA7A+BC, or direct targeting of SEMA7A, could improve prognosis for these high-risk populations. We have identified several targets in pre-clinical models of SEMA7A+BC that include clinically available, FDA approved drugs, as well as novel inhibitors that exhibit efficacy. In published studies, we have shown that venetoclax, a Bcl-2 inhibitor, reverses ER+SEMA7A+BC resistance to endocrine therapy in mouse models. In unpublished studies, we have extended our observations in ER+SEMA7A+BC to show that alpelisib and a novel PI3K kinase inhibitor, GCT-007, both inhibit growth of human and mouse mammary tumor cells. Furthermore, in models of ER-SEMA7A+BC where we have shown cells to be resistant to chemotherapy, we have utilized age matched cell lines from AA and CA women to dissect the downstream pro-survival signaling that is mediated by SEMA7A and we have shown that anti-PD-1 and anti-PD-L1 therapies are efficacious in reducing tumor growth in vivo. Finally, we have developed a novel monoclonal antibody-based therapy that directly targets SEMA7A signaling via pro-survival pathways and inhibits tumor growth in vivo and in vitro. Collectively our results suggest that SEMA7A+BC should be identified clinically, and alternative treatments advised for this high-risk subset of breast cancer.

PO3-09-06

Role of Obesity-Related Biomarkers on Mortality Among Black Breast Cancer Survivors in the Women's Circle of Health Followup Study

Presenting Author(s) and Co-Author(s):

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

C. Hong. Roswell Park Comprehensive Cancer Center, United States

A. George. Roswell Park Comprehensive Cancer Center, United States

K. Attwood. Roswell Park Comprehensive Cancer Center, United States

B. Quin. Rutgers Cancer Institute of New Jersey, United States

N. Zeinomar. Rutgers Cancer Institute of New Jersey, United States

Y. Lin. Rutgers Cancer Institute of New Jersey, United States

C. Ambrosone. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

K. Demissie. SUNY Downstate Medical Center, United States

E. Bandera. Rutgers Cancer Institute of New Jersey, United States

Background: Central obesity and higher adiposity have been recently associated with higher all-cause and breast cancer-specific mortality in Black breast cancer survivors participating in the Women's Circle of Health Followup Study. Adipose tissue is a dynamic organ producing adipocytokines, including leptin, adiponectin, adiponin, resistin, lipocalin-2/NGAL, plasminogen-activator inhibitor type 1 (PAI-1) and CXCL11, TNF α , and IL-6, which modulate inflammatory markers in obesity, including the release of proinflammatory C-reactive protein (CRP). These circulating biomarkers play important roles linking obesity with insulin resistance, hyperinsulinemia, chronic inflammation, and altered immunity, which may impact overall and breast cancer mortality. The goal of this analysis was to determine if circulating adipocytokines and obesity-related biomarkers of systemic inflammation are associated with breast cancer and overall survival in Black breast cancer survivors. Methods: Circulating biomarkers were assayed for 460 Black breast cancer survivors who provided a blood sample 2 years post-diagnosis in the Women's Circle of Health Followup Study, a population-based cohort of Black breast cancer survivors in New Jersey enrolled within 12 months of diagnosis. Associations between biomarkers (by tertiles) and overall survival were assessed using multivariable Cox regression models. Breast cancer specific survival was assessed based on competing risk analyses using the Fine and Gray subdistribution hazard model. Multivariable models were adjusted for age, body mass index as a measure of overall adiposity, education, menopausal status, stage, grade, subtype, and chemotherapy, hormonal therapy, and radiation treatments received. All tests were two-sided. Analyses were conducted at P=0.05. Results: In multivariable analyses, lipocalin-2, CXCL11, and CRP, biomarkers of adipose tissue inflammation closely related to insulin resistance, were associated with worse overall but not breast cancer specific survival. Compared to women in the lowest tertile of lipocalin-2, women in the highest tertile had a 3-fold increased risk of dying from any cause (T3 vs T1, HR=3.08, 95% CI: 1.29-7.39, p= 0.004) and a ~2-fold increased risk of dying from breast cancer, which was not statistically significant (HR= 1.84, 95% CI: 0.59-5.79, p=0.30). Similarly, women in the highest tertile of CXCL11 were at 2-fold increased risk of dying of any cause (HR: 2.10, 95% CI: 0.96-4.57, p=0.06) but no associations were observed with risk of dying from breast cancer (HR:1.31, 0.42-4.13, p=0.64). Circulating CRP, as a marker of systemic inflammation, was also associated with worse overall survival (T3 vs T1 HR: 2.51, 95% CI: 1.07-5.89, p=0.03), showing a borderline significant association with increased breast cancer specific survival (T3 vs T1 HR:

4.32, 95% CI: 0.87-21.38, $p=0.07$). No associations with overall or breast cancer specific mortality were observed for any of the other adipocytokines examined. Conclusion: In this population-based cohort study of Black breast cancer survivors, biomarkers associated with adipose tissue related inflammation and insulin resistance were associated with reduced overall survival. Relationships with breast cancer survival were not significant, possibly due to limited sample size.

PO3-09-07

When We Tri(al): Reaching, Motivating, & Effectively Engaging Black Women In Breast Cancer Clinical Trial Research

Presenting Author(s) and Co-Author(s):

R. Fairley. TOUCH, the Black Breast Cancer Alliance, United States

E. Powers. TOUCH, The Black Breast Cancer Alliance, Portland, Maine, United States

H. Brown. TOUCH, The Black Breast Cancer Alliance, Annapolis, Maryland, United States

According to the American Cancer Society, Black women in the United States are 41% more likely to die from breast cancer than non-Hispanic white women. A systematic review of participation in clinical trials found that Black patients comprised less than 4% of all patients enrolled in clinical trials for emerging immune-based cancer treatments. The physiology of Black women has not been a significant consideration in clinical trial research. Clinical trial education, recruiting, and participation are not commensurate with the burden of disease.

TOUCH, The Black Breast Cancer Alliance (TOUCHBBCA) launched the When We Tri(al) Movement (WWT) in January 2022 with robust multi-media support and nationwide community event activations to educate and empower Black women with culturally-agile messaging from the trusted voices of Black Breast Cancer survivor/thrivers. WWT provides an innovative and engaging learning platform that clearly depicts how clinical trials work, explains standard of care, dispels historical myths, establishes trust, and empowers self-advocacy. To date, whenwetrial.org has garnered over 108,000 visits and sent nearly 11,000 Black women to clinical trial portals. One-third of unique website visitors have gone into clinical trial search portals.

Over a sixteen day period in late June and early July of 2023, TOUCHBBCA conducted research among Black women who joined the When We Tri(al) movement using a pre-experimental, retrospective pre-then-post test (RPTP) survey design to assess growth in knowledge and behavior change among Black women exposed to the Movement. This survey received 113 respondents who self-identified as Black and assigned female at birth. Following exposure to WWT, 34.5% of respondents reported an increase in their understanding of how breast cancer clinical trials work, 31.9% reported an increase in their understanding of standard of care in breast cancer clinical trials, and 40.7% reported an increased understanding of why clinical trials are important for Black women. 32.7% of survey respondents were more likely to consider participating in a clinical trial after interacting with the WWT movement. After interacting with the movement, 31% of respondents took active steps to participate in a clinical trial—specified as searching for clinical trials in a portal, asking about clinical trial options, talking to a doctor about clinical trials, etc. Another 17.7% of respondents reported supporting a loved one in taking steps to participate in a clinical trial only after interacting with WWT.

The majority of respondents reported first hearing about WWT through social media (59.2%), followed by “Other” (the majority of write-in responses named Google or a friend) (19.5%). Respondents reported that the most convincing WWT messages were delivered via social media (26.6%) and in-person conversations (20.4%).

Not only is When We Tri(al) educating and equipping Black women with critical clinical trial knowledge, but the movement is driving significant behavior change by Black women around clinical trial participation.

PO3-09-08

Using Social Determinants of Health to Improve Surgical Delays for Breast Cancer Patients at Rush University Cancer Center

Presenting Author(s) and Co-Author(s):

H. Tingley. Rush University Medical Center, United States

M. McIntosh. Rush University Medical Center, United States

M. Klee. Rush University Medical Center, United States

M. Gladman. Rush University Medical Center, United States

A. Coogan. Rush University Medical Center, United States

A. Madrigrano. Rush University Medical Center, United States

Introduction

Delays to surgery in the treatment of breast cancer can lead to worse disease specific mortality and overall survival. Previous work has shown a woman's time to surgical treatment is influenced by income, which may be secondary to social determinants of health (SDOH) including health literacy, safety, stress, access to health care and transportation, housing, and ability to pay utilities. This study sought to evaluate a screening process for SDOH to assess and address barriers to care for women newly diagnosed with breast cancer.

Methods

A SDOH screening tool consisting of 7 yes/no questions was developed and used by trained breast oncology nurses via phone call made to all new patients prior to their first visit. Based on patient response, patients are provided with community resources or referred to the hospital social work team. Primary outcome included the SDOH screening results, and secondary outcome included time to surgery.

Results

118 patients were screened, of which 60 patients had surgery as their first treatment and were included in this analysis. Twenty-seven patients screened positive for SDOH need. Ten patients reported >3 SDOH concerns and were referred to social work. The most common concerns were food insecurity and trouble paying utilities. Of the 27 patients who screened positively, 18 identified as Black or African American, 3 were Hispanic, 1 Asian and 5 White. The mean household income for these patients based on their reported zip codes was \$55,615.78. Average time to surgery for patients with a positive SDOH screen was 37.7 days and negative SDOH screen was 42 days. For patients with a positive SDOH screen, those with 2 or fewer SDOH needs had an average time to surgery of 41.9 days and those with 3 or more SDOH needs had an average 30.6 days until surgery.

Discussion

Patients who screened positive for SDOH need and were provided resources had a faster time to surgery than patients who initially screened negative for SDOH. Patients referred to social work had the fastest time to surgery. Early identification of SDOH is necessary for all patients to improve equity and outcomes in breast cancer treatment.

PO3-09-09

Interventions to improve adherence to oral endocrine therapy for prevention or treatment of breast cancer in African American women of low socioeconomic status

Presenting Author(s) and Co-Author(s):

C. Johnson. University of Houston College of Pharmacy, Houston, Texas, United States

A. Adigwe. University of Houston College of Pharmacy, United States

N. Ekezie. University of Houston College of Pharmacy, United States

B. Fatima. University of Houston College of Pharmacy, United States

Z. Majd. University of Houston College of Pharmacy, United States

K. Houk. University of Houston Jack J. Valenti School of Communication, United States

T. Patel. MD Anderson Cancer Center, United States

R. Shimko. University of Houston School of Theatre & Dance, United States

O. Ononogbu. University of Houston College of Pharmacy, United States

S. Abughosh. University of Houston College of Pharmacy, United States

M. Trivedi. University of Houston College of Pharmacy, United States

Introduction: Adherence to oral endocrine therapy (OET) for the prevention and treatment of hormone receptor-positive breast cancer (BC) is important as they reduce the risk of new or recurrent BC. OET adherence is greatly compromised in women of lower socioeconomic status (SES). We have recently reported that patients belonging to the African American race, with longer time on OET, and using OET in the prevention setting are more likely to be non-adherent to OET. Therefore, our study aims to design unique patient-centered interventions and pilot test their feasibility, acceptability, and effectiveness in improving OET adherence in African American women of low SES.

Patients and Methods: This prospective study includes adult, African American women on OET for either the prevention or treatment of BC at Harris Health System in Houston, Texas, serving the underserved patient population with low SES. The first intervention is a motivational interviewing (MI) based telephone intervention consisting of an initial phone call followed by five monthly follow-up calls with an MI-trained pharmacy student. The second intervention is a theatre-based educational video with a script developed by a local African American playwright, featuring African American women. Three African American BC survivors with experience in taking OET consulted with the study team to convey their BC journey and explain challenges with taking OET. They provided feedback on the script and production of the educational video. Informed consent was obtained verbally via phone in the MI intervention and electronically for the educational video intervention. Individuals in both intervention groups were compensated with Walmart eGift cards. Pre- and post-intervention adherence was measured using the proportion of days covered (PDC) over 6-12 months and compared using a paired t-test. Participants also complete a survey at the end of the interventions to determine their acceptability. The survey responses were summarized descriptively.

Results: For the MI intervention initiated in 20 patients, the median age and BMI of study participants was 61 years (range: 49-71) and 30.8 (range: 22.3-57.8) respectively. All participants identified their ethnicity as non-Hispanic or Latino. The majority of participants had hypertension (n=13, 65%) and/or hyperlipidemia (n=11, 55%) with depression (n=3, 15%) and diabetes (n=8, 40%) being less common. The most common stage of BC cancer was stage I

(n=9, 45%), followed by stage II (n=4, 20%), stage 0 (n=3, 15%) and then stage III (n=2, 10%) and IV (n=2, 10%). Letrozole was the most common OET (n=13, 65%), followed by tamoxifen (n=3, 15%), anastrozole (n=2, 10%) and exemestane (n=2, 10%). Most participants were not on a CDK 4/6 inhibitor (n=18, 90%). The median number of years on therapy was 2.8 (0.6-4.5). The median pre-intervention PDC for OET was 0.7 (range: 0.2-0.9). The MI intervention is expected to be complete by October 2023 for all patients. For the educational video intervention, 7 out of the anticipated 25 participants have been enrolled in the intervention. All patients were taking OET for BC treatment and not prevention. Letrozole (n=3, 43%) and anastrozole (n=3, 43%) were the most utilized OET, followed by exemestane (n=1, 14%). While 5 participants (71%) in this intervention reported not missing any OET doses in the past week, 2 patients (29%) reported missing all 7 doses within the past week. After watching the educational video, most participants (n=6, 86%) reported that they strongly agreed to take their OET regularly. The recruitment of study participants for this intervention is ongoing.

Conclusion: In this study, we report that MI and educational video interventions are feasible. The interventions and analysis of their effectiveness and acceptability are ongoing.

PO3-09-10

Minority participation in breast cancer therapeutic trials at an NCI-CCC affiliated safety-net system: Advancing equity in clinical research.

Presenting Author(s) and Co-Author(s):

N. Qureshi. UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER SIMMONS CANCER CENTER, Dallas, Texas, United States

F. Robles. UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER SIMMONS CANCER CENTER, Dallas, Texas, United States

Authors: Nasir Qureshi, MBBS Fabian Robles, MS Mai Badran, MBBS Nisha Unni, MD Hsiao C Li, MD Samira Syed, MD Glenda Delgado-Ramos, MD Sangeetha Reddy, MD Heather McArthur, MD Navid Sadeghi, MD **Title:** Minority participation in breast cancer therapeutic trials at an NCI-CCC affiliated safety-net system: Advancing equity in clinical research. **Introduction:** Participation of under-represented minorities (URMs) in clinical trials enhances the generalizability of the findings and can also improve clinical outcomes. Multiple factors, such as access, language barrier, distrust, and misconceptions, negatively impact URM enrollments in cancer clinical trials. Here we describe our approach to increase participation of breast cancer URMs in therapeutic trials at an academic-affiliated safety-net system. **Methods:** Parkland Health (PH) is a large safety-net system in Dallas County, Texas, and is affiliated with the NCI-CCC designated Harold C. Simmons Comprehensive Cancer Center (SCCC) at UT Southwestern. A dedicated team of SCCC research coordinators support the clinical trial operations at PH. In 2020, several steps were taken to increase access and enrollment of URMs in breast cancer trials at PH including review and optimization of the trial portfolio (more trials in curative intent setting), proactive screening, increasing provider awareness, and addition of a bilingual (English/Spanish) patient navigator to the research team. Data for 2018-2019 (pre-intervention) and 2021-2022 (post-intervention) is presented here. Data for 2020 is excluded due to the impact of COVID-19 pandemic on trial operations. **Results:** Racial and ethnic minorities composed the majority of breast cancer patients at PH (52% Hispanics, 32% Blacks). Ten percent of new patients at PH presented with metastatic disease. In 2018-2019, PH's portfolio included 13 therapeutic trials, 5 of which (38%) were in metastatic setting and 3 required a biomarker. A total of 47 breast cancer patients were enrolled in 11 therapeutic trials at PH, accounting for an average annual accrual rate of 6.1% (7.6% in 2018 and 4.5% in 2019). Accrual to trials in the metastatic setting accounted for 11% (5/47) of enrollments. Two trials in the metastatic setting had zero accruals. In 2021-2022, 16 trials were open at PH, including 7 cooperative group, 4 industry-sponsored (ISTs), and 5 Investigator-Initiated trials (IITs). Five trials (31%) were in metastatic setting and 4 required a genomic biomarker. A total of 87 patients were enrolled in 2021-22, representing an 85% increase in the accruals over the baseline (2018-2019). The annual accrual rates for 2021 and 2022 were 10.5% (43/409) and 10.4% (44/423), respectively. In 2021-22, 63 were enrolled in cooperative group studies, 20 in IITs, and 4 in ISTs. Accrual to trials in the metastatic setting accounted for 6% (5/87) of enrollments. Two studies had zero accruals. The majority of the trial participants (77/87; 89%) belonged to URMs (64 Hispanic, 13 Black). Overall participation rate was 67% (87/129) and was significantly higher in Hispanics compared to Blacks (77% vs 41% - $p < 0.001$). Among Black patients who declined participation, 42% (8/19) cited lack of interest as the reason, which may reflect distrust or misperceptions regarding clinical trials. **Conclusions:** The collaboration between academic centers and safety-net systems provides a unique opportunity to promote equity in clinical trials by increasing access and enrollment of URMs. Developing a balanced portfolio that matches the patient population, enhanced screening, and incorporating clinical trial patient navigation at our institution resulted in a sustained increase in the number of URM

trial participants. Given the lower participation rate among eligible Black patients, we aim to expand our clinical trial navigation program to better address the distrust and misperceptions regarding clinical trials, as a strategy to further improve trial participation at our institution.

PO3-09-11

Age Group Analysis of Breast Cancer Patterns in Brazil: Findings from Population-Based Registries

Presenting Author(s) and Co-Author(s):

J. da Silva. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

A. De Melo. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

L. de Albuquerque. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

M. Rodrigues. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

L. Thuler. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

Background: The rising breast cancer (BC) incidence among young women is potentially influenced by modifiable genetic and reproductive risk factors, as well as the increased incidence among older women may be associated with lifestyle-related factors and screening programs. This study examines BC incidence and mortality rates across different age groups in Brazil, focusing on clinicopathological and sociodemographic variations.

Patients and methods: By using data from 13 Brazilian Population-Based Cancer Registries spanning the period 2010-2015, this study analyzed incidence trends among women with BC. Crude incidence ratios (CIRs) and the annual average percent change (AAPC) were computed. Additionally, clinical and sociodemographic information from 348 Hospital-Based Cancer Registries covering 2000-2019 was incorporated. Mortality data for the years 2000-2020 were obtained from the National Mortality Information System. Comparative analyses were conducted across three predefined age groups: < 40, 40-69, and ≥ 70 years. Statistical significance was defined as a p-value < 0.05, while a threshold of more than 5% difference in proportional values was used as a criterion to identify clinically relevant differentials.

Results: Between 2010 and 2015, a total of 205,966 newly diagnosed cases of BC were documented. The CIRs were 7.1/100,000 for the age group < 40, 156.5/100,000 for the age group 40-69, and 247.5/100,000 for the age group ≥ 70 years. Within the scope of the analyzed age groups, it was observed that solely the age group < 40 years exhibited a noteworthy and persistent increase in the rate of occurrence (AAPC +1.6; 95% CI: 1.0 to 2.2; p < 0.001). This age group also displayed a significantly higher proportion of black women (53%, p < 0.001), a higher prevalence of alcohol consumption (20.5%, p < 0.001), and a greater likelihood of receiving multiple treatment modalities (60.7%, p < 0.001). In contrast, the age group ≥ 70 years experienced a more extended time delay of > 60 days from diagnosis to treatment onset (54%, p < 0.001), while exhibiting a higher utilization rate of hormone therapy (45.3%, p < 0.01). The mortality rates witnessed a significant increase across all age categories, with the age group < 40 years manifesting the most substantial escalation (AAPC +1.8%; 95% CI: 1.6 to 2.1; p < 0.001). This rise was comparatively more than double the rate observed in the 40-69 age group (AAPC +0.7%; 95% CI: 0.5 to 0.8; p < 0.001) and exactly twice as high as the rate recorded in the age group > 70 years (AAPC +0.9%; 95% CI: 0.7 to 1.1 ; p < 0.001).

Conclusion: This study reveals substantial disparities in BC incidence and mortality rates, as well as significant differences in clinicopathological and sociodemographic features, among women aged < 40 compared to those in the 40-69 and ≥ 70 years in Brazil.

Keywords: Breast cancer; age groups; incidence; mortality.

PO3-09-12

Exploring Gender-Specific Patterns of Breast Cancer in Brazil: A Comparative Epidemiological Study

Presenting Author(s) and Co-Author(s):

M. ANTONINI. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, Sao Paulo, Sao Paulo, Brazil

G. PANNAIN. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

S. Buttenbender. Hospital do Servidor Publico Estadual, Sao Paulo, Brazil, United States

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

R. COELHO LOPES. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

O. FERRARO. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

Introduction: Male breast cancer constitutes approximately 1% of all breast cancer cases, and limited studies have focused on this population, resulting in a lack of understanding of the disease in men. This study aims to describe the epidemiological profile of male breast cancer in Brazil and compare it with female breast cancer. Methods: A comprehensive observational cross-sectional study was conducted using retrospective data from the DATASUS database (SISCAN/Cancer Information System) spanning the period from 2017 to 2021. Male and female patients diagnosed with breast cancer (ICD C50) during this period were included. Statistical analysis involved absolute values, percentages, and a 95% confidence interval ($p < 0.05$). Results: Analysis of the study period revealed 4,326 cases (1.8%) of male breast cancer and 236,597 cases (98.2%) of female breast cancer in Brazil. The southeast region had the highest concentration of cases for both sexes, while the northeast region showed a higher prevalence in males ($p < 0.0004$). Noteworthy findings include a higher mean age among males (59.5 years) compared to females (55.7 years) and a higher prevalence of advanced stages at diagnosis in males (72.8% vs. 59.3%). Diagnostic approaches, subtype distribution, and treatment modalities also differed between the genders. Conclusions: Male breast cancer presents with more advanced stages at diagnosis compared to females, necessitating more aggressive surgical interventions. However, males benefit from earlier initiation of treatment. These findings contribute to a better understanding of male breast cancer, enabling the development of tailored management strategies for this unique patient population.

Comparison between male and female MC

Variable	Male (n=4,326)		Female (n=233,793)		95% CI	P-value
	N	%	n	%		
Age						
Mean (years) [SD]	59,5 [10,3]		55,7 [9,8]			
Age Groups						
Below 40 years	519	12.1	27,611	11.8	-1.022 (0.832 - 1.121)	0.37
40 - 54 years	826	19.1	84,162	36.0	0.430 (0.389 - 0.453)	0.002
55 - 69 years	1,787	41.3	83,563	35.8	0.068 (0.075 - 0.040)	0.000
Above 69 years	1,194	27.6	38,507	16.3	-0.111 (-0.124 - -0.098)	0.001
Diagnostic Approach						
Symptoms	2,716	62.8	73,828	31.6	-0.12 (-0.128 - -0.097)	<0.001
Screening	-	-	79,861	34.1		
Imaging (other)	1,619	37.2	80,104	34.3	-0.031 (-0.048 - -0.017)	<0.001
Image Findings						
Nodule	2,780	63.8	105,441	45.1	0.044 (0.030 - 0.059)	0.003
Microcalcifications	458	10.6	55,843	23.8	0.296 (0.248 - 0.295)	0.002
Focal asymmetry	122	2.8	40,212	17.2	0.238 (0.227 - 0.248)	0.003
Architectural Distortion	966	22.8	32,497	13.9	-0.011 (-0.024 - 0.000)	0.051
Type of Biopsy						
Thick needle	2,171	50.2	157,978	68.0	0.099 (0.084 - 0.114)	0.02
Incisional	147	3.4	7,481	3.2	-0.008 (0.011 - -0.000)	0.04
Excisional	537	12.4	23,080	10.3	-0.026 (-0.048 - -0.020)	<0.001
Intraoperative	2,885	34.0	47,359	18.5	-0.489 (-0.499 - -0.471)	<0.001
Histological Type						
Invasive carcinoma	3,850	89.2	170,668	73.0	-0.239 (-0.248 - -0.229)	<0.001
Lobular carcinoma	177	4.1	34,601	14.8	0.090 (0.084 - 0.096)	<0.001
Carcinoma in situ	44	1.0	2,194	9.0	0.069 (0.066 - 0.072)	<0.001
Other	288	5.7	22,631	3.2	0.793 (0.788 - 0.800)	<0.001
Histological grade						
G1	1,042	24.1	11,220	48.0	0.186 (0.173 - 0.198)	<0.001
G2	2,163	50.0	81,827	35.0	-0.186 (-0.202 - -0.173)	<0.001
G3	1,121	25.9	39,746	17.0	-0.107 (-0.120 - -0.094)	<0.001
Subtypes						
Luminal	3,720	86.0	140,276	60.0	-0.260 (-0.274 - -0.243)	<0.001
TNBC	363	8.4	51,434	22.0	0.136 (0.123 - 0.148)	<0.001
HER-2	243	5.6	42,083	18.0	0.123 (0.111 - 0.132)	<0.001
Clinical Staging						
0	44	1.0	16,365	7.0	0.052 (0.048 - 0.054)	<0.001
I	294	6.8	28,756	12.3	0.041 (0.033 - 0.048)	<0.001
II	839	19.4	50,031	21.4	0.003 (0.015 - 0.008)	0.073
III	2,548	58.9	123,442	52.8	-0.118 (-0.133 - -0.103)	0.03
IV	601	13.9	15,199	6.5	-0.080 (-0.091 - -0.070)	<0.001
Treatment						
Surgical	3,417	79.0	210,413	90.0	0.011 (-0.000 - 0.024)	0.329
Conservative + SNB	324	7.5	110,584	47.3	0.346 (0.337 - 0.353)	<0.001
Conservative + AHD	809	18.5	31,562	13.5	-0.066 (-0.078 - -0.055)	<0.001
Mastectomy + SNB	1,808	41.6	43,251	18.5	-0.282 (-0.287 - -0.276)	<0.001
Mastectomy + AHD	432	10.0	3,9043	16.7	0.048 (0.039 - 0.057)	<0.001

Source: Panel-Oncology Brazil (accessed 15/04/2023)

PO3-10-01

How The Financial Toxicity of Metastatic Breast Cancer Affects Single Mothers with Young Children: Where Disparities Lie and Outcomes For Quality of Life

Presenting Author(s) and Co-Author(s):

R. Lombardi. Infinite Strength, Inc., Madison, Connecticut, United States

m. lustberg. Yale Cancer Center, New Haven, Connecticut, United States

PURPOSE

Financial Toxicity in underserved/underrepresented single mothers living with Metastatic Breast Cancer (MBC) diminishes patients' quality of life. The purpose of this abstract is to determine which demographic experiences financial toxicity the most and understand how assisting this patient population financially improves their physical, mental and emotional health, ultimately contributing to a better quality of life for them and their young children.

METHOD

From July 2022 to April 2023, we invited underserved/underrepresented single mothers living with MBC to apply for a six month financial grant to help pay for rent/mortgage. To be eligible, applicants needed to be 200 percent of the federal poverty level, and have children under the age of 18 for whom they were solely responsible. The patients applying were receiving treatment in different healthcare systems from premier cancer hospitals to small rural hospitals and lived in different states within the US. We were able to assess demographic factors, employment status, and familial support of each patient by the information requested on the application to determine qualification for financial assistance.

RESULTS

48 women qualified for our grant based on the criteria stated above. Of those 48 qualified applicants, 26 were African American (54%), 8 were Latina (16%), 2 were Asian Pacific (4%) and 12 were caucasian (25%). All applicants were either no longer working due to treatment related illness or working significantly reduced hours. All were in need of rent/mortgage assistance or would face eviction and 7 were experiencing or had experienced homelessness. Those who had experienced homelessness were black. We provided each of these women with \$1,000.00 per month for six months for the expense of rent/mortgage. We provided the funds for those who were homeless to find housing. We also provided grocery cards and funds for children's clothing when requested. All 48 patients receiving grants were able to remain in their home or acquire housing if they had been living in a homeless shelter. All patients reported that having this significant support allowed them to have less stress and therefore, an improved quality of life mentally and emotionally. Once the six months of financial help was removed, 25 African American patients (52%), 3 Latina patients (6%) and 1 Caucasian patient (2%) went back to experiencing financial toxicity and quality of life diminished once again.

CONCLUSION

This work highlights the tremendous financial burden faced by single mothers living with MBC. Direct financial assistance can help provide stability and support families in this time of significant need. Additional expansion to all states is planned.

PO3-10-02

Cardiovascular Risk Factors and Outcomes in Native Americans who have Received Chemotherapy and/or Radiation: A Retrospective Single-center Study

Presenting Author(s) and Co-Author(s):

C. Kirby. University of New Mexico Health Sciences Center, Department of Internal Medicine, United States

J. Meyer-Hagen. University of New Mexico Health Sciences Center, Department of Pediatrics, United States

P. Andre. University of New Mexico Health Sciences Center, Department of Internal Medicine, Division of Cardiology, United States

U. Khan. University of New Mexico Health Sciences Center, Department of Internal Medicine, United States

N. Harris. University of New Mexico Health Sciences Center, Department of Internal Medicine, United States

E. Davila. University of New Mexico Health Sciences Center, Department of Internal Medicine, United States

M. Garcia. University of New Mexico Health Sciences Center, Department of Internal Medicine, Division of Cardiology, United States

J. Nemunaitis. University of New Mexico, UNM Comprehensive Cancer Center, United States

Introduction: There is scarce literature regarding cardiovascular risk factors and cardiovascular outcomes in Native American patients with breast cancer. Cardiovascular complications are known to be associated with cancer treatment. Certain medications, such as anthracyclines and HER-2 agents are directly cardiotoxic, while other modalities of treatment may lead to accelerated atherosclerosis. We have conducted a single-center retrospective study assessing cardiovascular risk factors and outcomes in Native American patients with breast cancer.

Methods: Data was extracted from the UNM Comprehensive Cancer Center tumor registry and PowerChart. Charts were selected based on if the patient was registered as a Native American with a breast cancer diagnosis from 2010-2020. Inclusion criteria were age 18 or older, identified as Native American, received a diagnosis of breast cancer between 2010-2020, received at least one chemotherapeutic agent, endocrine therapy, or radiation therapy. **Results:** The study included 89 participants. The median age at the time of diagnosis of breast cancer was 55 years. All were female. Cardiovascular risk factors prior to undergoing treatment were reported as follows: Hypertension (55.3%); diabetes (46.1%); hyperlipidemia (35.3%); smoking (25%); obesity (52.6%). Before initiating treatment, 3.5% of Native American breast cancer patients in our study population had coronary artery disease.

Cardiovascular disease incidence before and after undergoing treatment was as follows: myocardial infarction (1.2% vs 2.4%), stroke (4.7% vs 1.2%), heart failure with reduced ejection fraction (HFrEF) (2.3% vs 4.8%), heart failure with preserved ejection fraction (HFpEF) (1.2% vs 1.2%), peripheral arterial disease (1.2% vs 1.2%), atrial fibrillation or another arrhythmia (4.7% vs 5.9%). We also noted new diagnoses of hypertension and arrhythmia in 3.6% and 1.2% of our study patient population respectively after starting chemotherapy.

43% of all included patients had a transthoracic echocardiogram (TTE) or multigated acquisition scan (MUGA) recorded in the chart before chemotherapy and 45% had one afterward. Of those, when comparing ejection fraction between pre- and post-chemotherapy, a change in

mean EF (61.9% vs 57.8%) was seen.

37 patients (41.6%) received treatment with an anthracycline or a Her-2 agent. Mean EF prior to treatment was 65.0%, and mean EF after treatment was 59.1%. Pre- and post-treatment rates of HFrEF were 0% and 5.7%, respectively. Discussion: Hypertension, diabetes, hyperlipidemia, smoking, and obesity are highly prevalent in the Native American patient population who are treated for a diagnosis of breast cancer. Our study showed a change in mean EF after treatment (61.9% vs. 57.8%) in our Native American breast cancer patient population. For those receiving an anthracycline or Her-2 agent, EF changed from 65.0% to 59.1% after treatment. High rates of HFrEF, new onset hypertension, and arrhythmias post-treatment were also noted. These findings suggest that a thorough cardiovascular risk assessment prior to starting a treatment regimen for breast cancer may be important. Multidisciplinary management with cardiology may be critical in the care for these patients. Further investigation of cardiovascular risk factors and outcomes after cancer treatment is warranted in this population. There are several limitations of our study, one being that this was a single-center study which does not represent the Native American population throughout the United States and Canada. The small sample size also limits the power of the study. Many patients after initial evaluation at our facility received care at outside facilities, which limits data on treatments received, studies performed (e.g. TTE and MUGA), or cardiovascular events.

PO3-10-03

Nationwide Impact of Neighborhood Poverty Hotspots on Breast Cancer Mortality

Presenting Author(s) and Co-Author(s):

I. Nwigwe. Johns Hopkins Bloomberg School of Public Health, United States

M. Desjardins. Johns Hopkins Bloomberg School of Public Health, United States

K. Visvanathan. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, MD and Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States

Title: Nationwide Impact of Neighborhood Poverty Hotspots on Breast Cancer Mortality

Background: Poverty is known to lead to the worst breast cancer (BC) outcomes, at the individual and county level. However, we believe that the relationship between poverty and breast cancer mortality is more complex and can be influenced by the economic status and available resources of the surrounding neighborhoods. Our goal is to understand to what extent poverty in the surrounding neighborhood may contribute to breast cancer mortality on a national scale and the county areas at the highest risk. Methods: This study examines the association between neighborhood effects of poverty on overall and BC mortality among women diagnosed between 2005 and 2019 from NCI SEER. We also obtained county-level five-year poverty estimates from the American Community Survey. Counties with poverty estimates above or below the national mean were high-poverty (H) or low-poverty (L) counties, respectively. We then used local indicators of spatial autocorrelation (LISA) analysis with Local Moran's I of the poverty estimates and their H- and L-county categorization to define four neighborhood poverty environments for US counties. Specifically, H-counties among other H-counties were classified as poverty hotspots (HH) counties, L-counties among other L-counties were classified as poverty cold spots (LL), H-counties among LL-counties were HL-counties, and L-counties among HH-counties were LH-counties. Non-Hispanic White (NHW), Non-Hispanic Black, and Hispanic women at least 20 years of age diagnosed with local, regional, or distal stage BC between 2005-2009 and 2010-2014 that survived more than one year after diagnosis were aggregated by county of residence at diagnosis to determine their neighborhood poverty environment at BC diagnosis. Women included in the study had a Local Moran's I p-value less than or equal to 0.3 for their county of residence. A Poisson regression model that adjusts for age at diagnosis, race/ethnicity (NHW vs. not-NHW), BC stage, year of diagnosis (2005-2009 vs. 2010-2014), both local and systemic treatment except for hormone therapy, and Estrogen Receptor (ER) status (negative vs. positive) was used to assess the effects of county-level poverty cluster types on BC mortality. Results: Our analysis includes 24,070 women diagnosed with BC, of which 6,919 women died, and 2,262 of these deaths were specific to BC. In total, 4,528 women were in HH counties from CA, GA, KY, LA, NM, UT, and HI; 14,112 women were in LL counties; 4,338 women were in HL counties; 1,092 women were in LH counties. Women in HH, LH, and HL counties had a 1.28 (95%CI:1.15,1.42), 1.23 [95%CI:1.01-1.48], and 1.05 [CI: 0.93, 1.17] relative risk of cause-specific BC death respectively when compared to deaths in LL counties after adjustment for year of diagnosis, age at diagnosis, race/ethnicity, stage at diagnosis, treatment, and estrogen receptor status. When stratified by ER status or BC stage at diagnosis, the relative risk of BC mortality for women in HH counties diagnosed with ER-positive, local or regional stage had a 1.35 (95% CI: 1.19,1.52), 1.32 (95%CI: 1.13,1.54), and a 1.21 (95%CI:1.02, 1.43) when compared to women in LL counties, respectively. Our analysis also showed that total death trends were similar to the trends observed in cause-specific deaths. In addition, we observed similar total and cause-specific BC death trends when using a p-value of 0.05 for the LISA analysis. Conclusion: We use LISA spatial clustering to demonstrate the impact national poverty neighborhood environments have on BC mortality,

thus identifying counties of worst BC outcomes through neighborhood poverty environments. Our findings suggest that prioritization of resource allocations to HH counties would significantly improve BC outcomes.

PO3-10-04

Palliative Care, Healthcare Utilization, and Disparities in Deceased Breast Cancer Patients in U.S. Hospitals: Analysis of National Inpatient Sample

Presenting Author(s) and Co-Author(s):

R. Patel. Community hospital of San Bernardino, CA, United States

Z. Patel. University of California, Riverside, United States

M. Patel. Trumbull regional medical center, Ohio, United States

D. Patel. Rush University, Illinois, United States

A. Onyechi. SSM St Mary's hospital, United States

A. Chitkara. University of California, Riverside, United States

F. Patel. University of California, Riverside, United States

Objective:

This study aims to explore the characteristics of receiving palliative care and the patterns of utilization among breast cancer patients using a large-scale representative population-based sample.

Methods:

A retrospective analysis was performed on hospitalization data obtained from the National Inpatient Sample (NIS) covering the period from January 2016 to December 2019. The objective of the study was to investigate the characteristics and disparities associated with the provision of palliative care to breast cancer patients who had passed away, and to evaluate its impact on healthcare utilization as indicated by discounted hospital charges and length of stay (LOS). To achieve this, multivariate linear and logistic regression analyses were conducted, with the data stratified according to age, race, Charlson comorbidity index, insurance status, patient's zip code, and hospital characteristics. The classification and identification of the study population were performed using ICD-10 codes.

Results:

In the study, a total of 6,325 deceased breast cancer patients were identified from hospitalization records. Among them, 59.16% (n=3,742) received palliative care during their hospital stay.

Multivariate linear regression analysis revealed that patients who received palliative care experienced a significant reduction in LOS by an average of 0.67 days (-1.246 to -0.898, $p = 0.02$) compared to those who did not receive palliative care. Furthermore, the palliative care group exhibited lower total charges, with a mean decrease of \$21,392 (-28205 to -14578, $p=0.00$) compared to the non-palliative care group.

Multivariate logistic regression analysis indicated that patients with black race had lower odds of receiving palliative care, while those with higher household income and patients admitted to larger hospitals had higher odds of receiving palliative care. Additionally, patients with private insurance had a higher probability of receiving palliative care compared to other insurance groups.

Conclusion:

Palliative care has demonstrated its benefits in reducing healthcare utilization costs and length

of stay for breast cancer patients. However, disparities exist in access to palliative care, particularly among Black patients and those with lower household income. Larger hospitals and patients with private insurance show higher rates of palliative care utilization. Addressing these disparities is crucial to ensure equitable access, optimize patient outcomes, and improve resource allocation. Integrating palliative care into breast cancer hospitalizations requires targeted interventions. Further research and implementation efforts are needed to enhance the availability and delivery of palliative care services for all patients, regardless of their demographics or socioeconomic backgrounds. Health policymakers should consider these findings in their resource allocation decisions as palliative care plays an increasingly important role in cancer treatment.

Odds of Receiving Palliative care among deceased breast cancer patients

<i>Odds of Receiving Palliative care among deceased breast cancer patients</i>			
	Odds ratio	95% CI	P value
Race	Reference	Reference	Reference
White	Reference	Reference	Reference
Black	0.7783	0.6705 - 0.9035	0.001
Hispanic	0.8445	0.6890 - 1.0352	0.104
Asian or Pacific Islander	0.8754	0.6510 - 1.1772	0.379
Native American/Other	0.9576	0.4277 - 2.1443	0.916
Other	0.8184	0.5865 - 1.1420	0.238
Insurance status	Reference	Reference	Reference
Medicare	Reference	Reference	Reference
Medicaid	1.1407	0.9664 - 1.3464	0.12
Private insurance	1.655	1.4583 - 1.8783	0.000
Self-Pay	0.8563	0.5911 - 1.2406	0.412
Census division	Reference	Reference	Reference
New England	Reference	Reference	Reference
Middle Atlantic	0.3422	0.2378 - 0.4925	0.000
East North Central	0.4213	0.2932 - 0.6052	0.000
West North Central	0.5775	0.3894 - 0.8565	0.006
South Atlantic	0.4487	0.3145 - 0.6402	0.000
East South Central	0.3038	0.2026 - 0.4554	0.000
West South Central	0.3868	0.2674 - 0.5594	0.000
Mountain	0.3435	0.2246 - 0.5253	0.000
Pacific	0.4341	0.3028 - 0.6224	0.000
Location/teaching status of hospital	Reference	Reference	Reference
Rural	Reference	Reference	Reference
Urban nonteaching	1.3531	1.0630 - 1.7222	0.014
Urban teaching	1.7439	1.4008 - 2.1710	0.000
Hospital Bedsize	Reference	Reference	Reference
Small	Reference	Reference	Reference
Medium	1.1031	0.9151 - 1.3296	0.303
Large	1.2974	1.0878 - 1.5473	0.004
Median household income	Reference	Reference	Reference
0-25th percentile	Reference	Reference	Reference
26th to 50th percentile	1.0098	0.8672 - 1.1759	0.900
51st to 75th percentile	1.12	0.9541 - 1.3147	0.166
76th to 100th percentile	1.2697	1.0734 - 1.5020	0.005

Length Of Stay and Total Charges

<i>Length Of Stay and Total Charges</i>				
Crude Length Of Stay	Mean (days)	Standard error	95% CI	
No Palliative Care Utilized	7.4	0.28	6.86 - 7.94	
Palliative Care Utilized	6.54	0.19	6.18 - 6.91	
Adjusted Length Of Stay	Coefficient (days)	Standard error	95% CI	P-value
No Palliative Care Utilized	Reference	Reference	Reference	Reference
Palliative Care Utilized	-0.67	0.29	(-1.25 - -0.09)	0.024
Crude Total Charges	Mean (\$)	Standard error	95% CI	
No Palliative Care Utilized	96794	2950	(91010-102578)	
Palliative Care Utilized	72836	1887	(69134-76537)	
Adjusted Total Charges	Coefficient (\$)	Standard error	95% CI	P-value
No Palliative Care Utilized	Reference	Reference	Reference	Reference
Palliative Care Utilized	-21392	3475	(-30590 - -17325)	0.000

PO3-10-06

Parenting While Living with Cancer - Providing Better Outcomes for Families During the Cancer Journey

Presenting Author(s) and Co-Author(s):

A. Kabir. Kesem, Covina, California, United States

For over 20 years, Kesem has been dedicated to supporting children impacted by a parent's cancer. To better understand the stresses on a family navigating cancer, Kesem completed a several month research program rooted in Diversity, Equity, and Inclusion (DEI) and consisting of ethnographic research, quantitative surveys, focus groups, benchmarking, and data analytics. We are using this research to develop a deeper understanding of the personal stories of families impacted by a cancer diagnosis and of the current data from experts in the field. Kesem is sharing our research findings in order for the general oncology space to better serve parents living with cancer.

The research included three weeks of ethnographic research completed in rural Mississippi, the Pacific Northwest, and southern Nevada. The research team completed 124 interviews in 18 cities, gathering deep insights about being a parent while living with cancer. The team also reviewed over 30 databases and conducted a survey of approximately 150 parents with cancer.

Little has been published about parental cancer in the past decade. Using literature reviews and data such as the 2020 decennial census, we have been able to generate a more accurate assessment of need than ever, confirming earlier estimates that there are approximately five million children in the United States who have a parent with cancer. This means that the average percentage of children under 18 who have experience with parental cancer is between 3.6%–5.5%.

The following key takeaways from this research are helpful for all who support patients, including oncologists, nurse navigators, and patient advocates:

- There are over 5 million children in the United States who have a parent
- We need to build greater trust with people living with cancer, particularly in underrepresented communities.
- Families are uncertain about how and where to find support for their children and want early access to information.
- Families are looking for more resources and support for parents.
- Families want more frequent opportunities to connect in person and virtually.
- Families seek increased psychosocial support to help children navigate isolation and challenging times.
- Current offerings need greater flexibility to incentivize new families to join.

Based on this research and our ongoing internal survey results, we know that patients generally have less anxiety when they know their children will receive a lifetime of support. Children who are supported are more likely to create a community of support for themselves, do better academically, and have increased mental health. This leads to better outcomes for the entire family.

PO3-10-07

Leveraging AI to identify factors influencing access to care and their association with overall survival- a multiracial Breast Cancer cohort.

Presenting Author(s) and Co-Author(s):

M. Safran. Leal Health, United States

Y. Lapidot. Leal Health, United States

T. Bader. Leal Health, United States

A. Gaziel. Leal Health, United States

Introduction: Data from the Centers for Disease Control and Prevention (CDC) labels each US state based on its 5-Year Relative Survival of Breast Cancer (BC) patients (pts). Data is categorized into four "survival groups", each representing a range of 5-year survival percentages. Using real-world data, this study characterized the populations in each survival group, examining pt knowledge and education about their disease as well as preferences and factors influencing their decision to explore clinical trial (CT) opportunities.

Methods: Leal is an AI-based platform that employs self-reported medical profiles to match cancer pts with CTs. This study involved a diverse cohort of 14,509 BC pts who completed the questionnaire. The geographic distribution of pts across US states was analyzed, taking into account the state's 5-year BC survival %. Four groups were defined as follows: Group A (86.4 - 89.4%), Group B (89.4 - 90.4%), Group C (90.4 - 91.5%), and Group D (92.0 - 95.0%). Parameters such as race, willingness to travel, insurance coverage, performance of genetic testing, and biomarker knowledge were considered in the analysis.

Results: We found significant variations in registration rates on the Leal platform across groups. The Highest registration rate was recorded for Group D which has the highest 5-year survival rate ($p < 0.0001$). Group A which has the lowest 5-year relative survival had a significantly higher proportion of African Americans compared to group D (14% vs 4%, $p < 0.0001$). Moreover, while there was no difference in the percentage of pts undergoing Next-Generation Sequencing (NGS) in both groups, a larger proportion of pts in Group D demonstrated proficiency in interpreting the test reports ($p = 0.05$). Although no significant differences were found in the proportion of pts who were aware of their treatment (tx) history between the two groups, whites in both groups exhibited greater knowledge of their tx ($p = 0.001$). Additionally, pts in Group D showed a significantly higher willingness to travel longer distances to participate in CTs ($p=0.001$), and a larger percentage of them had insurance coverage.

Conclusions: This study used data from CDC that categorized US states into four groups based on BC pts' 5-Year Survival. CT participation is associated with better clinical outcomes, especially for pts with poorer prognosis. In agreement, we show a higher signup rate to the Leal platform in States with higher 5-year relative survival, possibly pointing to higher CT education and knowledge among pts in those states. This is further supported by higher proficiency in interpreting NGS reports, resulting in better-optimized CT options on the Leal platform. Group A was also characterized by a reduced willingness to travel for a CT and a larger proportion of pts without health insurance. Those are significant barriers for CT enrollment, and ultimately limit access to optimal care and may impact outcomes. Gaps in knowledge of key disease parameters such as tx history were observed for African Americans, regardless of geographic location, highlighting the need to focus on minority populations even in states where the survival rate is relatively high. In agreement, the proportion of African Americans in group A

was markedly higher, correlating with current disparities in access to tx and poorer outcomes. AI-based platforms are optimized for the exact identification of barriers to access to care and for enabling relevant healthcare and support organizations to effectively address individual patient issues, consequently increasing access to CTs, particularly among different racial and ethnic populations.

PO3-10-08

Long-term uptake rate of a breast cancer screening program in Fukushima, Japan, following the 2011 Triple Disaster: a retrospective observational study.

Presenting Author(s) and Co-Author(s):

K. Gonda. Department of Breast and Thyroid Surgery, Jyoban Hospital of Tokiwa Foundation/Department of Gastrointestinal Tract Surgery, Fukushima Medical University, Fukushima, Japan

A. Ozaki. Medical Governance Research Institute, Japan

K. Tachibana. Fukushima Medical University, Department of Breast Surgery, Fukushima-shi, Fukushima, Japan

M. Wada. Utsunomiya Central Clinic/Department of Breast and Thyroid Surgery, Jyoban Hospital of Tokiwa Foundation, Japan

H. Saito. Medical Governance Research Institute, Japan

Y. Kaneda. Hokkaido University School of Medicine, Japan

Y. Nishikawa. Department of Internal Medicine, Hirata Central Hospital, Japan

M. Murakami. Present address: Center for Infectious Disease Education and Research, Osaka University/Department of Health Risk Communication, Fukushima Medical University, Japan

K. Hirai. Present address: Center for Infectious Disease Education and Research, Osaka University/Department of Health Risk Communication, Fukushima Medical University, Japan

H. Ohira. Department of Surgery, Minamisoma Municipal General Hospital, Japan

T. Sawano. Department of Breast and Thyroid Surgery, Jyoban Hospital of Tokiwa Foundation/Department of Radiation Health Management, Fukushima Medical University/Department of Surgery, Jyoban Hospital of Tokiwa Foundation, Japan

T. Kurokawa. Department of Medical Epigenomics Research Fukushima Medical University/Department of Surgery, Jyoban Hospital of Tokiwa Foundation, Japan

M. Tsubokura. Research Center for Community Health, Minamisoma Municipal General Hospital/Department of Radiation Health Management, Fukushima Medical University, Japan

K. Kono. Department of Gastrointestinal Tract Surgery, Fukushima Medical University, Japan

T. Ohtake. Department of Breast Surgery, Fukushima Medical University, Japan

S. Takenoshita. Department of Drug Research for Astatine-221 Targeted Alfa Therapy, Fukushima Medical University, Japan

Introduction

There has been a growing concern over the past few years about the effects of disasters and crises on breast cancer screening, an argument that has been further enhanced by the novel coronavirus disease 2019 (COVID-19) pandemic. However, little is known about how crises might affect the long-term uptake of breast cancer screening programs. This study aimed to clarify the long-term trend of breast cancer screening program uptake in Minamisoma City following the 2011 Triple Disaster in Fukushima, Japan (earthquake, tsunami, and nuclear disaster), and to evaluate the factors associated with this uptake.

Material and Methods

This study retrospectively analyzed data from the Basic Resident Registry and Breast Cancer Screening Program in Minamisoma City following the Triple Disaster. We calculated the annual

breast cancer screening uptake rate for women aged 40–74 years who were of an even-numbered age at the end of each fiscal year and the incidence of at least one instance of uptake of the breast cancer screening initiative during the biennial intervals. We further performed cross-sectional and longitudinal regression analyses for the biannual screening uptake and investigated its associated factors.

Results

Breast cancer screening participation rates were 19.8% and 18.2% in 2009 and 2010, respectively. They decreased to 4.2% in 2011, and gradually increased thereafter, reaching the pre-disaster level of 20.0% in 2016. Similar but longer decrease of the uptake was observed in the biannual screening uptake rate. No pre-disaster screening uptake between 2009 and 2010, those living alone, or those who were evacuated, were factors that were found to be associated with non-uptake of the breast cancer screening program following the 2011 disaster.

Conclusion

This study showed a long-term decline in breast cancer screening uptake in the area affected by the Triple Disaster, which was the most severe among those under evacuation, those who were isolated, and those without previous uptake. The insights emerging from this study could be used to increase awareness of this issue and establish potential countermeasures. Nonetheless, we lack a complete understanding of the effects and variations of disasters on cancer screening in the affected areas. Therefore, global efforts should be intensified to conduct further studies on this topic.

PO3-10-09

The allocation of US \$2.6 billion in global funding for breast cancer research between 2016 – 2020: are we investing wisely for breast cancer patients?

Presenting Author(s) and Co-Author(s):

S. McIntosh. Queen's University Belfast, United States

E. Copson. University of Southampton, Southampton, England, United Kingdom

R. Cutress. University of Southampton, United States

M. Head. University of Southampton, United States

Background: Breast cancer is a global health challenge and the highest incident cancer globally, with over 2 million new cases and 685,000 deaths in 2020, making it the highest incident cancer globally. Furthermore, it is the most prevalent cancer, resulting in the loss of more disability-adjusted life years than any other malignancy. Research is thus crucial to improving outcomes and reducing suffering for breast cancer patients worldwide. This study aimed to analyse global patterns of funding for breast cancer research. Methods: We have previously created a comprehensive database of awards for human cancer research in this period using publicly available data on research funding awards. From this database we extracted all awards relating to breast cancer research, and categorised these by cancer type, cross-cutting research theme and phase of research. Findings: We identified 7051 awards with a total investment of \$2.6 billion in 2016-2020, representing 11.2% of all global public and philanthropic cancer research funding during this period. Breast cancer research funding fell year on year, from \$773.4 million in 2016 to \$243.8 million in 2020. The majority of the investment was in pre-clinical research (\$1.9 billion, 73.9%), with clinical trials (\$276 million, 10.7%) and public health (\$269.2 million, 10.5%) receiving roughly equivalent amounts of funding. The USA accounted for 66.9% of all global breast cancer research investment, with China (\$110.4 million, 4.3%) and the UK (\$96.6 million, 3.8%) the next largest funders. By research theme, cancer biology research received most funding (\$926.2 million, 37.5% of investment), with drug treatment the next best funded research area (\$600.5 million, 23.4%), and diagnosis, screening and monitoring third (\$396 million, 15.4%). Surgery (\$65.2 million, 2.5%) and radiotherapy (\$35.3 million, 1.4%) accounted for only a small proportion of research investment. There was minimal investment into breast cancer as a global health issue (\$8.1 million, 0.3%). Research into metastatic disease received a greater proportion of investment in breast cancer than in the overall cancer portfolio (23.2% in breast cancer, \$597.4 million, compared with 11.7% across all cancers). Conclusions: Breast cancer public and philanthropic research funding is largely invested in pre-clinical research in high-income countries, with the main areas of investment being cancer biology research and drug treatment. The direct benefit to patients from such research is likely to be low and only apparent after a substantial time lag (if at all). Despite their pivotal role in the treatment of the majority of breast cancer patients, surgery and radiotherapy research received a tiny proportion of the overall research investment. Furthermore, relatively little investment is directed towards cancer prevention and early detection, despite their acknowledged key role in cancer control globally. Finally, more equitable research funding is required to align with the global burden of breast cancer, with increased funding for low- and middle-income countries, which account for an increasing proportion of this burden. These data should be considered by funders and policymakers in the allocation of finite resources, which must be invested wisely.

PO3-10-10

Are we adequately integrating patient reported outcomes in breast cancer clinical trials?

Presenting Author(s) and Co-Author(s):

Y. Rina. University of Kentucky, Lexington, Kentucky, United States

Z. Huang. University of Kentucky, Lexington, Kentucky, United States

J. Moss. University of Kentucky, United States

G. Gupta. University of Kentucky, Lexington, Kentucky, United States

Background: Integrating patient reported outcomes (PROs) in cancer care enhances clinical outcomes and creates a paradigm shift in providing patient-centered care. Several studies performed in the past 15 years have demonstrated that systematic monitoring of patients using PROs through surveys improve patient-clinician communication, clinician awareness of symptoms, symptom management, patient satisfaction, quality of life, and overall survival. There has been uncertainty over the type of PRO system to implement in cancer care, how to evaluate PRO in clinical trials, and how to compare this to the clinician common terminology criteria for adverse events (CTCAE). The PRO concept was first introduced in 1975 with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) survey. In May 2018, the National Cancer Institute established the PRO-CTCAE to be utilized for cancer patients to report and grade their treatment related adverse events, like that of clinician reported CTCAE. The goal of our study was to evaluate frequency of PRO incorporation in phase III breast cancer clinical trials. Methods: New England Journal of Medicine, Journal of Clinical Oncology, and Lancet were systematically searched to identify phase III breast cancer clinical trials published between January 2018 and June 2023. A total of 113 phase III studies were identified, 87 of which had reported protocols. Studies that did not demonstrate protocols on these search engines were not included in the review. Of these 87 clinical trials, 36 studies documented evaluation of PRO. These studies were segregated by year of publication. For each year, the number of total phase III breast cancer clinical trials that were published were compared to those that were published and evaluated PRO. A percentage was generated and allowed for a longitudinal trend to be analyzed over a 5-year period to assess if there was improved frequency of PRO integration into breast cancer clinical trials. Summary statistics were calculated using SAS 9.4. Results: 36 of 113 trials demonstrated PRO use and 26 utilized EORTC-QoL, 1 used PRO-CTCAE, and 9 used another measure of PRO assessment within their study protocol (such as FACT-B and PHQ-9. Additionally, in 2018, 33% of published breast cancer studies included PRO data. Since then, there have been fluctuations in breast cancer studies collecting PRO; 2019: 33%, 2020: 47%, 2021: 43%, 2022: 73%, and since the start of 2023: 9%. Conclusions: Our data suggests a trend towards improvement in frequency of PRO data collection in breast cancer clinical trials over the past 5 years, exemplified by the marked increase in 2022. There remains a need to incorporate PROs in clinical trials and routine care to improve patient experience and provide patient-centered care.

PO3-10-11

Mujeres Avanzando a la Sobrevida (MAS: women going forward in survival): Breast Cancer Characteristics and Delays in Care in Honduras

Presenting Author(s) and Co-Author(s):

S. Prathibha. University of Minnesota, United States

A. Molina. Hospital San Felipe, Honduras

J. Siryi. Hospital San Felipe, Honduras

K. Gaitán. La Liga Contra el Cáncer, Honduras

M. Raudales. La Liga Contra el Cáncer, Honduras

M. Maldonado. La Liga Contra el Cáncer, Honduras

T. Tuttle. University of Minnesota, United States

S. Bejarano. La Liga Contra el Cáncer, Honduras

Introduction: Low and middle-income countries have exceedingly high breast cancer mortality rates primarily due to delays to diagnosis and treatment. The Breast Health Global Initiative (BHGI) recommends a diagnostic interval (time from initial provider visit to receiving a diagnosis) of < 60 days. Honduras is one of the poorest countries in the western hemisphere and has a paucity of published breast cancer research. Our objective was to understand delays in breast cancer diagnosis and treatment in Honduras. **Methods:** We initiated a prospective cohort study (Mujeres Avanzando a la Sobrevida (MAS: Women Going Forward in Survival)) in 2021 at two hospitals in two major cities in Honduras. All patients with newly diagnosed breast cancer were invited to participate. We prospectively collected demographic, cancer, and treatment data through patient interviews and surveys. We also determined several time intervals including: onset of symptoms to initial provider visit (patient interval), initial provider visit to biopsy (diagnostic interval), and biopsy to first treatment (treatment interval). Patients also completed the Unger-Saldana Delay Survey to assess their perceptions of any delays in cancer care and reasons for these delays. **Results:** We enrolled 95 patients with an average age of 54 years. 73% of patients reported an income of < 1 minimum wage (< 8,448 lempiras/month). 93% were housewives, and 35% were married. The majority of patients had an elementary school education or no education (61%). The most common first symptom was a breast lump (81%). The majority of patients had advanced stage disease (Stage III and IV: 64%). The mean patient interval was 185 days. The mean diagnostic interval was 153 days, and the mean treatment interval was 139 days. Most patients (61%) thought their symptoms were slightly serious or not serious at all, and 78% did not think their symptoms were due to cancer. Most patients (60%) thought they were able to see a physician immediately or soon after symptoms developed (63%). Patient stated reasons for not seeking care earlier included believing their symptoms would self-improve, being unsure which health service to go to, lack of money, and fear. Similarly, most patients (67%) thought the time between seeing their first provider and visiting the cancer hospital was immediate or soon but not immediately. Reasons for this delay included lack of information, lack of money, wait times to appointment or tests, incorrect initial diagnosis, and fear. **Conclusion:** In this prospective cohort study, nearly two-thirds of patients in Honduras were diagnosed with stage III/IV breast cancer. We found marked delays in patient, diagnostic, and treatment intervals, even though patients perceived their care to be immediate. Importantly, the diagnostic interval far exceeded 60 days, as recommended by the BHGI. This study provides initial insight into delays in breast cancer care in Honduras and provides an opportunity to target obstacles to early diagnosis and treatment and to improve

breast cancer survival.

PO3-11-01

Single centre experience of the adoption of self-administered HER2-directed therapy in patients with breast cancer

Presenting Author(s) and Co-Author(s):

W. Ng. Mount Vernon Cancer Centre, Northwood, England, United Kingdom

V. Dodhia. Mount Vernon Cancer Centre, Northwood, England, United Kingdom

A. Guppy. NHS Foundation Trust and Mount Vernon Cancer Center, United States

S. Sutherland. Mount Vernon Cancer Centre, Northwood, United Kingdom

M. Wojtas. Mount Vernon Cancer Centre, Northwood, England, United Kingdom

K. Harrold. Mount Vernon Cancer Centre, Northwood, England, United Kingdom

A. Aolat. Mount Vernon Cancer Centre, Northwood, England, United Kingdom

T. Tapiwa. Mount Vernon Cancer Centre, Northwood, England, United Kingdom

D. Miles. Mount Vernon Cancer Centre, Northwood, United Kingdom

Single centre experience of the adoption of self-administered HER2-directed therapy in patients with breast cancer

Background: Programs to promote the self-administration of systemic anti-cancer therapy (SACT) offer greater convenience and shared decision making for patients with the opportunity to alleviate pressures on cancer services.

Aims and Objective:

The aims of this study were to quantify the uptake/acceptability of self-administration (SA) of subcutaneous trastuzumab (sc T), to evaluate safety, patients' perception of the programme and the chair capacity released as a consequence.

Methods:

Patients receiving T for the treatment of HER2 +ve breast cancer were offered training in SA. The competency-based training programme, under the supervision of a chemotherapy-trained nurse, consisted of a minimum of 3 training sessions. Patients were also provided with printed and electronic material (via an App) on how to self-administer sc T, with 24/7 contact details in the event of an adverse event or device failure. Once trained and deemed competent, sc T was shipped to the patients' home in a temperature-controlled environment, in a pre-filled syringe. All patients were assessed by telephone one day before and one day after SA using the Common Terminology Criteria for Adverse Events (CTCAE). Analysis of the total number of administrations of sc T, between February 2022 and June 2023 was conducted. A telephone survey using a validated questionnaire Self-Management Assessment scale (SMASc) was also undertaken.

Results

Of 46 breast cancer patients receiving single agent sc T, 32 agreed to participate in the program and were trained. 2 patients were undergoing training at data analysis. 6 patients declined and 6 were ineligible for the programme on the basis of inclusion criteria.

The median age of the 32 patients that participated was 62, (range 27-77). The average distance from their home address to the cancer centre was 11.7 miles (range 3.5-27.9). 25

(78%) patients were Caucasian, 4 (13%) were Asian and 3 (9%) were of African/Caribbean origin. Patients had received an average of 10 sc injections in the hospital environment (median 5, range 1-103) before starting the training sessions. They required an average of 3 training sessions before sign-off (median 3, range 1-4). In the 32 patients studied, a total of 302 SA injections were delivered median 9 (range 1- 24) No Grade 3 or 4 CTCAE toxicities or infusion-related reactions were reported.

During the 17-month period, a total of 302 hours of chair time was saved.

25 of the 32 patients responded to SMASc questionnaires utilising the six-point Likert scale. Patients reported average scores of 5.32 (median 6) and 5.56 (median 6) respectively, for questions relating to having information about their condition and sufficient training to self-administer. They felt that they had sufficient support to participate in the programme (average 5.56 median 6).

80% of the patients would recommend this programme and 88% felt they had benefited. Comments from patients themed around the value of the support provided, ease of administration and time saved.

Discussion

Programs such as these empower patients and carers to take a more active role in managing their condition with consequent reduced hospital attendance. Safety and acceptability for those patients who agreed to the program has been confirmed. Success of this program with sc T has enabled expansion to incorporate self-administration of Phesgo (sc trastuzumab and pertuzumab) with 31% (14/45) of the current P patient cohort enrolled onto the programme within 2 weeks of roll out and the first patients self-administering their treatment from August 2023. With the continued expansion of SACT treatments, we encourage stakeholders to consider self-administration of SACT as an option. Formulation of treatments conducive to patient self-administration is a key component to this.

PO3-11-02

Characterizing Breast Cancer Care Fragmentation Among Young Black Women Diagnosed with Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Roberson. University of North Carolina, United States

J. Brown. University of North Carolina of Chapel Hill, United States

B. Taffe. UNC-Chapel Hill, United States

A. Weidner. Vanderbilt University Medical Center, United States

L. Venton. Vanderbilt University Medical Center, United States

S. Reid. Vanderbilt-Ingram Cancer Center, United States

T. Pal. Vanderbilt University Medical Center, United States

Introduction Fragmented cancer care is defined as receiving care across multiple institutions. The National Academy of Medicine has identified cancer care fragmentation as a priority area for cost reduction. However, little is known about the role of fragmented care on receipt of guideline-recommended care patient-reported outcomes, particularly among populations affected by health inequities like Black women. The objective of this study was to characterize breast cancer care fragmentation among a population-based cohort of young Black women with breast cancer. **Methods** Study participants were a population-based sample of self-identified Black women diagnosed with invasive breast cancer at or below age 50, recruited since 2017 through the Florida and Tennessee state cancer registries. As part of the study, participants completed baseline questionnaires about their cancer care delivery experiences. Participants were eligible if they self-reported the locations where they received their cancer treatment (i.e., diagnosis, surgery, chemotherapy, and radiation). Indicator variables for care fragmentation were created to identify participants who received their diagnosis, surgery, chemotherapy, and radiation within the same health system and those who received their cancer care across multiple health systems. Chi-squared tests were used to assess the relationship between care fragmentation, receipt of guideline-recommended genetic testing, and self-rated health. Self-rated health was dichotomized into Excellent/Very Good/Good and Fair/Poor. **Results** A total of 183 Black women diagnosed breast cancer \leq age 50 were included in the analysis. Among the included participants, 11% (n=20) only had surgery, 15% (n=27) had surgery and radiation, 17% (n=31) had surgery and chemotherapy, and 57% (n=105) had surgery, chemotherapy, and radiation. Among the 105 women who had surgery, chemotherapy, and radiation, 17% (n=17) received all cancer treatment within the same health system of diagnosis, 21% (n=21) received all cancer treatment within the same health system but were diagnosed within a different health system, and the remaining 62% of participants received their cancer treatment across different health systems, representing care fragmentation. In chi-squared analyses, fragmented care was not associated with lower receipt of genetic testing (p=0.33) or self-rated health (p=0.28). **Conclusion** In this population-based study, most participants had fragmented breast cancer care, however fragmentation was not associated with lower self-rated health or receipt of guideline-recommended germline genetic testing. Current approaches for assessing care fragmentation are often too coarse to capture the complexity of breast cancer care delivery and service availability. Patient-centered conceptual models of what drives cancer care fragmentation and the specific aspects of fragmentation that have the potential to drive adverse outcomes are critical.

PO3-11-03

A Randomized Controlled Trial to Assess the Benefit of Art & Music Therapy on Quality of Life in Patient with Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Herran. Cleveland Clinic Florida - Maroon Cancer Center, Weston, Florida, United States

M. Mohanna. Cleveland Clinic Florida, United States

S. Sabbagh. Cleveland Clinic Florida - Maroon Cancer Center, Weston, Florida, United States

B. Dominguez. Cleveland Clinic Florida, United States

K. Sarna. Center for Clinical Research, Cleveland Clinic Foundation, United States

R. Upton-Rice. Cleveland Clinic Florida - Department of Hematology Oncology, United States

A. Burdine. Cleveland Clinic Florida - Maroon Cancer Center, United States

Z. Nahleh. Cleveland Clinic Florida - Maroon Cancer Center, Weston, Florida, United States

Introduction: Quality of life (QoL) in oncology captures the well-being of a patient and is considered a significant outcome criterion. Breast cancer (BC) is the most diagnosed cancer in women, however, standardizing integrative therapies to alleviate the burden of cancer and improve QoL is still an unmet need. Art and music therapy might mitigate psychological and emotional distress. We sought to evaluate their efficacy compared to control among patients with BC during or after active therapy. Methods: Seventy-six treated patients with Stages I-III BC were randomly assigned to art, music therapy, or routine oncology care standard of care arm (SOC) for 3 months and received two sessions per month by a licensed therapist (including in-person/virtual and group sessions). The primary outcome was an improvement in QoL measured by the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire and secondary outcomes included: cognitive function measured by Functional Assessment of Cancer Therapy–Cognition (FACT-Cog), response to a 4-component Cleveland Clinic Visual Analog Scale (CCVAS), indicators of anxiety and depression assessed by the Generalized Anxiety Disorder-7 item (GAD-7) and Patient Health Questionnaire-9 item (PHQ-9). All questionnaires were assessed at baseline, 30, 90, and 180 days. Statistical considerations included stratified randomization, and a mean difference in 15 points between either of the interventions. SOC arm was considered relevant at the 3-month mark. Mean improvement within groups was performed using paired t-tests whereas independent t-tests were used to evaluate mean improvement between interventions (1 or 2 vs. SOC arm). All analyses were performed using SPSS version 26 (IBM, Armonk, NY). Results: Forty-five participants completed the study to date and were included in the interim analysis. Median age was 58 (57-59), white race (51.1%), patients on active treatment (45%), art therapy group (n=16), music therapy (n=15) and standard of care (n=14). Significant improvement was noted in the art therapy arm at 3 months in FACT-B physical well-being (p=0.04), functional well-being (p=0.008) domains as well as GAD-7 (p=0.003), PHQ-9 (p=0.04) and FACT-Cog section “impact on quality of life” (p=0.03). At 6 months, the art therapy arm demonstrated lower scores in the CCVAS questionnaire total score, emotional distress (p=0.01) and anxiety (p=0.004) scales. Music therapy participants reported a significant improvement only in GAD-7 index (p=0.04) at 3 and 6 months compared to SOC. No significant difference was found between art and music therapy arms. Conclusion: Art therapy patients exhibited significant improvement in overall QoL (including anxiety, depression, improvement in cognitive function) and 4-scale CCVAS (emotional distress, anxiety, depression, and pain). Music therapy improved anxiety scores (GAD-7). Art and music therapy should be considered in the care of patients to manage cancer associated distress and improve their quality of life.

Table 1. Comparison of test changes from 3 months to baseline within groups

Table 1. Comparison of test changes from 3 months to baseline within groups

	Art (n=16)			Music (n=15)			Standard (n=14)		
	Baseline	3 months	p-value	Baseline	3 months	p-value	Baseline	3 months	p-value
GAD7, mean ± SD	3.5±2.8	1.6±1.6	0.0030	6.9±6.5	4.7±4.7	0.0452	4.0±4.5	4.7±6.0	0.3674
PHQ9, mean ± SD	4.6±3.4	2.9±3.2	0.0431	6.0±5.2	6.0±5.7	0.6432	5.8±5.2	5.6±6.8	0.6692
Physical well-being, mean ± SD	5.0±3.8	3.4±2.8	0.0403	7.1±7.0	7.1±6.9	0.5395	6.2±5.5	5.7±5.0	0.8116
Functional well-being, mean ± SD	20.6±3.9	23.0±3.9	0.0080	17.2±8.2	16.9±7.5	0.6477	21.4±5.1	21.4±6.4	0.9258
Impact quality of life, mean ± SD	2.6±3.0	1.3±2.1	0.0362	4.5±5.2	4.5±4.6	0.9232	1.9±2.6	1.4±2.3	0.4410

Table 2. Comparison of test changes from 6 months to baseline within groups

Table 2. Comparison of test changes from 6 months to baseline within groups

	Art(n=13)			Music(n=10)		
	Baseline	6 months	p-value	Baseline	6 months	p-value
CCVAS1, mean ± SD	3.0±2.1	0.9±1.2	0.0156	2.3±2.4	2.7±3.2	0.7215
CCVAS2, mean ± SD	3.7±1.9	1.3±1.9	0.0045	2.7±2.8	2.4±2.8	0.8114
CCVAS total, mean ± SD	9.9±5.6	3.8±4.2	0.0058	9.1±6.7	9.2±10.0	0.9775

PO3-11-05

Sexual dysfunction among Brazilian women with early breast cancer on adjuvant endocrine therapy (ET)

Presenting Author(s) and Co-Author(s):

- D. Assad-Suzuki. Hospital Sírio-Libanês, Brasília, Brazil, Brazil
- F. Moura. Hospital Sírio-Libanês, Brasília DF, Brazil , Instituto Hospital de Base do Distrito Federal, DF, Brazil, Brazil
- D. Santos. Hemolabor, Goiânia, Goiás, Brazil, Goiânia, Goiás, Brazil
- S. Oliveira. Liga Norte Riograndense contra o Câncer , RN, Brazil, Brazil
- C. Souza. Hospital de Câncer de Barretos, Barretos, Brazil
- H. Resende. Hospital Jardim Amália, United States
- A. Shimada. Hospital Sirio Libanês, São Paulo , Brazil, Brazil
- A. Galvão. Uniceub, DF, Brazil, Brazil
- B. Souza. DASA Oncologia/Hospital Brasilia, Brasília, DF, Brazil, Brazil
- A. Castro. Hospital Sírio-Libanês, Brasília DF, Brazil, Brazil
- M. Andrade. Liga Norte Riograndense contra o Câncer , RN, Brazil, United States
- Y. Beckedorff. Hospital Sirio Libanês, São Paulo, Brazil, Brazil
- M. Magalhães. Hospital Universitário Evangélico Mackenzie, CURITIBA, Parana, Brazil
- C. Paiva. Barretos Cancer Hospital, Barretos, Brazil
- A. Rodrigues. Universidade Federal de Minas Gerais, Brazil; ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, United States
- D. Pereira. ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, Brazil
- D. Rosa. Hospital Moinhos de Vento, RS, Brazil, United States
- R. Barroso-Sousa. Dasa Oncology, United States

Background:

Sexual dysfunction is a common health problem in women, and it can occur during breast cancer treatment and survivorship. This study aims to determine the frequency of sexual dysfunction among Brazilian women with early breast cancer on adjuvant endocrine therapy and to explore its relationships with patients' clinical and social characteristics, adherence to ET, quality of life, return to work and healthcare insurance.

Methodology:

Women with history of early-stage ER+ invasive carcinoma of the breast on adjuvant endocrine therapy for at least 6 months were invited to participate of this study. Sexual dysfunction was evaluated using the Female Sexual Function Index questionnaire (FSFI). A score of < 26.55 in FSFI indicates sexual dysfunction. We evaluated sexually active patients (women should have at least one sexual intercourse in the previous four weeks). Demographic and medical information, site of treatment (private versus public), degree of education (completed high school vs not) were reviewed from medical records. Quality of life was assessed using EORTC QLQ C30 and BR-23 forms and adherence to ET was assessed by the Morisky Medication Adherence Scale (MMAS-8). Additionally, patients were interviewed about return to work. Data collection was performed using RedCap software and statistical analyzes were performed on the software R (R Core Team (2022)). Qualitative variables were compared between groups

using the Chi-square or exact Chi-square test and for quantitative variables the non-parametric Mann-Whitney test was used. Multivariable analysis was performed using Poisson regression. $P < 0.05$ was considered significant. Analyses were performed in SAS 9.4.

Results:

From June 2021 to May 2023, a total of 461 women with ER+ early-stage breast cancer from 12 Brazilian institutions were included in this analysis. The mean age was 56.0 years (range 22-93), 47.7% were non-white and 38.7% were premenopausal. A total of 233 women (50.6%) had private insurance and the remaining were treated in public institutions. Median duration of ET use was 2.78 years (range 6 months- 9.61 years). Only 249 (54%) out of 461 patients who accepted to participate in this study declared to have sexual intercourse in the previous 4 weeks before evaluation and composes the population of this analysis. Sexual dysfunction according results of FSFI questionnaire was found in 113 (53.3%) participants. Age was significantly associated with sexual dysfunction with women > 40 years-old having higher rates (95.3%) compared with versus younger patients (4.71% $p=0.0069$). Patients without sexual dysfunction had significantly higher EORTC QLQ C30 Global health status, Physical Functioning, Emotional Functioning, Sexual Functioning and Sexual Enjoyment scores than those with sexual dysfunction ($p = 0.0060$, $p = 0.0242$, $p = 0.0353$, $p = 0.0002$ and $p < 0.0001$ respectively). ET duration between 2 and 5 years vs < 2 years, higher vs lower education level, EORTC QLQ-BR23 breast symptom and sexual functioning higher scores were significantly associated with the occurrence of sexual dysfunction in multivariate analysis ($p < 0.05$).

Conclusion:

In our study, only 54% of women evaluated had sexual intercourse in the previous four weeks and from those women 53.3% reported sexual dysfunction. Factors related to sexual dysfunction were higher education level, ET duration between 2 and 5 years, breast symptom and sexual functioning higher scores.

div style=margin-top:10px; margin-bottom:20px;>Characteristic with adjusted prevalence ratios for the occurrence of sexual dysfunction

Variables	Adjusted Prevalence ratio	
	PR (CI 95%)	p-value
Healthcare insurance		<0.0001
No	2.73 (1.78; 4.18)	<0.0001
Yes	1	
Age		<0.0001
≤60	1	
>60	2.05 (1.43; 2.92)	<0.0001
EORTC QLQ-C30 physical functioning score	0.99 (0.98; 1.00)	0.0045
EORTC QLQ-BR23 arm symptoms score	1.01 (1.00; 1.01)	0.0161

PR: prevalence ratio , EORTC: European Organisation for Research and Treatment of Cancer

PO3-11-06

Return to work in Brazilian women on adjuvant endocrine therapy

Presenting Author(s) and Co-Author(s):

- D. Assad-Suzuki. Hospital Sírio-Libanês, Brasília, Brazil, Brazil
- A. Shimada. Hospital Sirio Libanês, São Paulo , Brazil, Brazil
- D. Santos. Hemolabor, Goiânia, Goiás, Brazil, Goiânia, Goiás, Brazil
- C. Souza. Hospital de Câncer de Barretos, Barretos, Brazil
- F. Moura. Hospital Sírio-Libanês, Brasília DF, Brazil , Instituto Hospital de Base do Distrito Federal, DF, Brazil, Brazil
- S. Oliveira. Liga Norte Riograndense contra o Câncer , RN, Brazil, Brazil
- A. Galvão. Uniceub, DF, Brazil, Brazil
- B. Souza. DASA Oncologia/Hospital Brasília, Brasília, DF, Brazil, Brazil
- A. Castro. Hospital Sírio-Libanês, Brasília DF, Brazil, Brazil
- M. Andrade. Liga Norte Riograndense contra o Câncer , RN, Brazil, United States
- Y. Beckedorff. Hospital Sirio Libanês, São Paulo, Brazil, Brazil
- M. Magalhães. Hospital Universitário Evangélico Mackenzie, CURITIBA, Parana, Brazil
- C. Paiva. Barretos Cancer Hospital, Barretos, Brazil
- H. Resende. Hospital Jardim Amália, United States
- D. Pereira. ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, Brazil
- A. Rodrigues. Universidade Federal de Minas Gerais, Brazil; ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, United States
- D. Rosa. Hospital Moinhos de Vento, RS, Brazil, United States
- R. Barroso-Sousa. Dasa Oncology, United States

Background: Breast cancer is the most common cancer in women and its diagnosis and treatment may adversely impact the return to work (RTW). Previous work showed that RTW varies from as low as 27% to as high as 93%. There are few data about RTW in Latin America population. This study aims to investigate the RTW in Brazilian woman with early breast cancer treated with adjuvant endocrine therapy (ET) and its relations to patients' characteristics, duration of ET, healthcare insurance, quality of life (QOL), sexual dysfunction and adherence. **Methodology:** Women with a past history of early-stage estrogen receptor-positive (ER+) invasive carcinoma of the breast on adjuvant endocrine therapy for at least 6 months were invited to participate in this study and evaluated about RTW. We interviewed patients and asked about employment before cancer diagnosis and about absence from work (yes/no) after diagnosis, return to work (yes/no), time off (< 06 months, 6-12 months, 13-24 months, > 24 months), and difficulties in RTW (yes/no). EORTC QLQ C30 and BR-23, female sex function index questionnaires (FSFI) and adherence to endocrine therapy (MMAS-8) were evaluated. Demographic and medical information, having or not private health insurance (yes versus public), degree of education (completed high school vs not) were reviewed from medical records. Data collection was done with RedCap software. Qualitative variables were compared between groups using the Chi-square or exact Chi-square test and for quantitative variables the non-parametric Mann-Whitney test was used. Multivariable analysis was performed using Poisson regression. $P < 0.05$ was considered significant. Analyses were performed in SAS 9.4. **Results:** From June 2021 to May 2023, a total of 461 women with ER+ early-stage breast

cancer from 12 Brazilian institutions were included in this analysis. The mean age was 56.02 years (range 22-93), 47.7% were non-white and 38.7% were premenopausal. A total of 233 women (50.6%) had private insurance and the remaining were treated in public institutions. Median duration of ET use was 2.78 years (range 6 months- 9.61 years). A total of 266 (64.88%) of women worked before cancer diagnosis and were evaluated about RTW. RTW rates at 6 months, 12 months and 24 months after diagnosis were 32.7%, 53% and 69.9% respectively. A total of 31.2% of women did not RTW at 2 years. A total of 53 (37.5%) of women reported to face difficulties to RTW. Characteristics associated with RTW were age >60 years (p=0.004), white race (p=0.014), higher education level (p< 0.0001), stage I disease (p=0.018), private healthcare insurance (p< 0.0001). In the multivariable analysis, not having private health insurance, younger age, lower EORTC QLQ-C30 physical functioning score and higher EORTC QLQ-BR23 arm symptoms scores were associated with not returning to work in this population (p < 0.05). Conclusion: Almost one third of the patients who were employed before cancer diagnosis did not RTW after treatment in Brazil. At 12 months, RTW rate was 53% higher than previous data in Latin America. Healthcare insurance, age and quality of life were related to RTW. It is crucial to identify the barriers and improve work conditions to increase RTW after breast cancer treatment as RTW have been shown to be beneficial to patients' physical, mental health and quality of life.

Variables with adjusted prevalence ratios for the occurrence of absence from work

Variables	Adjusted Prevalence ratio	
	PR (CI 95%)	p-value
Healthcare insurance		<0.0001
No	2.73 (1.78; 4.18)	<0.0001
Yes	1	
Age		<0.0001
≤60	1	
>60	2.05 (1.43; 2.92)	<0.0001
EORTC QLQ-C30 physical functioning score	0.99 (0.98; 1.00)	0.0045
EORTC QLQ-BR23 arm symptoms score	1.01 (1.00; 1.01)	0.0161

PR: Prevalence ratio; EORTC : European Organisation for Research and Treatment of Cancer

PO3-11-07

Dose-response association between post-diagnosis exercise and clinical outcomes among survivors of breast cancer (BC)

Presenting Author(s) and Co-Author(s):

- D. Soldato. Gustave Roussy, Villejuif, France, United States
- I. Vaz Luis. Gustave Roussy, Villejuif, France
- J. Havas. Gustave Roussy, Villejuif, France, United States
- A. Di Meglio. Gustave Roussy, Villejuif, France, Paris, France
- N. Iyengar. Memorial Sloan Kettering Cancer Center, New York, New York, United States
- B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France
- P. Cottu. Institut Curie, United States
- F. Lerebours. Institut Curie, United States
- C. COUTANT. Centre Georges-François Leclerc, France
- A. Bertaut. Centre Georges François Leclerc, Dijon, France, United States
- O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France
- L. Vanlemmens. Centre Oscar Lambret, Lille, France
- C. Jouannaud. Institut Godinot, Reims, France
- I. Hrab. Centre François Baclesse, Caen, France, United States
- S. Everhard. Unicancer, Paris, France, United States
- A. Martin. Unicancer, Paris, France, United States
- F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France
- L. Jones. Memorial Sloan Kettering Cancer Center, United States

Background: Higher levels of pre and post-diagnosis physical exercise lead to reduced risk of death among survivors of BC. However, the effect of exercise on recurrence remains unclear. Furthermore, previous studies assumed a linear relationship between exercise and clinical outcomes, used discrete classifications of exercise and did not report results according to BC subtype. The aim of this study was to investigate the dose–response relationship of exercise and clinical outcomes among survivors of BC and by BC subtypes.

Methods: We included pts diagnosed with stage I-III BC from the CANTO cohort (NCT01993498). CANTO collects longitudinal data, including self-reported exercise exposure using the Global Physical Activity Questionnaire (GPAQ-16), at diagnosis (dx), 1 (T1), 2 (T2) and 4 (T3) years after dx. Exercise exposure in travel and leisure time was calculated according to GPAQ16 guidelines to derive a total MET-hours per week (MET-h/w) at dx and T1 and absolute change in exercise was computed between these timepoints. Outcome of interest was distant relapse-free interval (DRFI) according to STEEP criteria. Restricted cubic splines from unadjusted Cox models assessed the dose-response relationship between exercise and DRFI in the overall cohort and by BC subtype. Kaplan-Meier estimator, log-rank test and multivariate Cox models assessed the prognostic role of exercise.

Results: In the overall cohort with available data on exercise at dx (N=10,359) mean (SD) age and BMI were 56.3 (11.2) years and 25.9 (5.4) kg/m², 38.7% of pts were premenopausal,

52.9% received chemotherapy and 81.9% hormonal therapy, 57.1% were meeting WHO exercise recommendations at dx. At a median (IQR) follow-up of 5.5 (3.9-6.5) years, 541 DRFI events were observed. In the overall cohort, the spline showed a significant non-linear relationship between exercise at dx and DRFI: exposure greater than ≈ 5 MET-h/w was associated with an inverse linear risk reduction up to ≈ 25 MET-h/w. A similar relationship was observed in the HR+/HER2- and HR-/HER2- cohorts. On this basis, exercise was categorized as 'no exercise' (0 MET-h/w) and 'exercise' (≥ 5 MET-h/w). Pts reporting exercise ≥ 5 MET-h/w had longer DRFI compared to those reporting no exercise in the overall (log-rank $p < 0.0001$), HR+/HER2- (log-rank $p < 0.0113$) and HR-/HER2- (log-rank $p < 0.0001$) cohorts. In multivariate analyses, reporting exercise ≥ 5 MET-h/w was associated with a significant lower risk of DRFI events in the overall (HR 0.75, 95%CI 0.62-0.90) and HR-/HER2- cohorts (HR 0.54, 95%CI 0.37-0.80). Absolute change in exercise exposure from dx to T1 was available in 8,516 pts: 34.2% increased exercise (≥ 5 MET-h/w), 25.9% decreased exercise (≤ -5 MET-h/w) and 39.8% maintained exercise (> -5 and $< +5$ MET-h/w). The spline showed a non-significant relationship between change in exercise and risk of DRFI events and change in exercise was not significantly associated with risk of DRFI events in multivariate analyses.

Conclusions: In this large, prospective cohort of survivors of BC, higher exercise at diagnosis was associated with reduced risk of DRFI events. The relationship between exercise dose and clinical outcomes appears non-linear and to differ based on subtype. Change in exercise after breast cancer diagnosis does not appear to impact on clinical outcomes. Future studies should aim at validating these findings in independent cohorts.

Kaplan-Meier estimates of disease recurrence-free interval (DRFI) according to baseline exercise.						
5 year DRFI (95%CI)	Overall cohort (n=10,359; 541 events)		HR+/HER2- cohort (n=7,846; 324 events)		HR-/HER2- cohort (n=984; 129 events)	
	0 MET- h/week	≥ 5 MET- h/week	0 MET- h/week	≥ 5 MET- h/week	0 MET- h/week	≥ 5 MET- h/week
		92.2 (91.1-93.2)	94.7 (94.0-95.3)	94.1 (93.0-95.1)	95.5 (94.7-96.2)	79.4 (74.2-83.6)

Multivariate Cox models of distant recurrence-free interval (DRFI)*						
Physical activity (≥ 5 vs 0 MET/h-week)	Overall cohort (n=10,359; 541 events)		HR+/HER2- cohort (n=7,846; 324 events)		HR-/HER2- cohort (n=984; 129 events)	
	HR	95%CI	HR	95%CI	HR	95%CI
	0.75	0.62-0.90	0.89	0.69-1.14	0.54	0.37-0.80

HR: hormone receptor, HER2: human epidermal growth factor receptor 2, MET: metabolic equivalent of task, h: hours, DRFI: distant recurrence-free interval, HR: hazard ratio, 95%CI: 95% confidence interval.

*All models included and were adjusted for age at dx (continuous), menopausal status (post vs premenopausal), smoking behavior at dx (former vs never smoker, current vs never smoker), BMI at dx, tumor stage (II vs I, III vs I), Charlson comorbidity index (≥ 1 vs 0), Receipt of chemotherapy (yes vs no), hormonal therapy (yes vs no), antiHER2 therapy (yes vs no) and radiotherapy (yes vs no) were included as appropriate in the model according to the analyzed cohort.

PO3-11-08

High Risk of Metabolic Dysfunction in Non-Obese Breast Cancer Survivors

Presenting Author(s) and Co-Author(s):

P. PERRONI FILHO. State University of Sao Paulo, United States

D. Buttros. State University of Sao Paulo, United States

E. Petri Nahas. State University of Sao Paulo, United States

Much literature already depicts the relationship between metabolic syndrome (MS), obesity, and breast cancer. Despite that, up to one-third of non-obese individuals may exhibit undiagnosed MS or metabolic dysfunction, posing an independent cancer risk and worse outcomes even for those with a body mass index (BMI) < 30kg/m². In that manner, our study aims to evaluate the metabolic profile of non-obese women with postmenopausal breast cancer compared to non-obese women without breast cancer. In this cross-sectional clinical study at the State University of São Paulo Medical School - UNESP. The study group (n=130) included women aged ≥ 45 and < 75 years, in amenorrhea for at least 12 months, BMI ≤ 30kg/m², histological diagnosis of breast cancer, without metastatic disease, and without established cardiovascular disease (CVD). The control group (n=130) comprised women with all the same criteria except for breast cancer diagnosis. The groups were matched by age and menopause time in a ratio of one case to one control (1:1). We aimed to analyze their clinical, biochemical, and oncological data to establish relationships between these groups. We presented the data in tables 1 - 3. The groups showed homogeneity in age, time since menopause, BMI, waist circumference (WC), and cholesterol levels. There was a higher occurrence of MS and hypertension (HTN) among women treated for breast cancer compared to the control group (30.8% vs. 20.0% and 25.4% vs. 14.6%, respectively) (p< 0.05). Similarly, a higher percentage of women treated for breast cancer had abnormal values for total cholesterol and glucose (56.2% vs. 43.1% and 29.2% vs. 15.4%, respectively) (p< 0.05). In the analysis of metabolic profile risk-adjusted for age time since menopause and BMI, women treated for breast cancer showed an increased risk for MS (OR=2.76, 95% CI 1.48-5.15), elevated glucose (OR=2.69, 95% CI 1.46-4.96), and HTN (OR=3.03, 95% CI 1.51-6.10). In the evaluation of factors influencing the metabolic profile, women with breast cancer had significantly higher mean values of WC (82.6±8.5 vs. 79.9±6.4 cm, p=0.048), systolic and diastolic blood pressure (129.2±17.1 and 77.7±8.8 mmHg vs. 118.2±15.1 and 73.6±8.8 mmHg, p=0.0002 and p=0.01, respectively), and glucose (99.7±32.5 vs. 86.6±7.6 mg/dL, p=0.0002) compared to control group. We conducted a sub-analysis among women with BMI < 25kg/m² from both groups. Women with breast cancer (n=64) had a higher occurrence of MS compared to women without breast cancer (n=53) (17.2% vs. 1.9%, respectively). Even though this sub-analysis did not reach the minimum number of patients with BMI < 25 kg/m² to achieve p value < 0,05, this analysis reveals a significant difference in MS incidence between the groups (p=0.007). This reinforces the hypothesis that oncological diagnosis substantially affects metabolic health, and therefore, breast cancer patients should receive special attention regarding their metabolic profile, regardless of their BMI. Conclusion: Non-obese women with breast cancer showed a higher risk of MS, HTN, and diabetes, with a worse metabolic profile than non-obese postmenopausal women without breast cancer. These findings suggest that postmenopausal women diagnosed with breast cancer, even in the absence of obesity, exhibit significant metabolic dysfunction characterized by a higher occurrence of MS and its components. The findings highlight the importance of a comprehensive assessment of metabolic health in women with breast cancer, regardless of their body mass index, to ensure appropriate and individualized care for these patients.

Table 1 - Comparison of clinical and laboratory characteristics among 130 non-obese postmenopausal women with breast cancer and 130 non-obese postmenopausal women (control) (average values ± standard deviation).

Table 1. Comparison of clinical and laboratory characteristics among 130 non-obese postmenopausal women with breast cancer and 130 non-obese postmenopausal women (control) (average values ± standard deviation).

Parameters	Breast Cancer (n=130)	Control (n=130)	p* value
Age (years)	57.5 ± 9.4	55.9 ± 7.2	0.098 ^b
Menopause age (Years)	47.7 ± 4.1	47.5 ± 4.4	0.681 ^a
Time since menopause (years)	10.7 ± 8.6	8.9 ± 6.5	0.067 ^b
BMI (kg/m ²)	25.1 ± 3.1	25.6 ± 2.9	0.128 ^a
WC (cm)	87.8 ± 9.3	85.9 ± 8.1	0.244 ^a
SBP (mmHg)	132.3 ± 17.1	123.4 ± 15.3	<.0001 ^a
DBP (mmHg)	81.0 ± 10.5	76.1 ± 9.7	<.0001 ^a
Total Cholesterol (mg/dl)	204.4 ± 34.9	201.3 ± 32.1	0.452 ^a
HDL (mg/dl)	55.4 ± 12.3	56.5 ± 14.0	0.489 ^a
LDL (mg/dl)	121.5 ± 29.0	117.6 ± 30.8	0.292 ^a
Triglycerides (mg/dl)	141.6 ± 62.6	134.4 ± 64.5	0.357 ^b
Glucose (mg/dl)	101.4 ± 32.3	90.0 ± 10.6	<.0001 ^b

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure, DBP, diastolic blood pressure, HDL, high-density lipoprotein, LDL, low-density lipoprotein.

*Significant difference if p<0.05 (a Student's t-test or b Gamma Distribution).

Table 2 - Comparison of categorized clinical and laboratory characteristics that influence the metabolic profile between 130 non-obese postmenopausal women with breast cancer and 130 non-obese postmenopausal women (control).

Characteristics	Breast Cancer (n=130)	Control (n=130)	P value*	Glucose (mg/dl)		
				≥ 150	37 (28.5)	50 (38.5)
				< 100	92 (70.8)	110 (84.6)
				≥ 200	38 (29.2)	20 (15.4)
						0.001
Values expressed as number and percentage in parentheses.						
CA, cancer; WC, waist circumference; MS, metabolic syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.						
*Significant difference p<0.05 (Chi-square Test).						
Smoking			0.166			
Yes	22 (16.9)	31 (23.8)				
No	108 (83.1)	99 (76.2)				
Exercise			0.482			
Yes	32 (24.6)	37 (28.5)				
No	98 (75.4)	93 (71.5)				
WC			0.163			
≤ 88cm	73 (56.1)	84 (64.6)				
> 88cm	57 (43.9)	46 (35.4)				
Presence of MS			0.001			
Yes	40 (30.8)	26 (20.0)				
No	90 (69.2)	104 (80.0)				
Blood Pressure (mmHg)			0.001			
< 135/85	97 (74.6)	111 (85.4)				
≥ 135/85	33 (25.4)	19 (14.6)				
Cholesterol (mg/dl)			0.027			
< 200	57 (43.8)	74 (56.9)				
≥ 200	73 (56.2)	56 (43.1)				
HDL (mg/dl)			0.236			
≥ 50	82 (63.1)	91 (70.0)				
< 50	48 (36.9)	39 (30.0)				
LDL (mg/dl)			0.333			
< 160	80 (61.5)	86 (65.7)				
≥ 160	50 (38.5)	44 (34.3)				
TG (mg/dl)			0.087			
< 150	93 (71.5)	80 (61.5)				
≥ 150	37 (28.5)	50 (38.5)				

Values expressed as number and percentage in parentheses. CA, cancer; WC, waist circumference; MS, metabolic syndrome; HDL, high-density lipoprotein, LDL, low-density lipoprotein; TG, triglycerides.

*Significant difference p<0.05 (Chi-square Test).

Table 3. Association between the presence of Metabolic Syndrome, and its clinical and laboratory components, among the 130 non-obese postmenopausal women with breast cancer and the 130 non-obese postmenopausal women (control).

Table 3. Association between the presence of Metabolic Syndrome, and its clinical and laboratory components, among the 130 non-obese postmenopausal women with breast cancer and the 130 non-obese postmenopausal women (control).

Parameters	Groups		OR (IC 95%)*
	Breast	Control	
	Cancer		
	n (%)	n (%)	
Metabolic syndrome	40 (30.8)	26 (20.0)	2.76 (1.48-5.15)
WC (> 88cm)	57 (43.9)	46 (35.4)	1.43 (0.86-2.35)
HDL (<50 mg/dl)	48 (36.9)	39 (30.0)	1.37 (0.81-2.29)
TG (≥150mg/dl)	37 (28.5)	50 (38.5)	1.64 (0.73-2.17)
Glucose (≥100 mg/dl)	38 (29.2)	20 (15.4)	2.69 (1.46-4.96)
BP (≥ 135/85 mmHg)	33 (25.4)	19 (14.6)	3.03 (1.51-6.10)

Values expressed as number and percentage in parentheses.

CA, cancer; BP, blood pressure; WC, waist circumference; TG, triglycerides.

*Odds ratio (OR) adjusted for age, menopause duration and BMI.

**Significant difference if $p < 0.05$ (Logistic Regression).

Values expressed as number and percentage in parentheses.

CA, cancer; BP, blood pressure; WC, waist circumference; TG, triglycerides.

*Odds ratio (OR) adjusted for age, menopause duration and BMI.

**Significant difference if $p < 0.05$ (Logistic Regression).

PO3-11-09

Cross-cultural adaptation and psychometric validation of lymphedema patient-reported outcome measurements in Chinese breast cancer patients

Presenting Author(s) and Co-Author(s):

Y. Zhou. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, 200032 China, United States

B. Xiu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

Q. Zhang. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Background: Lymphedema is one of the most common complains reported by breast cancer survivors, which negatively affects the quality of life (QoL). Various internationally recognized patient-reported outcome measurements (PROMs), such as the Upper Limb Lymphedema 27 (ULL-27), Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF), Lymphedema Quality of Life Questionnaire for upper limbs (LYMQOL-ARM), and Lymphedema Life Impact Scale Version 2 (LLIS), have been translated into different languages and widely used to assess QoL in patients with breast cancer-related lymphedema (BCRL). However, limited evidence has proved the efficiency of these tools in Chinese patients. In this study, we performed cross-cultural adaptation and psychometric validation of these four PROMs within the Chinese context. Additionally, we also compared the accuracy in detecting BCRL for early diagnosis. **Methods:** A process of forward-backward translation and cultural adaptation was conducted based on international standards. Content validity was assessed through patient interviews. Internal consistency was evaluated by Cronbach's alpha coefficient. The correlation analysis of the MOS item short form health survey (SF-36) and each BCRL QoL questionnaires was utilized to indicate the convergent and divergent validity. Clinical validity was assessed by comparing scores among patients with different BCRL stages. Furthermore, questionnaires scores and the known group of lymphedema or not were compared to generate receiver operator characteristic (ROC) curves of these instruments. **Results:** A total of 204 female breast cancer patients were recruited in this study. Among them, 104 patients (61 with lymphedema and 43 without lymphedema) finished LYMQOL-ARM and ULL-27 questionnaire, while 100 patients (59 with lymphedema and 41 without lymphedema) were assessed by Lymph-ICF and LLIS. The internal consistency was high, with Cronbach's alpha coefficients above 0.9 for all subscales and global scales. The content validity was generally good, except for a few issues reported by the patients. Convergent and divergent validity confirmed the hypotheses of correlation between the tested questionnaire and SF-36 to varying degrees: 100% for ULL-27, 80% for Lymph-ICF, nearly 70% for LLIS, and only 50% for LYMQOL-ARM. LLIS and Lymph-ICF demonstrated strong clinical validity, with significant differences found in total and subscale scores among participants in different BCRL stages ($P < 0.05$). There were no significant differences between stages for the mood dimension ($P=0.132$) of LYMQOL-ARM, psychological dimension ($P=0.506$), social dimension ($P=0.083$), and total score ($P=0.057$) of ULL-27. Only the physical concerns and global scale of LLIS and the symptom subscale of Lymph-ICF exhibited acceptable AUC values near 0.7 (AUC 0.725, 95% CI 0.625-0.825, $p < 0.029$; AUC

0.680, 95% CI 0.573-0.787, $p < 0.002$; AUC 0.734, 95% CI 0.633-0.834, $p < 0.001$, respectively). In contrast, other subscales and questionnaires displayed lower AUC values. Conclusion: Lymphedema is a chronic disease that has a relatively low mortality risk but significantly affects the quality of life. Therefore, it is crucial to prioritize patient-reported outcomes in the assessment of lymphedema. Among the four PROMs, LLIS not only showed high internal consistency and content validity more suitable for Chinese patients, but also exhibited better performance in reflecting the presence and severity of lymphedema patients. Consequently, the validated and reliable Chinese version of LLIS is recommended for clinical and scientific practices in the assessment of BCRL, which will help to provide better interventions with a patient-centered focus.

PO3-11-10

Second primary non-breast cancers in young breast cancer survivors

Presenting Author(s) and Co-Author(s):

- B. Zhang. Harvard Medical School, United States
- K. Brantley. Dana-Farber Cancer Institute, United States
- S. Rosenberg. Weill Cornell Medicine, New York, New York, United States
- G. Kirkner. Medical Oncology, Dana-Farber Cancer Institute, United States
- L. Collins. Beth Israel Deaconess Medical Center, United States
- K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States
- R. Tamimi. Weill Cornell Medicine, New York, NY, USA, United States
- L. Schapira. Stanford Cancer Institute, Palo Alto, CA, USA, United States
- V. Borges. University of Colorado Anschutz Medical Center, United States
- E. Warner. Sunnybrook Odette Cancer Centre, Toronto, Ontario, Canada
- S. Come. Beth Israel Deaconess Medical Center, Boston, MA, USA, United States
- E. Winer. Yale Cancer Center, New Haven, Connecticut, United States
- A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Adolescent and young adults (AYAs) (15-39 years) have a heightened risk of developing a second primary malignancy due to extended periods of survivorship, higher incidence of germline cancer predisposing variants, and increased susceptibility to treatment-induced malignancies. Research on survivors of specific AYA cancer types, including breast cancer (BC) survivors, is limited. Among BC survivors, while much survivorship research focuses on risk of locoregional recurrence or contralateral BC, little is known about overall risk, and risk factors, of developing second non-breast primaries.

This prospective cohort study examined women diagnosed with BC from 2006-2016 at age ≤ 40 years enrolled in the Young Women's BC Study (YWS) (N=1297). Women were excluded from the analytic cohort if initially diagnosed with Stage IV breast cancer (N=64). To enable investigation of how BC treatments may impact second primary risk, women were also excluded if they reported another cancer before primary BC diagnosis (N=3). Patient characteristics, treatment information, and clinical events were collected via serial surveys. Tumor characteristics and detailed treatment data were obtained from medical record review. Five- and 10-year risk of second non-breast primary was estimated via the cumulative incidence function after applying the Fine-Gray competing risks model with time starting at primary BC diagnosis. Death, metastasis, or diagnosis with a second primary BC were considered as competing events. Univariate and multivariate Fine-Gray sub-distribution models were used to estimate sub-distribution hazard ratios (sHRs) and 95% confidence intervals (CI) for second non-breast primary cancer risk. Risk factors considered included age, race, body mass index, smoking, alcohol use, income, family history of cancer, germline pathogenic variant (PV) carrier status, tumor stage, grade, and ER status, primary surgery type, and receipt of radiation, chemotherapy, or endocrine therapy (yes/no). Multivariate models tested individual associations with additional adjustment for radiation therapy and PV carrier status, as both are consistently associated with second primary in the literature.

Over a median follow-up of 10.1 years (inter-quartile range (IQR) =7.9-12.1 y), 47 patients (4%)

developed a second non-breast primary cancer. Median age at second non-breast primary was 43 years (IQR=39-46), and median time between primary BC and second non-breast primary was 7.3 years (IQR=4.1-9.3). Second primary types included melanoma (n=10), thyroid (n=10), ovarian (n=4), sarcoma (n=4), uterine (n=3), rectal (n=3), bladder (n=2), cervical (n=2), head and neck (n=2), lung (n=2), lymphoma (n=2), pancreatic (n=2), and kidney (n=1). During the study, 22 patients (2%) developed a second primary BC, 167 (19%) developed metastasis, and 15 (1%) died from causes other than BC. Among the patients who developed a second primary BC, two later developed another non-breast cancer (ovarian and brain cancer). When incorporating competing risks, five and 10-year cumulative incidence of second non-breast primary was 1.4% and 3.2%, respectively. No patient or treatment factors were statistically significantly associated with second non-breast primary in univariate or multivariate models, including radiation and PV carrier status.

In this population of young BC survivors, 10-year cumulative incidence of second non-breast primary cancer was 3.2%, with the most common second cancers being melanoma and thyroid cancer. Incidence rates of all second primary cancer types in this cohort were higher than population-based incidence rates for healthy women under 50 years of age, highlighting the importance of long-term surveillance for other cancer events in this young population. While risk of second non-breast primary was not associated with primary BC treatment in this study, cases were limited, and the follow-up interval was relatively short.

PO3-11-11

Reproductive concerns of Japanese young women with breast cancer: a longitudinal study

Presenting Author(s) and Co-Author(s):

C. Watanabe. Showa University, United States

H. Bando. University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan

A. Kataoka. The Cancer Institute Hospital of JFCR, Koto-ku, Tokyo, Japan

M. Okazaki. Breast-Thyroid-Endocrine Surgery, University of Tsukuba Hospital, United States

T. Shien. Okayama University Hospital, Okayama-city, Okayama, United States

E. Tokunaga. Department of Breast Oncology, NHO Kyushu Cancer Center, Japan

T. Kuwayama. Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine, United States

C. Shimizu. Department of Breast and Medical Oncology, National Center for Global Health and Medicine, Tokyo, Japan

Background: Treatment-related infertility is one of the major concerns of young women with breast cancer. We explored the longitudinal change and factors associated with reproductive concerns of Japanese young women in a prospective cohort study.

Method: Women under the age of forty with newly diagnosed, histologically confirmed, operable breast cancer were recruited to "Hope for YBC Project" (UMIN000034481). The participants were asked to respond to anonymous self-written questionnaire regarding reproductive concern, anxiety and depression, perception of motherhood and socio-economic status at baseline and 6M.

Result: Among 215 participants who were enrolled in the study, the mean age of 143 participants who responded to both the questionnaire at baseline and 6M was 35.7 (range 25-39): 78 (54.5%) had a university degree or higher, 104 (72.7%) had a partner, 65 (45.5%) had more than one child, and 84 (58.8%) had a household income more than 5 million yen. 57 (39.9%) had desire for having a baby, 37 (25.9%) were unsure and 43 (33.6%) were not interested. Among 143, 33 (23%) attempted fertility preservation. Baseline score of Reproductive Concerns After Cancer scale (RCAC) had weak correlation with the total scores of Hospital Anxiety and Depression Scale (HADS) ($r=.397$, $p<.001$) and Decision Conflict Scale (DCS) ($r=.365$, $p<.001$), respectively. Perceived "sufficient explanation of the risk of recurrence" and "sufficient explanation of the necessity and benefit of pharmacotherapy" were significantly associated with reduced DCS score at baseline ($p<0.001$). The desire for having a baby changed in 15 women (10.5%) at 6M. Although both DCS and HADS significantly lowered at 6M, there was no difference between RCAC score at baseline and at 6M. RCAC score at 6M had correlation with RCAC ($r=.793$, $p<.001$), DCS ($r=.439$, $p<.001$), and HADS ($r=.401$, $p<.001$) scores at baseline. RCAC score at 6M was also associated with younger age ($r=.311$), non-existence of partner ($p=.001$), non-existence of child ($p=.014$), desire for having a baby ($p<.001$) at baseline, attempt of fertility preservation ($p=.025$) and not receiving endocrine treatment ($p=.047$).

Conclusion: Reproductive concerns of young women remained throughout the treatment, and concerns at later treatment phase were associated with decision conflict and anxiety at diagnosis. These results shows that young women, especially those who have higher risk of

having reproductive concern, need psychological and decision support at diagnosis, including thorough explanation of risk of recurrence and benefit of systemic treatment from oncologists.

PO3-11-12

A Pragmatic Randomized Trial Comparing Morning versus Evening Dosing of Endocrine Therapy for Early Breast Cancer: Final Results (REaCT-CHRONO Study).

Presenting Author(s) and Co-Author(s):

M. Savard. The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada, United States

M. Ibrahim. Northern Ontario School of Medicine University, United States

G. Pond. McMaster University, United States

D. Saunders. Ottawa Hospital Research Institute, United States

L. Vandermeer. Ottawa Hospital Research Institute, Ontario, Canada

L. Fallowfield. Brighton and Sussex Medical School, University of Sussex, United States

T. Ng. The Ottawa Hospital Cancer Centre, Ottawa, Ontario, Canada

A. Awan. The Ottawa Hospital Cancer Centre, Canada

S. Sehdev. University of Ottawa, Ottawa Hospital Research Institute, United States

A. Beltran-Bless. University of Ottawa, Ontario, Canada

M. Clemons. Ottawa Hospital, Ottawa, Ontario, Canada

Background. Interventions to improve tolerability and adherence to endocrine therapy (ET) are critical to the global improvement of breast cancer (BC) survivorship. The optimal time of day to take ET in terms of quality of life, side effects and adherence is unknown. This study compared a morning dose versus an evening dose of ET in patients with early-stage BC (EBC). **Methods.** In this pragmatic, open-label, multicenter trial, patients with hormone receptor-positive (HR+) EBC were randomized (1:1) to receive either a morning dose (within 1 hour of the patient wake up time) or an evening dose of ET (within 1 hour of patient bedtime). The primary endpoint was endocrine toxicity/tolerability measured by the change in total Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES) score from baseline (commencement of ET) to 12 weeks. The secondary endpoints included: ET toxicity/tolerability and quality of life (FACT-ES and FACT-B) from baseline to 4, 8, 12 and 52 weeks, non-persistence or non-adherence, and patient timing preference. **Results.** Between June 2021 and March 2022, 245 eligible patients were randomized, 122 to morning (122/245, 49.8%) and 123 to evening (123/245, 50.2%) dosing. Mean age was 61 [standard deviation (sd) 11.9], 181 patients (73.9%) were postmenopausal, 188 (76.7%) received tamoxifen, 58 (23.7%) received an aromatase inhibitor and 22 (9%) received luteinizing hormone-releasing hormone. The mean changes in the FACT-ES score from baseline to 12 weeks following the beginning of ET were -2.0 (sd=14.3) vs -5.4 (sd=16.8) in the morning vs evening arms respectively (Wilcoxon two-sample rank sum test p-value=0.22). Also, the proportion of patients with a clinically important increase (Fisher's exact test p-value=0.54 0.89) or decrease (p-value= 0.89) in FACT-ES Scores was not statistically different between the arms. At 52 weeks, the mean changes in the FACT-ES score from baseline were -2.5 (sd=18.8) vs -4.8 (sd=15.5) in the morning vs evening arms respectively (p-value=0.23). There was no statistical difference in FACT-ES and FACT-B scores over the 52 weeks of the study. At 12 weeks, 94.5% (69/79) vs 98.7% (78/79) were still taking the ET (p-value=0.2), whereas at 52 weeks, 92.1% (58/63) vs 85.4% (41/48) were still taking ET (p-value=0.36), in the morning vs evening arms respectively. Also, 13.7% (10/73) vs 7.6% (6/79) and 3.2% (2/62) vs 12.5% (6/48) interrupted their ET at least once, in the morning vs evening arms, at 12 and 52 weeks respectively. At week 52, 57.9% (62/107) in the morning arm vs 13.5% (14/104) in the evening arm strongly preferred an ET morning dose, whereas 7.5% (8/107) vs 42.3% (44/104) strongly preferred an ET evening dose. No significant preference

changes were observed in dose timing from baseline to week 52 (p-value=0.081). Conclusions. These results suggest no significant difference in quality of life or adherence if ET is taken in the morning or in the evening. Patients should be reassured that they can take ET at their preferred time. Clinical Trial Registration: NCT04864405

Table 1. Mean changes between FACT scores at 12 weeks and 52 weeks from baseline for patients receiving ET morning vs evening dose.

	All patients	Morning	Evening	p-value
12 weeks				
FACT-ES, mean (sd)	-3.7 (15.7)	-2.0 (14.3)	-5.4 (16.8)	0.22
Decrease, n (%)	88 (41.5)	44 (40.7)	44 (42.3)	
Stable, n (%)	66 (31.1)	32 (29.6)	34 (32.7)	
Increase, n (%)	58 (27.4)	32 (29.6)	26 (25.0)	
FACT-B, mean (sd)	0.8 (13.9)	2.4 (13.6)	-0.9 (14.1)	0.087
52 weeks				
FACT-ES, mean (sd)	-3.6 (17.3)	-2.5 (18.8)	-4.8 (15.5)	0.23
Decrease, n (%)	97 (46.2)	45 (42.1)	52 (50.5)	
Stable, n (%)	47 (22.4)	23 (21.5)	24 (23.3)	
Increase, n (%)	66 (31.4)	39 (36.5)	27 (26.2)	
FACT-B, mean (sd)	1.5 (16.3)	2.2 (18.0)	0.8 (14.3)	0.29

A positive value indicates the FACT score increased over time.
FACT ES: Endocrine Subscale; FACT B: breast

PO3-12-01

Breastfeeding After Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Litwiniuk. Greater Poland Cancer Centre, Poznan; University of Medical Sciences, Poznan, Poland, Poznań, Wielkopolskie, Poland

M. Bartoszkiewicz. Medical University of Poznań, United States

J. Kufel-Grabowska. University Hospital of H. Świącicki, Lusowo, Wielkopolskie, Poland

Breast cancer (BC) in young women (< 40 years of age) accounts for only 6-8% of all breast cancers, but it is the most common oncological disease in the reproductive age group. For many young patients, it is important to have children after breast cancer treatment. The results of retrospective studies and the POSITIVE trial indicate that pregnancy and childbirth do not increase the risk of BC recurrence. While we have more data on the course of pregnancy, maternal and child health, limited information is available about breastfeeding experiences in BC survivors.

The aim of this study was to retrospectively analyze the breastfeeding experiences of women who had previously been treated for breast cancer. Method: The study took the form of a survey. A questionnaire regarding diagnosis, treatment, pregnancy, and breastfeeding was sent to women associated with patient organizations. Data on cancer and treatment were obtained from the patients. Results: We received 44 completed questionnaires. The mean age of the patients at diagnosis was 30 years (23-35). The majority of patients underwent mastectomy (59%), and almost all patients received chemotherapy (91%). Hormonal treatment was used in 61% of cases, and trastuzumab in 41%. The average time from diagnosis to pregnancy was 44.6 months (0-120). Most babies were born at term (86.4%), with an average birth weight of 3444.4 grams (2360-4220). Out of the 44 patients, 33 breastfed their babies. In 80% of women, milk appeared in the healthy breast, and in every fourth patient after conserving treatment. 20% of these patients attempted to breastfeed with the affected breast, but these attempts failed after a few days. Among the patients who breastfed with the healthy breast, 27% breastfed for 3 to 6 months, 24% for 6 to 12 months, and 30% for more than a year (12% for more than 2 years). Babies were gaining weight normally, but 65% of mothers opted for additional formula feeding. Patients who did not start breastfeeding cited concern for the proper development of their children and fear of recurrence of the disease as the main reasons. Two patients were unable to breastfeed because they had to resume adjuvant hormonal treatment that had been interrupted in order to become pregnant and deliver a child. Shockingly, 36% of patients did not receive sufficient information on the possibility of breastfeeding after breast cancer treatment, and only 23 patients (52%) had meetings with a lactation consultant after giving birth. Conclusions: Women who give birth after breast cancer treatment should be informed about the possibility of breastfeeding. They should also be aware that one breast can produce enough milk for their baby, and they should have access to lactation consultants for guidance and support.

PO3-12-02

SAFETY AND TOLERANCE OF THE USE OF SHOCK WAVE THERAPY IN LYMPHEDEMA SECONDARY TO THE TREATMENT OF BREAST CANCER

Presenting Author(s) and Co-Author(s):

P. Ventura. Universidade Federal do Estado de São Paulo, United States

C. Haddad. Universidade Federal de Sao Paulo, Brazil

V. Sanvido. Universidade Federal de São Paulo/ Hospital do Coração (Hcor), United States

A. Nazário. Universidade Federal de São Paulo, United States

G. Facina. Universidade Federal de São Paulo, United States

A. Estevao. Universidade Federal de Sao Paulo, United States

S. Lopes de Almeida Rizzi. Universidade Federal de Sao Paulo, United States

Introduction: Lymphedema is a very common complication of breast cancer treatment. The first-line therapeutic method for lymphedema is Complex Physical Therapy. An option currently mentioned as an adjuvant and non-invasive treatment for lymphedema secondary to breast cancer is Shockwave Therapy. **Objectives:** To evaluate the safety and tolerance of shockwave therapy for the treatment of upper limb lymphedema secondary to breast cancer treatment. **Methods:** This is a quasi-experimental study carried out with 17 women who underwent breast surgery associated with axillary lymphadenectomy or Sentinel Lymph Node Biopsy and who had upper limb lymphedema secondary to the treatment of breast cancer. All were treated with complex physical therapy prior to the study. Four sessions of Shockwave Therapy were applied, 4000 shocks at 0.06 mJ/mm², 1 time per week for 4 consecutive weeks. For that, the participants were evaluated through the application of questionnaires and physical examination and underwent shock wave therapy for the upper limb ipsilateral to the surgery. **Results:** After the intervention, none of the participants had skin lesions, blisters, desquamation or hyperthermia of the limbs, and 17.65% had skin redness. Most patients reported no change in their social life and that they felt safer in daily activities and very satisfied with the treatment. The patients showed improvement in upper limb functionality after the intervention versus baseline ($p=0.02$). No difference in limb volume and shoulder range of motion over time for all movements performed was found after the intervention and at the evaluated intervals. In addition, improvements were observed in some domains of the quality-of-life questionnaires. **Conclusion:** Shockwave Therapy proved to be safe and tolerable in patients with lymphedema, with improved functionality and no significant change in the volume of the affected limb. **Keywords:** Extracorporeal shock wave therapy; Lymphedema; Breast cancer.

PO3-12-03

SAFETY AND TOLERABILITY OF SHOCKWAVE THERAPY FOR TREATMENT OF BREAST CANCER-RELATED LYMPHEDEMA: A SYSTEMATIC REVIEW

Presenting Author(s) and Co-Author(s):

P. Ventura. Universidade Federal do Estado de São Paulo, United States

C. Haddad. Universidade Federal de Sao Paulo, Brazil

A. Nazário. Universidade Federal de São Paulo, United States

G. Facina. Universidade Federal de São Paulo, United States

V. Sanvido. Universidade Federal de São Paulo/ Hospital do Coração (Hcor), United States

A. Estevas. Universidade Federal de Sao Paulo, United States

S. Lopes de Almeida Rizzi. Universidade Federal de Sao Paulo, United States

Introduction: Breast cancer is currently the most common malignancy among women, after non-melanoma skin cancer. Upper limb lymphedema is the most feared complication of breast cancer treatment. Currently, the approach described in the literature as the most effective for the treatment of lymphedema is Complex Physical Therapy. In the search for more efficient therapeutic actions, Shockwave Therapy emerges as an alternative in the treatment of upper limb lymphedema secondary to breast cancer. Objective: to systematically review the available literature and verify the safety, tolerance and efficacy of using Shockwave Therapy (ESWT) in the treatment of upper limb lymphedema secondary to breast cancer. Methods: The following databases were used: PubMed; PEDro, The Cochrane Library, EMBASE, Web of science and Scopus and through manual search of articles. The PICO research method was adopted, and the descriptors adjusted according to the respective database. This study was registered in PROSPERO: CRD42020209588. Results: Combined searches, including reference lists, manual searches, and database searches, yielded 64 articles, of which 35 articles were duplicates, 23 studies were excluded by title, abstract, or full reading. Six full-text articles were selected. Of these, only 3 randomized clinical trials and 3 non-randomized clinical trials met all established inclusion criteria and were analyzed in this systematic review. Two more RCTs were added by manual search of references from other articles. None of the studies found had safety and tolerability as their primary objective, and one reported transient redness with the use of the device. Shockwave Therapy, combined with other resources, can significantly improve lymphedema volume and shoulder range of motion, but there is not enough evidence to support the use of ESWT as a substitute for complex physical therapy (CPT). Final considerations: There is evidence that it can improve ROM and upper limb volume when used in association with CPT, which is the gold standard for the treatment of lymphedema.

Keywords: Lymphedema, Breast Cancer, Extracorporeal Shockwave Therapy.

PO3-12-04

Pulmonary Complication related to Trastuzumab Deruxtecan. A pharmacovigilance study from 2022-2023 FAERS Database

Presenting Author(s) and Co-Author(s):

N. Neupane. Rochester General Hospital, United States

H. Kharel. Rochester General Hospital, United States

S. Thapa. Westchester Medical Center, United States

Background: The horizon of Trastuzumab Deruxtecan (T-DXd), an antibody-drug conjugate, has been expanding. After its promising results in HER2-positive/HER2-low Breast cancer, it has been on trial for other cancers, such as HER2-negative breast cancers, Gastrointestinal, lung, colorectal, urothelial, etc., and it has shown promising results in clinical trials. However, there have been reports of pulmonary adverse events associated with T-DXd, including interstitial lung disease (ILD) and pneumonitis. Understanding the occurrence and characteristics of these pulmonary complications is essential for optimizing patient care and ensuring the safe use of T-DXd. Using the FAERS (FDA Adverse Event Reporting System) database for 2022-2023 aims to see T-DXd-related pulmonary complications and guide healthcare professionals in monitoring and managing these adverse events effectively.

Methods: We conducted a retrospective analysis of all reported cases of respiratory complications in patients using TDXD, utilizing data reported to the FDA Adverse Event Reporting System (FAERS) database for January 2022 to March 2023. We included patients of more than 18; these cases were identified and classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. **Results:** In this study, a total of 296 cases of adverse events were reported in patients using TDXD. Among these cases, 74 (27%) were respiratory adverse events. The most frequently observed respiratory complications were interstitial lung disease (ILD) and pneumonitis, with 21 cases each, accounting for 56% of the total respiratory complications. Out of the 14 reported deaths in this cohort, pneumonitis was the most commonly seen respiratory complication, occurring in 8 patients, followed by pulmonary embolism and ILD, each reported in 4 patients. **Conclusion:** Respiratory complications were the most frequent among the reported adverse events, accounting for 27% of all cases. ILD and pneumonitis were the most common complications, with 14 deaths reported in this group. These findings underline the importance of closely monitoring and managing pulmonary adverse events in patients treated with T-DXd. Healthcare professionals can use this information to optimize patient care and ensure the safe use of T-DXd. However, it is important to note that this study was based on a database and has limitations such as underreporting bias and lack of a control group, which hinders establishing a causal relationship. Additional research is needed to identify risk factors and improve patient outcomes.

PO3-12-05

Patient (pt)-provider communication challenges about side effects/toxicities from metastatic breast cancer (mBC) treatments

Presenting Author(s) and Co-Author(s):

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

K. Shanahan. Metavivor Research and Support, Inc, Annapolis, MD, United States

F. Chino. Memorial Sloan Kettering Cancer Center, New York, New York, United States

D. Trapani. European Institute of Oncology, IRCCS, University of Milano, Milan, Lombardia, Italy

D. Carroll. Sermonix Pharmaceuticals, United States

M. Kozlowski. Sermonix Pharmaceuticals, United States

E. Attias. Sermonix Pharmaceuticals, United States

N. Kuderer. Advanced Cancer Research Group, United States

Introduction: Treatment decisions for ER+/HER2- mBC may be influenced by pt knowledge about treatment side effects, which is shaped by pt-provider communication. We conducted a survey of pts with ER+/HER2- mBC to better understand pt expectations and experiences of treatment toxicities, the extent they were discussed by the pts' medical team (MT), and the sources/types of side effect information pts prefer.

Methods: The 55-question, online ESR1 QUALity of Life Survey 3 (EQUALS 3) survey was emailed to US pts from the Cure Media Group and authors' contacts, and posted to private BC Facebook and Twitter pt groups for 2 weeks in June 2023. Eligible pts had ER+/HER2- mBC and reported changing treatments due to progression. Pts received a \$10 gift card at survey completion. Survey answers were descriptively summarized.

Results: 213 pts completed the survey; they were < 60 yrs of age (77%), White (44%) or Hispanic/Latino (48%), peri-/postmenopausal (54%), and urban-area residents (51%); and had college education (71%) and household income >\$50K (66%). Most pts were on 2nd (36%) or 3rd+ (51%) therapy lines. Current mBC treatments were endocrine therapy ± targeted agent (70%), antibody-drug conjugate (8%), chemotherapy (11%), and others (10%). Most pts' oncologists were female (65%), BC specialists (51%), and from an academic hospital (61%).

Only half (49%) of surveyed pts felt extremely/very comfortable discussing side effects with their MT. Although 86% felt well informed about treatment toxicities, MTs did not proactively ask about pts' greatest concerns on side effects for 15% of pts, nor about what side effects pts would find tolerable or intolerable for 25%. Oncologist/MT inquired about acceptability of side effects most often with treatment change (25%) or when brought up by the pt (20%), and at every single visit for only 19% of pts.

Most pts felt extremely prepared for treatment toxicities (78%) and well prepared to manage them (86%), but 19% of pts still felt that their MT did not provide optimal guidance on managing potential side effects. Pt-centered conversations were most often missing: what rare but serious

side effects to expect (44%), how to deal with potential side effects (39%), and what common side effects to expect (32%). Pts also reported that the likelihood of experiencing side effects (40%), what rare but serious side effects to expect (39%), and how to deal with potential side effects (28%) were not well presented.

To facilitate treatment decisions, pts would like more time discussing treatment options (48%) or side effects (39%); additional written or visual resources on side effects (29%, 23%, respectively) or efficacy (39%, 8%); and the ability to ask questions and receive meaningful answers (39%), talk to other pts (20%), or listen to videos of their stories (11%). Pt testimonials (45%), toxicity descriptions/examples (42%), and toxicity management strategies (36%) were the most common additional forms of information that pts would like to have had on side effects.

Conclusion: In this survey of pts with ER+/HER2- mBC, not all pts were comfortable discussing treatment toxicities with their MT, but MTs are mostly addressing side effects. However, there is still room for communication improvement and additional forms of toxicity information are needed for optimal decision-making. Despite generally feeling well prepared for toxicities, a significant proportion of pts report that the range and specifics of side effects and how to manage them were missing or not well presented in MT discussions. This survey highlights the need to improve both provider and pt education with the goal of effectively communicating toxicity specifics of mBC therapies, as well as the need for standardized pt education tools detailing risks and benefits of mBC therapies to assist pts in shared decision-making conversations.

PO3-12-06

The pilot study for a mobile-based monitoring solution to manage menopausal symptoms of premenopausal breast cancer patients with endocrine therapy

Presenting Author(s) and Co-Author(s):

D. Shin. Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Seoul, Republic of Korea

J. Ryu. Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam, Ulsan-gwangyoksi, Republic of Korea

B. Chae. Breast Division, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, United States

J. Lee. Samsung Medical Center, United States

S. Kim. Breast Division, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, United States

S. Nam. Breast Division, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, United States

J. Yu. Breast Division, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, United States

Background

Endocrine therapy (ET) is the most important treatment for hormone receptor (HR)-positive breast cancer (BC) patients. Each of the endocrine medications, such as aromatase inhibitors (AIs), luteinizing hormone-releasing hormone (LHRH) analogs, and selective estrogen receptor modulators, has its own set of side effects, and these might lead to poor drug adherence and eventual discontinuation. There are few systematic monitoring systems for menopausal symptoms of patients on ET. We conducted a prospective, pilot study through the mobile platform-based monitoring solution which contains a questionnaire about menopausal symptoms to assess the feasibility of the solution.

Methods

We screened and collected data from HR-positive BC patients who underwent surgery at a single institution from May 2022, until recruiting a total of 20 patients. Patients scheduled for postoperative ET at age 50 or younger were included. Preoperatively confirmed metastatic BC patients were excluded. A total of 19 patients were enrolled, excluding one patient who self-discontinued medication. Menopause Rating Scale (MRS) surveys were periodically administered to the patients using a mobile platform-based solution to collect responses during first 3 months of ET. The primary endpoint of this study was the response rate of the patients, and the second endpoint was MRS scores and patient satisfaction. At the time of initial enrollment before the start of ET, MRS was collected using a paper questionnaire. The concordance rate of MRS response using a paper questionnaire and this solution was compared. We also conducted a user evaluation at the end of the third month of ET to determine satisfaction. The data collected from the solution were used by physicians to assist in patient care for clinical use.

Results

The median age of the cohort was 39 (range 29-47). Six patients were treated with Tamoxifen alone, Tamoxifen with LHRH analog in 12 patients, and AI with LHRH analog in 1 patient. There were 3 (15.8%) of pTis, 13 (68.4%) of pT1, and 3 (15.8%) of pT2, as well as 18 (94.7%)

of pN0 and 1 (5.3%) patients of pN1. The total response rate of patients to the solution during the study period was 84.5%. Each symptom has different response rates and MRS scores, from 70.2% for sex-related symptoms to 95.4% for joint pain, and from 1.24 out of 4 for sleep disturbances to 0.45 out of 4 for vaginal dryness. The match rate between mobile and paper surveys was 90.0%. The overall satisfaction score for the solution of patients was 8.06 out of 10, with the highest score (8.79 out of 10) given in terms of using patients' responses in outpatient appointments with the physician.

Conclusion

The analysis of MRS using this mobile solution in premenopausal BC patients undergoing postoperative ET is expected to be feasible for clinical use and should be analyzed in a large-scale study in the future.

PO3-12-07

Utility of Volumetric Measurement for Clinical Diagnosis of Breast Cancer-Related Lymphedema

Presenting Author(s) and Co-Author(s):

F. Bhimani. Montefiore Medical Center, New York, United States

S. Feldman. Montefiore Medical Center, United States

Y. Chen. Montefiore Medical Center, United States

A. Gupta. Montefiore Medical Center, United States

J. Pastoriza. Albert Einstein College of Medicine, Bronx, New York, United States

A. Shihabi. Montefiore Medical Center, United States

M. McEvoy. Montefiore Medical Center, United States

Background: Early detection of Breast cancer-related lymphedema (BCRL) is crucial since it can significantly reduce the negative impact on a patient's quality of life after breast cancer treatment. Several objective screening methods have been used in prior studies but have not proven accurate due to a lack of standardization. Bioimpedance spectroscopy (BIS), which assesses tissue resistance to an electric current and converts it into a score to measure interstitial fluid content, has proven to be an accurate tool in diagnosing lymphedema. SOZO[®] is a BIS device that generates quantitative results in real time and provides a Lymphedema Index (L-Dex) score by measuring the patient's extracellular fluid volume. However, there is a paucity of literature highlighting its clinical applicability. Thus, we aimed to evaluate the clinical utility of SOZO[®] in diagnosing BCRL in patients undergoing breast cancer surgery.

Materials & Methods: A retrospective chart review was carried out of patients who underwent axillary surgery from January 2019 to December 2022. Demographic information such as age, body mass index (BMI), gender, ethnicity, disease pathology, cancer stage, type of axillary surgery, neoadjuvant and adjuvant treatment received was recorded. Patients undergoing sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND) were assessed for their preoperative L-Dex score, and they were followed up postoperatively with repeated measurements of their L-Dex score to diagnose lymphedema for a year at 3 months intervals. Clinical lymphedema was defined as those having an absolute L-Dex score of more than +10 and an increase in L-Dex score by 6.5 from the baseline. SOZO[®] scores measured at each follow-up were compared to their preoperative baseline scores.

Results: A total of 200 patients' data was evaluated whose mean age and BMI were 57.5+10.9 years and 29.6+5.6 kg/m², respectively. Eighty-five percent of the patients belonged to ethnic minority groups. Furthermore, 84.5% (n=169) of the patients had SLNB, and 15.5% (n=31) had ALND. All the patients included in the study had their preoperative and postoperative quarterly L-Dex scores recorded. Pre- and post-operative L-Dex scores had a mean of -0.20+6.6 and 0.61+6.8, respectively. A total of 20 (10%) patients developed lymphedema without symptoms detected by SOZO[®], with 19 (9.5%) resolving at their respective 3-month follow-up and 1 (0.5%) patient with persistent lymphedema at the end of the 24-month follow-up. All 20 patients were treated with a compression sleeve. Of the 20 patients with lymphedema, 4 patients underwent ALND, whereas 16 patients had SLNB. When compared to their preoperative baseline scores, all patients' SOZO[®] measurements had an absolute score of more than 10 and an increase of 6.5 from their baseline score. Additionally, 21 other patients had an increase

in score of 6.5 from their baseline measurements but did not meet the cut-off range of an absolute score of +10. Therefore, we excluded them from the diagnosis of BCRL, and none of these patients later developed any signs of BCRL, such as swelling, pain, or discomfort.

Conclusion: SOZO[®] procedure can accurately detect BCRL. In our study, 1 patient developed clinical lymphedema after undergoing SLNB and was diagnosed using SOZO[®]. Additionally, 19 patients who were initially diagnosed with lymphedema were later categorized as transient due to the resolution of lymphedema on follow-up. Early identification of transient lymphedema using SOZO[®] resulted in the prevention of a potentially life-long debilitation in our patients. Moreover, our findings underscore that an increase in SOZO[®] score from the baseline by > 6.5 with an absolute score of more than +10 should be the threshold to clinically diagnose lymphedema. Future studies with larger sample sizes and longer follow-up duration are necessary to understand better the utility of SOZO[®] in diagnosing BCRL.

Table 1: Baseline characteristics and follow-up data of the patients included in the study.

Table 1: Baseline characteristics and follow-up data of the patients included in the study.

Total Patients	200
SLNB	169 (84.5%)
ALND	31 (15.5%)
Patients with lymphedema	
3-month	4 (2%)
6-month	7 (3.5%)
9-month	1 (0.5%)
12-month	0
15-month	1 (0.5%)
18-month	4 (2%)
21-month	2 (1%)
Total	20 (10%)
Resolution on 3-month	19 (9.5%)
Persistent lymphedema	1 (0.5%)

PO3-12-08

Hypersensitivity reactions to paclitaxel and carboplatin in breast cancer: safety and effectiveness of desensitization.

Presenting Author(s) and Co-Author(s):

R. Villarreal-González. Oncology Service, Centro Universitario Contra el Cáncer, Hospital Universitario "Dr. José Eleuterio González", Faculty of Medicine, Universidad Autónoma de Nuevo León., Nuevo Leon, Mexico

O. Vidal-Gutiérrez. Oncology Service, Centro Universitario Contra el Cáncer, Hospital Universitario "Dr. José Eleuterio González", Faculty of Medicine, Universidad Autónoma de Nuevo León., Nuevo Leon, Mexico

J. Martínez-Moyano. Oncology Service, Centro Universitario Contra el Cáncer, Hospital Universitario "Dr. José Eleuterio González", Faculty of Medicine, Universidad Autónoma de Nuevo León., Nuevo Leon, Mexico

M. Madrazo-Morales. Oncology Service, Centro Universitario Contra el Cáncer, Hospital Universitario "Dr. José Eleuterio González", Faculty of Medicine, Universidad Autónoma de Nuevo León., Nuevo Leon, Mexico

K. Sáenz-Cantú. Oncology Service, Centro Universitario Contra el Cáncer, Hospital Universitario "Dr. José Eleuterio González", Faculty of Medicine, Universidad Autónoma de Nuevo León., Nuevo Leon, Mexico

P. Rodríguez-Niño. Oncology Service, Centro Universitario Contra el Cáncer, Hospital Universitario "Dr. José Eleuterio González", Faculty of Medicine, Universidad Autónoma de Nuevo León., Nuevo Leon, Mexico

Introduction. Taxanes and platinums are first line treatment of breast cancer for early stages and metastatic disease and constitute the most commonly implicated chemotherapeutics in hypersensitivity reactions.¹ Clinical manifestations range from mild skin reactions to anaphylaxis.² Hypersensitivity reactions (HSR) to paclitaxel and carboplatin occur in a significant percentage of patients, with estimates of 30% and 40% respectively,^{3,4,5} leading to discontinuation of treatment.⁶ Using alternative drugs can be poorly tolerated or much less effective, entailing to high morbidity and mortality.⁷ Desensitization is the procedure performed to achieve a tolerance to the drug to which a HSR previously occurred, in order to maintain first-line treatment.⁸ The evaluation of the oncological response remains in the importance of assessing the shrinkage of the tumor and the time of progression of the disease.⁹

Objective: To describe the hypersensitivity reactions to paclitaxel and carboplatin, and the safety and effectiveness of desensitization protocols after anaphylaxis in patients with breast cancer.

Materials and Methods: Original, retrospective, descriptive, and analytical study, approved by the Bioethics and Research Committee ON23-00016 code, included patients >18 years with breast cancer who developed a hypersensitivity reaction to first-line chemotherapy and performed a 3-bag-12-step desensitization according to the Brigham and Women's Hospital, Dana Farber Institute, Boston protocol.

Results: Forty-five desensitization to paclitaxel or carboplatin were performed in 8 women with breast cancer, mean age 38.6 years. 6 patients developed HSR to paclitaxel, 83% of which

were in the first application, and 2 patients developed HSR to carboplatin after several cycles.

The most predominant symptom of HSR was cutaneous in 87% of the cases, and all patients presented cardiovascular HSR to paclitaxel.

No patients developed HSR during desensitization. Currently, only 1 patient developed disease progression, while the rest presented a complete response to treatment.

Discussion. HSR to paclitaxel appear in the 1-2 cycle,¹⁰ while to platinum after various exposures (>6 cycles) similar to our study.^{3,4} The symptoms associated with paclitaxel are cardiovascular^{10,11} while urticaria is the most frequent in carboplatin.^{3,11} The desensitization protocol implemented did not develop HSR in any of the patients. Neoadjuvant chemotherapy in breast cancer has been shown to yield better disease-free interval results alongside improved pathological response.¹²

Conclusions. The program implemented in our hospital's chemotherapy desensitization clinic, replicating the model of the Dana-Farber Cancer Institute, Brigham, and Women's Hospital in Boston, has enabled cancer patients to continue with first-line treatment, thus improving their prognosis and quality of life, opening new areas of opportunity in the multidisciplinary management of these patients to improve overall survival.

Characteristics of patients with hypersensitivity reactions

Patient	1	2	3	4	5	6	7	8
Gender	Female	Female	Female	Female	Female	Female	Female	Female
Age	38	45	48	32	37	38	45	27
Atopy	Yes	Yes	No	Yes	No	No	No	No
Drug	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Carboplatin
HSR cycle	1	1	1	1	1	2	10	7
Symptoms								
Cutaneous	Urticaria	Urticaria	No	Flushing	Flushing	Pruritus	Urticaria	Urticaria
Cardiovascular	Hypotension, bradycardia	Chest pain	Chest pain	Hypertension, presyncope	Chest pain, hypertension	Chest pain	No	Tachycardia
Respiratory	Dyspnea	Dyspnea, wheezing	Wheezing	Dyspnea	Dyspnea	No	No	Dyspnea
Oropharyngeal	No	Yes	No	Yes	No	Yes	No	No
Gastrointestinal	Nausea/vomiting, abdominal pain	Nausea/vomiting, abdominal pain	No	Nausea/vomiting	Abdominal pain	No	No	Nausea/vomiting
Neuromuscular	Back pain	Visual disturbances	Back pain	Back and pelvic pain	Head and pelvic pain	No	No	No
Atypical	No	No	No	No	Chills and rigors	No	No	No
Brown classification ⁸	3	2	2	3	2	2	1	2
Desensitization cycles	12	12	9	2	2	1	6	1
HSR during desensitization	No	No	No	No	No	No	No	No
Oncologic diagnosis	Infiltrating ductal carcinoma	Infiltrating ductal carcinoma	Infiltrating ductal carcinoma	Infiltrating ductal carcinoma	Infiltrating ductal carcinoma	Infiltrating ductal carcinoma	Infiltrating ductal carcinoma	Infiltrating ductal carcinoma
Clinical stage	IB	IA	IA	IB	IB	IA	IV	IIC
TNW	T2N1cM0	T2N0Mx	T1aN1M0	T4cN2M0	T2N1M0	T2N0M0	T4cN2M1	T2cN2M0
Metastasis	No	No	No	No	No	No	Pulmonary	No
Surgery	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Radiotherapy	Yes	No	Yes	Yes	Yes	ND	Yes	Yes
Disease free intervals	29m (2.4 yrs)	ND	50m (4.2 yrs)	10m	11m	64m (5.3 yrs)	ND	11m
RECIST 1.1	Complete response	ND	Complete response	Complete response	Complete response	Complete response	Progression	Complete response

HSR: hypersensitivity reactions

ND: No data

m: months

yrs.: years

Desensitization protocol to Paclitaxel IV (300 mg)

	Volume per bag	Concentration (mg/mL) per bag	Amount (mL) of bag infused	Dose infused (mg) per bag
Solution 1	250	0.012	9.38	0.112
Solution 2	250	0.12	18.75	2.25
Solution 3	250	1.191	250	297.63

Step	Solution	Rate mL/h	Time (min)	Volume infused (mL)	Dose infused (mg)	Cumulative dose (mg)
1	1	2.5	15	0.625	0.0075	0.0075
2	1	5	15	1.25	0.015	0.0225
3	1	10	15	2.5	0.03	0.05
4	1	20	15	5	0.06	0.11
5	2	5	15	1.25	0.15	0.26
6	2	10	15	2.5	0.3	0.56
7	2	20	15	5	0.6	1.16
8	2	40	15	10	1.2	2.36
9	3	10	15	2.5	2.98	5.34
10	3	20	15	5	5.96	11.3
11	3	40	15	10	11.91	23.21
12	3	80	174.4	232.5	276.79	300 mg
Total dose: 300 mg						Total time: 5.67 h

IV: intravenous
mg: milligram
mL: milliliter
h: hour

PO3-12-09

De-Escalating Extent of Sentinel Lymph Node Biopsy in Patients with Ductal Carcinoma in Situ Undergoing Mastectomy

Presenting Author(s) and Co-Author(s):

A. Ayub. Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, United States

K. Senol. Uludag University, Medical Faculty, General Surgery, Bursa, Turkey

M. Eleftherios. Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, United States

M. Cowher. Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, United States

R. Johnson. UPMC Magee Women's Hospital, United States

K. Lupinacci. Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, United States

Q. Sabih. University of Pittsburgh, United States

J. Steiman. UPMC Magee Women's Hospital, United States

E. Diego. University of Pittsburgh, United States

P. McAuliffe. UPMC Magee-Womens Hospital, United States

A. Soran. UPMC Department of Surgery, Breast Health Working Group International, United States

Background: Sentinel lymph node (SLNB) biopsy for axillary staging in patients (pts) with ductal carcinoma in situ (DCIS) undergoing mastectomy is debated due to low positivity rate and potential morbidity. Standard SLNB entails removing all LNs with a radioactive count >10% of the most radioactive node, contain blue dye or are palpably suspicious. In this study, we hypothesize that judicious SLNB with attempt to remove only the SLN with the highest radioactive count provides sufficient pathologic information while minimizing morbidity.

Method: A single institution prospective database was retrospectively reviewed to identify women with core biopsy showing DCIS (cTis) who underwent mastectomy and SLNB between 2010–22. Pt characteristics, number of SLNs retrieved, pathologic results and long-term upper extremity complications were collected.

Results: A total of 743 LN's were removed in 324 pts. Median [IQR] age was 62 [51–70] years. Dual tracer technique, with Technetium-99m labeled radiocolloid and blue dye, was used in 311 (96%) pts, whereas single agent (radioisotope or blue dye alone) was utilized in 9 (2.8%) and 4 (1.2%) pts respectively. Median [IQR] number of SLN removed was 2 [1-3] (range 1-9). In 99% of cases, the SLN with the highest radioactive count was identified among the first 3 dissected LNs. Final pathology revealed upstaging to invasive cancer in 27.5% (n=89) of the breasts and nodal positivity in 1.9% (n=6) of the patients. In all 6 cases, metastatic disease was identified in the LN with highest radioactive count among the LNs retrieved. No additional metastatic nodes were identified after >3 SLN had been removed. At median follow-up of 57 (range 28-87) months, 8.3% (n=27) of pts complained of long-term upper extremity symptoms. 7.1% (23 pts) were referred to physical therapy for symptoms such as swelling, fullness, heaviness, stiffness or sensory discomfort in the upper extremity and/or axillary cording. Long-term upper extremity complications were higher when >3 SLNs compared to <3 SLNs were removed (10.4% vs

6.5%, p=0.005).

Conclusion: In this cohort of pts with DCIS (cTis) undergoing mastectomy who had upstaging on final pathology to invasive cancer with LN involvement, the SLN with the highest radioactive count provided sufficient information for axillary staging. Acknowledging that the “hottest” LN is not always the first one removed, these data support an increased likelihood of developing long-term complications when more than three SLNs are removed. Rather than comprehensive removal of all SLNs meeting the standard “10% rule,” prioritizing the sequence of removal to the highest count provides the same prognostic information with reduced morbidity.

Table 1

Variable	(N = 324)
Age [IQR]	62 [51-70]
Race	
White	292 (90.1%)
Black	21 (6.5%)
Other	11 (3.4%)
LN yield	
Median [IQR], range	2 [1-3], 1-9
≤3	276 (85.2%)
>3	48 (14.8%)
Number of pts with positive LN	6 (1.9%)
Final pathology on mastectomy	
DCIS	235 (72.5%)
Invasive	89 (27.5%)
Follow-up, mo [IQR]	57 [28-87]
Complications (swelling, fullness, heaviness, axillary cording)	23 (7.1%)

Patient and lymph node characteristics

PO3-12-10

Cryotherapy to Prevent Taxane-Induced Sensory Neuropathy of the Hands and Feet

Presenting Author(s) and Co-Author(s):

P. Advani. Mayo Clinic, United States

J. Harvey. Mayo Clinic Florida, Florida, United States

I. Vilches. Mayo Clinic, United States

A. hochwald. Mayo Clinic, United States

D. Hodge. Mayo Clinic, United States

A. Arnold. Mayo Clinic, United States

M. weidner. Mayo Clinic, United States

D. Haley. Mayo Clinic, United States

T. Pai. Mayo Clinic, United States

S. Chumsri. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

R. Rao. Mayo Clinic, Jacksonville, United States

K. Sideras. Mayo Clinic, Jacksonville, Florida, United States

C. Tofthagen. Mayo Clinic, United States

A. Moreno-Aspitia. Mayo Clinic, Jacksonville, Florida, United States

Background: Taxane based chemotherapy (chemo) forms a critical part of breast cancer (BC) treatment in early and metastatic settings. Taxanes can cause peripheral neuropathy (CIPN)-sensory and motor, primarily of the hands and feet, resulting in quality of life decline and negative impact on BC survival. Acral cryotherapy has shown benefit in reducing in minimizing the incidence and severity of CIPN. However, these studies have included limited number of patients (pts) with inconclusive evidence to change US practice guidelines, have been primarily conducted in Asia, and did not include racially diverse patients.

Methods: We conducted a single arm non randomized study at Mayo Clinic that included early BC pts who underwent standard of care paclitaxel or docetaxel based chemo. Pts had ECOG performance status 0-2, no sensory peripheral neuropathy at study entry and were able to give signed informed consent. Pts with metastatic BC, Raynaud's and peripheral vascular disease, cryoglobulinemia, cold intolerance, prior exposure to neurotoxic or taxane chemotherapy were excluded. Participating pts wore frozen gloves and socks (-20 to -10°C) on both hands and feet, 15 min before, during and until 15 min post taxane infusion. During chemo, grade (G) of CIPN (sensory) per CTCAE v5 was collected prior to each cycle of chemo, end of and 3 months after chemo. Schedule of events is listed in Table 1. Continuous variables were summarized using mean and standard deviation, and categorical variables were summarized with number and percentage of patients. Numeric variables were compared with t tests (paired and unpaired), and categorical variables were compared with Chi-Squared test for independent data and McNemar's test for dependent data. All statistical tests were two-sided and were performed using R Statistical Software (version 4.1.2; R Foundation for Statistical Computing).

Results: A total of 95 patients were included in this study. Median age is 54 years, 66.3% pts were White (W), 23.2% African American (AA), 4.2% Asian (A) and 4.2% Hispanic (H). Median BMI was 27.7. Most pts had stage I/II (75.8%), ER positive (64.9%) and HER2 negative

(55.3%) BC and got adjuvant chemo (52.6%). Only 10.6% pts had diabetes, 55.3% used alcohol. Vitamin D3 use seen in 65.6%, B12 in 6.2% and folate, B12 and D3 in 6.2% pts. A total of 41 pts (44.1%) developed neuropathy at some point during chemo, of which 27 pts were W (43%), 10 pts AA (45%), 2 pts H, 1 Asian and 1 other. CIPN was G1 in 37 pts (90%). G2 CIPN was seen in 4 pts, at or after cycle 10 of weekly paclitaxel. Cold intolerance was seen in 24 pts (25%), G1 in 20 and G2 in 4 pts, all seen in cycle 1 with 1 pt withdrawal. Recovery to G0 was seen in 15 W pts at chemo end and 2 additional pts at 3 month after chemo. None of the AA pts, one H and one A pt had CIPN recovery to G0. In 4 AA pts who had G1 CIPN during chemo, G2 CIPN was noted at 3 month follow up. No Statistically significant differences in baseline characteristics and neuropathy results for W vs nonwhites (NW) were seen except Charleson score (p-value 0.023).

Conclusion: Acral cryotherapy was found to be effective in reducing the incidence and severity of CIPN from taxane in our study. This is the only study with diverse racial/ethnic pt inclusion and incidence of CIPN was similar in W and NW. However, majority of G2 CIPN pts were AA and recovery to G0 CIPN was not seen in AA pts. Majority (63%) of W pts recovered to G0 at end of follow up. Analysis of objective testing of all pts is underway. Continued research into risk factors for AA pts to develop CIPN and its mitigation are warranted.

	Baseline	End of chemotherapy	3 months post chemotherapy
Consent	X		
FACT-G questionnaire (Q)	X	X	X
FACT/GOG-NTX Q	X	X	X
CIPN-R-ODS	X	X	X
Timed Up and Go Test	X	X	X
Quantitative Sensory Testing	X	X	X
Clinical Data and CIPN grade	X	X	X

PO3-12-11

A phase-3 randomized controlled study to evaluate the role of hydroxyprogesterone in prevention of chemotherapy induced neurotoxicity in women with breast cancer.

Presenting Author(s) and Co-Author(s):

R. Badwe. Tata Memorial Centre, Mumbai, India

S. Joshi. Tata Memorial Hospital, United States

R. Hawaldar. Tata Memorial Centre, United States

T. Panhale. Tata Memorial Hospital, United States

N. Nair. Tata Memorial Centre, Mumbai, India

S. Sawant. Tata Memorial Centre, Mumbai, India

V. Vanmali. Tata Memorial Hospital, United States

M. Engineer. Tata Memorial Centre, Mumbai, India

A. Daptardar. Tata Memorial Centre, Mumbai, India

V. Parmar. Tata Memorial Centre, United States

S. Gulia. Tata Memorial Centre, United States

S. Gupta. Tata Memorial Center, United States

Introduction Chemotherapy induced peripheral neuropathy (CIPN) is seen in 60% breast cancer patients who receive paclitaxel-based chemotherapy with no conclusively known pathophysiology. Hydroxyprogesterone is known to have neuroprotective and neuro-regenerative potential. We conducted a randomized controlled trial assessing the role of hydroxyprogesterone in reducing the incidence and severity of CIPN. **Methodology** Histologically proven, post-menopausal, non-metastatic breast cancer patients without pre-existing neuropathy, planned to receive paclitaxel (with or without trastuzumab) in the adjuvant or neoadjuvant setting were screened and consented. They were randomized to receive depot hydroxyprogesterone injection 500 mg followed by 250 mg injection every 2 weekly (trial arm) versus 1 ampoule (2 ml) of vitamin-B complex (B1-100mg, B6-100mg and B12-1000µg) injection every 2 weekly (control arm) during the entire course of paclitaxel-based chemotherapy. The primary end point was cumulative incidence of grade II-IV CIPN, at the last cycle of chemotherapy as assessed by CTCAE-V4. Secondary end point was EORTC-QLQ-CIPN20 assessment 8 weeks after last cycle of chemotherapy. Patients were stratified for stage, diabetes mellitus, and frequency of paclitaxel administration. Sample size was calculated for a 20% reduction in CIPN from 60% with $\alpha=0.05$ and power of 80%, for 2-sided significance of $p=0.05$, with a drop-out rate of 10%. **Results** A total of 240 patients were randomized between November 2015 and February 2023- 120 each on the trial and control arm. The median age was 54 (43-73) and 55 (43-74) years; 35% and 31.7% patients were early breast cancer (cT1-2, N0-1) in the trial and control arms respectively. The median pT size was 2.6 cm and 65% patients were node positive overall. The incidence of grade II-IV CIPN (motor and/or sensory) at the end of chemotherapy was 55.9% and 56.8% in the trial and control arms respectively ($p=0.90$, 95%CI-0.12-0.13). Overall, chemotherapy related adverse events (CTCAE-V4) were seen in 41.39 and 39.9% in trial and control arms respectively. The average EORTC-QLQ-CIPN20 score at 8 weeks after last cycle of chemotherapy for motor neuropathy was 11.18 (0-70) and 13.53 (0-74), for sensory neuropathy was 8.51 (0-76) and 9.27 (0-81) and that for autonomic neuropathy was 4.94 (0-67) and 4.65 (0-67) in the trial and control arms respectively ($p=NS$). **Conclusion** Hydroxyprogesterone did not reduce the incidence of paclitaxel related CIPN when assessed immediately post-chemotherapy. The absolute

incidence of CIPN (any grade) was 61% in our study which is like that reported in literature. Long term follow-up of these patients will assess the recovery of CIPN and long-term impact of the study interventions on CIPN. The study was approved by Institutional Review Board and Drug Controller General of India (CTRI/2015/11/006381).

PO3-12-12

Axial Neuropathy in Two Breast Cancer Patients receiving Fam-trastuzumab deruxtecan: A Case Report

Presenting Author(s) and Co-Author(s):

L. Botero. Montefiore Einstein Cancer Center, United States

K. McNeill. Montefiore Einstein Cancer Center, United States

D. Makower. Montefiore Medical Center, United States

Introduction. Fam-trastuzumab deruxtecan (T-DXd) is FDA approved for metastatic HER2-positive (HER2+) and HER2-low breast cancer (BC). Peripheral neuropathy is a side effect of T-DXd, with an incidence of 13%. Here we discuss two BC patients (pts) who presented with paresthesias of the trunk after receiving T-DXd.

Case 1. A 51-year-old female with Stage IIIB cT4N2M0 left BC, estrogen receptor positive (ER+), progesterone receptor positive (PR+) and HER2+ was treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP), followed by mastectomy and axillary lymph node dissection, with downstaging to ypT3N2a disease. She was enrolled on a clinical trial comparing T-DXd with standard treatment for HER2+ BC with residual disease after neoadjuvant therapy, and was randomized to T-DXd arm. She also received adjuvant proton radiation therapy to the chest wall. One week after her third cycle of T-DXd she developed Grade 3 paresthesias on her trunk and proximal upper and lower extremities, stating she could not bend over or perform activities of daily living. She did not experience associated weakness or peripheral neuropathy. Symptoms improved to Grade 1 after initiation of gabapentin and delay of cycle 4 T-DXd by one week. She resumed T-DXd with dose reduction per protocol, and increase in gabapentin dose. She was seen by neurology who localized her sensory findings to T5-T9. She was recommended to undergo MRI spine, but was unable to do so, due to presence of tissue expander. Paresthesias have been controlled on dose reduced T-DXd and continued gabapentin.

Case 2. A 56-year-old female with ER+, PR+, HER2-negative BC initially diagnosed in 1990, with local recurrence in 2005, treated with mastectomy, adjuvant chemotherapy, and adjuvant endocrine therapy, followed by development of metastatic disease to lung, liver, bone and skin in 2017. She received multiple lines of endocrine therapy, including aromatase inhibitors and fulvestrant, with cdk4/6 inhibitors and everolimus, but either progressed or was intolerant to all treatments. Skin biopsy in 2022 confirmed metastatic BC, which was ER+, PR+, and HER2 low (IHC2+, FISH nonamplified). She then received T-DXd, with clinical and radiographic response to treatment. After cycle 8 T-DXd, the patient was hospitalized for severe burning pain of her trunk and skin. Radiologic evaluation, including CT chest, abdomen, pelvis, and MRI spine, did not show an etiology of her pain, and showed stable metastatic disease to liver and bones, without evidence of cord or nerve root compression. Symptoms improved on pregabalin. She received an additional cycle of T-DXd with dose reduction, but ultimately declined further treatment. Symptoms resolved within 5 months of discontinuation of T-DXd.

Discussion. These cases represent unusual events of axial neuropathy in two BC patients receiving T-DXd. Given the similarity of their symptoms, these findings may represent an unusual adverse effect of T-DXd. As the indications for T-DXd continue to expand, clinicians should be aware of this uncommon potential toxicity.

PO3-13-01

ONTARGET: Phase 3 randomized, double-blind, placebo-controlled trial evaluating crofelemer for the prophylaxis of diarrhea in adult patients with solid tumors receiving targeted therapies with or without standard chemotherapy

Presenting Author(s) and Co-Author(s):

L. Schwartzberg. William N. Pennington Cancer Institute - Renown Health, United States

P. Okhuysen. The University of Texas MD Anderson Cancer Center, Houston, TX, Houston, Texas, United States

E. Roeland. Oregon Health & Science University, United States

G. Vidal. The West Clinic, Germantown, United States, United States

K. Harnden. Inova Schar Cancer Institute, United States

R. Zuniga. New York Cancer and Blood Specialists, Port Jefferson, NY, United States

S. Bosnjak. Institute for Oncology and Radiology of Serbia, Belgrade, Serbia, United States

S. Daggubati. Texas Oncology, San Antonio Region, TX, United States

D. Bursac. Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica,, United States

Background: Cancer therapy-related diarrhea (CTD) can result in fluid and electrolyte losses, malnutrition, unexpected hospitalization, and poor quality of life (QoL) of patients with cancer. CTD can also limit response to cancer therapy due to treatment interruption, discontinuations, or dose modifications. CTD is a common side effect of targeted therapies (TTx) (e.g., inhibitors of tyrosine kinases, EGFR, CDK4/6, VEGFR) with or without concomitant chemotherapy (ChemoRx) for treating various solid tumors, including breast cancer (BRCA). TTx induce CTD by increasing intracellular cAMP or Ca⁺⁺ leading to activation of two intestinal Cl⁻ channels, CFTR and CaCC, increasing luminal secretion of Cl⁻ and accompanying loss of Na⁺ and fluids. For most patients with cancer, CTD management with dietary modifications and antimotility agents is suboptimal. New drugs are needed to prevent or mitigate CTD, a huge unmet medical need.

Since the mechanism of CTD is mostly secretory, we hypothesized that crofelemer (CRO) an oral botanical drug purified from the latex of the *Croton lechleri* tree that modulates both intestinal Cl⁻ ion channels, CFTR and CaCC, may benefit preventing CTD. CRO is negligibly absorbed orally and is FDA-approved for symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy. In a phase 2 study in 51 women with BRCA receiving THP/TCHP (HALT-D), CRO given daily, compared to standard of care (SOC), for 2 cycles resulted in grade ≥ 2 diarrhea in significantly fewer subjects (9.0% vs. 33.3%, $p=0.0361$) in cycle 2 and was 1.8 times more likely to resolve diarrhea ($p=0.0425$) (Pohlmann et al. 2022; NCT02910219)

Methods: ONTARGET ([NCT04538625](https://clinicaltrials.gov/ct2/show/study/NCT04538625)) is a randomized, multicenter, international, double-blind, placebo-controlled pivotal trial evaluating CRO for the prophylaxis of diarrhea in adults with solid tumors receiving 1 of 24 diarrheagenic TTx known to cause any grade diarrhea in $\geq 50\%$ of patients. This study is designed to show a 40% reduction in loose/watery (LW) stools in patients randomized 1:1 CRO to placebo (1-sided $\alpha=0.025$) and stratified by tumor type (lung, breast, other) and TTx type (CDK4/6i, TKIs, or other). Eligible patients require a new TTx, ECOG 0-2, lack baseline diarrhea and can complete patient-reported outcome (PRO) diary using a mobile device. Key exclusions include immunotherapy, neratinib or irinotecan (due to

required SOC antimotility prophylaxis), colitis/ostomy/abdominal surgery ≤ 3 months, or antidiarrheal/laxative/antibiotic use ≤ 7 days. Oral CRO 125 mg or a matching placebo is administered twice daily concomitant with TTx initiation and continued for 12 weeks, with the option to continue blinded treatment through 24 weeks. Rescue antidiarrheal medication is permitted when participants have ≥ 4 LW stools and can continue thereafter. PRO diaries capture clinical and QoL outcomes. The primary endpoint is the mean weekly number of LW stools over 12 weeks based on PRO diary using the Bristol Stool Form Scale. Key secondary endpoints include time to TTx/ChemoRx dose reduction or discontinuation, time to ≥ 4 LW stools for 2 consecutive days, fecal incontinence episodes, and time to durable responder status (≤ 7 LW stools/week). PRO diaries capture: 1) LW stool frequency daily; 2) TTx/ChemoRx dose reduction/discontinuation, use of antimotility drugs, fecal incontinence daily; and 3) CTD's impact on QoL weekly.

Results: Enrollment is complete with 287 patients from 46 sites in 5 countries from 8/2020 through 5/2023. Primary cancer diagnoses were breast (183; 64%), lung (37; 13%), renal (36; 12.5%), liver (12; 4%) and other (19; 6.5%). Most frequent TTx were CDK 4/6 and EGFR inhibitors. To our knowledge this trial evaluating CRO is the first prospective, randomized double blind study for prevention of targeted therapy CTD. Topline results for the study are expected in Q4 2023 and will be reported at the meeting.

Funded by Napo Pharmaceuticals (a Jaguar Health Co.)

PO3-13-02

Genomic and intrinsic subtype correlates of serum thymidine kinase activity in patients with metastatic breast cancer treated with palbociclib and fulvestrant in the PYTHIA trial

Presenting Author(s) and Co-Author(s):

S. Tyekucheva. International Breast Cancer Study Group Statistical Center, Department of Data Science, Dana-Farber Cancer Institute and Department of Biostatistics, Harvard T.H. Chan School of Public Health,, Boston, Massachusetts, United States

T. Crestani. Breast International Group, Belgium

M. Ignatiadis. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Brussels Hoofdstedelijk Gewest, Belgium

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

M. Colleoni. Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Lombardia, Italy

S. Henry. CHU UCL Namur - Site Ste Elisabeth, United States

K. Papadimitriou. Multidisciplinary Oncologic Centre Antwerp (MOCA), Antwerp University Hospital, Antwerp, Belgium

A. Bernardo. ICS Maugeri, United States

E. Seles. Ospedale Degli Infermi, Ponderano, Italy

F. Duhoux. Cliniques Universitaires Saint-Luc, Bruxelles, Belgium, United States

I. Macpherson. University of Glasgow - Institute of Cancer Sciences, United Kingdom

A. Thomson. Royal Cornwall NHS Trust, United States

D. Davies. Department of Oncology, South West Wales Oncology Center, Swansea, United Kingdom

M. Bergqvist. Biovica International AB, United States

I. Migliaccio. Translational Research Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

G. Zoppoli. Department of Internal Medicine and Medical Specialties DiMI, University of Genoa, Italy

R. Kammler. ETOP IBCSG Partners, Bern, Bern, Switzerland

H. De Swert. Breast International Group (BIG)-aisbl, Brussels, Belgium, Brussels, Belgium

B. Ruepp. ETOP IBCSG Partners Foundation, Coordinating Center, Bern, Switzerland

A. Guerrero. Instituto Valenciano de Oncologia, Spain

A. Llinas. Cancer Computational Biology Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

D. Fimereli. Breast Cancer Translational Research Laboratory J.-C. Heuson, Institut Jules Bordet, Belgium

A. Arahmani. Breast International Group (BIG)-aisbl, Brussels, Belgium, Brussels, Belgium

D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

M. Piccart. Institut Jules Bordet, Anderlecht, Brussels Hoofdstedelijk Gewest, Belgium

M. Regan. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

M. Benelli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

L. Malorni. Translational Research Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy, United States

Background: Serum thymidine kinase activity (sTKa) is a novel non-invasive proliferation biomarker providing prognostic, predictive and monitoring information in patients (pts) with metastatic breast cancer (MBC). We have shown in PYTHIA that high baseline sTKa and lack of sTKa clearance at day 15 of the first cycle of treatment with palbociclib (P)+ fulvestrant (F) are poor prognostic factors in terms of PFS. Here we characterized the molecular features of tumor samples from PYTHIA, and their relation with sTKa. **Methods:** PYTHIA (IBCSG 53-14/BIG 14-04; NCT02536742) is a phase II biomarker discovery trial downstream of the AURORA molecular program (BIG 14-01; NCT02102165) which enrolled 122 pts with endocrine-resistant, ER+ and HER2 - MBC receiving P+F. Intrinsic subtypes of metastatic samples from 24 pts were estimated using RNA-Seq. Somatic mutations (mut) from 66 pts were identified using an NGSpanel of 411 cancer-related genes (36 primary and 48 metastatic samples). sTKa was measured using DiviTum^o TKa (Biovica International) before treatment (D0) and at day 15 (D15) of cycle 1 of P+F. sTKa clearance at D15 was defined as sTKa below the limit of detection (LOD). Intrinsic subtypes and ESR1 mut were assessed in metastatic samples, PIK3CA and TP53 mut were derived from a combined cohort, wheremetastatic samples were used when available and primary samples otherwise. Association of mut and continuous sTKa with PFS was assessed using Cox regression. **Results:** In metastatic samples, sTKa levels at D0 tended to be higher in luminal B and HER2-enriched subtypes. Lack of sTKa clearance at D15 was observed in 14% of the cases, all classified as luminal B. PIK3CA and TP53 were the most frequently altered genes (38% and 27%, respectively). ESR1 mut were found in 8% of primary and 25% of metastatic samples. Only TP53 was associated with worse PFS. sTKa levels at D0 tended to be higher in pts with TP53 mut vs wild-type (wt) and lower in PIK3CA mut vs wt. Interestingly, lack of sTKa clearance at D15 was more frequent in TP53 mut vs wt and less frequent in PIK3CA mut vs wt. Levels of sTKa were similar in pts with ESR1 mut vs wt both at D0 and at D15 (Table 1). The inclusion of TP53 as a predictor of PFS in bivariate Cox models with sTKa at either D0 (likelihood ratio test p=0.44) or D15 (p=0.21) did not add to the prognostic value provided by sTKa alone. **Conclusions:** Tumors with high proliferation and poor prognostic features (luminal B, HER2-enriched and TP53 mut) tend to have higher baseline sTKa and less sTKa response on-treatment, in line with sTKa being a circulating dynamic biomarker of tumor cell proliferation. After accounting for sTKa values, TP53mutational status did not contribute to prognosis. This suggests that high sTKa at D0 and lack of sTKa clearance at D15 might be associated with a worse prognosis independently of TP53 status. Further validation in larger datasets is warranted.

Table 1: Results summary

	DL N (%)	*TKa DD (Mean)† median (IQR)	P-val* †	D15 N (%)	Lack of TKa D15 clearance	P-val**	Univariate association with PFS: HR (95% CI), P-val
Her2/neu subtype							
LumA	3 (12.5%)	<LOD (-<LOD, 50)		3 (14%)	0 (0%)		Not assessed
LumB	32 (50%)	222 (85, 457)		33 (52%)	3 (27%)		
HER2+	7 (29%)	87 (43, 213)		5 (24%)	0 (0%)		
Basal	2 (8.5%)	49 (13, 64)		2 (10%)	0 (0%)		
total	24 (100%)	144 (62, 252)		21 (100%)	3 (14%)		
TPS2 mut	38 (27%)	158 (87, 918)	0.07	35 (26%)	3 (3%)	0.33	3.82 (1.02, 9.24), P 0.04
TPS2 wt	48 (63%)	84 (21, 270)		43 (24%)	6 (14%)		
total	66 (100%)			58 (100%)			
PIK3CA mut	20 (48%)	75 (13, 220)	0.35	23 (48%)	0 (0%)	0.008	0.77 (0.44-0.94), P 0.87
PIK3CA wt	41 (52%)	344 (16, 1035)		32 (42%)	3 (10%)		
total	66 (100%)			58 (100%)			
ESR1 mut	32 (25%)	149 (79, 1043)	0.4	30 (24%)	2 (2%)	3	3.31 (0.66-2.65), P 0.44
ESR1 wt	36 (27%)	91 (27, 233)		28 (46%)	7 (27%)		
total	48 (100%)			42 (100%)			

*-Wilcoxon test; **-Fisher's exact test; †-LOD: 20 Divisum unit (Dsu)/A

PO3-13-03

RNAScope: a practical approach and promising alternative to immunohistochemistry to quantify HER2 expression in breast cancer

Presenting Author(s) and Co-Author(s):

X. Li. Emory University, United States

J. Lee. Georgia Institute of Technology, United States

Y. Gao. Emory University, United States

J. Zhang. Emory University, United States

K. Bates. Yale School of Medicine, United States

D. Rimm. Yale University, New Haven, Connecticut, United States

H. Zhang. University of Rochester Medical Center, Rochester, NY, USA, United States

G. Smith. Emory University, United States

D. Lawson. Emory University, United States

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

J. Chang. Houston Methodist Hospital, United States

L. Huo. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T-DXd has been approved by the FDA to treat patients with metastatic HER2-low and -positive breast cancer. The utility of current HER2 immunohistochemistry (IHC) assays in evaluating HER2-low tumors is not clear. A simple and objective method to evaluate HER2 expression in breast cancer is urgently needed. RNAScope can detect HER2 RNA levels by in situ hybridization using one regular unstained FFPE slide and processed using the Leica BOND-III autostainer that is readily available in many clinical laboratories. RNA level detected by RNAScope can be quantified by dots/cell using publicly available software. Therefore, RNAScope is a practical assay and could be a promising alternative to IHC to quantify HER2 levels in breast cancer.

We evaluated HER2 levels in 605 breast cancer tissue microarray cores using RNAScope and the two most commonly used FDA approved HER2 IHC assays: Ventana PATHWAY (PATHWAY) and Dako HercepTest (HercepTest). Clinical data were available for 505 cores from 347 patients. RNA level (dots/cell) by RNAScope was quantified using publicly available software QuPath. IHC assays were scored as 0, ultralow (UL, >0% but ≤10% incomplete membranous staining), 1+, 2+ and 3+. In addition, HER2 protein levels (AQUA protein level) were quantified from 100 cores through regression analysis, using AQUA score against cell line arrays with pre-calibrated HER2 protein levels determined by mass spectrometry. We used ANOVA to assess the differences in RNAScope results among the five IHC scores, and linear regressions to correlate RNAScope with HER2 AQUA protein levels. We finally evaluated 41 RNAScope whole-slide images (IHC 1+: n=5; 2+: n=26; 3+: n=10) of metastatic tumors from 31 patients treated with T-DXd.

No significant differences of RNAScope results were observed among the 0, UL, and 1+ cores in both IHC assays, indicating the current IHC assays cannot differentiate HER levels in HER2-low tumors. However, statistically significant differences ($p < 0.0001$) were found among the IHC 1+, 2+, and 3+ cores and higher RNAScope dots/cell was associated with higher stage of the tumors. There was a strong correlation ($R^2 = 0.610$) between the RNAScope results and

quantitative HER2 AQUA protein level in the 100 cores. There were significantly higher HER2 RNA levels in the 41 metastatic biopsies with higher IHC scores ($p < 0.05$). When we used RNAScope to measure HER2 levels in metastases right before T-DXd treatment, there was numerically ($p = 0.881$) higher HER2 RNA levels in responders (5.60 ± 8.82 dots/cell) vs non-responders (5.20 ± 5.31). Interestingly, the HER2 RNA levels in bone metastases was statistically higher ($p = 0.030$) in non-responders (5.24 ± 2.87 , $n = 3$) than in responders (1.55 ± 0.81 , $n = 5$); although number of patients was low. For the non-bone metastases (esophagus, lymph node, liver, brain, lung), HER2 RNAScope values were numerically higher ($p = 0.261$) in responders (9.65 ± 2.87 , $n = 5$) than non-responders (5.19 ± 5.74 , $n = 15$). In these non-bone metastatic cases, the response rates by IHC scores were 100% in 1+ cases, 24% in 2+ and 33% in 3+. When we used AI assisted categories based on RNAScope results, the response rates were 20% in RNAScope 1+ cases, 20% in 2+, 50% in 3+ cases.

Our study shows that current IHC assays are unable to differentiate HER2 levels between IHC 0 and 1+ breast cancer cases, which is a critical issue in properly identifying patients who will benefit from T-DXd treatment. RNAScope results strongly correlate with HER2 protein levels and showed similar RNA levels among IHC 0 and 1+ cases. RNAScope is a simple and objective assay to quantify HER2 levels by dots/cell using publicly available software and may help better identify which patients benefit from T-DXd treatment. Other factors besides HER2 level may also contribute to the response rate in patients treated with T-DXd.

RNAScope results in association with immunohistochemistry (IHC) scores by PATHWAY, HercepTest, and in biopsies from patients treated with T-DXd (T-DXd cohort).

IHC Score	RNAScope dots/cell				
	0	UL	1+	2+	3+
PATHWAY	0.33 ± 0.59 ($n = 189$)	0.34 ± 0.42^{ns} ($n = 46$)	0.45 ± 0.43^{ns} ($n = 72$)	$4.4 \pm 4.6^{****}$ ($n = 17$)	$17.0 \pm 10.6^{****}$ ($n = 23$)
HercepTest	0.35 ± 0.62 ($n = 180$)	0.28 ± 0.29^{ns} ($n = 59$)	0.49 ± 0.52^{ns} ($n = 72$)	$6.6 \pm 6.0^{****}$ ($n = 15$)	$17.0 \pm 11.0^{****}$ ($n = 21$)
T-DXd cohort	NA	NA	1.8 ± 1.7 ($n = 5$)	$4.1 \pm 4.0^*$ ($n = 20$)	$8.2 \pm 11.3^*$ ($n = 5$)

No significant (ns) difference of RNAScope dots/cell were seen among 0, UL and 1+ cases by both PATHWAY and HercepTest assays. There were significant differences of dots/cell comparing 1+, 2+ and 3+ cases. Note: ns not significant ($p > 0.05$), * $p < 0.05$, *** $p < 0.001$, **** $p < 0.0001$

PO3-13-04

The role of sphingolipids in cancer progression and its microenvironment in breast cancer patients

Presenting Author(s) and Co-Author(s):

A. Hattori. Hyogo Medical University, United States

M. Nagahashi. Hyogo Medical University, United States

A. Oshiro. Hyogo Medical University, United States

A. Mitsuyoshi. Hyogo Medical University, United States

H. Kanaoka. Hyogo Medical University, United States

A. Bun. Hyogo Medical University, United States

R. Fukui. Hyogo Medical University, United States

Y. Fujimoto. Hyogo Medical University, United States

T. Higuchi. Hyogo Medical University, United States

A. Nishimukai. Hyogo Medical University, United States

K. Murase. Hyogo Medical University, United States

Y. Takatsuka. Hyogo Medical University, United States

Y. Miyoshi. Dept of Surgery, Division of Breast and Endocrine Surgery, Hyogo Medical University, Nishinomiya-hama, Hyogo, Japan

Background: Sphingosine-1-phosphate (S1P) is a lipid mediator, and although it is a lipid, it acts as a signaling molecule similar to proteins by stimulating specific receptors. In the cell, ceramide (Cer), a component of the cell membrane, is converted to sphingosine (So), and So is phosphorylated by specific enzymes, named sphingosine kinases 1 and 2, to produce S1P. Based on the results of previous basic and translational researches, it is believed that S1P contributes to cell survival, and ceramide contributes to cell death, such as apoptosis, and that the balance of these sphingolipids regulates cell survival and death. Because sphingolipids are lipids, it is technically difficult to measure their concentration in patients, and their clinical significance has not yet been fully elucidated. The purpose of this study was to quantify sphingolipids in the blood of breast cancer patients and compare them with clinicopathological factors to determine their clinical significance.

Methods: Among breast cancer patients who underwent surgery at our hospital from September 2019 to April 2021, 118 cases were included, excluding breast cases with ductal carcinoma in situ and cases who received neoadjuvant chemotherapy. Plasma was collected from preoperative breast cancer patients, and cryopreserved samples were subjected to lipidomics analysis by mass spectrometry. As sphingolipids, So, dihydro-So (DHSO), S1P, DHS1P, and Cer (C14:0, C16:0, C18:0, C18:1, C20:0, C22:0, C24:0, C24:1, C26:0, C26:1, total Cer) levels were quantified, and S1P/Cer ratios were determined, and those data were compared with clinicopathological factors.

Results: The median age of the 118 patients was 58 years (range 29-86), and the types of breast cancer included 103 luminal, 8 HER2-positive, and 7 triple-negative cases. No significant associations were found between age, subtype, and the levels of any of the sphingolipids. Compared to the negative group, the positive lymphatic invasion group had higher So and DHSO levels, and S1P/Cer ratios ($p=0.0262$, $p=0.0167$, and $p=0.002$, respectively) and lower

total Cer ($p=0.0401$). Total Cer was lower in the vascular invasion-positive group than in the negative group ($p=0.0365$). The lymph node-positive group tended to show higher C24:0 levels ($p=0.0867$). No association was found between tumor diameter, nuclear grade, or tissue grade and sphingolipid levels. Interestingly, analysis of the association between sphingolipids and tumor-infiltrating lymphocytes (TILs) showed significant differences: So and DHSo levels, and S1P/ceramide ratio were significantly higher in the TILs-high group ($p=0.0063$, $p=0.0011$, and $p=0.0171$, respectively). DHS1P also tended to be higher with higher TILs ($p=0.072$), and S1P showed a similar trend, although not statistically significant.

Conclusion: Our data revealed that plasma sphingolipid concentrations were significantly associated with lymphatic invasion and TILs. These findings suggest that sphingolipids may be involved in shaping the tumor microenvironment in breast cancer patients.

PO3-13-05

PD-L1 and PD-L2 Protein Expression is Frequently Discordant in Breast Cancer

Presenting Author(s) and Co-Author(s):

L. Chaudhary. Medical College of Wisconsin, Milwaukee, Wisconsin, United States

J. Jorns. Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Y. Sun. Medical College of Wisconsin, United States

S. Kamaraju. Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Y. Cheng. Medical College of Wisconsin, United States

A. Kong. Medical College of Wisconsin, United States

T. Yen. Medical College of Wisconsin, United States

C. Patten. Medical College of Wisconsin, United States

C. Cortina. Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin, United States

I. Chervoneva. Thomas Jefferson University, United States

C. Chitambar. Medical College of Wisconsin, United States

H. Rui. Medical College of Wisconsin, United States

Background: In neoadjuvant setting, PD-1 inhibitors have shown significantly higher pathological responses in patients (pts) with early-stage triple-negative breast cancer (TNBC) irrespective of PD-L1 status. However, durable responses are less common in estrogen receptor-positive (ER+) pts. Most breast cancer (BC) clinical trials of PD-1 inhibitors have thus far focused on PD-L1 expression for patient eligibility. The alternative PD-1 ligand, PD-L2, with reported ~4-fold greater affinity for PD-1, has been largely understudied. We recently reported that high cancer cell protein levels of PD-L2 in pts with treatment-naïve ER+ BC was an independent predictor of shorter progression-free survival. PD-L2 expression was significantly high in ER- group as well, however, given the low numbers of ER- pts, the study was not powered enough to determine the correlation of PD-L2 with PFS in the ER- subgroup. These findings suggest that PD-L2 has an important role in BC and combined PD-L1/PD-L2 status may help improve BC pt selection for PD-1 inhibitors. We therefore initiated efforts to determine baseline expression patterns of PD-L1 and PD-L2 in BC.

Methods: PD-L1 and PD-L2 protein levels in cancer cells and tumor-infiltrating immune cells were prospectively analyzed by immunohistochemistry (IHC) using validated antibodies in diagnostic core biopsies of 31 consecutive pts diagnosed with localized or locoregional ER+/HER2- BC or TNBC. Percent positivity of PD-L1 and PD-L2 in cancer cells and immune cells was determined by our breast pathologist. Detectable PD-L1 or PD-L2 expression in $\geq 1\%$ of cancer cells or stromal immune cells was considered positive. Spearman correlation and Wilcoxon paired analyses were used to measure and correlate PD-L1 and PD-L2 protein expression in cancer and immune cells.

Results: There was no significant correlation between PD-L1 and PD-L2 expression, neither across all cases (N=31), nor within ER+ (N=22) or TNBC (N=9) cases. However, PD-L1 and PD-L2 expression patterns in BC differed in several ways. PD-L1-positivity in immune cells was higher than in cancer cells (median=5.0% vs. 0.0%; $p=0.001$), whereas PD-L2-positivity was higher in cancer cells than in immune cells (median=30% vs. 5.0%; $p<0.001$). PD-L1 positivity in cancer cells and immune cells were positively correlated in TNBC ($\rho=0.69$, $p=0.04$) but not

in ER+ BC. Conversely, PD-L2 positivity in cancer cells and immune cells were positively correlated in ER+ BC ($\rho=0.68$, $p=0.001$) but not in TNBC. TNBC diverged from ER+ BC by displaying higher PD-L1 positivity in immune cells (median=20.0% vs. 1.0%; $p=0.004$). By the conventional cut point for positivity of $\geq 1\%$ for PD-L1 and PD-L2 in cancer cells or immune cells, all TNBC tumors were PD-L1-positive (9/9), with 8 also being PD-L2-positive. Of the 22 ER+ cases, 16 were PD-L2-positive, of which only 9 were also PD-L1-positive. Table 1. shows cross tabulation data for PD-L1 and PD-L2 status by BC subtype.

Conclusions: PD-L1 and PD-L2 proteins show divergent expression and are not correlated in BC. Discordant PD-L2 and PD-L1 expression may be more common in ER+ BC than in TNBC. This finding justifies efforts to explore PD-L2 as a complementary marker to PD-L1 for improved prediction of response to PD-1 inhibitors, which may benefit patients with aggressive ER+ BC that are eligible for chemotherapy.

Table 1. PD-L1 vs. PD-L2 Status by Breast Cancer Subtype

Table 1. PD-L1 vs. PD-L2 Status by Breast Cancer Subtype					
Subtype		PD-L2			
		Neg	Pos	Total	
ER+	PD-L1	Neg	2	7	9
		Pos	4	9	13
	Total		6	16	22
TNBC	PD-L1	Neg	0	0	0
		Pos	1	8	9
	Total		1	8	9
All	PD-L1	Neg	2	7	9
		Pos	5	17	22
	Total		7	24	31

PO3-13-06

TILs are an independent prognostic factor in early-stage TNBC patients achieving pathologic complete response after neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

M. Dieci. University of Padova, United States

C. Vernieri. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Lombardia, Italy

D. Massa. Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy, United States

L. Nicolè. Department of Medicine (DIMED), University of Padua, Padova, Italy, United States

G. Griguolo. Department of Surgery, Oncology and Gastroenterology, University of Padua; Division of Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy

F. Miglietta. Department of Surgery, Oncology and Gastroenterology, University of Padua; Division of Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Italy

A. Vingiani. Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori, United States

R. Lobefaro. Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, United States

F. Girardi. Division of Medical Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

G. Vernaci. Medical Oncology 2, Istituto Oncologico Veneto IOV IRCCS, United States

T. Giarratano. Division of Medical Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

C. Giorgi. Division of Medical Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padua, Veneto, Italy

G. Pruneri. University of Milan, Fondazione IRCCS Istituto Nazionale dei Tumori, Spain

M. Fassan. University of Padua, Department of Medicine (DIMED), United States

F. De Braud. University of Milan, Fondazione IRCCS Istituto Nazionale dei Tumori, Spain

V. Guarneri. Department of Surgery, Oncology and Gastroenterology, University of Padua; Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Veneto, Italy

Introduction: In patients with triple negative breast cancer (TNBC) the achievement of pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) is associated with better long-term clinical outcomes. However, the attainment of pCR does not guarantee cure, since ~ 10% of patients undergo disease relapse. Higher levels of tumor infiltrating lymphocytes (TILs) are associated with better prognosis in TNBC patients undergoing upfront surgery and in patients with residual disease after NACT. However, the prognostic role of TILs among TNBC patients undergoing pCR during NACT has not been investigated so far.

Methods: We included 134 TNBC patients (ER cutoff < 10%) who achieved pCR after NACT. These cases were identified from a cohort of 348 TNBC patients who received NACT at Istituto Oncologico Veneto (Padova) and Istituto Nazionale Tumori (Milano) from April 2004 to April 2021. TILs were quantified in pre-NACT tumor biopsy according to International guidelines. We assessed the association between TILs and relapse-free survival (RFS) or overall survival (OS).

Results: Main patients characteristics were: median age 48 years; ductal histotype 92.8%; histologic grade 3 95.2%; stage I 9.7%, stage II 71.6%, stage III 18.7%. Almost all patients received anthracyclines (98.5%) and taxanes (99.3%) as part of NACT for a median number of 4 cycles each; 55.2% of patients received carboplatin. At a median FU of 4.6 years, the 5-yr RFS and OS rates were 90.4% and 94.4%, respectively. As a continuous variable (1% increment), TILs were independently associated with better RFS and OS after adjusting for patient age and tumor stage: HR 0.90 (95%CI 0.83-0.98), $p=0.015$ and HR 0.89 (95%CI 0.80-1.00), $p=0.041$, respectively.

The best prognostic TILs cut-off in this cohort was 20%. Patients with TILs>20% showed a 100% 5-yr RFS rate (0/63 events) vs 82.6% (12/71 events) for patients with TILs< 20% (log-rank $p < 0.001$). OS rates at 5 years were 100% and 90.1% for high vs low TILs (log-rank $p=0.007$).

Conclusions: This is the first demonstration of an independent prognostic role of baseline TILs in TNBC patients achieving pCR after NACT. Baseline TILs may discriminate patients who are cured after achieving pCR from patients at risk of disease relapse despite the achievement of pCR. These latter may be candidate to treatment escalation in the context of clinical trials. Our work provides relevant data in the ongoing debate on the role of adjuvant therapy (primarily pembrolizumab) following pCR.

PO3-13-07

MUC1-C INTEGRATES CHRONIC ACTIVATION OF INTERFERON PATHWAYS WITH CHROMATIN REMODELING IN TREATMENT RESISTANCE OF TRIPLE-NEGATIVE BREAST CANCER

Presenting Author(s) and Co-Author(s):

N. Yamashita. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, Koto-ku, Tokyo, Japan

Y. Morimoto. Osaka University, United States

A. Fushimi. Jikei University School of Medicine, United States

R. Ahmad. Harvard Medical School, United States

A. Bhattacharya. Harvard Medical School, United States

Y. Inoue. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States

H. Withers. Roswell Park Comprehensive Cancer Center, United States

G. Shapiro. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

T. Yoshizumi. Kyushu University, United States

T. Ueno. Breast Surgical Oncology, Breast Oncology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan, Tokyo, Tokyo, Japan

S. Ohno. Breast Oncology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

M. Long. Roswell Park Comprehensive Cancer Center, United States

D. Kufe. Dana-Farber Cancer Institute, Harvard Medical School, United States

Chronic inflammation is intimately linked to cancer progression and resistance to treatment. Triple-negative breast cancer (TNBC) is a recalcitrant malignancy largely unresponsive to cytotoxic, targeted and immunotherapeutic agents. The Mucin1 (MUC1) transmembrane heterodimeric protein, which is aberrantly expressed in TNBCs, evolved in mammals to provide protection of epithelia from the external environment. With loss of homeostasis, the (i) MUC1 N-terminal (MUC1-N) subunit is shed and released into serum as detected by the CA15-3 assay, and (ii) MUC1 C-terminal (MUC1-C) subunit is activated and thereby induces inflammatory, proliferative and remodeling signaling pathways associated with wound healing. However, prolonged MUC1-C activation in settings of chronic inflammation promotes cancer progression and treatment resistance. The SWI/SNF PBAF chromatin remodeling complex includes the polybromo-1 (PBRM1) subunit and drives DNA damage resistance and immune evasion in certain cancer cells through mechanisms that remain unclear. Recent studies in TNBCs have demonstrated that MUC1-C drives intrinsic activation of type II interferon (IFN) pathway that is linked to chronic inflammation and immune evasion. In extending this work, we have found that MUC1-C activates the type I IFN pathway, which contributes to genomic instability and DNA damage tolerance in TNBC cells. Importantly, our results further demonstrate that MUC1-C interacts with interferon regulatory factor 1 (IRF1) as a key regulatory node in integrating activation of the type I and II IFN pathways. Here, we report that MUC1-C is necessary for PBRM1 expression and that it forms a nuclear complex with PBRM1 in TNBC cells. Analysis of global transcriptional (RNA-seq) and chromatin accessibility (ATAC-seq) profiles further demonstrated that MUC1-C and PBRM1 drive STAT1 and IRF1 expression by increasing chromatin accessibility of promoter-like signatures (PLS) on their respective genes. We also found that MUC1-C, PBRM1, and IRF1 increase the expression and

chromatin accessibility on PLSs of the (i) type II IFN pathway IDO1 and WARS genes and (ii) type I IFN pathway RIG-I, MDA5, cGAS, STING and ISG15 genes that collectively contribute to DNA damage resistance and immune evasion. In support of these results, targeting MUC1-C in wild-type BRCA1/2 TNBC cells enhanced carboplatin-induced DNA damage and loss of self-renewal capacity. In addition, MUC1-C was necessary for DNA damage resistance, self-renewal and tumorigenicity of olaparib-resistant BRCA1-mutant TNBC cells. Analysis of TNBC clinical samples corroborated that (i) MUC1 and PBRM1 are associated with decreased responsiveness to chemotherapy and (ii) MUC1-C expression is associated with the depletion of tumor-infiltrating lymphocytes. These findings demonstrate that MUC1-C activates PBRM1, and thereby chromatin remodeling of IFN-stimulated genes that promote chronic inflammation, DNA damage resistance, and immune evasion. These findings have identified MUC1-C as a potential target for the treatment of TNBC that have limited therapeutic options. To that end, the generation of MAb 3D1 against the MUC1-C extracellular domain provided an opportunity for the development of agents that target MUC1-C on the cancer cell surface. As one example, an allogeneic anti-MUC1-C CAR T cell using MAb 3D1 sequences is undergoing Phase I evaluation for the treatment of MUC1-C-expressing cancers (NCT05239143: P-MUC1C-ALLO1 Allogeneic CAR-T Cells in the Treatment of Subjects with Advanced or Metastatic Solid Tumors). In addition, anti-MUC1-C huMAb3D1-MMAE ADCs are under development by the NCI NExT Program for IND-enabling studies and performing early phase clinical trials in patients with TNBC.

PO3-13-08

D17104: Aryl Hydrocarbon Receptor Signaling and Other Biomarkers of Fat Metabolism in Human Mammary Adipose Tissue from Women with Malignant Breast Disease

Presenting Author(s) and Co-Author(s):

A. Ephraim. Dartmouth Hitchcock Medical Center / Dartmouth Cancer Center, United States

J. Pirruccello. Dartmouth Hitchcock Medical Center / Dartmouth Cancer Center, United States

S. Palisoul. Dartmouth Cancer Center, United States

J. Marotti. Dartmouth Hitchcock Medical Center / Dartmouth Cancer Center, United States

M. Chamberlin. Dartmouth Hitchcock Medical Center / Dartmouth Cancer Center, United States

Background: Obesity is a recognized risk factor for the development of metabolic disease and breast cancer possibly due to chronic inflammation mediated by cytokines secreted by adipose tissue. Given this, our group examined differential expression of several markers of chronic inflammation in adipose tissue of both benign and malignant breast tissue from patients. The aryl hydrocarbon receptor (AhR) is an important cytosolic, ligand-dependent transcription factor found within hepatocytes and adipocytes that is upregulated in many types of cancer. AhR promotes the initiation, progression, and metastasis of cancer cells allowing certain cancers to evade immune recognition (Xue et al. *Front. Immunology* 2018). Indoleamine 2,3-dioxygenase 1 (IDO1) is an enzyme that generates kynurenine (KYN) from tryptophan (TRP), which acts as an AhR agonist. We sought to determine expression of IDO1 via immunohistochemistry (IHC) in mammary adipose tissue associated with benign or malignant breast. We hypothesized that adipose tissue adjacent to malignant breast tissue may have heightened expression of IDO1 in addition to Cyp1b1, and SPP1; both of which are also markers of increased aryl-hydrocarbon transcriptional activity, compared to adipose tissue noncontiguous to malignant lesions. KYN affects gene expression for insulin resistance and levels are elevated in plasma of older obese women compared to lean women; however, the relationship to breast malignancy is not known.

Methods: IDO1 (Cell Signaling, 1:200), Cyp1b1 (Thermo Fisher, 1:300), and SPP1 (Thermo Fisher, 1:200) IHC was performed according to the manufacturers' protocols. Adipose tissue immediately adjacent to, and >2 mm away from, tumors (three DCIS, 11 invasive carcinomas) was evaluated in 14 patients. Adipose tissue in separate tissue blocks from benign breast tissue (three ipsilateral, 11 contralateral) in the same patients was also evaluated. Human plasma KYN levels were assayed by HPLC in the Dartmouth Clinical Pharmacology Shared Resource as described previously (Rojas et al. *Obesity* 2021).

Results: In this preliminary pilot study, there was no difference in staining pattern for IDO1 in adipose tissue present in malignant and benign samples. Two patients showed increased Cyp1b1 and SPP1 staining immediately adjacent to the invasive carcinoma (Figure 1). Patients with benign breast disease did not show increased Cyp1b1 or SPP1 staining. Results will be confirmed using qPCR for mRNA. Plasma samples from patients with benign disease showed a lower level of KYN expression on average (0.370 ug/mL, N = 8) compared to plasma from patients with malignant disease (0.424, N = 10). Additionally, the ratio of KYN:TRP was lower in the benign group (0.065) compared to the cohort with malignancy (0.080). Univariate linear regression will be used to further assess relationships between continuous variables in the study population (e.g., patient age, BMI, KYN plasma levels, benign vs malignant breast disease). Regression lines and the associated slope estimates (b-value) and p-values for regression models will be provided on scatter plots.

Conclusions: While there was no difference in IDO1 staining patterns in adipose tissue of malignant and benign samples in this group, tissue samples from patients with invasive carcinoma demonstrated increased Cyp1b1 and SPP1 staining adjacent to the malignant tumor; while benign tissue samples did not show a positive stain. This suggests

increased aryl-hydrocarbon transcriptional activity in invasive breast carcinoma—further linking AhR signaling with adipose tissue immune dysregulation and invasive malignancy. Additionally, KYN plasma levels were higher in patients with malignant disease indicating a possible relationship between insulin resistance and breast malignancy. Additional research may offer new insights relating to this important pathway and ultimately treatments aimed at blunting its nefarious effects.

PO3-13-09

Personalized ctDNA testing for detection of molecular residual disease in patients with localized HR+ breast cancer: temporal dynamics and impact on clinical outcomes

Presenting Author(s) and Co-Author(s):

A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States

E. Denault. Massachusetts General Hospital, United States

Z. Ephrem. Massachusetts General Hospital, United States

D. Micalizzi. Massachusetts General Hospital Cancer Center, United States

Y. Bar. Massachusetts General Hospital, United States

R. Abelman. Mass General Cancer Center/Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Comander. Mass General Cancer Center / Newton-Wellesley Hospital, United States

J. Knape. Massachusetts General Hospital, United States

M. Liu. Natera, United States

A. Rodriguez. Natera, United States

S. Isakoff. Cancer Center, Massachusetts General Hospital, United States

B. Moy. Massachusetts General Hospital, United States

L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background: Molecular residual disease (MRD) describes detectable circulating tumor DNA (ctDNA) after definitive surgery and is an expanding field in breast oncology. Multiple studies have demonstrated detectable MRD to be poorly prognostic, and clinical trials are now underway assessing the efficacy of therapeutic interception. However, most retrospective studies did not obtain baseline imaging at the time of MRD detection, such that the proportion of patients with detectable ctDNA and concurrent radiographically evident recurrent disease is not known. Furthermore, the role of serial ctDNA testing in the adjuvant setting remains unclear. Meanwhile, tumor-informed assays such as the Signatera™ platform are now covered by Medicare. To address these outstanding clinical questions, we aimed to determine the temporal dynamics of MRD detection in HR+/HER2- breast cancer, association with radiographic recurrence, and impact on clinical outcomes. **Methods:** Patients with HR+/HER2- breast cancer who underwent MRD testing either as part of a clinical trial or via an expanded access program were reviewed for MRD positivity and assessed alongside clinically annotated data. All patients completed surgical resection prior to MRD testing. Whole exome sequencing of primary tumor tissue and personalized ctDNA primers were designed for multiplex PCR targeting up to 16 single nucleotide variants for MRD testing via the Signatera™ platform. Clinical data was determined through focused chart review. **Results:** Among 185 patients with HR+/HER2- breast cancer who underwent MRD testing, 37 patients (20%) did not complete testing due to factors including tumor tissue not meeting pathology parameters, insufficient quantity of primary tissue, or tumor/normal discordance. 14 patients (8%) had detectable ctDNA (1, 5, and 8 patients had stage I, II, and III breast cancer, respectively). Among the 6 patients

who did not have stage III disease, 3 had other high-risk features (Oncotype 40; grade 3 disease x2). Overall, 71% (n=10) of the +MRD population tested positive at the first test, while 29% (n=4) tested positive only on serial sampling. Median time from surgery to positive test was 3.5 years (range: 1 month – 10.2 years). Twelve patients (86%) were on adjuvant endocrine therapy at the time of detectable MRD. Among the 14 +MRD patients, 9 underwent staging scans shortly after positive MRD testing, and among these patients, 3 (33%) had radiographic evidence of asymptomatic metastatic recurrence (2 bone-only; 1 visceral); two of these pts had 1 MRD test, while the other had a negative test followed by a positive test 11 months later. The other 3 patients with radiographic recurrences had scans prompted only by clinical symptoms >6 months after +MRD. Among the 4 patients with serial data after first +MRD testing, none experienced subsequent ctDNA clearance. Serial testing occurred over a median of 11.5 months (range 1.1-21.7 months). With median follow up of 8.6 months, 43% (n=6) of patients with +MRD had distant disease recurrence. **Conclusions:** Personalized tumor-informed ctDNA testing identified patients with high risk of recurrence, including patients without classic high-risk clinical, pathologic, or genomic features, suggesting a complementary role of MRD testing for risk assessment. Serial monitoring was necessary to identify MRD in more than a quarter of patients. Furthermore, one-third of patients with +MRD disease had asymptomatic metastatic recurrence, highlighting the importance of staging scans in studies and clinical trials assessing therapeutic interception in the adjuvant setting.

PO3-13-10

Proteogenomic characterization of primary invasive breast tumors from young women compared to matched tumors from older women

Presenting Author(s) and Co-Author(s):

P. Raj Kumar. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

J. Liu. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

A. Soltis. Center for Military Precision Health, Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, United States

N. Bateman. Women's Health Integrated Research Center/ Gynecologic Cancer Center of Excellence, Department of Gynecologic Surgery and Obstetrics, Uniformed Services University of the Health Sciences, Walter Reed National Military Medical Center, Bethesda, MD, United States

Q. Chen. Center for Biomedical Informatics and Information Technology, National Cancer Institute, Rockville, MD, United States

L. Sturtz. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

B. Deyarmin. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

M. Pierobon. George Mason University, United States

T. Abulez. Women's Health Integrated Research Center/ Gynecologic Cancer Center of Excellence, Department of Gynecologic Surgery and Obstetrics, Uniformed Services University of the Health Sciences, Walter Reed National Military Medical Center, Bethesda, MD, United States

A. Praveen-Kumar. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States

X. Zhang. Center for Military Precision Health, Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, United States

T. Nguyen. Center for Biomedical Informatics and Information Technology, National Cancer Institute, Rockville, MD, United States

C. Yan. Center for Biomedical Informatics and Information Technology, National Cancer Institute, Rockville, MD, United States

Y. Hu. Center for Biomedical Informatics and Information Technology, National Cancer Institute, Rockville, MD, United States

K. Guion. Departments of Medicine, Chemical Engineering and Material Sciences, and Quantitative and Computational Biology, University of Southern California, Los Angeles, CA, United States

J. Hooke. Henry Jackson Foundation, Rockville, Maryland, United States

A. Kovatich. HJF, Bethesda, Maryland, United States

L. Fantacone-Campbell. Murtha Cancer Center Research Program, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, United States

- B. Mostoller. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States
- L. Kvecher. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States
- S. Somiari. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States
- P. Steeg. Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States
- S. Rajagopal. Cancer Data Sciences Laboratory, Center for Cancer Research, National Cancer Institute, Bethesda, MD, United States
- K. Darcy. The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, United States
- J. Lee. Departments of Medicine, Chemical Engineering and Material Sciences, and Quantitative and Computational Biology, University of Southern California, Los Angeles, CA, United States
- C. Dalgard. USU, United States
- T. Conrads. Women's Health Integrated Research Center/ Gynecologic Cancer Center of Excellence, Department of Gynecologic Surgery and Obstetrics, Uniformed Services University of the Health Sciences, Walter Reed National Military Medical Center, Bethesda, MD, United States
- E. Petricoin. George Mason University, Manassas, Virginia, United States
- D. Meerzaman. Center for Biomedical Informatics and Information Technology, National Cancer Institute, Rockville, MD, United States
- M. Wilkerson. USU, United States
- A. Research Network. Murtha Cancer Center Research Program, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, United States
- X. Lin. Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW), Windber, PA, United States
- C. Shriver. Uniformed Services University, Bethesda, Maryland, United States
- S. Lipkowitz. Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States
- H. Hu. Chan Soon-Shiong Institute of Molecular Medicine at Windber, United States

Introduction: Breast cancer (BC) in women < 40 years old accounts for ~5% of BC diagnosed in the U.S. However, young women have more aggressive tumors and worse outcomes, including higher rates of recurrence and lower disease-free and overall survival, compared to older women. To better understand mechanisms for these disparities, an integrated proteogenomic study of tumors from young (< 40) and older (≥ 60) women was performed through the Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) program.

Methods: 34 pairs of retrospectively collected, untreated primary breast tumors from young and older women, matched by immunohistochemistry (IHC) subtype and race, were selected from the Clinical Breast Care Project. Median patient follow-up was 7 years. Tumor cells were enriched by laser microdissection and analyzed using RNA sequencing, whole genome sequencing, global proteomics, phosphoproteomics, and reverse phase protein array (RPPA). Molecular and clinical data from tumors from young and old patients in the TCGA-BC and METABRIC studies, matched by IHC subtype and race, were used to corroborate findings from

our cohort. Results are presented comparing young women and their tumors to their older counterparts.

Results: Young women have worse clinical outcome measured by progression-free interval. Despite matching for IHC subtypes, tumors from young women are enriched for intrinsic basal-like subtype, BRCA1/2 germline mutations, and had fewer invasive lobular BCs.

Differentially enriched molecules and pathways: A number of significantly differentially expressed genes (DEGs) and proteins were detected, which were able to separate luminal subtypes of BC by patient age. IRS1 and IRS2 were enriched at both transcript and protein levels; IRS1 has been reported to promote tamoxifen resistance. We observed limited overlap of DEGs between the APOLLO, TCGA, and METABRIC datasets. In contrast, 14 of the 28 significantly upregulated Cancer Hallmark pathways were also enriched in TCGA-BC and METABRIC datasets; suggesting targeting pathways, vs genes, may be more effective for therapeutic intervention.

Integrated pathway/network analysis: Integrated pathway analysis of RNA and protein levels identified 5 Hallmark pathways upregulated in younger women, including ER response and proliferative pathways, and 6 downregulated immune-response pathways; 10 of the 11 were supported by the public datasets. Immune scores were also lower. Kinase substrate enrichment analysis identified 4 kinases with increased activity in tumors from young women.

ESR1/ER: We identified for the first time a significant reduction of ER protein expression while confirming previously reported lower ESR1 gene expression and copy number variations. Surprisingly, integrated pathway analysis identified elevation of early and late estrogen responses in young women. ER activation, indicated by phosphorylated ER (pS118) normalized to total ER protein, was elevated in LumA tumors from young women.

Conclusions: This first-ever integrated proteogenomic study shows that BC in young women is enriched for more aggressive molecular subtypes and for genes that promote tamoxifen resistance, exhibits lower immune pathways and immune scores, and shows enhanced ER responses despite lower gene and protein expression of ER. These findings may contribute to the understanding of the molecular mechanisms underlying worse outcomes of BC in young women, and offer new insight to therapeutic strategies.

Disclaimer: The contents of this publication are the sole responsibility of the authors and do not necessarily reflect the views, opinions or policies of USUHS, HJF, the DoD or the Departments of the Army, Navy or Air Force. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

PO3-13-11

Quantitative Multiplex Immunofluorescence Assay for TROP2 and HER2 Expression in Breast Cancer: Towards Guiding Patient Selection for Antibody Drug Conjugate Therapies

Presenting Author(s) and Co-Author(s):

C. Robbins. Yale, United States

M. He. Yale University, New Haven, Connecticut, United States

R. Khaimova. Alexion, AstraZeneca Rare Disease, United States

K. Bates. Yale School of Medicine, United States

N. Chan. Yale School of Medicine, New Haven, Connecticut, United States

D. Liebler. Inotiv, Inc., United States

R. Fulton. Array Science, LLC, United States

D. Rimm. Yale University, New Haven, Connecticut, United States

Emerging antibody drug conjugate (ADC) therapies targeting human trophoblast cell-surface antigen (TROP2) and human epidermal growth factor receptor 2 (HER2) are transforming the treatment landscape for breast cancer. Sacituzumab govitecan (SG) and trastuzumab deruxtecan (T-DXd) have gained approval for an overlapping set of "HER2-low" metastatic breast cancers, including hormone receptor (HR)-positive HER2 non-amplified and "triple-negative" subtypes. Nevertheless, the optimal selection of patients and treatment sequencing for these ADC therapies remains a clinical challenge. Clinical trial objective response rates to SG are approximately 30%, compared to 30-90% for T-DXd depending on HER2 expression levels. While both drugs are thought to be targeted therapies, the value of measuring the target and the best methods to do so are still not established. We believe that quantitative measurement of TROP2 and HER2 antigen expression levels could establish thresholds for responders, enabling more effective patient selection for ADC therapies. Here, we present a TROP2, high-sensitivity HER2, and cytokeratin (CK) quantitative immunofluorescence (QIF) multiplex assay. Using a ten-cell line standard array and proteomic mass spectrometry, we can convert tumor compartment QIF intensity to protein concentration in fmol/mm^2 for tissue specimens. Anti-HER2, anti-TROP2 antibodies, and fluorescence detection systems were titrated and combined to maximize signal-to-noise ratio on our cell line standard array and breast cancer tissue microarrays (TMA). The multiplex assay was designed for automated slide stainers (Leica BOND Rx) and fluorescence slide scanning (Rarecyte CyteFinder II HT). We perform our analyses in QuPath using an image processing plugin developed for automated QIF/IHC analysis (Qymia). Reproducible TROP2 and HER2 QIF scoring ($R^2 > 0.95$) was achieved across multiple staining batches using serial sections of breast cancer TMAs and cell standard arrays. This assay has a TROP2 linear range between 0.63 - 9.17 fmol/mm^2 (about 1 million TROP2 receptors/cell) and HER2 linear range between 0.09 - 0.565 fmol/mm^2 (about 60,000 HER2 receptors/cell). We then applied this multiplex assay to two serial retrospective primary breast cancer cohorts from Yale University to quantitatively measure TROP2 and HER2 expression (338 clinical cases). We find a weak negative correlation between TROP2 and HER2 expression in our breast cancer cohorts (Pearson $r = -0.14$, $p = 0.0097$, $n = 338$). TROP2 expression levels were above the limit of detection (LOD) in 90.2% of cases, with 4.1% exceeding the limit of linearity (LOL), and a mean TROP2 expression of 4.05 fmol/mm^2 . For HER2, 67.2% of cases were above the LOD, with 7.1% exceeding the LOL, and a mean HER2 expression of 0.186 fmol/mm^2 . Both TROP2 and HER2 were below the LOD in 3.0% of cases,

which we define as “negative”. We found 29.9% expressed TROP2 and were HER2-negative, and 6.8% expressed HER2 and were TROP2-negative. Our future studies will aim to quantitatively define expression thresholds for T-DXd and SG response with the goal to produce a clinical grade assay for ADC patient selection and determine the value of the assay to help select which ADC to give first.

HER2 and TROP2 protein expression summary in Yale breast cancer cohort

Table 1: Summary of HER2 and TROP2 protein expression levels in serial retrospective primary breast cancer cohort of 338 cases using our high-sensitivity HER2 and TROP2 multiplex immunofluorescent assay

	HER2	TROP2
Limit of Linearity (LOL)	0.565 fmol/mm ²	9.17 fmol/mm ²
Limit of Detection (LOD)	0.09 fmol/mm ²	0.635 fmol/mm ²
Mean	0.186 fmol/mm ²	4.05 fmol/mm ²
Standard deviation	0.216 fmol/mm ²	2.63 fmol/mm ²
Single marker (n = 338)		
Above LOD	24 (7.1%)	14 (4.1%)
Linear range	203 (60.1%)	291 (86.1%)
Below LOD	111 (32.8%)	33 (9.8%)
HER2 – TROP2 Combination (n = 338)		
Hi – Hi	0 (0%)	
Hi – Q	19 (5.6%)	
Hi – Neg	5 (1.5%)	
Q – Hi	10 (3.0%)	
Q – Q	175 (51.8%)	
Q – Neg	18 (5.3%)	
Neg – Hi	4 (1.2%)	
Neg – Q	97 (28.7%)	
Neg – Neg	10 (3.0%)	

Hi: above LOD, Q: within linear range, Neg: below LOD

Summary of HER2 and TROP2 protein expression levels in serial retrospective primary breast cancer cohort of 338 cases using our high-sensitivity HER2 and TROP2 multiplex immunofluorescent assay

PO3-13-12

ER-positive/HER2-negative breast cancer in Adolescent & Young Adult (AYA) age group has a specific biological feature and worse outcome compared to other generations

Presenting Author(s) and Co-Author(s):

M. Oshi. Roswell Park Comprehensive Cancer Center, United States

A. Yamada. Yokohama City University Graduate School of Medicine, United States

M. Sasamoto. Yokohama City University Graduate School of Medicine, United States

K. Kawashima. Department of Breast and Thyroid Surgery, Yokohama City University Medical Center, United States

Y. Fujiwara. Department of Breast and Thyroid Surgery, Yokohama City University Medical Center, United States

S. Adachi. Department of Breast and Thyroid Surgery, Yokohama City University Medical Center, United States

S. Yamamoto. Department of Breast and Thyroid Surgery, Yokohama City University Medical Center, United States

K. Narui. Yokohama City University Medical Center, United States

T. Ishikawa. Tokyo Medical University, United States

I. Endo. Yokohama City University Graduate School of Medicine, United States

K. Takabe. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

Background: Adolescents & Young Adults (AYA) is commonly defined as patients younger than 40 years old. Breast cancer patients in AYA has been reported to have poor outcome compared to other generation, however, the clinicopathological and biological features of AYA breast cancer remains controversial partly because many previous studies did not consider the difference in subtypes by age. We aim to clarify the features of AYA compared with the other age group in ER-positive/HER2-negative breast cancer, assuming the effects of age-related hormonal status.

Material and Methods: Each analyzed cohort were divided into four age groups; AYA (15-39yo), perimenopausal (40-55yo), menopausal (55-65yo), and old (65+yo). Clinicopathological and biological features were analyzed using gene set variation analysis and the xCell algorithm using mRNA expression profiles of large independent public databases (METABRIC; n = 1,903, GSE96058; n = 3,273).

Results: We found that both clinical and pathological T-category of AJCC staging were larger in AYA and Old compared from the other groups. Pathological N-category as well as pathological Stage were higher in AYA. Nottingham histological grade 3 was significantly higher in the AYA compared with the other older groups. Among the subtypes, AYA breast cancer was significantly associated with higher rate of triple-negative breast cancer compared to the others, as expected. Considering the whole cohort, ER and PgR positivity trended to be lower, but HER2-positivity trended to be higher in AYA. Within the ER-positive/HER2-negative subtype, PgR positivity was higher in the AYA and Perimenopausal groups compared to others. AYA had poorer disease-specific survival than other groups ($p = 0.010$ and $p = 0.002$, respectively), as well as overall survival, especially compared to perimenopausal group. The survival difference was more pronounced in ER-positive/HER2-negative breast cancer patients. In biological analysis in ER-positive/HER2-negative subtype, we found that estrogen response

late signaling level decreased as the age group gets older. AYA breast cancer had significant enrichment in cell proliferation-related gene sets (G2M checkpoint, E2F targets, and MYC target v1), other pro-cancerous gene sets (MTORC1, unfolded protein response, and PI3K/ACT/MTOR signaling), consistently in two cohorts (all $p \leq 0.028$), when compared to the other age groups. Interestingly, the features were observed even in the small tumor size (T1/T2) subgroup. Furthermore, AYA breast cancer showed significantly high BRCAness (all $p \leq 0.002$) and DNA repair (all $p \leq 0.023$) compared to other age groups. The infiltration fraction of several immune cells: CD8+ T cells, M1 macrophages, regulatory T cells, helper type 2 T cells, were significantly higher, and M2 macrophages were significantly lower in AYA, consistently in two cohorts.

Conclusion: ER-positive/HER2-negative breast cancer in AYA was highly proliferative with high immune cell infiltrations compared to other generations. This may be related to the difference in outcomes in each age group. Considering these unique features may enable us to fine tune treatment strategies for AYA.

PO3-14-01

Heterogeneity of tumor immune microenvironment to predict everolimus efficacy in premenopausal women with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer

Presenting Author(s) and Co-Author(s):

Y. Tan. Chinese Academy of Medical Sciences and Peking Union Medical College, United States

F. Ma. Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

J. Wang. Chinese Academy of Medical Sciences and Peking Union Medical College, United States

P. Zhang. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

L. Xue. Chinese Academy of Medical Sciences and Peking Union Medical College, United States

Y. Fan. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Objective

Everolimus (EVE), a mammalian target of rapamycin (mTOR) inhibitor, has been shown to prolong survival of patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-), advanced breast cancer (ABC) with endocrine resistance. Preclinical studies have suggested that mTOR is closely associated with the tumor immune microenvironment (TME). We aimed to explore the tumor heterogeneity of TME between patients with different response to everolimus (EVE), and identify potential markers to predict efficacy of EVE in premenopausal patients with HR+/HER2-, advanced breast cancer (ABC) suffering endocrine resistance.

Methods

Patients were divided into two groups according to the best response to EVE: the responsive subgroup (RS) and the non-responsive subgroup (NRS). Postoperative tumor tissue from patients who received EVE was collected for whole exome sequencing. Transcript abundance of 126 distinct tumor regions of interest (ROIs) were quantitated using digital spatial profiling, including 42 tumor cell zones (TCZs), 42 immune cell zones (ICZs), and 42 stroma cell zones (SCZs). Based on investigation in multiple discrete areas, differences in cell components, function and pathway, gene expression and immune cell infiltration between RS and NRS were investigated.

Results

Totally, 93 differentially expressed genes (DEGs) were identified in the ICZs, 174 DEGs in the TCZs, and 197 DEGs in the SCZs, using $p < 0.05$ and $|\log_2FC| > 1$ as the screening criterion. Among all the subgroup analyses on different ROIs, the statistical significance of PIP gene was the highest (ICZs: $p=2.6E-12$, TCZs: $p=1.25E-20$, SCZs: $p=2.0E-18$) in the comparison of RS and NRS. Moreover, we found that PIP was highly expressed in NRS and patients with a progression-free survival < 1 year. The receptor-legend analysis showed that, the intra-and inter-cellular communication in RS was mainly mediated by interaction between CCL-CCR

family, while NRS mainly by COL family complex. Comparing all cell components extracted from each ROI, no statistical differences were found between RS and NRS, only a statistical trend in the SCZs ($p=0.098$). Further cell classification analysis showed fibroblasts highest in TCZs and SCZs, macrophages in ICZs. Compared to NRS, in TCZs, fibroblasts were significantly increased ($p=0.01$), and plasma cells ($p=0.02$) and neutrophils ($p=0.03$) were decreased in RS. In SCZs, the downregulated fibroblasts ($p=0.04$) and enhanced plasma cells ($p=0.01$) were observed in NRS. In ICZs, pDCs ($p=0.048$) and neutrophils ($p=0.006$) were significantly elevated in NRS compared with RS.

Conclusion

The utility of digital spatial gene expression profiling might provide some references to predict the efficacy of EVE in premenopausal patients with HR+/HER2- ABC with endocrine resistance.

PO3-14-04

Prognostic value of systemic inflammatory markers in neoadjuvant chemotherapy for breast triple negative cancer with pembrolizumab: development of a nomogram

Presenting Author(s) and Co-Author(s):

F. Giovanardi. IRCCS AUSL Reggio Emilia, Emilia-Romagna, Italy

G. Bisagni. IRCCS AUSL Reggio Emilia, United States

E. Gasparini. Azienda USL-IRCCS di Reggio Emilia, United States

A. Bologna. Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

R. Di Cicilia. IRCCS AUSL Reggio Emilia, United States

G. Moretti. IRCCS AUSL Reggio Emilia, United States

C. Degli Esposti. IRCCS AUSL Reggio Emilia, United States

C. Pinto. IRCCS AUSL Reggio Emilia, United States

Introduction:

Systemic inflammatory markers derived from peripheral blood cells, such as the neutrophil-lymphocyte ratio (NLR), derived neutrophil-lymphocyte ratio (dNLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR), have shown promise as prognostic markers for various cancer types. Inflammation plays a crucial role in cancer development, progression, metastasis, and resistance to treatment. However, only a few preoperative biomarkers have been identified as independent prognostic markers. Systemic inflammatory markers offer a reliable and easily accessible approach for prognosis evaluation. Materials and Methods:

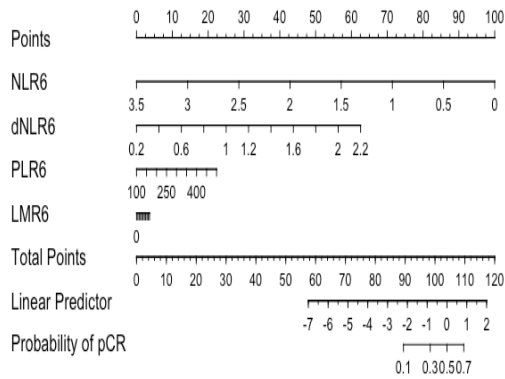
This study evaluated two groups of patients who received neoadjuvant chemotherapy for triple-negative breast cancer outside of clinical trials. The first group underwent neoadjuvant chemotherapy in 2021 with the EC X4 and weekly paclitaxel regimen, whereas the second group received neoadjuvant chemotherapy in 2022 following the KEYNOTE-522 study protocol with pembrolizumab. A total of 44 patients were included, with 23 patients in the pembrolizumab group. The NLR was defined as the absolute blood neutrophil count divided by the absolute lymphocyte count, and the derived neutrophil/lymphocyte ratio (dNLR) was defined as the absolute neutrophil count divided by the derived lymphocyte count (absolute leukocyte count — neutrophil count). The PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. The LMR was defined as the absolute lymphocyte count divided by the absolute monocyte count. The association between systemic inflammatory markers (NLR, dNLR, PLR, and LMR) and pathological complete response (pCR) was analyzed using statistical tests. Inflammatory markers were evaluated at the time of diagnosis, at the time of chemotherapy regimen change, and two weeks before surgery. The χ^2 test or Fisher's exact test was used to analyze the correlation between the inflammatory indices and clinicopathologic parameters. Student's t-test was used to compare different groups of continuous parametric data. Results:

The pCR rates were 67% in the standard therapy group and 87% in the pembrolizumab group. There were no significant differences in other clinical characteristics between the two groups. The NLR, dNLR, PLR, and LMR at 6 months showed statistically significant differences compared to baseline levels. This difference was more evident in patients undergoing pembrolizumab therapy. ROC curves for the pembrolizumab group demonstrated an area under the curve (AUC) of 0.737, indicating a strong correlation between these systemic inflammatory markers and pCR. Based on these data, a nomogram was constructed to predict the likelihood of achieving pCR in patients undergoing neoadjuvant pembrolizumab therapy.

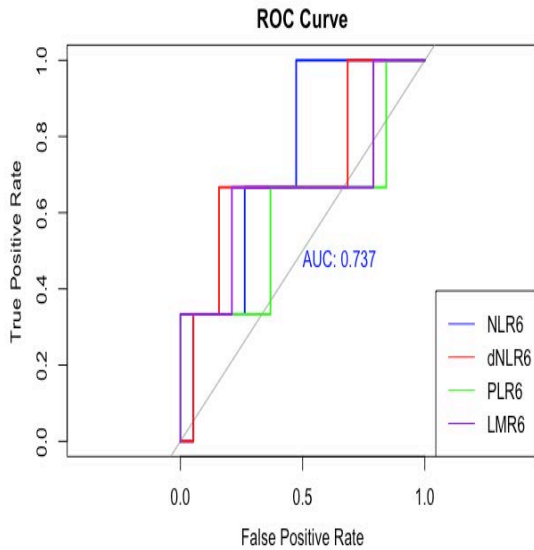
Conclusion:

This study highlights the potential of systemic inflammatory markers as prognostic indicators in patients with TNBC undergoing neoadjuvant chemotherapy. The significant differences observed in the pembrolizumab group and the high AUC of the ROC curves suggest the utility of these markers in predicting treatment response. The developed nomogram provides a practical tool for clinicians to estimate the probability of pCR based on NLR, dNLR, PLR, and LMR. Further research and validation are required to confirm the clinical utility of these markers in larger patient cohorts.

Nomogram



ROC curve



PO3-14-05

Integration of metabolomics and transcriptomics to Reveal Potential Biomarkers Associated with Treatment Response of Neoadjuvant Therapy in HER2+ Breast Cancer

Presenting Author(s) and Co-Author(s):

N. Zhang. Chongqing University Cancer Hospital, United States

Y. Huang. Chongqing university cancer hospital, United States

G. Wang. Chongqing university cancer hospital, United States

Y. Xiang. Chongqing university cancer hospital, United States

Z. Jing. Chongqing university cancer hospital, United States

J. Zeng. Chongqing university cancer hospital, United States

F. Yu. Chongqing university cancer hospital, United States

X. Pan. Chongqing university cancer hospital, United States

W. Zhou. Chongqing university cancer hospital, United States

X. Zeng. Chongqing University Cancer Hospital, Chongqing, Chongqing, China (People's Republic)

Background: Neoadjuvant therapy (NAT) has become the standard treatment for early human epidermal growth factor receptor 2 positive (HER2+) breast cancer. For patients with HER2+ breast cancer, achieving a pathologic complete response (pCR) is highly indicative of their prognosis. However, not all HER2+ breast cancer patients could benefit from the NAT, about 40%-50% patients could not achieve pCR at surgery, even if they used the present standard neoadjuvant regime of TCbHP (taxane, carboplatin, trastuzumab and pertuzumab). This study was conducted to explore potential indicators associated with neoadjuvant efficacy of TCbHP in HER2+ breast cancer.

Methods: Consecutive HER2+ breast cancer patients, who received and completed NAT with TCbHP regime and subsequent surgery at Chongqing University Cancer Hospital were prospectively enrolled. LC-MS and GC-MS platform-based untargeted metabolomics were performed to determine the metabolic profiles of plasma samples from these patients at different time points during treatment period. Random forest (RF) was used to establish predictive models based on pre-therapeutic metabolic traits. The potential monitors for the treatment response were obtained by time series analysis. Transcriptome analysis was performed in available samples to identify differentially expressed genes (DEGs) before treatment. qRT-pCR was used to detect DEGs in trastuzumab-sensitive and -resistant cell lines. Metabolic and transcriptomic data were integrated to explore substantially altered pathways that might be responsible for drug resistance.

Results: From July 20, 2020 to May 28, 2021, a total of 40 HER2+ breast cancer patients with 120 plasma samples were eligible and recruited for this study. Of whom 21 (52.5%) patients achieved pCR and 19 (47.5%) achieved non-pCR, there are no significant difference in baseline clinicopathological features between pCR and non-pCR patients. There were significant differences in plasma metabolic profiles between non-pCR and pCR groups before and during treatment. A total of 100 differential metabolites were identified between pCR and non-pCR patients at pre-therapeutic period, which were markedly enriched in 40 metabolic pathways. Four key metabolites [sophorose, N-(2-acetamido)iminodiacetic acid, taurine and 6-hydroxy-2-aminohexanoic acid] were selected by RF analysis. The AUC value to discriminate

pCR and non-pCR group to NAT of the single potential metabolite or combined panel of these metabolites were more than 0.910. 18 metabolites exhibit a potential for monitoring efficacy. Among 163 DEGs identified by RNA-seq, some genes might associate with trastuzumab resistance detected by qRT-PCR in cell lines. 39 altered pathways were found abnormally expressed at both the transcriptional and metabolic levels, including ABC transporters, protein digestion and absorption, mineral absorption, et al.

Conclusion: By metabolomics analysis, we have both offered a road map of the molecular alterations underlying NAT of TCbHP regime in HER2+ breast cancer and a preliminary analysis of a unique metabolic signature that might be used to distinguish non-pCR from pCR patients. Metabolomics integrated with transcriptomics analysis could assist for gaining new insights into biochemical pathophysiology and might facilitate the development of new treatment targets for insensitive patients.

PO3-14-06

Immunologic features and association with prognosis in hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (MBC) treated with chemotherapy (CT) or CDK4/6-inhibitors (CDK4/6i) + endocrine therapy (ET)

Presenting Author(s) and Co-Author(s):

F. Schettini. Medical Oncology Department, Hospital Clínic of Barcelona, Barcelona, Spain ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain and Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, United States

M. Palleschi. Department of Medical Oncology, IRCCS- Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy, United States

F. Mannozi. Unit of Biostatistics and Clinical Trials, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

F. Brasó-Maristany. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), United States

L. Ceconetto. Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

P. Galván. Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

M. Mariotti. Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy, United States

A. Ferrari. UO Medicina Oncologia - Ospedale Ramazzini - Azienda USL di Modena - Carpi, Italy, United States

E. Scarpi. Biostatistics and Clinical Trials Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST);Dino Amadori, Via P.Maroncelli 40, 47014 Meldola, Italy, United States

A. Miserocchi. Unit of Biostatistics and Clinical Trials, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy, United States

O. Nanni. Unit of Biostatistics and Clinical Trials, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy, United States

E. Sanfeliu. SOLTI Breast Cancer Research Group, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Faculty of Medicine and Pathology Department, Hospital Clínic of Barcelona, University of Barcelona, Barcelona, Spain., Catalonia, Spain

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

A. Rocca. Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy, United States

U. De Giorgi. Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Italy

Purpose: Little is known regarding the prognostic and predictive role of tumor immunological features in HR+/HER2- MBC treated with CT or CDK4/6i+ET. **Methods:** The Italian KENDO phase 2 trial randomized CT-naïve patients with HR+/HER2-neg. MBC with aggressive characteristics to receive CDK4/6i+ET (arm A) or CT+/-ET (arm B). Primary endpoint was progression-free survival (PFS). A tumor sample from the primary or metastatic tumor (archived or newly-obtained) was mandatory for inclusion. In this correlative biomarker analysis, tumor-infiltrating lymphocytes (TILs) and tertiary lymphoid structures (TLS) were detected on baseline

tumor samples by hematoxylin&eosin staining, while immune genomic signatures were assessed with the nCounter BC360 panel. Immune pattern at immunohistochemistry was defined as inflamed (IF), excluded (IE) or desert (ID). TILs and signatures were dichotomized (high vs. low) with the maximally-selected rank statistics (MSRS) method. Survival analyses were conducted with the Kaplan-Meier (KM) method and differences were tested with log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated with Cox regression. Significance was set at $p \leq 0.05$. Since the trial was stopped earlier due to slow accrual all analyses were exploratory. **Results:** Forty-nine patients were randomized, 17 (34.7%) in arm A and 32 (65.3%) in arm B. No significant clinicopathological differences were observed at baseline between the two arms, except for tumors in arm B showing more TLS (50.0% vs. 12.5%, $p=0.013$). Median PFS (mPFS) with CT+/-ET was numerically shorter than mPFS with CDK4/6i+ET (11.2 vs. 19.9 months, HR: 1.41, 95%CI: 0.75-2.64, $p=0.289$). The median OS (mOS) for arm A was not estimable (NE) vs. 30.6 months in arm B ($p=0.283$). In arm A, median TILs levels were 3% (interquartile range [IQR]: 1-5%) and TLS, with/without germinal centers, were present in 2 cases (12.5%). These were also the only IF tumors in the arm, whereas the rest (87.5%) were ID. In arm B, 7 (25.0%) tumors were IF, 19 (87.5%) ID and 2 (7.1%) IE. Median TILs were 4.5% (IQR: 2-12.8%) and TLS were present in 50% cases. In arm A, ID tumors showed lower mPFS than IF (15.8 vs. 27.5 months), with concordant trend at the OS KM curve. In arm B there was no clear difference in PFS, but IF tumors did not reach mOS, differently from ID (28.7 months) and IE (28.1 months). High vs. low TILs levels were significantly associated with better PFS ($p=0.003$) and OS ($p=0.005$) in arm A. High levels of a TGF β gene expression signature were significantly associated with better PFS ($p=0.020$) and OS ($p=0.005$) in arm A and PFS ($p=0.03$) in arm B; higher levels of a cytokine/chemokine signature were associated with better PFS ($p=0.02$) in arm A, and higher levels of a mast cells signature was associated with worse OS in both arms ($p=0.02$ and $p=0.03$). In arm B, higher levels of a macrophage ($p < 0.001$) and antigen presentation signatures ($p=0.04$) were associated with worse and better OS, respectively, whereas higher levels of an immune infiltration and a cytotoxic cells signature were associated with better PFS ($p=0.03$ both). TLS presence was numerically associated to longer mPFS (23.5 vs. 15.8 months) in arm A, with consistent OS KM curve's trend, and longer mOS (44.5 vs. 28.1 months) in arm B. **Conclusions:** The KENDO trial further supports CDK4/6i+ET use in aggressive CT-naïve HR+/HER2- MBC. Biomarkers of immune activation such as IF tumors, higher TILs and presence of TLS pointed towards better survival outcomes. Genomic immunological features also showed prognostic effect, with differences according to treatment arm and/or the immune process or cell line tracked. Further research on larger cohorts is needed to confirm these preliminary findings.

PO3-14-07

Characterizing Immune Infiltration in Metastatic Hormone Receptor-Positive/HER2-Negative Breast Cancer: A Comprehensive Translational Analysis from four SOLTI Clinical Trials

Presenting Author(s) and Co-Author(s):

E. Seguí. SOLTI Cancer Research Group; Hospital Clínic Barcelona; IDIBAPS, Barcelona, Catalonia, Spain

E. Sanfeliu. SOLTI Breast Cancer Research Group, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Faculty of Medicine and Pathology Department, Hospital Clínic of Barcelona, University of Barcelona, Barcelona, Spain., Catalonia, Spain

F. Brasó-Maristany. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), United States

B. González-Farré. Pathology Department, Hospital Clínic of Barcelona, Barcelona, Spain ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, United States

F. Salvador. SOLTI Cancer Research Group, United States

L. Angelats. Hospital Clínic Barcelona/IDIBAPS, United States

L. Villanueva. SOLTI Cancer Research Group, Barcelona, Spain, United States

A. Espinosa. SOLTI Cancer Research Group, Catalonia, Spain

P. Galván. Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

E. Fernández. SOLTI Cancer Research Group, Barcelona, Spain., United States

X. Gonzalez-Farré. Instituto Oncológico Dr. Rosell, Hospital General de Catalunya, Catalonia, Spain

S. Escrivá-de-Romaní. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

N. Chic. Peter McCallum Cancer Centre, Melbourne, Australia ; SOLTI Breast Cancer Research Group, Barcelona, Spain, United States

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

L. Manso. Hospital Universitario 12 de Octubre, Madrid, Spain

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

J. Tabernero. Vall d'Hebron University Hospital. Vall d'Hebron Institute of Oncology (VHIO), Spain

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

T. Pascual. SOLTI Cancer Research Group, Barcelona, Spain /Department of Medical Oncology, Hospital Clínic de Barcelona, Spain / Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

Background: Hormone Receptor-positive (HR+)/HER2-negative (HER2-) metastatic breast cancer (BC) is a highly heterogeneous disease. Non-luminal subtypes within HR+/HER2- BC have been linked to poor survival in the metastatic setting. However, these subtypes might exhibit higher expression of immune-related genes, tumor-infiltrating lymphocytes (TILs), and APOBEC signatures. This study aimed to investigate the presence of tertiary lymphoid structures (TLS), TILs and immune gene expression (GE) across PAM50 intrinsic subtypes (IS) in metastatic samples from patients (pts) with HR+/HER2- BC.

Methods: We included pts with HR+/HER2- metastatic BC who participated in the molecular prescreening of the SOLTI-1904-ACROPOLI (NCT04802876), SOLTI-1502-ARIANNA (NCT04142060), SOLTI-1718-NEREA (NCT04460430) and SOLTI-1716-TATEN (NCT04251169) studies, providing metastatic samples for analysis. The proportion of TILs was centrally evaluated by a single pathologist using standard criteria. GE analysis was performed on the same FFPE tumor block using a panel of 72 genes, including 10 immune genes and the PAM50 IS. In a subset of patients, we conducted additional GE analysis using a panel of 192 genes, including the 14-gene B-cell/IgG (IGG) signature, while also retrospectively assessing the presence of TLS. Descriptive statistics, significance analysis of microarrays (using False Discovery Rate [FDR]) and logistic regressions were used to investigate the association between TLS, TILs, immune GE and PAM50 IS.

Results: A total of 401 pts were included. Distribution across IS was: 53.4% Luminal B (n=197), 27.1% Luminal A (n=100), 16% HER2-enriched (n=59), 2.7% basal-like (n=10) and 0.8% normal-like (n=3). TILs were evaluated in 375 samples (93.5%). Median (m) TILs proportion was 2% (IQR: 1-4, range 0-80). Non-luminal subtypes exhibited a higher enrichment of TILs compared to luminal subtypes (m=3% vs m=1%, p=0.002). Moreover, significant differences of TILs were also seen according to the site of metastasis (M1): m=6.5% in lymph nodes vs m=4.5% in lung M1 vs m=1% in liver M1 (p< 0.001). Immune GE was significantly higher in samples with a high proportion of TILs (>10%), although the correlation between TILs and immune genes was moderate (e.g. coefficient=0.44, p< 0.001, between CD8A and TILs). TLS were evaluated in 147 samples and detected in 16 pts (10.9%). Compared to TLS-negative tumors, TILs were significantly higher in TLS-positive (TLS+) tumors (m=1.5% vs m=10%, p< 0.001). In addition, the presence of TLS was significantly higher in non-luminal subtypes compared to luminal subtypes (18% (11/61) vs 5.8% (5/86), p=0.019). TLS+ tumors had a significant enrichment of genes related to activated B-cells (CD19, CD79A), plasma cells (CD27), immunoglobulins (IGKC, IGLV), and T-cells (CD8A, PDCD1). Notably, the IGG signature as a continuous variable demonstrated a significant association with TLS presence, independently of the PAM50 IS and TILs (p=0.033, ROC AUC=0.817). Finally, higher expression of some immune genes was observed in non-luminal subtypes vs luminal subtypes (e.g., CD19 (p=0.016) and CD274/PDL1 (p< 0.001)).

Conclusions: Our translational analysis reveals that non-luminal subtypes within metastatic HR+/HER2- BC exhibit a higher enrichment of TILs, immune GE, and presence of TLS. Importantly, we identified the IGG signature as a robust immune GE pattern that is strongly associated with TLS across PAM50 IS, independent of TILs. These findings highlight the potential significance of the IGG signature as a novel biomarker for precisely measuring TLS and selecting pts who might be more likely to derive benefit from immunotherapy.

PO3-14-08

Metaplastic Breast Cancer: Whole Genome Sequencing Analysis and Emerging Therapeutic Targets

Presenting Author(s) and Co-Author(s):

F. Pareja. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, United States

A. Gazzo. Memorial Sloan Kettering Cancer Center, New York, New York, United States

H. Dopeso. Memorial Sloan Kettering Cancer Center, New York, New York, United States

D. Brown. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, United States

P. Selenica. Memorial Sloan Kettering Cancer Center, United States

Y. Zhu. Memorial Sloan Kettering Cancer Center, New York, New York, United States

J. Blanco-Heredia. Memorial Sloan Kettering Cancer Center, New York, NY, USA, United States

L. Gusain. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, United States

X. Pei. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

G. Montagna. Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, United States

N. Abuhadra. Memorial Sloan Kettering Cancer Center, United States

H. Wen. Memorial Sloan Kettering Cancer Center, United States

E. Brogi. Memorial Sloan Kettering Cancer Center, United States

N. Riaz. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

M. Scaltriti. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, United States

L. Norton. Memorial Sloan Kettering Cancer Center, United States

S. Powell. MSKCC, United States

J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States

B. Weigelt. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Metaplastic breast cancer (MpBC) is a rare histologic subtype of triple negative breast cancer (TNBC) with an aggressive behavior and poor outcome. Previous studies by whole-exome and targeted sequencing showed that MpBCs display a dominant mutational signature 3, associated to homologous recombination (HR) deficiency (HRD). Tumors displaying HRD are associated with response to therapies causing double strand breaks. Nonetheless, MpBCs consistently display significantly lower rates of response to neoadjuvant chemotherapy than non-metaplastic TNBCs and effective therapeutic alternatives are an unmet clinical need. Here we sought to assess the HR features of MpBCs using whole-genome sequencing (WGS), and to evaluate the expression in MpBCs of antigens that are targets of novel antibody drug conjugates (ADCs) in common forms of breast cancer. In addition, we

sought to assess the efficacy of ADCs and drugs targeting the DNA damage response (DDR) using preclinical MpBC models. Materials and Methods: We subjected 25 primary MpBC to WGS. HRDetect, the 'gold standard' tool for assessment of HRD, was utilized. Mutational signatures were inferred using Signal. 31 MpBCs were subjected to RNA-sequencing to assess the gene expression levels ADC targets compared to non-MpBCs from The Cancer Genome Atlas (TCGA). Efficiency of ADCs and DDR drugs was evaluated using the MpBC cell models HCC1806, BT549 and Hs578T in vitro and/or using HCC1806 xenografts in athymic mice in vivo. Results: Although the majority of MpBCs (13/25) displayed a dominant SBS mutational signature 3, only a small subset of cases (3/25) were classified as HRD by HRDetect. These three bona fide HRD cases were found to harbor bi-allelic inactivation of BRCA1 (n=2) or RAD51C (n=1), and displayed various genomic features of HRD, including deletions with microhomology, enrichment in tandem duplications, rearrangement signatures 3 and 5, and high large scale state transitions (LST) and telomeric allelic imbalance (NtAI) scores. Most MpBCs (22/25), however, were not classified as HRD by HRDetect displaying an incomplete HRD phenotype, with only partial genomic features of HRD. 52% of MpBCs (13/25) displayed APOBEC mutagenesis exposure, which was present in the three bona fide HRD MpBCs. RNA-sequencing analyses revealed detectable ERBB2 and TROP2 expression in all MpBCs interrogated, although at lower levels than in non-MpBCs from TCGA. The HCC1806, BT549 and Hs578T MpBC cell models were found to be sensitive to Sacituzumab Govitecan and Trastuzumab Deruxtecan (T-DXd) in cell viability and colony formation assays, and to T-DXd in vivo. These MpBC cell models were also found to be sensitive to DDR compounds, such as ATR, WEE1 and PKMYT1 inhibitors in vitro, alone and in combination with T-DXd or Sacituzumab Govitecan. Conclusions: Most MpBCs display an incomplete HRD genomic scar, except for those cases harboring bi-allelic inactivation of HRD genes. APOBEC mutagenesis is operative in MpBCs and co-exists with HRD. MpBCs express ERBB2 and TROP2, and MpBC cell models are sensitive to T-DXd and Sacituzumab govitecan, as well as DDR compounds, targeting the incomplete HRD phenotype of MpBCs, alone and in combination. Taken together, these findings warrant further studies in patients with MpBCs testing the therapeutic efficacy of agents targeting the incomplete HRD phenotype, as well as the expression of ADC targets in these aggressive rare forms of TNBCs.

PO3-14-10

A single-center prospective cohort study to evaluate circulating tumor cells as a monitoring tool in women with breast cancer treated with neoadjuvant chemotherapy: final results of baseline data

Presenting Author(s) and Co-Author(s):

R. chehade. Sunnybrook Odette Cancer Centre, University of Toronto, United States

A. Jain. Synnybrook Research Institute, United States

V. Moravan. VM Stats, United States

G. Di Caro. Epic Sciences, United States

M. Slade. Epic Sciences, California, United States

N. Hartmann. EPIC SCIENCES, United States

R. Wenstrup. Epic Sciences, United States

A. Lohmann. London Health Sciences Centre, United States

W. Tran. Odette Cancer Centre - Sunnybrook Health Sciences Centre, United States

K. Jerzak. Sunnybrook Health Sciences Centre, United States

Background: The presence of liquid biomarkers such as circulating tumor cells (CTCs) among women undergoing neoadjuvant chemotherapy (NAC) for breast cancer may be associated with treatment response and/or an increased risk of recurrence, but limited data is available. **Objectives:** To detect and enumerate CTCs in blood samples from women with a new diagnosis of non-metastatic breast cancer of any subtype both i) at baseline (prior to commencing NAC), and ii) after completion of NAC and surgery using the Epic Sciences platform. **Methods:** Women with non-metastatic breast cancer of any subtype who have not yet commenced NAC were included, irrespective of age. Those with a prior history of another invasive cancer (apart from non-melanoma skin cancer identified 5+ years prior to enrollment) were excluded. Blood samples were obtained to measure CTCs prior to commencing NAC, and after completion of NAC and surgery (at least 4 weeks post-operatively). As previously described, CTC identification was based on immunofluorescence analysis using the Epic Sciences platform (Ueno et al 2017). Clinical/pathological data and clinical outcomes were abstracted from patients' medical records. Associations between CTC detection and clinical/pathologic characteristics were evaluated using Fisher's exact test for categorical variables and t-test or Wilcoxon rank sum tests for numerical variables. All analyses were performed using the R software package. **Results:** 50 participants who met eligibility criteria were included; a baseline blood sample was evaluable for CTC detection and enumeration for 47 patients. The median age at breast cancer diagnosis was 52 (29-75). Among them, 18 (38.3%) had HER2+ breast cancer, 17 (36.1%) had hormone receptor (HR)+/HER2- breast cancer and 12 (25.5%) had triple negative breast cancer (TNBC). The majority of patients (91%) received anthracycline and taxane-based NAC. A total of 68 samples were tested for CTC enumeration (5 mL equivalent per sample) including 47 pre-treatment and 21 post-treatment samples. CTCs were detected in 37 (79%) of patients for whom a baseline (pre-NAC) sample was available with a mean of 4.2 (SD 17.0) CTCs/mL and a range of 0 - 115.4 CTCs/mL. Detection of CTCs at baseline was highest among patients with TNBC (n=10/12, 83%), followed by those with HER2+ (n=14/18, 78%) and HR+/HER2- (n=13/17, 76%) breast cancer. CTCs were detected in 43% (n=9/21) of post-treatment samples, with a mean of 1.2 (SD 3.6) CTCs/mL and range of 0 – 16.4 CTCs/mL. Among the 20 patients for whom matched pre- and post-treatment CTC results were available, 16 (80%) had detectable CTCs pre-treatment and 8 (40%) had detectable levels post-NAC and

surgery; of the 8 patients with post-treatment CTCs, 4 (50%) had HR+/HER2- breast cancer, 2 had HER2+ (25%) and 2 (25%) had TNBC. Three patients had numerically higher CTC levels after completion of NAC and surgery compared to baseline levels, 2 of whom had HR+/HER2- breast cancer and one of whom had TNBC. To-date, only 8 patients (19% of 43 who have undergone surgery) have achieved a pathological complete response (PCR) to NAC, among whom 3 had matched pre- and post-treatment CTC results available. None of these 3 patients had detectable CTCs post treatment. Conclusions: Approximately 4 in 5 women with non-metastatic breast cancer who undergo NAC have detectable CTCs at baseline (pre-treatment) using the Epic Sciences Platform. Given that CTCs remain detectable in a high proportion (40%) of patients after NAC and surgery, evaluation of CTCs as a potential measure of minimal residual disease warrants further evaluation in this patient population.

PO3-14-11

Association between BRCA alterations detected by circulating tumor DNA and germline mutations in breast cancer patients: a retrospective mono-institutional analysis.

Presenting Author(s) and Co-Author(s):

L. Pontolillo. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, United States

E. Nicolò. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

L. Munoz Arcos. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, New York, United States

C. REDUZZI. Weill Cornell Medicine, United States

M. Serafini. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA; , United States

A. Strickland. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA; , United States

N. Bayou. Faculty of Medicine-University of Tunis El Manar, Department of Human Genetics/Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

J. Donahue. Weill-Cornell, New York, New York, United States

E. Molteni. Department of Medicine, University of Udine, Italy/Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

D. Giannarelli. Biostatistic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy., Italy

E. Andreopoulou. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

E. Bria. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, United States

M. Cristofanilli. Weill Cornell Medicine, United States

Background: PARP inhibitors (PARPi) are a standard of care for breast cancer (BC) patients (pts) with germline BRCA (gBRCA) mutation, with benefit demonstrated also in patients with somatic (s) BRCA1/2 mutations. The use of circulating tumor (ct) DNA testing allows to detect resistant and actionable alterations in BC, but it could be associated with the incidental identification of germinal mutations. The aim of this study was to describe the incidence of both, somatic and germinal BRCA1/2 alterations, and the impact on the therapeutic outcomes in a retrospective BC cohort with clinical ctDNA testing for their BC.

Materials and methods: A retrospective cohort of 245 BC pts that underwent ctDNA analysis (Guardant 360) between August 2014 and May 2023 at Weill Cornell Medical College was identified. Pts with at least a BRCA1/2 alteration, including variant of uncertain significance (VUS) and synonymous, were enrolled in the study. A descriptive analysis was performed.

Results: Among 35 patients included, 34 had metastatic disease, the median age was 61 years old (IQR 40-67), and 65.7% were post-menopausal at diagnosis. 57.1% of pts had hormone

receptor positive/HER2 negative (HR+/HER2-) BC, 20% had HER2 positive disease and 22.9% were triple-negative (TN) BC.

Ten (28.6%) and 20 (57.1%) pts had a sBRCA1 or a sBRCA2 alteration on ctDNA, respectively; 5 pts (14.3%) had a coexisting sBRCA1/2 mutation. The median variant allele frequency (VAF) was 1.2% for BRCA1 and 2.7% for BRCA2 alterations. Furthermore, 53.3% and 6.7% of sBRCA1 and 40% and 8% of sBRCA2 mutations were identified as VUS and synonymous, respectively.

The most common associated genomic alterations included TP53 (62.9%), ESR1 (20%) and PI3KCA (52%) with a median number of 4 variants (IQR 2-7).

Next generation sequencing (NGS) testing on tissue was available for 3 patients: two demonstrated concordance with BRCA alterations detected by ctDNA, whereas no alteration in BRCA1/2 genes was found for the third patient despite the tissue analysis was performed at the same time of the ctDNA.

Germline testing was available for 24 (69%) pts; a corresponding gBRCA1 mutation was found for 3 pts (VAF 48.6%-84.3%), and a gBRCA2 for 8 pts (VAF 26.7%-49.5%). Due to the small sample size, a univocal VAF cut-off to detect gBRCA1/2 mutations could not be calculated. Twenty-nine pts had a sBRCA1/2 mutation detected by ctDNA test before starting a new therapy; of these 55.2% had HR+/HER2- disease, while 17.2% and 27.6% were HER2 positive and TN BC, respectively.

The median progression free survival (mPFS) was 10.3 (3.2-17.4) months (ms) and the 1-year and 2-year overall survival (OS) rates were 82.3% and 70.5%, respectively. The mPFS was 10.3 ms (0-25.0) for patients (n=16) that underwent chemotherapy, 5.6 ms (0-15.1) for those who had received endocrine therapy (n=9), and not reached for patients treated with PARPi (n=4).

Conclusions: ctDNA analysis allows the detection of sBRCA1/2 mutations that could be missed by tissue-based testing. The identification of BRCA alterations on ctDNA could guide the use of germline testing even when these are present at a lower VAF than expected, with relevant impact on the therapeutic choices and family screening. Further evaluation to establish the impact of sBRCA1/2 detected by ctDNA on the therapeutic algorithm decision are needed.

PO3-14-12

SIRT3 as a new potential predictive biomarker for response to CDK4/6 inhibition in ER+/HER2- metastatic breast cancer patients

Presenting Author(s) and Co-Author(s):

M. Manai. Pasteur Institute of Tunis, Laboratory of Transmission, Control and Immunobiology of Infections, Tunis, Tunisia

G. Sahraoui. Salah Azaiez Institute, Anatomic Pathology Department, Tunis, Tunisia

R. Doghri. Salah Azaiez Institute, Anatomic Pathology Department, Tunis, Tunisia

L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

P. D'Amico. Northwestern University, United States

Y. Zhang. Northwestern Medicine Northwestern University, Chicago, Illinois, United States

J. Donahue. Weill-Cornell, New York, New York, United States

A. Shah. Northwestern University - Feinberg School of Medicine, United States

C. REDUZZI. Weill Cornell Medicine, United States

W. Qiang. Northwestern University, United States

M. Cristofanilli. Weill Cornell Medicine, United States

Background: Several prospective, randomized clinical trials showed that the CDK4/6 inhibitor palbociclib in combination with either letrozole or fulvestrant significantly improves progression-free survival (PFS) in patients with ER+/HER2- metastatic breast cancer (MBC). However, in some cases, there is development of endocrine resistance and ultimate disease progression. Molecular analysis performed in tissue specimens collected in the PALOMA-3 study, comparing fulvestrant and Palbociclib versus fulvestrant placebo, demonstrated that one of the genes associated with an increased clinical benefit is SIRT3 (Sirtuin 3) which is thought to control mitochondrial integrity and metabolism (Cristofanilli M. et al., Lancet Oncol. 2016). This study aimed to evaluate in preclinical models the predictive role of SIRT3 in ER+/HER2- breast tumors.

Methods: Using lentiviruses we generated MCF-7 and T47D cells stably expressing either control shRNA (sh ctr) or shRNA targeting SIRT3 (shSIRT3). With these models, we studied cell viability, tumor growth, apoptosis, and autophagy in MCF-7 cells treated with fulvestrant and palbociclib as a single treatment or in combination, these either alone or in combination with shSIRT3 (knockdown). Nude mice were used for our in vivo studies, and sh ctr or shSIRT3 MCF7 cells were injected.

Results: We showed in vitro that the response to palbociclib was significantly associated with levels of SIRT3 expression as high or low in ER+ cells ($p < 0.0001$). Furthermore, we found that irreversible cell growth inhibition mediates the beneficial effect of palbociclib in SIRT3 high expressing cells compared to low expression ($p < 0.001$). Then, we evaluated the mechanistic activity of SIRT3. We showed that SIRT3-low expression cells induced enhanced sensitivity to palbociclib by targeting the reactive oxygen species (ROS)/autophagy axis: (i) SIRT3 regulated the mitochondrial homeostasis (e.g. glucose, lactate, pyruvate, succinates), (ii) ROS levels were lower in sh ctr comparing and shSIRT3 in treated and untreated cells ($p < 0.001$), (iii) in terms of senescence, a higher level of positive cells for β -gal activity was found ($p \leq 0.05$) and (iv) for autophagy, our western blot analysis showed cleaved LC3 proteins. Our in vivo studies

showed that SIRT3 regulated treatment response to palbociclib with a significant decrease in tumor weight and tumor volume ($p < 0.01$) and importantly, after immunohistochemistry analysis, we validated the role of SIRT3 in regulating the proteins involved in the autophagy/senescence balance, was mainly in epithelial cells compared to stromal cells.

Conclusion: Our preclinical studies demonstrated that elevated SIRT3 expression levels sensitizes ER+/HER2- breast tumors to palbociclib treatment. This study suggested that SIRT3 expression could represent a potential predictive biomarker in HR+ MBC patients treated with Palbociclib.

PO3-15-01

Overexpression of N-glycosylation related gene OST4 promotes chemotherapy resistance in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

W. Wang. Shanghai General Hospital, United States

D. Liu. Department of Breast and Thyroid Surgery, Shanghai General Hospital, Shanghai JiaoTong University School of Medicine, United States

S. Ding. Shanghai General Hospital, United States

Y. Fang. Shanghai General Hospital, United States

J. Wu. Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, United States

L. Zhu. Department of Breast and Thyroid Surgery, Shanghai General Hospital, Shanghai JiaoTong University School of Medicine, United States

Triple-negative breast cancer (TNBC) is one of the most aggressive subtypes of breast cancer, with high malignancy and poor outcome. Resistance to chemotherapy leads to treatment failure. How to overcome drug resistance is the key point in TNBC treatment. Previously, we initiated a prospective multicenter single-arm NeoPath clinical study (ClinicalTrials.gov identifier: NCT03907800) to assess the efficacy and safety of nab-paclitaxel combined with carboplatin in the neoadjuvant therapy of triple negative and HER2-positive early breast cancer. A total of 99 TNBC patients were enrolled and the pCR rate in TNBC was 33.78%. Samples before and after treatment were collected. RNA-sequencing results showed that OST4 was of high-expression in drug-resistant TNBC tumor tissues compared with chemo-sensitive samples. To verify the clinical significance of OST4 expression levels in TNBC, we tested the expression of OST4 by immunohistochemical technique on a tissue microarray including 87 TNBC cases treated with chemotherapy. We found that high expression of OST4 was associated with poor tumor differentiation, and patients with high OST4 expression had more relapse after chemotherapy. Ex-vivo proliferation assay and foci formation assay further confirmed that over-expression of OST4 promoted chemo-resistance, whereas down-regulating OST4 could reverse resistance in TNBC cell lines. As an oligosaccharyltransferase, it is reported that OST4 played parts in N-glycosylation. So we try to elucidate the relationship between N-glycosylation and drug resistance. Glycoproteomics results verified the existence of differential N-glycosylation atlas in drug-resistant tumor tissues compared with drug sensitive samples. NGS1 was identified as a potential target of OST4 by co-immunoprecipitation and mass spectrometry. In conclusion, high expression of OST4 could promote chemotherapy resistance in TNBC through N-glycosylation regulation. Targeting OST4 may help reverse drug-resistance and improve therapeutic effect in TNBC.

PO3-15-02

TP53 GENE POLYMORPHISM AT CODON 72 AS A RESPONSE PREDICTOR FOR NEOADJUVANT CHEMOTHERAPY

Presenting Author(s) and Co-Author(s):

J. Vieira. UNIFESP, aracaju, Sergipe, Brazil

A. Nazário. Universidade Federal de São Paulo, United States

J. Pesquero. UNIFESP, sao paulo, Sao Paulo, Brazil

Introduction: Breast cancer is one of the most prevalent in women in the world and has shown extensive changes in treatment in recent decades. More patients are undergoing neoadjuvant chemotherapy in order to achieve pathological complete response (CPR) and perform less aggressive surgeries. CPR increases overall and disease-free survival and the decrease in tumor size increases the chances of conservative surgery. We have numerous studies that propose to discover CPR markers. Predictive factors of response to chemotherapy are important for treatment planning and the P53 gene, apoptosis-inducing gene, plays a role in inducing response to chemotherapy drugs that act by inducing apoptosis. The presence of mutations and genetic polymorphisms act by modulating this response. Among these, the codon 72 polymorphism is one of the most studied, as its polymorphic variants Arg/Arg, Arg/Pro and Pro/Pro encode a p53 with different functioning at the cell level. So, individuals with different polymorphisms will have different apoptotic action and different response to chemotherapy treatments. **Objectives:** Based on this knowledge, the study sought to correlate the polymorphism variants at codon 72 with the complete pathological response to neoadjuvant chemotherapy. **Casuistic and Methods:** The study was carried out at an oncology center in the state of Sergipe, in northeastern Brazil. A total of 206 patients with breast cancer who underwent neoadjuvant chemotherapy and core needle biopsy of the breast at the beginning of treatment were included in the study, in the period from 2019 to 2022. From these patients, oral swab samples were collected for PCR evaluation of the P53 polymorphism at codon 72. The polymorphisms were studied using the Sanger technique at the Sao Paulo School of Medicine of the Federal University of São Paulo (UNIFESP). Patients were prospectively evaluated after surgery to verify the surgical pathological response after chemotherapy. Pathologic response was assessed using the RECIST criteria. The study was evaluated and approved by the ethics and research committee of UNIFESP and all patients signed an informed consent form. **Results:** Of the 206, 18.4% met the exclusion criteria (did not undergo surgery, interrupted chemotherapy treatment, insufficient genetic material in the swab, loss of follow-up). Of the 168 patients analyzed, 44.6% were Arg/Arg, 17.3% Pro/Pro and 38.0% Arg/Pro. Complete pathological response (PCR) was obtained in 21.4% of the patients, 10.1% had progressive disease (PD), 13.7% had stable disease (SD) and 54.2% had partial pathological response (PPR). Of the patients who achieved RPC, 47.2% were Arg/Arg, 38.9% Arg/Pro and 13.9% Pro/Pro without statistical significance, among the variants of polymorphisms. The only predictor of CPR in multivariate regression was immunohistochemistry ($p < 0.001$). The only predictor of CPR in multivariate regression was immunohistochemistry ($p < 0.001$) **Conclusion:** The P53 polymorphism at codon 72 is not a predictor of complete pathological response, but the Arg/Pro and Pro/Pro polymorphisms increase the chances of stable disease after neoadjuvant chemotherapy.

PO3-15-03

Abemaciclib is effective in palbociclib resistant estrogen receptor positive breast cancers

Presenting Author(s) and Co-Author(s):

J. Navarro-Yepes. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

N. Kettner. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

X. Rao. The University of Texas MD Anderson Cancer Center, United States

T. Bui. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

C. Bishop. Yale University, United States

H. Wingate. Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, United States

A. Singareeka Raghavendra. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Y. Wang. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Wang. MD Anderson cancer center, United States

A. Sahin. UT MD Anderson cancer center, Houston, TX, Texas, United States

F. Meric-Bernstam. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Damodaran. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Keyomarsi. Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Introduction: Hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (Her2)-negative breast cancer constitutes the majority of breast cancer cases and is commonly treated with endocrine therapy (ET). However, resistance to ET is a significant clinical challenge in metastatic breast cancer (MBC). The addition of cyclin-dependent kinase 4/6 inhibitors (CDK4/6is), such as palbociclib, ribociclib, and abemaciclib, to ET has shown promise in delaying disease progression. Nonetheless, resistance to CDK4/6is remains a concern, necessitating the exploration of alternative treatment strategies. This study aims to investigate the distinct mechanisms of resistance between palbociclib and abemaciclib and evaluate the sequential use or targeting of differentially altered pathways to delay disease progression in HR-positive/HER2-negative tumors.

Models: In vitro models of palbociclib-resistant (PR) and abemaciclib-resistant (AR) cell lines were generated to elucidate the pathways leading to resistance. Patient-derived xenografts (PDX) and ex vivo PDX-derived organoids (PDXOs) from MBC patients who experienced progression on CDK4/6is were also employed.

Results: PR and AR cells exhibited unique transcriptomic and proteomic profiles, with 14 similarly and 30 differentially altered pathways identified between PR and AR in vitro models. Epithelial-mesenchymal transition (EMT) and hypoxia were enriched in PR cells but not in AR cells, while oxidative phosphorylation (OXPHOS) and reactive oxygen species pathways were enriched in AR cells. Consequently, PR cells responded to abemaciclib, whereas AR cells showed sensitivity to OXPHOS inhibitors. Genomic alterations were heterogeneous and did not consistently predict palbociclib response. Furthermore, the use of organoids and PDX models confirmed that tumors with high expression of G2/M pathway genes remained responsive to abemaciclib. Clinical data from a cohort of patients with HR-positive/HER2-negative MBC demonstrated that sequential treatment with palbociclib and abemaciclib resulted in significantly longer overall survival (42.7 months versus 17.3 months) compared to non-sequential therapy.

Conclusion: Transcriptomic and proteomic analyses revealed distinct pathways in PR and AR models, suggesting that patients with enrichment of the G2/M pathway are likely to benefit from abemaciclib following palbociclib resistance, whereas those with enrichment of the OXPHOS pathway are most likely to be refractory. These findings support the need for prospective trials to evaluate the clinical benefit of abemaciclib after progression on a prior CDK4/6i regimen.

PO3-15-04

Oncotype DX Recurrence Score as an Informative Tool to Optimize Neoadjuvant Therapy in HR-positive, HER2-negative Breast Cancers

Presenting Author(s) and Co-Author(s):

L. Luzhna. BC Cancer Vancouver, Vancouver, British Columbia, Canada

S. Chia. British Columbia Cancer Agency, Vancouver, British Columbia, Canada

M. Pauls. BC Cancer, United States

N. Levasseur. BC Cancer - Vancouver, United States

Oncotype DX Recurrence Score as an Informative Tool to Optimize Neoadjuvant Therapy in HR-positive, HER2-negative Breast Cancers

Background: Neoadjuvant therapy (NAT) in HR+/HER2- breast cancers rarely leads to pathological complete response (pCR) and often doesn't achieve substantial tumor shrinkage. Therefore, neoadjuvant therapy in HR+/HER2- breast cancers has the most value in the assessment of in vivo treatment response. For this purpose, biomarkers that can predict clinical and pathological response to systemic therapy could help inform treatment. The role of Oncotype DX testing in the management of early-stage HR+/HER2- breast cancer has been widely recognized in the adjuvant setting. However, no large prospective studies evaluating the Oncotype DX test in the neoadjuvant setting have clearly shown its predictive or prognostic utility to date. In this study, we evaluated the effect of the recurrence score (RS) on systemic treatment recommendations and its correlation to NAT response.

Methods: Patients with clinically selected T2-T4 and/or clinically node positive HR+/HER2- breast cancer who were referred to BC Cancer Vancouver for consideration of NAT between September 2021 – April 2023 were screened for study eligibility. Suitable candidates who agreed to participate in the study had Oncotype DX testing on core biopsy specimens and Ki-67 testing on the core biopsy and final resection specimen. Clinico-pathological information, treatment regimens, operative details, and clinical, radiologic, and pathological responses were recorded.

Results: Of the 66 patients who met eligibility criteria, 40 enrolled in the study comprising the accrual rate of 60.6 %. There were multiple factors that influenced patients and/or Oncologists participation in the study highlighting the low uptake of NAT in HR+/HER2- tumors. Technical feasibility of obtaining Oncotype DX from core biopsy samples was 95% which correlates with our previously reported data on a smaller cohort. The mean turnaround time from patient consent to RS report was 18.5 calendar days. The mean time from the initial consult to the start of NAT was 18.8 calendar days.

Amongst all tumors tested, 28 % had RS equal or greater than 26 while only 2 % of participants had a score less than 10. Overall, 32 % of treatment recommendations were changed based on RS. Approximately 31% of patients who were initially recommended to receive neoadjuvant chemotherapy were spared from this treatment based on low RS. Conversely, 23.8% of patients who were recommended to pursue upfront surgery were escalated to chemotherapy due to a high RS.

Approximately 88 % of the participants who were treated with neoadjuvant chemotherapy had a favourable clinical response and 38.5% had a complete clinical response. There were no pCR

observed amongst patients who completed surgery after neoadjuvant chemotherapy, but half of them were rendered eligible for less surgery (either spared a mastectomy and/or an axillary dissection).

Conclusions: Oncotype DX testing changed systemic treatment recommendations in one third of neoadjuvant patients and presents a unique opportunity for personalized medicine. Pre-operative testing thus influenced clinical decision-making, allowing treatment de-escalation and omission of chemotherapy in those with a low RS and conversely an earlier escalation of systemic therapy for those with a high RS. Turnaround time of the Oncotype DX assay on a core biopsy sample was acceptable and did not significantly delay treatment initiation. The benefit of the Oncotype DX assay prior to NAT was valuable for predicting in vivo response although pCR was not observed in any of the patients enrolled. Analyses are ongoing to further correlate RS to neoadjuvant response and to dynamic Ki-67 and MRI changes.

PO3-15-05

B cell immunology predict response and survival in PD-1/PD-L1 targeting immune checkpoint inhibition of metastatic breast cancer

Presenting Author(s) and Co-Author(s):

C. Fremd. Medical Oncology, National Center for Tumor Diseases Heidelberg, NCT (DKFZ and University Hospital), Heidelberg, Baden-Wurttemberg, Germany

M. Schulze. Merck KGaA, Darmstadt, Germany, United States

M. Cetin. German Cancer Research Center (DKFZ), United States

H. Boehm. German Cancer Research Center (DKFZ), United States

B. Lenoire. German Cancer Research Center (DKFZ), United States

O. akilli-Oeztuerk. TRON Mainz, United States

I. Zörnig. NCT Heidelberg, United States

P. Charoentong. NCT Heidelberg, United States

Y. Lyu. German Cancer Research Center Heidelberg, Germany, United States

C. Collaborators. DKFZ/UKHD, United States

D. Hübschmann. German Cancer Research Center, United States

F. Kommos. Department of Pathology, University Hospital Heidelberg, Germany, United States

V. Thewes. National Center for Tumor Diseases (NCT) Heidelberg, a partnership between DKFZ and Heidelberg University Medical Center, Heidelberg, Germany, Heidelberg, Baden-Wurttemberg, Germany

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

M. Zapatka. German Cancer Research Center (DKFZ), United States

F. Hartmann. German Cancer Research Center, United States

P. Lichter. Division of Molecular Genetics, German Cancer Research Center (DKFZ), Heidelberg, Germany, Germany

Critically understudied in the era of T cell immunotherapies, aggregation of B cells within tertiary lymphoid structures (TLS) has recently been linked to improved response and survival in immune checkpoint inhibition (ICI). While this has been reported for several cancers, including melanoma, lung cancer, bladder and renal cell cancer, there is an unmet need to understand molecular patterns in tumors with limited mutational burden (TMB) and low overall abundance of tumor infiltrating lymphocytes (TILs). Here, we report on the landscape of B cells in metastatic breast cancer, inferred by bulk sequencing (WGS/RNAseq) and multiplexed ion beam imaging (MIBI-TOF) in 203 patients across the breast cancer biology (ER/PR/HER2), collected from real world data (CATCH diagnostic and register study, NCT05652569). Median age was 53 years (range, 23-79), with a median of 3 systemic treatment lines for advanced or metastatic disease. The majority of biopsies were taken from the liver (49%), followed by breast (15%), lymph node (13%), skin (6%) and lung (6%). Immunohistochemistry based subtyping revealed 61% of the HR+/HER2- (or Luminal HER2-), followed by 26% of HR-/HER2- (TNBC), and 15% of HER2+ subtype. Immunological subtyping by stromal TILs and CD8+ infiltrates defined 3 subgroups with 57% being desert, 18% inflamed and 19% of no special type (6% NA). The majority (52%) was scored CD20+ with minimal colocalization in 45% of samples.

MIBI-TOF demonstrated a continuum of coordinated B cell and T cell aggregation in the tumor microenvironment with lymphoid aggregates in 29% and mature TLS structures in 26% of patients. No correlation with conventional biomarkers for immunogenicity (PD-L1, TMB) has been observed. Chart review identified 21 patients treated by immune checkpoint blockade (ICI) targeting PD-1 (Pembrolizumab) or PD-L1 (Atezolizumab), either as monotherapy or in combination with chemotherapy/targeted therapy. Overall response rate (ORR) at week 12 was 57%, disease control rate (DCR) was 71%. RNA signature levels for germinal center signalling, B cell activation and antibody secretion correlated with quality of B cell aggregation and, importantly, significantly with response to ICI (Kruskal Wallis $p=0,028$). B cell derived prediction of response was independent of PD-L1 protein expression, breast cancer subtype, BRCA mutation status or TMB. Downstream single cell analysis, computational immunogenomics as well as spatial neighbourhoods will be reported at the meeting. These results extent B cell centered molecular insights to metastatic breast cancer and may pave the way for a composite biomarker, selecting patients for ICI who benefit meaningful and would not have been identified by the current standard of care.

PO3-15-06

Identification of a Novel Five Ferroptosis-Related Gene Signature as a Promising Prognostic Model for Breast Cancer

Presenting Author(s) and Co-Author(s):

T. Cheng. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, United States

J. Wu. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, United States

B. Zhu. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, United States

L. Zheng. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, United States

W. Chen. Department of Breast Surgery, the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213000, Jiangsu Province, China, Changzhou, Jiangsu, China (People's Republic)

Background: Breast cancer (BCa) is a major challenge for women's health worldwide. Ferroptosis is closely related to tumorigenesis and cancer progression. However, the prognostic value of ferroptosis-related genes in BCa remains unclear, and more accurate prognostic models are urgently needed. **Methods:** Gene expression profiles and clinical information of BCa patients were collected from public databases. LASSO and multivariate Cox regression analysis were utilized to construct the prognostic gene signature. Kaplan-Meier plotter, Receiver Operating Characteristic (ROC) curves, and nomogram were used to validate the prognostic value of the gene signature. Gene set enrichment analysis was performed to explore the molecular functions and signaling pathways. **Results:** Differentially expressed ferroptosis-related genes between BCa samples and normal tissues were obtained. A novel five-gene signature including BCL2, SLC40A1, TFF1, APOOL, and PRAME was established for prognosis prediction. Patients stratified into high-risk or low-risk group displayed significantly different survival. Kaplan-Meier and ROC curves showed a good performance for survival prediction in different cohorts. Biological function analysis revealed that the five-gene signature was associated with cancer progression, immune infiltration, immune response, and drug resistance. Nomogram including the five-gene signature was established. **Conclusions:** A novel five ferroptosis-related gene signature and nomogram could be used for prognostic prediction in BCa. **Key words:** breast cancer, ferroptosis, gene signature, overall survival, prognosis

PO3-15-07

False-negative results of hyperexpression of HER2 receptor in breast cancer at a public tertiary hospital in Brazil

Presenting Author(s) and Co-Author(s):

B. Batista. Pontificia Universidade Catolica do Parana, United States

S. Ioshii. Pontificia Universidade Catolica do Parana, United States

S. Padilha. Universidade Federal do Parana, United States

J. Nabhen. Universidade Federal do Parana, United States

T. Ostroski. Hospital Erasto Gaertner, United States

C. Batista. Hospital Erasto Gaertner, United States

Introduction: Breast cancer (BC) is the second leading cause of cancer death in women worldwide. One of the major advances in BC management was its molecular classification, especially regarding the Human Epidermal growth factor Receptor 2 (HER2). HER2 positive tumors are at greater risk of visceral metastasis and are associated with worse survival rates. Thus, the use of specific drugs to target this pathway is essential and false-negative have a high impact on patient care. HER2 status is usually accessed using immunohistochemistry (IHC), but false-negatives results occur. When IHC results are inconclusive, in-situ hybridization (ISH) testing is necessary. Objective: to determine if there is variability between the positivity rates between laboratories that performed the ISH, according to the IHQ, and to evaluate if there are false-negative results and possible prognostic impact. Methods: retrospective, observational study in a public hospital in the city of Curitiba (Brazil), followed by cross-sectional analysis of histological samples. All cases of BC that underwent HER2 assessment by IHC and ISH between January 2008 and December 2018 were included. Participants classified as HER2 negative by IHC and patients whose medical records were not available were excluded. A new analysis of all IHC slides and of cases with negative ISH was performed. Results: We identified 205 people with an average age of 53.52 (\pm 11.89) years. Most cases were classified as clinical stage I and II (68.3%), and the most prevalent histological features were Invasive Ductal Carcinoma (82.4%) and luminal molecular subtype (49.8%). Initial ISH testing was performed by four laboratories. There was a significant difference in HER2 positivity rates between these laboratories, even after individual reanalysis of all IHC slides. Of the 114 cases with negative ISH, it was possible to obtain histological material in 82 of them to perform a new standardized ISH. The false-negative rate for HER2 in this 82 patients was 41.46%, with 10 cases out of 24 for positive IHC (3+) and 22 out of 58 for inconclusive IHC (2+). In this paper, false-negative results did not impact in survival, most likely to differences between groups. Conclusion: our work showed different rates of positivity for HER2 among laboratories that performed confirmatory test with ISH. The performance of a second standardized ISH proved that the difference between the laboratories was due to false-negative results. There was no difference in recurrence and cancer-specific survival in this false-negative sample.

Keywords: breast cancer. Biomarkers. Health technology assessment. HER2 receptor.

Differences between laboratories re regarding HER2 false negatives

False negatives and true positives between laboratories. Note on more false negatives in A and B

	Laboratories			
	A	B	C	Total
	n (%)	n (%)	n (%)	n (%)
HER2 false neg	14 (41,2)	16 (47,1)	4 (11,8)	34 (100)
TRUE HER2	23 (28,7)	20 (25)	37 (46,3)	80 (100)
Total	37 (32,5)	36 (31,6)	41 (36)	114 (100)

PO3-15-08

Validation for prognostic staging based AJCC 8th edition with nuclear grade in Japanese breast cancer patients: A multicenter retrospective study

Presenting Author(s) and Co-Author(s):

K. Kaneshiro. Japan / Hamanomachi Hospital / Breast Center / St Mary Hospital / Breast surgery, United States

M. Yamada. Japan / Kyushu University / Department of Clinical Oncology and Breast Surgery, United States

S. Hayashi. Japan / Kyushu University / Department of Clinical Oncology and Breast Surgery, United States

K. Koga. Japan / Kitakyushu Municipal Medical Center / Department of Surgery, Breast Surgery, United States

M. Saimura. Japan / Kitakyushu Municipal Medical Center / Department of Surgery, Breast Surgery, United States

N. Otomo. Japan / Miyazaki Prefectural Miyazaki Hospital / Breast Surgery, United States

S. Umeda. Japan / JCHO Kyushu Hospital / Breast Surgery, United States

K. Anan. Kitakyushu Municipal Medical Center, Kitakyushu, Japan

M. Okido. Japan / Hamanomachi Hospital / Breast Center, United States

T. Morisaki. Japan / Kyushu University Hospital / Department of Breast Surgery, United States

M. Nakamura. Dept. Surgery and Oncology, Kyushu University, Japan

M. Kubo. Kyushu University graduate school of Medical Sciences, Kyushu University Hospital, Fukuoka, Fukuoka, Japan

Introduction.

The American Joint Committee on Cancer (AJCC) 8th edition of breast cancer classification introduced the concept of "prognostic stage," which is based on anatomic classification (TNM classification) plus four biomarkers: estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2), and histological grading (HG).

In Japan, however, the introduction of histological classification has been passive and slow, and the nuclear grading (NG) has been used so far.

Objective.

Our aim is to compare the prognostic staging classification in the AJCC, 8th edition which substitutes NG for HG (AJCC8th-NG) with the TNM classification, and to confirm the usefulness of AJCC8th-NG classification.

Methods.

We collected 5229 patients with primary breast cancer operated on between 2005 and 2013 at six institutions affiliated with Kyushu University Hospital in Japan, for whom prognosis was available.

We retrospectively evaluated the 7-year survival rates based on the TNM classification and the AJCC8th-NG classification, based on the pathological diagnosis of their surgeries.

Results.

Median age was 58 years (24-99), 5210 (99.6%) were female, and the 7-year survival rate of all eligible patients was 93.2%.

The changes in the number of cases by stage were observed as follows: Stage 0 (16.5%), Stage IA (42.3% to 56.2%), Stage IB (0.3% to 8.8%), Stage IIA (21.5% to 6.9%), Stage IIB (9.7% to 3.1%), Stage IIIA (3.9% to 3.5%), Stage IIIB (1.5% to 1.9%), Stage IIIC (2.1% to 0.9%), Stage IV (1.9%).

The changes in 7-year survival rates were observed as follows: Stage 0 (96.1%), Stage IA (96.8% → 96.5%), Stage IB (93.7% → 93.4%), Stage IIA (93.1% → 87.8%), Stage IIB (88.5% → 84.6%), Stage IIIA (86.9% → 80.4%), Stage IIIB (78.7% to 84.4%), Stage IIIC (79.8% to 58.4%), and Stage IV (51.9%). (TNM classification → AJCC8th-NG classification)

Both TNM classification and AJCC8th-NG classification were significantly associated with prognosis. AJCC8th-NG classification was more stratified. In AJCC 8th-NG Stage IB, which is the largest population in all patients, 42% of that were triple-negative type (TN) downstaging from TNM Stage IA and 58% were luminal type downstaging from TNM Stage II-III. In AJCC 8th-NG Stage IIIC, which was changed the most with biomarkers, 52% of that were TN upstaging from TNM Stage IIIA-IIIB. On the other hand, 50% of AJCC 8th-NG Stage IIIB with a favorable prognosis were ER-positive or HER2-positive downstaged from TNM Stage IIIC.

Discussion

TN breast cancer generally has a poor prognosis. However, HER2-positive breast cancer, which used to have a poor prognosis, is said to have a favorable prognosis after the availability of anti-HER2 drugs. This time, we examined cases after 2005 when anti-HER2 drugs became available in Japan, but the results did not show that HER2-positive breast cancer had a better prognosis than HER2-negative breast cancer. In this study, we were unable to confirm the use of anti-HER2 drugs. In the AJCC 8th classification, it seems necessary to consider whether or not treatment is being provided. If all patients are treated, the prognostic stratification will become clearer.

Conclusion.

Our study could show that AJCC8th-NG classification was useful for predicting prognosis same as AJCC8th classification in the relatively large cohort.

PO3-15-09

LobSig4 is a superior and readily implementable ILC-focussed prognostic biomarker set.

Presenting Author(s) and Co-Author(s):

L. Kalinowski. The University of Queensland and Sullivan Nicolaides Pathology, United States

J. Kutasovic. The University of Queensland, United States

S. Srihari. QIMR Berghofer, United States

Y. Feng. The University of Queensland, United States

S. Lal. The University of Queensland, United States

K. Ferguson. The University of Queensland, United States

H. Chittoory. The University of Queensland, United States

A. Sokolova. The University of Queensland and Sullivan Nicolaides Pathology, United States

M. Lim. The University of Queensland, United States

P. Kalita De Croft. The University of Queensland, United States

S. Lakhani. The University of Queensland and Pathology Queensland, United States

P. Simpson. The University of Queensland, United States

A. McCart Reed. The University of Queensland, United States

Invasive Lobular Carcinoma (ILC) is the most common special histological subtype of breast cancer. ILC typically present as Oestrogen and Progesterone Receptor positive cancers, without over-expression of HER2 and are defined by their invasive pattern of growth. Despite clinical and biological differences, including diverse sites of metastasis, ILC are managed in the same way as the more commonly diagnosed, Invasive Carcinomas of no special type. Previously, we derived the LobSig lobular specific gene signature in an attempt to prognosticate within an otherwise homogeneous tumour category. We showed that this set of genes could stratify Grade 2 and Nottingham Prognostic Index moderate tumours into high and low risk groups. Herein, we use a nanoString nCounter custom codeset and immunohistochemistry to validate the LobSig signature. Using a CoxBoost analysis we further refined the geneset to 14 genes of interest which we examined using Immunohistochemistry on a large panel of ILC with clinical follow up data. Four targets showed a significant association with breast cancer specific survival, with high levels correlating with the poorest outcomes. Considering the expression data for these 4 candidates together, we performed a Cox Proportional Hazard Regression resulting in a combined prognostic power of ($P=0.00034$, $HR=8.07$ (CI 2.58-25.30)), which has superior prognostic power over variables including tumor size and patient age. 'LobSig4' represents a readily implementable and informative biomarker set for prognostication in Invasive Lobular Carcinoma.

PO3-15-10

Enhanced Cancer Cell Proliferation and Aggressive Phenotype Counterbalance in Breast Cancer with High BRCA1 Gene Expression

Presenting Author(s) and Co-Author(s):

K. Chida. Department of Surgical Oncology, Roswell Park Comprehensive Cancer Center, United States

M. Oshi. Roswell Park Comprehensive Cancer Center, United States

A. Roy. Roswell Park Comprehensive Cancer Center, United States

I. Endo. Yokohama City University Graduate School of Medicine, United States

K. Takabe. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

Introduction: It is estimated that 5–10% of all breast cancer cases have a hereditary component with BRCA1 mutation being one of the most frequently observed gene mutations in breast cancer patients. BRCA1 plays a crucial role in DNA repair, and its mutation has been extensively studied. However, the clinical significance of BRCA1 gene expression remains largely unexplored. Given that heightened DNA repair mechanisms can potentially increase cancer cell proliferation, we hypothesized that breast cancer with high BRCA1 gene expression might be associated with aggressive tumor biology and worse survival. **Methods:** The clinical, pathological and gene expression levels of a total of 6,245 breast cancer patients were analyzed from three large independent cohorts: METABRIC (n = 1,903), GSE96058 (n = 3,273), and The Cancer Genome Atlas (TCGA, n = 1,069). The data was retrieved through cBioPortal. The xCell algorithm was used to correlate the BRCA1 gene expression with the stromal and immune cell fractions infiltrating the tumor microenvironment (TME). **Results:** BRCA1 gene expression was higher in breast cancer patients without BRCA1 mutation, and it correlated with the DNA repair activity (p = 0.026 and p < 0.01 respectively), however, it did not correlate with BRCA2 gene expression (p = 0.38). Breast cancer with high BRCA1 gene expression was associated with cancer cell proliferation as evidenced by higher Nottingham histological grade (p < 0.001), Ki67 expression (p < 0.001), significant enrichment of cell proliferation-related gene sets such as E2F Targets, G2M Checkpoint, MYC Targets V1 and V2, Mitotic Spindle (all FDR < 0.25), and significantly less infiltration of stromal cells such as adipocytes, fibroblasts, microvascular and lymphatic endothelial cells, and pericytes (all p < 0.05). High BRCA1 gene expression was associated with higher homologous recombination deficiency, intratumor genomic heterogeneity, and fraction altered (all p < 0.001); however, there was no correlation observed with mutation rates or neoantigens. It was observed that breast cancer with high BRCA1 gene expression had less infiltration of CD8 T cells, dendritic cells, regulatory T cells, and B cells and had higher infiltration of Th1 cells (all p < 0.05). To our surprise, there was no significant difference in overall survival regardless of the subtypes (except for ER+/HER2- subtype in METABRIC cohort, p = 0.03). Breast cancer with low BRCA1 gene expression enriched cancer aggravating pathway gene sets such as Cancer Stem Cell-related signaling pathways (NOTCH and HEDGEHOG), Angiogenesis, Epithelial Mesenchymal Transition, Inflammatory Response, and TGF-beta signaling (all FDR < 0.25). **Conclusion:** Contrary to our initial hypothesis, we did not find any significant association between BRCA1 gene expression and survival outcomes in breast cancer patients. Based on the results of our study, we speculate that the interplay between enhanced cancer cell proliferation and aggressive tumor characteristics may counterbalance the effect of high BRCA1 expression in breast cancer.

PO3-15-11

Soluble sFas, sFasL, sPD1, and sPD-L1 analyses in the blood peripheral of locally advanced breast cancer women before and after neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

C. Vasconcelos. Hospital de Cancer de Pernambuco - HCP, Recife, Brazil, Recife, Pernambuco, Brazil

M. Salgado. Hospital de Câncer de Pernambuco - HCP, Recife, Brazil, Pernambuco, Brazil

C. Anunciação. Hospital de Cancer de Pernambuco- HCP, Recife, Brazil, Recife, Pernambuco, Brazil

D. Viana. Hospital de Cancer de Pernambuco - HCP, Recife, Brazil, Pernambuco, Brazil

L. Torres. Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, Brazil; Hospital de Cancer de Pernambuco (HCP), Recife, Brazil; Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil, Recife, Pernambuco, Brazil

N. Valois Montarroyos de Moraes. Cancer Hospital of Pernambuco, recife, Pernambuco, Brazil

Assess soluble sFAS, sFASL, sPD1, and sPD-L1 levels in patients with HER2 or triple-negative (TN) breast cancer submitted to neoadjuvant chemotherapy. A prospective cohort study was performed with TN and HER2+ breast cancer patients between 2015 and 2018. Soluble levels of sFasL, sFas, sPD-L1, and sPD1 were collected before and after neoadjuvant chemotherapy (NAC). NAC regimens included a dense dose of Adriablastin and cyclophosphamide during four cycles, followed by Paclitaxel for 12 weeks. No clinical evidence of tumor in the breast and axillary lymph nodes was defined as a pathological complete response (pCR). Twenty-one women with TN (56,7%) and 16 (43,3%) HER2+ breast cancer were included. Twenty-one women (56.7%) presented complete pathological response (pCR) after neoadjuvant chemotherapy (NAC), defined as the absence of invasive disease in the breast and lymph nodes. High sPD1 and sFas levels in the TN and HER2+ patients compared to the control group ($P < 0.05$). In paired analysis, statistical differences of sFas and sFasL levels in TN and HER2+ patients before and after NAC ($P < 0.05$). Low levels of sPDL1 in HER2+ patients with pCR compared to non-pCR ($P < 0.05$). High sFasL levels in TN patients with pCR compared to the non-pCR group ($P < 0.05$). Conclusion: soluble sFas, sFas-L, sPD1, and sPD-L1 levels were apoptosis-related markers with potential predictive value of neoadjuvant chemotherapy response in TN and HER2+ breast cancer.

Keywords: breast cancer; FAS receptor; Programmed death 1, HER2+, Triple negative

PO3-15-12

Expression and co-expression patterns of TROP2 and HER2 in breast cancer: implications for bispecific antibody-drug conjugate therapy

Presenting Author(s) and Co-Author(s):

M. Onishi. National Cancer Center Hospital, Tokyo, Japan
T. Shimoi. National Cancer Center Hospital, Tokyo, Japan
Y. Kojima. National Cancer Center Hospital, United States
S. Yazaki. National Cancer Center Hospital, United States
T. Yamanaka. National Cancer Center Hospital, United States
R. Kitadai. National Cancer Center Hospital, United States
A. Kawachi. National Cancer Center Hospital, United States
H. Okuma. National Cancer Center Hospital, United States
M. Hoshino. National Cancer Center Hospital, United States
A. Saito. National Cancer Center Hospital, United States
M. Ito. National Cancer Center Hospital, United States
A. Maejima. National Cancer Center Hospital, United States
T. Nishikawa. National Cancer Center Hospital, United States
K. Sudo. National Cancer Center Hospital, United States
E. Noguchi. National Cancer Center Hospital, United States
Y. Fujiwara. National Cancer Center Hospital, United States
M. Yoshida. Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo, Japan, United States
K. Yonemori. Medical Oncology, National Cancer Center Hospital,, United States

Introduction: Antibody-drug conjugates (ADCs) targeting trophoblast cell surface antigen 2 (TROP2), such as sacituzumab-govitecan and datopotamab-deruxtecan, have recently been developed. A preclinical study has reported the efficacy of anti-human epidermal growth factor receptor 2 (HER2) and TROP2 bispecific ADCs in treating HER2 and TROP2 co-expressing tumors, including HER2-low tumors in various solid tumors (Chengzhang Shang et al: AACR 2023). In this study, we aimed to evaluate the expression of TROP2 by immunohistochemistry (IHC) at different sites and investigate the changing status and co-expression of HER2 and TROP2 among breast cancer patients.

Methods: We collected 244 archival paired samples of primary tumors and metastatic sites from 111 breast cancer patients treated in our hospital from 2000 to 2018. Estrogen receptor (ER), progesterone receptor (PgR), and HER2 status were determined from previous pathology reports. HER2 low was defined as HER2 IHC score of 1+ or 2+ with negative fluorescent in situ hybridization (ISH). In addition, we determined the expression of TROP2 using IHC assays and categorized the results based on the histochemical score (H-score).

Results: Among the samples, ER+HER2- was 139, ER+HER2+ was nine, ER-HER2+ was eight, and triple-negative (TN) was 88. HER2 3+ or 2+ with ISH positive was 17, HER2 low was 112, HER2 negative was 115. The median TROP2 H-score was 10, with a mean of 37.5 (range: 0-265). Overall, 27% of the samples had H-score of 0, 73% had H-score of 1< , 47%

had H-score of 10< , and 12% had H-score of 100< . No statistically significant association was observed between TROP2 expression and breast cancer subtypes (ER+HER2-; H-score of 0 24%, H-score of 1< 76%, H-score of 10< 44%, H-score of 100< 14%, TN; H-score of 0 30%, H-score of 1< 70%, H-score of 10< 54%, H-score of 100< 11%). On the other hand, samples from the metastatic site showed a higher rate of TROP-2 expression H-score of 1< compared to the primary site (primary site; H-score of 0 36%, H-score of 1< 64%, metastatic site; H-score of 0 18%, H-score of 1< 82%; $p < 0.01$). The rates of TROP2-positive expression defined as H-score of 1< , varied among the metastatic sites, with 100% in liver, 92% in brain, 89% in lymph nodes, 64% in lung, and 60% in bone. Regarding the co-expression of HER2 and TROP2, among HER2-positive samples, 35% had TROP2 H-score of 0, 24% had TROP2 H-score of 1< , and 41% had TROP2 H-score of 10< , while among HER2 low samples, 21% had TROP2 H-score of 0, 27% had TROP2 H-score of 1< , 39% had TROP2 H-score of 10< , and TROP2 H-score of 100< was found in 13% of patients. Based on the definition of co-expression such as TROP2 H-score of 1< and HER2 1+ or more, overall, 40% of the samples had co-expression of HER2 and TROP2, and the metastatic site had a higher rate of co-expression than the primary tumor (49%, 32% respectively, $p=0.002$).

Conclusions: This study demonstrates that TROP-2 expression by IHC in breast cancer varies between primary and metastatic sites in breast cancer. Metastatic sites and specific organs show higher rate of TROP2 expression. Additionally, 40% of the samples had the co-expression of HER2 and TROP2, suggesting a potential target for future bispecific ADCs therapy.

PO3-16-01

Personalized circulating tumor DNA assay precisely predicts the response of neoadjuvant chemotherapy in breast cancer patients

Presenting Author(s) and Co-Author(s):

J. Kim. Samsung Medical Center, United States

H. Jung. Samsung Medical Center, United States

J. Lee. Samsung Medical Center, Seoul, Republic of Korea

S. Kim. Breast Division, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, United States

H. Kim. IMBdx Inc., Seoul, Republic of Korea, United States

S. Heo. IMBdx, United States

J. Ahn. IMBdx, United States

T. Kim. Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; Cancer Research Institute, Seoul National University, Seoul, Republic of Korea; IMBdx Inc., Seoul, Republic of Korea, United States

Y. Im. Samsung Medical Center, Seoul, Republic of Korea

Introduction Circulating tumor DNA (ctDNA), which is detected in the blood as cell free DNA fragment from tumor cells, could indicate genomic landscape, tumor burden and treatment response during chemotherapy as a non-invasive method. Especially, personalized ctDNA assay by next-generation sequencing (NGS) is able to detect a trace amount of ctDNA and precisely figure out the change of the amount of ctDNA during NAC and follow up period after curative surgery. Here, we performed serial ctDNA evaluations in EBC patients who diagnosed as TNBC or HER2-positive BC and received NAC followed by curative surgery. We aimed to predict NAC response and detect minimal residual disease (MRD) using personalized ctDNA assay. **Methods** CtDNA was detected by AlphaLiquid[®]Detect, a tumor-informed personalized MRD detection assay exploring most of the mutations in tumor. Whole exome sequencing (WES) of tumor tissue and peripheral blood mononuclear cells (PBMCs) was performed. Patient-specific somatic mutations were selected using a proprietary algorithm. In brief, clonal variants were prioritized using integrated information including variant allele frequency, population allele frequency databases, somatic variant databases, variant pathogenicity, and genomic context. Up to 100 variants were selected for patient monitoring. A hybridization capture panel consisting of a pool of 4 patients' selected variants was synthesized. These bespoke panels (BSPs) were used for ctDNA detection. Patients with more than 2 tumor-derived mutations detected in plasma were considered as ctDNA positive.

Inclusion criteria included patient who diagnosed as stage IIA-IIIC BC planned to NAC followed by curative surgery. Among BC subtypes, TNBC and HER2-positive BC were allowed. Collection of specimens and associated clinical data used in this study was approved by the Institutional Review Board of Samsung Medical Center (IRB File No.2021-02-033), and we received informed consents for this study. **Results** From May 2021 to Sep 2022, 158 patients has been enrolled. Archival tissues were not available in 47 patients and tissue WES had failed in six patients. Therefore, 105 patients were enrolled and analyzed their ctDNA at diagnosis based on tissue WES data.

Of 105 patients, Median age of BC patients was 49.3 years of age (range: 26.1, 67.8). Thirty-six

patients (34.3%) were post-menopausal status and others (65.7%) were pre-menopausal status. In BC pathology at diagnosis, 56 (53.3%) were TNBC and other 49 (46.7%) were HER2-positive BC. Among HER2-positive BC, hormone receptor (HR)-positive were in 21 (20.0%). In clinical stage at diagnosis, stage II were 46 (43.8%) and stage III in 59 (56.2%).

In 105 patients, median number of somatic mutations was 60 (interquartile range [IQR]: 38.5, 91). CtDNA detection rate at BC diagnosis was 90.5% and all of BC which not be detected ctDNA was HER2-positive BC with clinical stage II. Median amount of ctDNA at diagnosis was 20 (IQR: 6, 44).

In the number of somatic mutations, there was no difference according to BC subtypes ($P=0.121$) and clinical stage ($P=0.700$) but the amounts of ctDNA at diagnosis was different. CtDNA was much more detected in TNBC compared to HER2-positive BC (Median: 34.5 vs. 15.9; $P < 0.001$) and clinical stage III compared to clinical stage II (Median 33.2 vs. 19.5; $P=0.002$). After NAC, ctDNA at curative surgery was tested in 70 patients. In 70 patients, pathologic complete response (pCR) was observed in 44 patients. CtDNA was detected in ten patients (14.3%) and eight did not achieve pCR and two with pCR (Specificity of assay: 95.5%, positive predictive value: 0.80, $P=0.032$). **Conclusions** Personalized ctDNA assay can precisely detected ctDNA at diagnosis and their detection rate was associated with BC subtypes and clinical stage. In addition, ctDNA at curative surgery also can predict NAC response in EBC patients. Long term ctDNA follow up of MRD would be warranted.

PO3-16-02

Trastuzumab and taxane chemotherapy in the first-line in MBC patients with a HER2-negative primary tumor and HER2-positive circulating tumor cells: a phase II trial

Presenting Author(s) and Co-Author(s):

N. Verschoor. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

M. Bos. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

I. de Kruijff. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

N. Van. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

J. Kraan. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

J. Drooger. Department of Internal Medicine, Breast Cancer Center South Holland South, Ikazia Hospital, Rotterdam, The Netherlands, United States

J. Zuetenhorst. Department of Medical Oncology, Franciscus Gasthuis & Vlietland, Rotterdam/Schiedam, the Netherlands, United States

S. Wilting. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

S. Sleijfer. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

A. Jager. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, Rotterdam, Netherlands

J. Martens. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, Rotterdam, Zuid-Holland, Netherlands

Purpose: HER2 overexpressing circulating tumor cells (CTCs) are observed in up to 20% of HER2-negative metastatic breast cancer patients. Since targeted anti-HER2 therapy has drastically increased the outcome of patients with HER2 positive breast cancer, we hypothesized that patients with HER2 overexpressing CTCs might benefit from the addition of trastuzumab to chemotherapy.

Methods: In this single-arm, phase II trial, HER2 negative patients with HER2-positive CTCs received trastuzumab as addition to first-line treatment with taxane chemotherapy (trastuzumab group). Patients with detectable CTCs but without HER2 overexpression and that received taxane chemotherapy only, were used as internal control group (taxane monotherapy group). The primary outcome measure was progression-free rate at 6 months (PFR6). The study was powered to reach a PFR6 of 80%; in this case this strategy was considered worth further investigation. In November 2022, the study was terminated early due to slow patient accrual.

Results: 63 HER2 negative patients with metastatic disease were screened, of which 8 patients had HER2-positive CTCs and were treated in the first line with trastuzumab in addition a taxane. Patients receiving taxane monotherapy were used as a control group (n = 27). The median number of CTCs was 15 (range 1 – 131) in patients with HER2-positive CTCs, compared to median 5 (range 1-1047) in the control group. PFR6 was 50% in the trastuzumab group and 64% in the taxane monotherapy group, with no significant difference in median PFS (8 versus 9 months, p=0.51). Excluding the patients that had no measurable CTCs, there was a borderline significant difference between median CTC count in the patients that did and that did not have HER2 positive CTCs (p=0.05). We confirmed a significant higher CTC-count in samples that had at least one HER2-positive CTC in an independent patient set (n=233, p< 0.001).

Conclusions: Although this study was performed in a limited number of patients, no clinical

benefit of trastuzumab was observed. Firstly, we conclude that our strategy was not feasible for clinical implementation due to high numbers needed to screen. And, second, due to the strong correlation between CTC numbers and detected CTC HER2 positivity, the prognostic value of the CTC numbers precludes judgement of any predictive value of the HER2 status of CTCs.

PO3-16-03

Investigating HER2DX genomic assay concordance within HER2-positive breast cancer

Presenting Author(s) and Co-Author(s):

F. Brasó-Maristany. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), United States

L. Paré. Reveal Genomics, United States

G. Villacampa. VHIO, London, England, United Kingdom

M. Marín-Aguilera. Reveal Genomics, United States

P. Spellman. UCLA, United States

A. Waks. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

I. Krop. Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, United States

E. Sanfeliu. SOLTI Breast Cancer Research Group, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Faculty of Medicine and Pathology Department, Hospital Clínic of Barcelona, University of Barcelona, Barcelona, Spain., Catalonia, Spain

Z. Li. DFCI, United States

P. Galván. Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

E. Hernández-Illán. Hospital Clínic Barcelona, United States

P. Jares. Pathology Department & Molecular Biology CORE, Hospital Clinic Barcelona, United States

J. Puig-Butillé. Hospital Clinic Barcelona, United States

A. Vivancos. Cancer Genomics Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain., Barcelona, Spain

P. Villagrasa. REVEAL GENOMICS, United States

J. Parker. University of North Carolina, United States

C. Perou. Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA., United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

O. Metzger. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

K. Polyak. Dana Farber Cancer Institute, Harvard Medical School, United States

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

Background: The HER2DX genomic assay, encompassing a 27-gene panel, provides prognostic (risk-score) and predictive (pathological complete response [pCR]-score) information while quantifying ERBB2 mRNA expression (ERBB2-score). This study aims to explore the variability of HER2DX scores within tumor samples and between paired diagnostic biopsies and surgical specimens. **Methods:** The standardized HER2DX assay was conducted on pretreatment FFPE biopsies from two distinct geographical areas within tumors (i.e., two different core biopsies) of patients enrolled in the 14-409 phase II study. This study assessed the impact of HER2 heterogeneity on treatment response in stage II-III HER2+ breast cancer patients treated with neoadjuvant T-DM1 and pertuzumab. Additionally, HER2DX was evaluated on paired biopsy-surgery FFPE samples from 6 patients who underwent primary surgery without pre-operative treatment. Variability and concordance of the three HER2DX

groups scores were calculated, and Pearson's correlation coefficient determined the correlation between scores at different sites/time points. Paired t-tests were performed between tumor samples for the HER2DX scores. **Results:** The HER2DX assay was evaluated in two different diagnostic pre-treatment core biopsies from 106 patients (n=212 HER2DX assays). Intra-tumor concordance rates of the three HER2DX groups (risk-score, pCR-score, and ERBB2-score) were 94.3%, 87.7%, and 91.5%, respectively. No significant differential expression of HER2DX scores was observed across paired core biopsies (p-values=0.327 [risk-score], 0.415 [pCR-score], and 0.451 [ERBB2-score]). The average score differences (core 1 - core 2 [scale from 0 to 100]) were 0.57 (risk-score), 0.63 (pCR score), and -0.63 (ERBB2-score). Correlation coefficients across paired core biopsies were 0.96 (risk-score), 0.91 (pCR-score), and 0.90 (ERBB2-score). Additionally, intra-patient variability of the HER2DX scores was evaluated. Average variability in risk-score was 3.38% (95% CI: 2.76-4.01), in pCR-score was 3.53% (95% CI: 2.84-4.23) and in ERBB2 was 3.87% (95% CI: 2.97-4.77). In 6 patients with cT1-2 cN0 disease, HER2DX was evaluated in a diagnostic core biopsy and a surgical specimen, with an average time interval of 8.5 weeks (range 4 to 12 weeks) between time points. The intra-patient concordance rates of the three HER2DX groups were 83.3%, 83.3%, and 100% for risk-score, pCR-score, and ERBB2-score, respectively. No significant differential expression of HER2DX scores was found across paired biopsy-surgery samples (p-values=0.814 [risk-score], 0.128 [pCR-score], and 0.607 [ERBB2-score]). The average score differences (core biopsy - surgical specimen [scale from 0 to 100]) were -0.67 (risk-score), -11.5 (pCR score), and 2 (ERBB2-score). Correlation coefficients across paired HER2DX assays were 0.97 (risk-score), 0.87 (pCR-score), and 0.94 (ERBB2-score). **Conclusion:** The HER2DX genomic assay demonstrates low variability within HER2+ breast cancer, supporting its reliability as a consistent tool for assessing prognosis, the probability of pCR and ERBB2 quantitative expression.

PO3-16-04

Distribution of intrinsic subtypes in endocrine-resistant and endocrine-sensitive breast cancer

Presenting Author(s) and Co-Author(s):

C. Schagerholm. Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden, United States

S. Robertson. Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, United States

E. Karlsson. Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, United States

E. Sifakis. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden, United States

J. Hartman. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden, United States

Background

Breast cancer (BC) is a heterogeneous disease that can be divided into intrinsic molecular subtypes. Among the four intrinsic subtypes, Luminal A and Luminal B are the most common and associated with the best outcome, whereas HER2-enriched and basal-like are less frequent. Tumors that are estrogen receptor α (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative (ER+/HER2-) are mostly found among the luminal subtypes. Despite that patients with ER+/HER2- tumors are offered adjuvant endocrine therapy, around one-third eventually develop endocrine resistance. The aim of this study was to explore the distribution of intrinsic subtypes in endocrine-resistant primary and relapse tumors, comparing these to endocrine-sensitive controls.

Materials and methods

Verified endocrine-resistant BC patients diagnosed in 2008-2012 were retrospectively collected at the Karolinska University Hospital, Stockholm, Sweden. Cases (N=70) were identified as patients with ER+/HER2- primary tumors and subsequent ER+/HER2- relapse tumors within 5 years and during endocrine therapy. Patients with primary ER+/HER2- tumors without progression or relapse at 10 years of follow-up were defined as controls (N=78), diagnosed in 2005-2006. Extracted RNA from formalin-fixed paraffin-embedded tumor tissue was analyzed by Affymetrix Clariom D Microarray and assessed by Transcriptome Analysis Console and R software.

Results

Among the controls, the distribution of Luminal A, Luminal B, and HER2-enriched subtypes was 65.4%, 34.6%, and 0%, respectively. In primary tumors, the distribution was in turn 55.4%, 43.1%, and 1.5%, and among relapse tumors 57.6%, 37.9%, and 4.5%, respectively. A total of 19 cases, accounting for 27.1%, switched intrinsic subtypes between the paired primary and relapse tumors. No tumors exhibited the basal-like subtype.

Conclusion

In this unique cohort, Luminal B and HER2-enriched subtypes were more common in primary and relapse tumors of verified endocrine-resistant patients than in primary tumors of endocrine-sensitive controls. Further, the HER2-enriched subtype, although sparse, was more frequently

found in patients' relapse tumors than in their corresponding primary tumors, and over one-fourth of cases switched subtypes during progression. These findings support the presence of subtype shifting in endocrine-resistant relapses and that endocrine-resistant tumors are more prone to be of Luminal B or HER2-enriched subtypes than endocrine-sensitive tumors.

PO3-16-05

Mitochondrial DNA mutation detection in tumors and circulating extracellular vesicles of triple negative breast cancer patients for biomarker development

Presenting Author(s) and Co-Author(s):

K. Vikramdeo. UNIVERSITY OF SOUTH ALABAMA, Alabama, United States

S. ANAND. UNIVERSITY OF SOUTH ALABAMA, United States

S. SUDAN. UNIVERSITY OF SOUTH ALABAMA, United States

P. PRAMANIK. UNIVERSITY OF SOUTH ALABAMA, United States

S. SINGH. UNIVERSITY OF SOUTH ALABAMA, United States

A. Godwin. University of Kansas Medical Center; Kansas Institute for Precision Medicine; The University of Kansas Cancer Center, United States

A. SINGH. UNIVERSITY OF SOUTH ALABAMA, United States

S. DASGUPTA. UNIVERSITY OF SOUTH ALABAMA, United States

Early detection of triple-negative breast cancer (TNBC) patients and their recurrence prediction are daunting tasks. We aim to develop mitochondrial DNA (mtDNA) based biomarkers to improve the management strategies of TNBC patients. We have undertaken mitochondrial genome (MG) enrichment and next-generation sequencing approaches to map the entire MG in 73 samples (64 tissues, 9 extracellular vesicle samples) from 32 highly-aggressive TNBC patients. Measurement of mtDNA and cardiolipin contents, in concert with NDUFB8 and SDHB proteins' expression, was carried out in tumors and matched extracellular vesicles (EVs) of all the above TNBC patients. Overall, we identified 168 nonsynonymous mtDNA mutations, of which 73% (123/168) were coding and 27% (45/168) were non-coding. Twenty percent of mutations were nucleotide transversions. Respiratory complex I (RCI) appears to be the key target, which harbored 44% (74/168) of the overall mtDNA mutations. A panel of 11 hotspot mtDNA mutations was identified among 19-38% TNBCs, each of which was detectable in the matched EV samples with 82% specificity. Overall, 38% of the metastatic tumor-signature mtDNA mutations were detectable in matched EVs of the TNBC patients. An appreciable number of mtDNA mutations were homoplasmic (18%, 31/168), novel (14%, 23/168), and potentially pathogenic (9%, 15/168). The overall and RCI-specific mtDNA mutational load was recorded to be higher in African American (AA) compared to European American (EA) women with an exclusive abundance of respiratory complex (RC) protein NDUFB8 (RCI) and SDHB (RCII) therein. Increased mtDNA ($p < 0.0001$) content was measured in both tumors and matched EV samples along with an abundance of cardiolipin ($p=0.0001$) content in the EVs of the TNBC patients. Lethal tumor-signature mtDNA mutation detection and measurement of altered mtDNA and cardiolipin contents in the EVs at an early time point bear the potential to formulate noninvasive early detection and recurrence prediction strategies in TNBCs to improve the overall survival of the patients.

PO3-16-06

Perceptions and experiences of patients and healthcare providers on genetic testing and treatment of early breast cancer: qualitative findings

Presenting Author(s) and Co-Author(s):

J. Earla. Merck & Co., Inc., Rahway, New Jersey, United States

E. Mulvihill. Cerner Enviza, an Oracle Company, United States

J. Lankin. Cerner Enviza, an Oracle Company, United States

L. Howell. Cerner Enviza, an Oracle Company, United States

A. Kissling. Cerner Enviza, an Oracle Company, United States

W. Li. AstraZeneca, Gaithersburg, Maryland, United States

J. Mejia. Merck & Co., Inc., Rahway, New Jersey, United States

Background: Olaparib is approved as adjuvant therapy for high-risk HER2-negative early breast cancer (eBC) patients with germline BRCA mutations (BRCAm). Understanding patients' preferences for genetic testing and treatment in the context of shared decision-making is needed to support optimal care in eBC. This study elicited the perspectives of patients with eBC and healthcare providers (HCP) treating eBC regarding treatment decision-making, and drivers and barriers to BRCA testing.

Methods: Semi-structured interviews were conducted in the United States from Jan-Feb 2023 with women (n=12) diagnosed with eBC from 2017-2021. Community and academic oncologists treating eBC (n=12) and genetic counselors (GCs; n=8) were also interviewed. Patients who were tested (n=7) and untested (n=5) for BRCAm were included. A content and thematic analysis was performed which identified key factors from the data; these analyses provided both a range and common responses that may influence BRCA testing and treatment decisions.

Results: BRCA-tested patients considered testing beneficial. In choosing to receive testing, >50% of patients reported HCP recommendation (n=7) and the opportunity to have "all of the information" about their eBC (n=7) as strong influencers. Patients declined genetic testing noting fear around negative impact to their insurance coverage (n=2) or mental health (n=3), or if they did not have family who would benefit from the information. Cost did not strongly influence testing choice.

In choosing a treatment, patients sought to maintain their quality of life (QoL) with fewer side effects while minimizing chance of recurrence. They expressed the dual goals of normalcy during treatment, including curtailing side effects that impact QoL, and returning to normalcy after treatment (n=7). Patients were willing to accept unpleasant side effects to have a more effective treatment if those side effects do not severely impact their QoL and the treatment is highly effective (n=9). Side effects that may lead to hospitalization were the least accepted as they disrupt normalcy.

HCPs reported that patients eagerly accept testing and face minimal familial or access barriers to testing. HCPs observed that among their non-Medicare patients, testing is usually covered by insurance with minimal out-of-pocket costs, thus alleviating financial constraints observed in previous years. HCPs believe BRCA testing is driven by updated hereditary cancer testing guidelines (e.g., NCCN), lower testing costs, closer collaborations of physicians and genetic counselors, and greater awareness among patients.

HCPs reported that they embrace patient-led decision-making in eBC, especially as it relates to patients with BRCAm considering additional prophylactic surgery, and GCs further emphasized patient autonomy. Oncologists mentioned that they discuss risk status starting at diagnosis and these conversations evolve over the patient journey as new information emerges. In HR+ eBC, oncologists offered most patients with BRCAm adjuvant olaparib, which they perceive as well tolerated. In triple-negative eBC, oncologists opted for neoadjuvant Keytruda regimen prior to considering adjuvant olaparib for gBRCAm patients.

Conclusions: Patients value information that empowers them to achieve their goals of normalcy and remission that can be achieved by addressing QoL, side effects, and patients' goals of living "normally". Though prior research highlighted insurance coverage and costs as significant barriers to BRCA testing, results from this study suggest that cost was not a major factor in testing decisions. Prior barriers to testing access have been mitigated making it more available and affordable than in the past, which could be broadly communicated to patients and HCPs to minimize misperception.

PO3-16-07

Strategies to Enact for Equitable and Unbiased Care of Black, Triple Negative Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

V. Leach. Tigerlily Foundation, United States

J. Regnante. Tigerlily Foundation & Patient3i LLC, United States

M. Karmo. Tigerlily Foundation, United States

S. Cooper. Tigerlily Foundation, United States

K. Peoples. Tigerlily Foundation, United States

L. Wittig. Tigerlily Foundation, United States

Background: Black women are at higher risk for early onset and increased breast cancer mortality, especially from the sub-type Triple-Negative Breast Cancer (TNBC), than their white peers. A patient experience survey has not been implemented or published for Black women diagnosed with TNBC. Tigerlily Foundation (TLF) conducted a TNBC survey of Black women to understand the patient experience throughout the cancer continuum of care. Methods: The survey instrument received an IRB exception and included 40 questions organized by the following themes: Demographics, Self-Detection/Early Assessment, Screening to Diagnosis, Diagnosis to Treatment, Post Treatment and Palliative Care/Survivorship, Emotional Trauma and Mental Health, and Trust/Bias. Data collection occurred between December 2022 and January 2023. Two methodological approaches influenced this innovative study design: 1) a Health Literate and Culturally Sensitive approach and 2) a Trusted Outreach approach. The survey was sent to leaders of patient-based organizations who shared the TLF survey with their constituents. Results: All participants (N = 106) racially identified as Black women diagnosed with TNBC. The age of participants ranged from 25 – 71. Participants were not always given information to manage their expectations before or after the screening process, as 38% reported they did not receive such information, while 45% reported they did. The number of times participants required diagnostic imaging ranged from only once (24%), two-three times (41%), four-five times (17%), or greater than six times (11%). Biopsies also varied among participants from one (25%), two-three times (40%), four-five times (15%), or greater than six times (8%). Biomarker testing was not equitably offered to all participants, as 30% reported they were not given the opportunity, while 48% were given the choice. While most participants reported a good understanding of their prognosis and treatment options (59%), other participants shared that the information they received could have been better (26%). Others stated they were given zero information to work with (15%). Many participants experienced a diagnosis change, and 57% were initially diagnosed with a different breast cancer subtype, while 24% were initially diagnosed with TNBC. Conclusions: Prospective implementation science is needed to ensure equitable care standards are sustainably provided to Black women. It is imperative to understand the cancer care continuum from the perspective of the patients, what they think of the care received. Equally important, it is necessary to know what education, resources and care the patients would have liked to receive before or upon diagnosis. Health equity is not achieved based on EHR, county-level beneficiary data, or SEER data alone. Gathering information regarding the patients' experience is a factor in achieving health equity. TLF successfully reached Black TNBC patients to share their authentic experiences and provided a framework for other research institutions and patient advocacy groups to do the same.

PO3-16-08

Real-World Treatment Patterns in Elderly Patients with HER2-Negative Early Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Earla. Merck & Co., Inc., Rahway, New Jersey, United States

A. Kurian. Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California, United States

K. Kponee-Shovein. Analysis Group, Inc., United States

A. Satija. Analysis Group, Inc., United States

Y. Song. Analysis Group, Inc., United States

N. Downes. Analysis Group, Inc., United States

M. Mahendran. Analysis Group, Inc., United States

Q. Hua. Analysis Group, Inc., United States

A. Kumar. Analysis Group, Inc., United States

J. Mejia. Merck & Co., Inc., Rahway, New Jersey, United States

Background: As the treatment landscape of human epidermal growth factor receptor 2-negative (HER2-) early breast cancer (BC) evolves, an understanding of treatments given in real-world settings to elderly patients with HER2- early BC is needed to gain insight into the potential unmet needs of this population for whom clinical data are limited. This study described demographics, clinical characteristics, and neoadjuvant and adjuvant treatment patterns in elderly patients with HER2- early BC in the United States.

Methods: This retrospective study used SEER-Medicare data (2010–2019) to identify patients aged ≥66 years with HER2- early (Stage I–III) BC receiving primary surgery. Patient characteristics were evaluated at primary surgery or at BC diagnosis. Neoadjuvant and adjuvant therapies were defined as any National Comprehensive Cancer Network-recommended regimens received between BC diagnosis and primary surgery, and during the 180-day period following primary surgery, respectively. Patient characteristics were described using means and standard deviations (SDs) for continuous characteristics, and frequencies and proportions for categorical characteristics. Neoadjuvant and adjuvant therapies were summarized using frequencies and proportions. All analyses were conducted for the overall population and stratified by breast cancer subtype (hormone receptor-positive [HR+]/HER2- vs. triple negative BC [TNBC]) and stage at diagnosis (Stage I vs. Stage II/III).

Results: Of 28,655 eligible patients, 25,899 (90.4%) had HR+/HER2- BC and 2,756 (9.6%) had TNBC; 17,961 (62.7%) had Stage I BC and 10,694 (37.3%) had Stage II/III BC. Mean (SD) age at diagnosis was 75.8 (6.4) years, mean (SD) National Cancer Institute comorbidity index was 1.9 (2.1), and 23.7% received single or multi-gene testing for a breast cancer gene 1 and/or 2 (BRCA1/2) mutation (HR+/HER2- BC: 24.6%; TNBC: 15.5%), with most (86.3%) testing occurring after primary surgery. Relative to HR+/HER2- BC patients, TNBC patients were less likely to present with Stage I disease (46.7% vs. 64.4%), had a larger mean tumor size at diagnosis (2.6 cm vs. 1.9 cm), and higher-grade tumors (Grade III or IV: 70.6% vs. 14.6%). TNBC patients were also more likely to receive neoadjuvant chemotherapy (90.9% vs. 35.3%) and adjuvant radiation therapy (81.2% vs. 66.4%) than HR+/HER2- BC patients (Table 1). By BC stage, neoadjuvant therapy was more common among Stage II/III patients relative to Stage

I patients (12.3% vs. 2.7%), with most (90.4%) neoadjuvant chemotherapy use observed among Stage II/III patients. Adjuvant therapy use was similar between Stage I and Stage II/III patients (87.4% vs. 88.1%) and the most common adjuvant therapies across both subgroups were endocrine therapy (85.2% vs. 82.2%) and radiation therapy (68.5% vs. 66.1%).

Conclusion: In elderly patients with HER2– early BC, treatment with adjuvant therapy was common, while neoadjuvant therapy was limited. Moreover, one in four HER2– early BC patients were tested for a BRCA1/2 mutation in real-world clinical practice. Our findings highlight the need for a better understanding of the role of increased and timely BRCA1/2 testing to inform optimal treatment strategies across neoadjuvant and adjuvant settings in this population.

Table 1. Treatment Patterns Among Patients with TNBC and HR+/HER2– Early Breast Cancer

	TNBC (N=2,756)	HR+/HER2– (N=25,899)
Neoadjuvant therapy, n (%)	384 (13.9)	1,421 (5.5)
Chemotherapy	349 (90.9)	501 (35.3)
Radiation therapy	31 (8.1)	196 (13.8)
Endocrine therapy	15 (3.9)	839 (59.0)
Adjuvant therapy, n (%)	2,050 (74.4)	23,077 (89.1)
Chemotherapy	1,189 (58.0)	3,513 (15.2)
Radiation therapy	1,664 (81.2)	15,314 (66.4)
Endocrine therapy	131 (6.4)	21,001 (91.0)

PO3-16-09

Real-World Experience with Trastuzumab Deruxtecan at a Diverse NCI Comprehensive Cancer Center

Presenting Author(s) and Co-Author(s):

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

M. Ratcliffe. Emory University, Atlanta, Georgia, United States

Background: Trastuzumab Deruxtecan (T-DXd) is an antibody-drug conjugate originally approved for use in patients with HER2-positive metastatic breast cancer (MBC). In June 2022, data from the DESTINY-Breast04 trial revealed a near-doubling of progression-free survival (PFS) and significantly improved overall survival (OS) for patients with HER2-low MBC (immunohistochemistry [IHC] grade 1+ or IHC2+ in situ hybridization [ISH]-negative) treated with T-DXd versus standard-of-care chemotherapy. The data from this clinical trial led to the approval of T-DXd for use in patients with HER2-low MBC. However, the DESTINY-Breast studies completed to date have included < 5% black patients. This retrospective study of patients at a racially diverse NCI Comprehensive Cancer Center was designed to study whether T-DXd in a real-world population are comparable to published data. Methods: A retrospective chart review was conducted and identified 72 patients with HER2-low and HER2-positive MBC who received T-DXd between December 2019 and March 2023 at the Winship Cancer Institute at Emory University. Data collected for all patients included demographics, prior breast cancer history, T-DXd -specific and post-T-DXd treatment, and clinical outcomes where applicable. Results: Of the 103 patients who were dosed with T-DXd, 55 (53.4%) had HER2-positive disease, and 48 (46.7%) patients had HER2-low disease. 71 (68.9%) patients had hormone-receptor positive disease and 32 (31.1%) patients had hormone-receptor negative disease. The overall study population was 46% Caucasian; 38% African American; 13% Asian; 4% Unreported. The average number of cycles received was 11 (on treatment an average of 8 months). Pneumonitis occurred in 5 patients (4.9%). HER2-positive patients were typically on T-DXd for a greater number of cycles than HER2-low patients (Table 1). Additionally, patients with brain metastases were, on average, treated with T-DXd longer than patients without brain metastases, 14.5 versus 9 cycles. The number of cycles of T-DXd received, the need for dose reduction, and incidence pneumonitis did not differ significantly between black and white patients. The data for this study is preliminary 48% of the patient population are still actively undergoing T-DXd treatment. Conclusion: This study reviewed and analyzed T-DXd treatment in a diverse population of both HER2-positive and HER2-low MBC patients, and in this study, outcomes of treatment did not differ by race. More attention to this topic is needed in future studies of larger populations, along with increased efforts to enroll diverse patient populations in clinical trials.

Table 1.

Table. 1

Covariate	HER2-low	HER2-positive	Brain metastases (Yes)	Brain metastases (No)	Pneumonitis (Yes)	Pneumonitis (No)	Prior Trodelvy (Yes)	Prior Trodelvy (No)
N	48	55	36	67	5	98	9	94
Race (%)								
<i>African American</i>	33.3	41.8	44.4	34.3	5.1	94.9	15.4	84.6
<i>Asian/Unknown</i>	16.7	16.4	11.1	19.4	0.0	100.0	0.0	100.0
<i>White</i>	50.0	41.8	44.4	46.3	6.4	93.6	6.4	93.6
P-value	0.649		0.444		0.844		0.156	
# of T-DXd Cycles	8.1	13.4	14.5	9.0	10.2	10.7	7.8	11.2
P-value	<0.001		<0.001		0.741		0.159	
Pneumonitis (%)	2.1	7.3	5.6	4.5	----	----	----	----
P-value	0.369		1.000		----		----	
Brain metastases (%)	16.7	50.9	----	----	----	----	8.3	91.7
P-value	<0.001		----		----		1.000	

PO3-16-10

Real-world outcomes with first-line ribociclib + endocrine therapy in patients with metastatic HR+, HER2– breast cancer: Fourth interim analysis of REACH AUT trial

Presenting Author(s) and Co-Author(s):

C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria

D. Egle. Department of Gynaecology, Medical University Innsbruck, Innsbruck, Austria, United States

R. Greil. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

E. Petru. Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria

L. Oehler. Department of Internal Medicine/Oncology, St Joseph Hospital, Vienna,, Austria

M. Balic. Clinical Department of Oncology, Medical University of Graz, Graz, Austria

L. Schöffmann. Department of Hematooncology, Leoben State Hospital, Leoben, Austria

G. Pfeiler. Medical University of Vienna, Austria, Vienna, Austria

M. Marhold. Medical University of Vienna, United States

C. Brunner. Department of Gynecology and Gynecological Oncology, Medical University of Innsbruck, Austria

K. Haider. Department of Surgery, Breast Health Center, State Hospital Wiener Neustadt, Wiener Neustadt, Austria

A. Galid. Department of Gynecology, Breast Center Hanusch KH, Vienna, Austria

U. Pluschnig. Department of Hematology and Internal Oncology, Klinikum Klagenfurt, Klagenfurt, Austria

F. Haslbauer. Department of Internal Medicine, Salzkammergutklinikum Hospital Vöcklabruck, Vöcklabruck, Austria, Austria

M. Hubalek. Department of Gynecology, Breast Health Center Schwaz, Schwaz, Austria, United States

A. Redl. Datamedrix GmbH, Vienna, Austria

J. Flatschacher. Novartis Oncology, Vienna, Austria

S. Uthman. Novartis Oncology, Vienna Austria, Austria

B. Mraz. Novartis Oncology, Vienna, Austria

R. Bartsch. Medical University of Vienna, Department of Medicine I, Division of Oncology, Vienna, Austria, Austria

Background: Ribociclib (RIB), a cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) in combination with endocrine therapy (ET) yielded significant improvement in progression-free survival (PFS) and overall survival (OS) across three phase III MONALEESA trials including patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) metastatic breast cancer (MBC) in first-line (1L) and second-line (2L) setting. In the previous interim analyses of REACH AUT trial, 1L RIB + ET showed tolerable

safety and favorable PFS results in a real-world setting. Results from the preplanned fourth interim analysis are reported here. Methods: REACH AUT is a noninterventional study conducted in Austria reporting data on the real-world clinical experience of RIB + ET (aromatase inhibitor [AI] or fulvestrant [FUL]) in premenopausal, perimenopausal, or postmenopausal pts with HR+, HER2– MBC. Pts with no prior ET for advanced disease and maximum up to 1 prior line of chemotherapy (CT) in the advanced setting were included. Results: At data cutoff (March 27, 2023) with a median duration of follow-up of 23.8 months, out of 281 analyzed pts (12.5% of premenopausal/perimenopausal and 85.1% of postmenopausal, 2.5% of unknown status) 31.7% of pts were receiving ongoing treatment. The most common reasons for treatment discontinuations (68.3%) were disease progression (39.1%) and adverse events (AEs, 22.1%). The median age was 63 years (< 65 years, n=156, 55.5%; ≥65 years, n=125, 44.5%) and ECOG PS ≥2: 1.8%. In 106 pts (37.7%), de novo metastatic disease was reported. Visceral metastases (lung, liver) were present in 116 pts (41.3%) and bone-only metastases in 80 pts (28.5%). Prior adjuvant therapy was received by 139 pts (49.5%): AI ± GnRH: n=80 (26.7% without and 1.8% with GnRH); tamoxifen ± GnRH: n=74 (21.7% without and 4.6% with GnRH); CT: n=56 (19.9%); antibody therapy n=3 (1.1%). In the metastatic setting, 1L RIB was prescribed in combination with an AI in 223 pts (79.4%; letrozole: n=139 [49.5%]; anastrozole: n=48 [17.1%]; exemestane: n=47 [16.7%]) and with FUL in 52 pts (18.5%). Prior CT for MBC was received by 5 pts (1.8%). The median PFS was 29.7 months in the overall population; 28.3 months in pts with bone only and 26.9 months in pts with visceral metastatic disease. In pts evaluable for response, the objective response rate and clinical benefit rate were 31.3% and 60.9%, respectively. The OS rates were 91.9%, 81.7%, and 63.7% at 12 months, 24 months, and 36 months, respectively. The trial is ongoing with ~40% of subjects end of documentation and ~27% of deaths. In total, 69.4% of pts had RIB dose interruptions and 48.8% of pts had a RIB dose reduction. The majority of all reported AEs were grade 1 (50.1%) or grade 2 (31.2%); the median time to first AE was 0.5 months. The most common AE was neutropenia (all grades: n=143, 50.9%; grade 1: n=39, 13.9%; grade 2: n=68, 24.2%; grade 3: n=98, 34.9%; grade 4: n=5, 1.8%). QTc prolongation of any grade was observed in 32 pts (11.4%; grade 1: n=24, 8.5%; grade 2: n=11, 3.9%; grade 3: n=1, 0.4%). Hepatobiliary toxicity of any grade was observed in 42 pts (14.9%; grade 1: n=12, 4.3%; grade 2: n=18, 6.4%; grade 3: n=22, 7.8%; grade 4: n=3, 1.1%). Overall, currently 101 pts (35.9%) received a follow-up therapy after progression on RIB + ET. The most common first subsequent therapies were targeted therapies + ET (40.0%), followed by cytotoxic chemotherapy (22.0%) and endocrine monotherapy (19.0%). Conclusion: 1L RIB + ET continues to show favorable efficacy and a tolerable safety profile in the routine clinical practice. The results are consistent with the data from MONALEESA trials. The OS is showing a positive trend but is still immature during this study follow-up.

Efficacy Outcomes With RIB + ET in Patients With HR+, HER2– MBC (Overall Population, Nf281)

Progression-free survival (PFS)	Median (months) + 95% CI	Events (%)
Overall	29.7 (24.1; 35.4)	49.5
PFS by metastases subgroup		
Bone only	28.3 (22.5; 39.8)	50.0
Visceral only	30.3 (11.6; 41.5)	47.2
Visceral any	26.9 (14.2; 36.0)	50.9
Overall survival (OS)		
	OS rate (%)	
12-month OS	91.9	
24-month OS	81.7	
36-month OS	63.7	
Best response		
	n	%
Complete response	28	10.0
Partial response	60	21.4
Stable disease	97	34.5
Progressive disease	39	13.9
Not available	57	20.3

ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; MBC, metastatic breast cancer; n, number of patients; OS, overall survival; PFS, progression-free survival; RIB, ribociclib.

PO3-16-11

Attrition rates from first- to third-line therapy in HER2+ metastatic breast cancer in Europe

Presenting Author(s) and Co-Author(s):

P. Hall. University of Edinburgh, Edinburgh, United Kingdom

S. Cheeseman. Leeds Teaching Hospitals NHS Trust, United States

P. Cottu. Institut Curie, Paris, Paris, Ile-de-France, France

M. Krebs. Comprehensive Cancer Center Mainfranken, University Hospital Würzburg, United States

C. Scholz. Department of Hematology and Oncology, Vivantes Klinikum Am Urban, United States

M. Vallet. Cancer Research UK Scotland Centre, The University of Edinburgh, United States

N. Niklas. IQVIA, United States

C. Hogg. IQVIA, United States

M. Lucerna. Daiichi Sankyo Europe GmbH, United States

S. Collin. AstraZeneca Pharmaceuticals, Cambridge, England, United Kingdom

A. Logue. AstraZeneca Pharmaceuticals, United States

G. Long. AstraZeneca Pharmaceuticals, Cambridge, England, United Kingdom

Background: Patients (pts) with human epidermal growth factor receptor 2 (HER2)-positive (HER2+) metastatic breast cancer (mBC) who experience progression with adjuvant first-line (1L) therapy (trastuzumab, pertuzumab, and a taxane) typically require treatment escalation. Trastuzumab emtansine was standard of care in the second-line (2L) setting until the recent approval (Jul 2022 in the EU) of trastuzumab deruxtecan in $\geq 2L$ settings. Receiving optimal targeted therapy in the earliest indicated setting is important to maximize the likelihood of durable clinical benefit. As new therapies become available, understanding subsequent lines of therapy may help guide treatment decision making and inform the optimal treatment paradigm for pts with HER2+ mBC. This study characterizes contemporary attrition rates in pts with HER2+ mBC receiving routine care in Europe. Methods: In this ongoing, multicenter, observational study, electronic medical record (EMR) data were collected from female pts ≥ 18 years old diagnosed with HER2+ mBC between Jan 1, 2017, and Jun 30, 2021, in the UK, France, Germany, Italy, and Spain. Structured EMR data and manually abstracted unstructured data from oncology centers were curated. Pts were followed for ≥ 12 months from mBC diagnosis. Data analysis is ongoing. The primary endpoint was attrition rate (percentage of pts who completed a line of therapy [LOT] but did not receive the subsequent LOT after 1L and 2L therapy). Documented reasons for attrition included death or move to end-of-life palliative care, end of study period, loss to follow up, or discontinuation due to toxicity. Reasons were categorized as 'other' if they did not meet these criteria, or if death or move to end-of-life palliative care occurred >30 days after treatment discontinuation. This abstract reports interim data from the UK, France, and Germany. Results: This interim analysis included data from 335 pts across five sites in three countries: two sites in the UK, one in France, and two in Germany (Table). Overall, 307 (91.6%) pts started 1L therapy and 172 (51.3%) pts started 2L therapy; overall attrition rates were 28.9% (70/242; 95% CI 23.3, 35.1) after 1L therapy and 33.1% (42/127; 95% CI 25.0, 42.0) after 2L therapy. The proportion of pts starting 1L and 2L therapy and attrition rates for each country are shown in the Table. Overall reasons for attrition were death (1L, n=28 [40.0%]; 2L, n=12 [28.6%]), move to end-of-life palliative care (1L, n=14

[20.0%]; 2L, n=5 [11.9%]), toxicity (1L, n=2 [2.9%]; 2L, n=1 [2.4%]), loss to follow up (1L, n=6 [8.6%]; 2L, n=4 [9.5%]), end of study period (1L, n=1 [1.4%]; 2L, n=4 [9.5%]), and other (1L, n=19 [27.1%]; 2L, n=16 [38.1%]). Further breakdown of results by country and hormone receptor (HR) status is shown in the Table. Conclusions: These data from routine clinical practice in the UK, France, and Germany indicate that a substantial proportion of pts with HER2+ mBC who completed 1L or 2L therapy did not receive a subsequent LOT (2L or 3L, respectively) for reasons other than death or move to end-of-life palliative care. Future analyses will focus on pooled and country-level treatment rates and real-world effectiveness.

Table. Results overall and by HR/HER2 status

	France			Germany			UK		
	All pts (N=115)	HR+ HER2+ (n=75)	HR- HER2+ (n=40)	All pts* (N=84)	HR+ HER2+ (n=65)	HR- HER2+ (n=17)	All pts (N=136)	HR+ HER2+ (n=91)	HR- HER2+ (n=45)
Age at mBC diagnosis, mean (SD), years	58.6 (15.1)	59.8 (15.1)	56.4 (14.9)	65.6 (13.9)	66.2 (13.0)	63.0 (17.8)	61.5 (15.7)	59.6 (15.0)	65.3 (16.4)
No. of metastatic sites, n (%)									
1	28 (24.4)	22 (29.3)	6 (15.0)	20 (23.8)	14 (21.5)	6 (35.3)	23 (16.9)	18 (19.8)	5 (11.1)
≥2	87 (75.7)	53 (70.7)	34 (85.0)	64 (76.2)	51 (78.5)	11 (64.7)	113 (83.1)	73 (80.2)	40 (88.9)
Stage IV at initial diagnosis, n (%)	76 (66.1)	45 (60.0)	31 (77.5)	48 (57.1)	41 (63.1)	6 (35.3)	90 (66.2)	58 (63.7)	32 (71.1)
Follow up, months (median Q1-Q3)	38.8 (21.3-51.4)	40.5 (21.9-50.6)	35.7 (20.1-53.0)	24.4 (12.1-44.5)	24.0 (13.0-48.8)	25.0 (4.2-30.7)	44.0 (27.8-54.0)	44.0 (30.6-56.2)	43.0 (24.4-50.2)
Pts who started LOT, n (%)									
1	115 (100)	75 (100)	40 (100)	79 (94.0)	64 (98.5)	14 (82.4)	113 (83.1)	75 (82.4)	38 (84.4)
2	71 (61.7)	51 (68.0)	20 (50.0)	35 (41.7)	28 (43.1)	7 (41.2)	66 (48.5)	44 (48.4)	22 (48.9)
Attrition rate, % (95% CI)									
After 1L	14.5 (7.7-23.9)	8.9 (3.0-19.6)	25.9 (11.1-46.3)	42.6 (30.0-55.9)	40.4 (26.4-55.7)	46.2 (19.2-74.9)	32.7 (23.5-42.9)	31.2 (20.2-44.1)	35.3 (19.7-53.5)
After 2L	26.1 (14.3-41.1)	23.3 (9.9-42.3)	31.2 (11.0-58.7)	42.3 (23.4-63.1)	45.0 (23.1-68.5)	33.3 (4.3-77.7)	34.5 (22.2-48.6)	30.6 (16.3-48.1)	42.1 (20.3-66.5)

*HR-missing/HER2+ mBC, n=2

+ , positive; -, negative; 1L, first line; 2L, second line; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LOT, line of therapy; mBC, metastatic breast cancer; pt, patient; Q, quarter; SD, standard deviation

PO3-16-12

European real-world experience of patients with HER2+ advanced/metastatic breast cancer accessing trastuzumab deruxtecan through a named patient program: first interim analysis of EUROPA T-DXd

Presenting Author(s) and Co-Author(s):

M. De Laurentiis. Istituto Nazionale dei Tumori IRCCS 'Fondazione Pascale, Napoli, Italy

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

G. Bianchini. IRCCS Ospedale San Raffaele, Milan, Lombardia, Italy

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

H. Wildiers. University Hospitals Leuven, United States

A. Allignol. Daichii Sankyo Europe GmbH, Munich, United States

A. Logue. AstraZeneca Pharmaceuticals, United States

M. Lucerna. Daiichi Sankyo Europe GmbH, United States

S. Stamenitis. Daiichi Sankyo Europe GmbH, Munich, United States

Background: In 2021, trastuzumab deruxtecan (T-DXd) monotherapy was conditionally approved in the EU for adult patients with human epidermal growth factor receptor 2-positive (HER2+) advanced/metastatic breast cancer (mBC). A named patient program (NPP) was initiated (March 2021) to enable eligible patients with an unmet medical need to gain access to T-DXd when not yet available locally, either commercially or through an appropriate clinical trial. Centers that treated / are treating patients under this NPP were invited to participate in EUROPA T-DXd real-world data (RWD) collection.

Methods: EUROPA T-DXd is an ongoing, multicenter (Ireland, Italy, and Spain), observational (retro- and prospective) study of RWD from approximately 200 adult patients with HER2+ advanced/mBC who had received ≥ 2 prior anti-HER2 regimens and for whom T-DXd was initiated through the NPP. Collection of RWD is optional and independent of eligibility for the NPP. The primary objective is to estimate real-world time to treatment discontinuation (rwTTD). Secondary objectives include real-world progression-free survival (rwPFS), reasons for T-DXd discontinuation, safety, and prior anti-HER2 treatment patterns.

Results: This first interim analysis included 84 evaluable patients. Patients had a mean (standard deviation) age of 53.4 (11.1) years; most were female (97.6%) and had HER2 immunohistochemistry 3+ (70.2%), and 44% had received >3 prior lines of anti-HER2 therapy in the metastatic setting (Table). At data cutoff (June 5, 2023), 50 (59.5%) patients were still receiving T-DXd. In total, 34 patients (40.5%) discontinued T-DXd (death, n=1 [1.2%]; adverse event, n=3 [3.6%]; disease progression, n=26 [31%]; or other, n=4 [4.8%]). Median rwTTD was 21.4 months (95% confidence interval 17.6, not estimated), and median rwPFS was not reached. The results of the wider cohort will be presented at the meeting, including adverse events.

Conclusion: Results from this first interim analysis confirm the efficacy of T-DXd in heavily pretreated patients with HER2+ mBC. Baseline characteristics and demographics are comparable to the clinical trial setting. Analyses are ongoing and will provide more mature

rwTTD and rwPFS.

Table. Patient demographics and baseline characteristics

	All patients (N=84)
Age, mean (SD), years	53.4 (11.1)
<65 years, n (%)	74 (88.1)
Female, n (%)	82 (97.6)
HER2 expression, n (%)	
IHC 1+	2 (2.4)
IHC 2+	20 (23.8)
IHC 3+	59 (70.2)
Missing	3 (3.6)
ISH+	26 (31.0)
ISH-	1 (1.2)
N/A	56 (66.7)
Missing	1 (1.2)
Hormone receptor, n (%)	
Positive	52 (61.9)
Negative	30 (35.7)
Missing	2 (2.4)
Site of metastatic disease, n (%)	
Lymph node	53 (63.1)
Lung	36 (42.9)
Bone	40 (47.6)
Liver	36 (42.9)
Brain	25 (31.0)
Other	24 (28.6)
Prior anti-HER2 therapy, n (%)	
Trastuzumab	81 (96.4)
T-DM1	75 (89.3)
Pertuzumab	69 (82.1)
Margetuximab	4 (4.8)
Lapatinib	39 (46.4)
Neratinib	10 (11.9)
Tucatinib	12 (14.3)
Lines of prior anti-HER2 therapy in metastatic setting, n (%)	
0	5 (6.0)
1	8 (9.5)
2	14 (16.7)
3	20 (23.8)
4	12 (14.3)
≥5	25 (29.8)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in-situ hybridization; N/A, not available; SD, standard deviation; T-DM1, trastuzumab emtansine

PO3-17-01

Brazilian Real-world data of HR+ HER2- early-stage Breast Cancer (BC) patients are poor when compared to control arms of recent adjuvant clinical trials

Presenting Author(s) and Co-Author(s):

A. Goncalves. Oncoclinicas Group / Oncoclinicas Institute, Rio de Janeiro, Rio de Janeiro, Brazil

T. Reinert. Oncoclinicas Group, United States

M. S.Mano. Grupo Oncoclínicas, United States

H. Cruz. ONCOCLINICAS DO BRASIL SERVIÇOS MEDICOS S.A, United States

C. Resende. Oncoclinicas Group / Oncoclinicas Institute, United States

G. Bretas. Oncoclinicas Group / Oncoclinicas Institute, United States

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

M. Costa e Silva. Grupo Oncoclinicas, Brazil

R. Paes. ONCOCLINICAS DO BRASIL SERVIÇOS MEDICOS S.A, United States

G. Silva. ONCOCLINICAS DO BRASIL SERVIÇOS MEDICOS S.A, United States

E. Martins. Grupo Oncoclínicas, Sao Paulo, Brazil

F. Koyama. Oncoclinicas Precision Medicine, United States

B. Ferrari. Grupo Oncoclinicas, United States

C. Ferreira. Grupo Oncoclínicas, United States

P. Aguiar Junior. ONCOCLINICAS DO BRASIL SERVIÇOS MEDICOS S.A, United States

R. Dienstmann. Oncoclínicas Group, United States

INTRODUCTION: In Brazil, BC is the most common neoplasm among women, with 73k new cases annually. Adjuvant hormone therapy (HT) options are evolving with personalized strategies based on risk stratification. Real-world data (RWD) plays a crucial role in understanding the outcomes in BC patients (pts) in low- and middle-income countries, where significant health disparities, access gaps, and barriers to the implementation of guidelines exist. This study aims to assess the epidemiologic profile, practice patterns, and real-world outcomes of pts with ER+ HER2- stage I-III BC treated in the largest network of private oncology services in Brazil and compare results with control arms of recent clinical trials evaluating CDK4/6 inhibitors in adjuvant setting. **METHODS:** Retrospective RWD study from Oncoclínicas Group with longitudinal EHR data from 2017 to 2022 merged in a platform where structured variables (demographics, tumor staging, pharmacy records) are integrated with unstructured data from physician notes and digitized pathology-molecular reports using technology-based abstraction performed by expert human curators that follow mCODE standards and predefined ontology. Treatment patterns and invasive disease-free survival (IDFS) outcomes were collected. Regarding risk stratification, pts were classified as high-risk (HR) if: (i) 4+ axillary lymph nodes (LN), or (ii) 1-3 LN and grade 3 and/or Ki67 >20% and/or high-risk ODX/Mammprint; intermediate-risk (IR) if: (iii) 1-3 LN with grade 1-2 and/or Ki67 < 20% and/or non-high-risk ODX/Mammprint, or (iv) N0 with grade 2-3 and/or Ki67 >20% and/or high-risk ODX/Mammprint; and low-risk (LR) if: (v) all other stages I and IIA not having the risk factors above. **RESULTS:** From over 30k BC pts in Oncoclínicas Database, 19k had HR+/HER2- early BC, 12k were treated in high-volume clinics, and 1,786 cases were selected

for the study (diagnosis and first treatment in the last 6 years, complete histopathology and pharmacy registries). The median age was 57 years (27-96), 566 (32%) pts were premenopausal, 1052 (59%) had stage I disease, 372 (21%) stage IIA, 165 (9%) stage IIB and 197 (11%) stage III BC. Regarding risk stratification, 1,179 (66%) were LR, 351 (20%) IR, and 256 (14%) HR. In post-menopausal pts, aromatase inhibitor (AI) was used by 74% of pts with LR, 79% with IR and 83% with HR. In premenopausal pts, ovarian function suppression (OFS) – combined with tamoxifen or AI – was prescribed to 18% of LR pts, 15% of IR pts, and 48% of HR pts. Chemotherapy (CT) was offered to 32%, 38%, and 73% of postmenopausal pts in LR, IR, and HR groups. In premenopausal pts, 55%, 57%, and 78% received CT in LR, IR, and HR groups. The 3-year iDFS in the general population was 85%, reaching 80% in premenopausal and 86% in postmenopausal pts. The overall 3y iDFS was 87% in the LR, 86% in IR, and 72% in HR. Among premenopausal pts, the 3y iDFS was 81% in LR, 92% in IR, and 64% in the HR group. While the risk distribution of our cohort is similar to recent clinical trials, the 3y iDFS outcomes were numerically lower to those observed in the control groups of the pivotal trials evaluating adjuvant CDK4/6 inhibitors. In the HR group, the 3y iDFS was 72% (versus 84% 3y iDFS in the control arm of the MonarchE trial). Combining the IR/HR groups, the 3y iDFS was 80% (versus 87% in the control arm of NATALEE trial). CONCLUSION: In this large RWD cohort treated in a private setting in Brazil, most pts are diagnosed with stage I and LR BC. In this cohort, a significant proportion of premenopausal pts with IR/HR are not treated with OFS and do not receive CT. Real-world survival outcomes of Brazilian women with HR+ HER2- early BC treated in private clinic are inferior to those observed in recent clinical trials, especially in the premenopausal pts. In public healthcare system, where prevalence of HR disease is higher and access to essential treatments more limited, outcomes might even be worsened compared to the ones presented here.

PO3-17-02

Analysis of clinical benefit in the real world of HER2-positive metastatic breast cancer following the development of anti-HER2 therapeutics over the past 20 years

Presenting Author(s) and Co-Author(s):

A. Ham. Ewha Womans University Medical Center, United States

S. Lee. Ewha Womans University Hospital, United States

J. Jo. Ewha Womans University Hospital, United States

S. Hong. Ewha Womans University Hospital, United States

J. Lee. Ewha Womans University Hospital, United States

H. Lee. Ewha Womans University Hospital, United States

S. Gwark. Ewha Womans University Hospital, United States

J. An. Ewha Womans University Hospital, United States

H. Kim. Ewha Womans University Hospital, United States

J. Lee. Ewha Womans University, School of Medicine,, Seoul, Seoul-t'ukpyolsi, Republic of Korea

J. Woo. Ewha Womans University College of Medicine/Ewha Womans University Mokdong Hospital, United States

W. Lim. Department of Surgery, Ewha Womans University School of Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

B. Moon. Ewha Womans University Hospital, United States

S. Ahn. Ewha Womans University Hospital, United States

H. Lee. Ewha Womans University Hospital, United States

K. Lee. Division of Hematology Oncology, Department of Internal Medicine, School of Medicine, Ewha Womans University, Republic of Korea

Analysis of clinical benefit in the real world of HER2-positive metastatic breast cancer following the development of anti-HER2 therapeutics over the past 20 years Ahrong Ham¹, Sewon Lee¹, Jungmin Jo¹, Soo Ji Hong², Ji Eun Lee², Haena Lee², Sungchan Gwark², Jeongshin An², Hyun Goo Kim², Jun Woo Lee², Joohyun Woo², Woosung Lim², Byung-In Moon², Sei Hyun Ahn², Hye Ah Lee³, Kyoung Eun Lee¹ ¹ Division of Hematology and Oncology, Department of Internal Medicine, Ewha Womans University Mokdong hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea

² Department of Surgery, Ewha Womans University Mokdong hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea

³ Clinical Trial Center, Ewha Womans University Mokdong hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea Purpose: Over the last two decades, treatment landscapes for human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer (MBC) have shown remarkable growth with the development of drugs targeting HER2. The standard of care for HER2+ MBC has continued to change with the ongoing development of new anti-HER2 therapies. We aimed to provide a comprehensive analysis of HER2-targeted therapies, clinical characteristics, and treatment outcomes in real-world practice of HER2+ MBC patients over the past 20 years. Methods: Patients who received palliative chemotherapy with HER2+ MBC between 2000 and 2022 were analyzed. We derived cohorts of two groups with or

without anti-HER2 containing therapies. Patients receiving multiple anti-HER2 therapies throughout the entire period of treatment were further analyzed according to treatment regimen. The progression-free survival for palliative first-line (PFS1), and overall survival (OS) were compared between groups. A multivariate Cox regression model was used to investigate predictors of survival outcome in HER2+ MBC. Results: A total of 185 patients were analyzed. Median age was 49 years (IQR, 42-56 years). 47 patients (25.4%) were initially diagnosed with de novo stage IV disease. Visceral metastases were found in 95 patients (51.4%). The median PFS1 was 3.9 months (without anti-HER2 therapy) versus 15.6 months (with anti-HER2 therapy) between two groups ($P < 0.001$). Likewise, the median OS was significantly improved in anti-HER2 therapy group (34.0 months vs. 70.5 months, $P=0.010$). As a result of confirming the difference in OS according to the type of anti-HER2 therapies during the entire period of treatment by correspondence analysis, significant improvement was found when two or three types of anti-HER2 were used (without anti-HER2 vs. 2 types of anti-HER2, $P=0.009$; without anti-HER2 vs. 3 types of anti-HER2, $P=0.010$). Interestingly, when analyzed by treatment regimen, trastuzumab (H) + pertuzumab (P), HP + TDM-1, and H + TDM-1 significantly improved OS over regimens without anti-HER2 (without anti-HER2 vs. HP, $P=0.009$; without anti-HER2 vs. HP + TDM-1, $P=0.013$; without anti-HER2 vs. H + TDM-1, $P=0.028$, respectively). HP + TDM-1 therapies significantly improved survival rate compared to H single containing regimen ($P=0.029$). Based on our multiple Cox regression model, visceral metastasis was a significant poor OS prognostic factor and two and three types of anti-HER2 therapies were associated better OS prognosis (visceral metastasis: HR=2.40, $P=0.003$; 2 types of anti-HER2: HR=0.29, $P=0.001$; 3 types of anti-HER2: HR=0.22, $P=0.018$, respectively). Conclusions: Anti-HER2 therapies significantly improved PFS1 and OS. Continuing treatment by changing anti-HER2 therapies may act as a better prognostic factor. Further prospective studies are required.

PO3-17-03

Impalpable breast lesion localisation device satisfaction in UK surgeons and radiologists: results of the iBRA-NET national practice questionnaire

Presenting Author(s) and Co-Author(s):

F. Mavor. Manchester Foundation Trust, United States

J. Harvey. Manchester Foundation Trust, United States

Introduction

A national practice questionnaire in 2020 collected quantitative data from UK breast surgeons on breast localisation device use and found wire to be the most frequently used localisation device for impalpable lesions (Somasundaram, et al., 2020). Wire localisation was found to be associated with significant logistical issues including displacement and delays in theatre scheduling.

Localisation device practice has changed greatly in the three years since the last questionnaire (Dave, et al., 2022). This study aimed to assess the change in device use, impact on logistics and to qualitatively assess surgeon and radiologist experience across the range of localisation devices.

Methods

The questionnaire was designed with identical questions to the 2020 study to allow for direct comparison of change, this collected information on demographics, logistics and device use. A pilot study was conducted to ascertain domains that were important to clinicians in differentiating between the quality of localisation device experience. The qualitative questions asked respondents to assign a Likert scale score of 0-10 for satisfaction in each identified domain. Two national practice questionnaires were created used SurveyMonkey® and were distributed to UK breast surgeons and radiologists via direct email, social media and the Association of Breast Surgery newsletter.

The means of the satisfaction responses were compared with the mean responses for wire as the standard using a two-sample t test using Microsoft Excel.

Results

The surveys were completed between August and December 2022. There were 157 completed questionnaires, with 76 responses being from surgeons and 81 from radiologists. There has been significant change in the use of localisation devices in the UK, from 83% wire, 5% radio-occult lesion localisation (ROLL), 2% radioiodine seed and 9% Magseed® in 2020 to 45% wire, 2% ROLL, 3% radioiodine seed, 30% Magseed®, 5% SAVI SCOUT, 12% Hologic LOCALizer® and 2% Sirius Pintuition® by 2022. In 2020 9% of patients had localisation performed prior to the day of surgery, by 2022 this had increased to 64% ($p < 0.05$). Changes in localisation techniques also allowed these patients to undergo surgery earlier on a list; 15% of units in 2020 could operate on a localisation patient prior to 9am, by 2022 this was 41%. The satisfaction scores for Magseed® were statistically significantly higher than for wire in six of eight domains for surgeons and seven of nine domains for radiologists ($p < 0.05$). Surgeons found SAVI SCOUT® and Hologic LOCALizer® to be preferable to wire in five and seven domains respectively ($p < 0.05$).

Discussion

The follow-up survey demonstrates a change in practice in the use of newer localisation devices. The outcomes of the change seem to be an ability to place devices in advance, earlier start times in theatre and higher clinician satisfaction.

The qualitative data demonstrates that clinicians are able to differentiate between the attributes of localisation devices. Due to a small sample size in some of the newer devices we are unable to directly compare between the newer devices, however, Magseed® scored significantly higher than wires in seven of the nine domains.

Table 1: Qualitative comparison of feedback on the performance of devices.

	Wire	Magseed®	ROLL	BSL	SAVI SCOUT®	Hologic LOCALizer®	Sirtas Pinpoint®
Surgeons							
Risk of device dislodging	5.8	6.8*	5.8	8.3*	6.6*	7.0*	6.5
Ease of detection during surgery	7.3	8.1*	9.0*	9.0*	7.5	8.3*	9.5*
Signal focus	4.9	7.8*	9.0*	9.0*	7.5*	7.5*	9.3*
Ease of detection in a deep breast	6.1	6.0	8.0*	9.0*	6.3	7.3*	8.3*
Ability to judge distance from a probe	4.1	6.7*	5.7	8.0*	7.7*	8.5*	9.5*
Ease of logistics	4.4	8.7*	4.3	7.7*	8.6*	8.8*	9.8*
Ease of bracketing of lesions	7.3	7.0	4.7	6.7	7.1	8.0	8.0
Overall	6.6	7.8*	7.3	8.3*	7.8*	7.6*	8.6*
Radiologists							
Reliability	8.2	8.0*	8.0	9.3*	8.3	8.8*	8.0
Ease of insertion with ultrasound	8.8	9.4*	10.0	9.1	8.6	7.6*	6.0
Ease of insertion with stereo	7.6	8.3*	10.0	8.3	8.3	7.0	6.0
Ease of use with ultrasound	8.8	9.3*	9.5	9.1	8.4	8.0*	7.0
Ease of use with stereo	7.5	8.4*	10.0	8.7*	8.0	7.2	6.0
Accuracy of deployment with ultrasound	8.9	9.2*	9.0	9.4	8.3	8.0*	8.0
Accuracy of deployment with stereo	7.4	8.0*	10.0	8.7*	8.2	7.0	6.0
Ease of logistics	5.9	9.1	8.0	6.7	9.1*	9.3	10.0
Overall	7.3	9.0	8.0	8.7*	8.0	7.8	7.0

This Table shows the means of the satisfaction scores for surgeons and radiologists in the eight and nine qualitative domains respectively. Localisation devices were compared to wire as the standard using a two-sample t test, statistically significantly different results ($p < 0.05$) are marked with an asterisk.

PO3-17-04

HER2-directed biosimilar Ogivri in the treatment of breast cancer: real world reporting of symptoms and wellbeing using electronic patient reported outcome (ePRO)

Presenting Author(s) and Co-Author(s):

A. Trojan. BreastCenter Zürichsee, Zürich, Zurich, Switzerland

S. Roth. University of Zürich, Zürich, Switzerland

R. Zenhäusern. Spital Oberwallis, Brig, Valais, Switzerland

Y. Kadwany. mobile Health AG, United States

C. Jackisch. Department of Obstetrics and Gynecology, Sana Klinikum Offenbach, Germany, Germany

M. Aapro. Clinique de Genolier, Genolier, Vaud, Switzerland

A. Eniu. Hôpital Riviera-Chablais, Rennaz, Vaud, Switzerland

Introduction: Trastuzumab has a major impact on the treatment of HER2 positive breast cancer (BC). Anti-HER2 biosimilars, such as OgivriTM, demonstrated safety and clinical equivalency to the reference product HerceptinTM in clinical trials. However, real-world reporting of side effects, quality of life (QoL) and outcome in patients treated with biosimilars has not yet been performed using electronic PROs. Here standardized and structured ePROs are dynamically recorded with the mediduxTM app during OgivriTM treatment and are applied to perform a comparative analysis with ePROs derived from 38 historical patients treated with HerceptinTM in two previous studies (NCT02004496, NCT03578731).

Methodology: In this prospective observational study, patients with HER2-positive BC were treated with OgivriTM alone +/- Pertuzumab, +/- Chemotherapy and hormone therapy in neo-adjuvant, adjuvant and non-curative settings. Over an observational period of 6 weeks, patients used the mediduxTM app to dynamically record symptoms (according to CTCAE), well-being, EQ-5D-5L, cognitive capabilities, and vital parameters. Comparative analysis was performed with historical data from 38 patients that had reported 5217 ePROs and more than 1400 reports of well-being in similar therapeutic settings.

Results: 52 females (age 37-86 yrs) were treated with OgivriTM. From 92 different symptoms available, 84 were entered (average > 2 symptoms/day) resulting in 10`532 individual patient entries. Among the most common symptoms reported in both groups were fatigue, taste disorder, nausea, diarrhea, dry mucosa, joint discomfort, tingling, sleep disorder, headache, appetite loss. As compared to HerceptinTM, overall, symptoms associated with OgivriTM were reported with a similar incidence and distribution among groups (p=0.68), although slightly but not significantly lower scores (p=0.24; CI: 0.08-0.31). Distribution of symptom grades in the OgivriTM cohort revealed that the vast majority of patients experienced mild and grade 1 toxicities, 13% grade 2, 2% grade 3 and 0.4% grade 4 toxicities, respectively. The latter finding could possibly also be attributed to a trend towards de-escalation in chemotherapeutic regimes during the past 5 years since data acquisition, affecting anthracyclines and taxanes, and that. Of note, when treatments were compared restricted to the trastuzumab antihormones and trastuzumab- paclitaxel therapies, this reported trend seemed weaker. Importantly, well-being of patients undergoing HER2 directed treatment did not differ (p=0.24; CI: 0.39-0.88) in both cohorts.

Conclusion: No difference was reported for symptoms, adverse events, and well-being with respect to the Trastuzumab biosimilar Ogivri™ in comparison with Herceptin™. The integration of ePRO into research and clinical practice provides reliable information when investigating real world tolerability and outcomes of similar therapeutic compounds.

PO3-17-05

Clinical Characteristics and Outcomes of Patients Receiving Adjuvant Paclitaxel and Trastuzumab (APT regimen) for HER2-Positive Early-Stage Breast Cancer in Brazil: A Real-World Evidence

Presenting Author(s) and Co-Author(s):

G. Carvalho. Instituto Nacional de Câncer, Brazil

R. Colombo Bonadio. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

P. Bergmann. Instituto Nacional de Câncer (INCA), Brazil

M. Nishimuni. Instituto D'Or de Pesquisa e Ensino (IDOR), Brazil

A. Rossi. Instituto do Câncer do Estado de São Paulo, United States

C. Souza. Hospital de Câncer de Barretos, Barretos, Brazil

G. Guimarães. Barretos Cancer Hospital, Barretos, Brazil, United States

L. Testa. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil

J. Bines. Instituto Nacional de Câncer (INCA), Brazil

Introduction: The APT trial established adjuvant paclitaxel and trastuzumab (TH) as the standard of care for HER2-positive early-stage breast cancer with tumor size ≤ 3 cm and no more than one lymph-node micrometastasis. This single-arm phase II trial demonstrated favorable long-term outcomes, with a 3-year invasive disease-free survival (IDFS) rate of 98.7% (95% CI 97.6 – 99.8%). In an updated follow-up analysis, the 10-year IDFS and overall survival (OS) rates were 91.3% (95% CI 88.3 – 94.4%) and 94.3% (95% CI 91.8 – 98.3%), respectively. Nevertheless, outcomes observed in real-world scenarios have frequently been less favorable than those observed in clinical trials. We aimed to characterize the population receiving the APT regimen in clinical practice and evaluate if real-world outcomes align with those observed in the pivotal clinical trial.

Methods: This retrospective cohort study included patients with HER2-positive early-stage breast cancer treated between 2015 and 2023 at four Brazilian cancer institutions, including public and private hospitals. Clinical and demographic data, treatment details, and outcomes were collected from electronic records. The primary endpoints were the 3-year and 7-year invasive disease-free survival (IDFS) rates. Secondary endpoints included overall survival (OS) and factors associated with IDFS. Survival analysis employed the Kaplan-Meier method, and Cox regression assessed prognostic factors.

Results: A total of 133 patients treated with the APT regimen were evaluated, with a median age of 56 years (range 20–83). The majority had no special type breast carcinoma (92.4%), grade 2 (63.4%) or grade 3 (34.3%) tumors, no angiolymphatic invasion (76.3%), positive estrogen receptor (69.9%), positive progesterone receptor (55.6%), and node-negative disease (94.7%). Tumor staging distribution was as follows: T1a (12%), T1b (23.3%), T1c (49.6%), and T2 (13.5%). Most patients (95.4%) received the APT regimen as per guideline recommendations, while 3.8% received it due to contraindication to other therapies. With a median follow-up of 45.8 months, 8 patients (5.8%) experienced an invasive disease event or death from any cause: 5 (3.8%) had distant recurrence, 1 (0.8%) had local recurrence, and 2 (1.5%) died without recurrence. Notably, these events occurred in patients receiving the APT regimen according to standard indications, except for one patient with N+ disease and a contraindication to another regimen. The recurrence rate according to the T stage is presented

in the Table. The 3-year IDFS rate was 100% (95% CI not applicable). All events occurred after the 3-year time point, resulting in a 7-year DFS rate of 80.8% (95% CI 62.7–90.7%). No prognostic factors related to IDFS were identified. Four patients died during the study period, yielding a 7-year OS rate of 88.0% (95% CI 61.6–96.6%).

Conclusion: While the baseline characteristics of this cohort resembled those of the APT trial, the long-term outcomes observed in the real-world setting were less favorable. Further investigation is required to determine the reasons for this discrepancy, underscoring the necessity for larger real-world data studies to validate these findings.

Recurrence rate according to T stage

Table. Recurrence rate according to T stage.

	T1a (n=16)	T1b (n=31)	T1c (n=66)	T2 (n=18)	T3 (n=2)
Local recurrence	0 (0%)	1 (3.2%)	0 (0%)	0 (0%)	0 (0%)
Distant recurrence	0 (0%)	1 (3.2%)	4 (6.1%)	0 (0%)	0 (0%)

PO3-17-07

Real-world experience with trastuzumab deruxtecan in patients with breast cancer: 6 month-interim analysis of an all-patient postmarketing surveillance in Japan

Presenting Author(s) and Co-Author(s):

J. Tsurutani. Advanced Cancer Translational Research Institute at Showa University, Tokyo, Shinagawa, Japan

H. Mizutani. Daiichi Sankyo Co., Ltd., United States

A. Tanabe. Daiichi Sankyo Co., Ltd., United States

Background: Trastuzumab deruxtecan (T-DXd) is an anti-human epidermal growth factor receptor 2 (HER2) antibody-drug conjugate. T-DXd has shown great efficacy in HER2-positive breast cancer, hence receiving approval in Japan in March 2020. In Japan, all-patient postmarketing surveillance (PMS) is underway to evaluate the risk of interstitial lung disease/pneumonitis (ILD/p) in patients with breast cancer treated with T-DXd. Due to the limited generalizability of results from clinical trials, there is a need for more information about ILD/p in a real-world setting. Herein we present an interim analysis of the large-scale all-patient PMS. Methods: This is an observational, multicenter, all-patient PMS (jRCT1080225197) with an observation period of 18 months that enrolled all patients treated with T-DXd for recurrent/advanced HER2-positive breast cancer. Patients who initiated T-DXd treatment between May 2020 (launch date of T-DXd) and May 2021 were included in the interim analysis to ensure the observation period of 6 months from the initial treatment of T-DXd. This interim analysis is based on safety data from the first 6 months of 1204 patients. Data collected includes baseline characteristics and information on ILD/p. All potential ILD/p (identified based on the AE terms) reported by physicians were adjudicated by an independent ILD adjudication committee. The incidence of ILD/p was calculated from adjudicated drug-related ILD/p. Results: The interim analysis set included 1204 patients with median age of 60 years. Three of the 1204 patients (0.2%) received T-DXd as a first-line treatment, 30 (2.5%) as second-line, 1159 (96.3%) as third- line or later treatment. At baseline, 105 (8.7%) of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) 2 or greater, 8 (0.7%) had severe renal impairment ($15 \leq$ creatinine clearance (CL_{cr}) < 30 mL/min), 4 (0.3%) had end-stage renal disease ($CL_{cr} < 15$ mL/min), 5 (0.4%) had severe liver impairment (total bilirubin > 4.5 mg/dL), and 32 (2.7%) had comorbid ILD/radiation pneumonitis. Those were defined as exclusion criteria in clinical trials of T-DXd. The median dose at the start of administration of T-DXd was 5.4 mg/kg (range:2.7-5.4). During the first 6 months from the initial treatment, T-DXd was discontinued in 403 (33.5%) of the 1204 patients. The most common reasons for discontinuation were disease progression in 232 (57.6%) of the discontinued 403 patients followed by ILD/p in 97 (24.1%) of the 403 patients. In the first 6 months, the incidence of all grade, grade ≥ 3 , and grade 5 ILD/p were 8.2% (n=99), 1.7% (n=20) and 0.4% (n=5), respectively. The incidence of ILD/p stratified by baseline characteristics identified as potential risk factors of drug-related ILD/p is shown in Table. Conclusion: This is the first report demonstrating real-world experience with T-DXd in Japan. The interim analysis revealed useful information including patient and treatment profiles of T-DXd and the incidence of ILD/p during the first 6 months from the initial treatment in a real-world setting in Japan. The final analysis of the ongoing PMS is warranted for further evaluation.

Incidence of interstitial lung disease/pneumonitis by patient baseline characteristics

Potential risk factor	Patients		
	N	ILD/p cases	
		n	% (95% CI)
All	1204	99	8.2 (6.7, 9.9)
Age group			
<65 years	786	54	6.9 (5.2, 8.9)
≥65 years	418	45	10.8 (8.0, 14.1)
Prior and/or current lung comorbidities*			
No	1097	87	7.9 (6.4, 9.7)
Yes	107	12	11.2 (5.9, 18.8)
Baseline renal function			
Normal (CL _{cr} ≥90 mL/min)	434	28	6.5 (4.3, 9.2)
Mild decrease (60 mL/min ≤ CL _{cr} < 90 mL/min)	531	45	8.5 (6.2, 11.2)
Moderate/Severe decrease (CL _{cr} <60 mL/min)	221	25	11.3 (7.5, 16.2)
Time since disease diagnosis			
<48 months	674	55	8.2 (6.2, 10.5)
≥48 months	514	43	8.4 (6.1, 11.1)
Baseline SpO₂			
<95%	35	3	8.6 (1.8, 23.1)
≥95%	902	80	8.9 (7.1, 10.9)

ILD/p: interstitial lung disease/pneumonitis, 95% CI: 95% confidence interval, CLCr: creatinine clearance using the Cockcroft-Gault equation

* includes ILD/p, pulmonary fibrosis, radiation pneumonitis, chronic obstructive pulmonary disease, emphysema, and Asthma

(Source: Powell CA, Modi S, Iwata H, et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open 2022;7(4):100554)

PO3-17-08

SAFETY AND TOLERABILITY OF SUBCUTANEOUS TRASTUZUMAB AS A TREATMENT IN PATIENTS WITH EARLY HER 2 POSITIVE BREAST CANCER : EXPERIENCE OF A CANCER CENTER IN PERU

Presenting Author(s) and Co-Author(s):

I. Otoyá. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Surquillo, Lima, Peru

N. VALDIVIESO. ecancer, Lima, Peru

Z. Morante. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

C. Castañeda. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

S. Neciosup. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

M. Calderón. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

BACKGROUND:

About 15% to 20% of breast cancers express positivity for human epidermal growth factor receptor 2 (HER2), a more aggressive breast cancer subtype with shorter survival.

Trastuzumab, a humanized monoclonal antibody was approved by the U.S. Food and Drug Administration (FDA) for therapeutic use in metastatic breast cancer in 1998 and HER2-positive early breast cancer in 2006. HER2 overexpression is associated with more aggressive tumor growth and worse prognosis compared to HER2-negative tumors. HER2-positive tumors occur more frequently in younger women and node-positive women and are often less responsive to cytotoxic therapies.

The primary objective of this study was to evaluate the tolerability of the subcutaneous formulation of trastuzumab in real life at the national institute of neoplastic diseases LIMA-PERU in patients with epidermal growth factor receptor 2 (HER2)-positive early breast cancer; efficacy was a secondary objective.

METHOD:

Female patients aged 18 years or older diagnosed between 2018-2019 with early epidermal growth factor receptor 2 (HER2)-positive breast cancer who received at least 1 dose of trastuzumab subcutaneously in a neo/adjuvant setting with or without chemotherapy were included. The treatment indication is 600 mg at a fixed dose every 3 weeks for 18 cycles.

RESULTS:

A total of 70 patients who received treatment with subcutaneous trastuzumab were included in the analysis. The mean age of the population was 52.6 ± 12.4 years, with the majority of patients being older than 50 years (54.29%). The mean number of subcutaneous trastuzumab cycles received was 11.4 ± 4.2 . Adverse effects such as arthralgia (47.62%), diarrhea (9.52%), fatigue (9.52%) and injection site reaction (9.52%) occurred in 30% of patients. The mean number of cycles received until the first occurrence of adverse effects was 5.2 ± 2.1 . It was observed that 97.14% completed treatment with trastuzumab subcutaneously, and 2.86% had to discontinue treatment. Cardiotoxicity and hypertension were the reasons why patients discontinued treatment.

Of the patients included in the study, 63.77% received subcutaneous trastuzumab in the

neoadjuvant setting, while the remaining 36.23% received it in the adjuvant setting. Of the patients, 45.71% started treatment with trastuzumab intravenously and received an average of 6 ± 3 cycles before switching to the subcutaneous presentation.

After 3 years of follow-up, 7.14% developed disease progression; 57.1% had progression at the cerebral level, 28.6% at the local level and 14.3% at the pulmonary/hepatic level. 98.57% of patients are alive.

CONCLUSIONS:

In a real-life setting, subcutaneous trastuzumab is a well-tolerated and effective treatment option for patients even in patients who started treatment with the intravenous presentation and made the switch during treatment.

Table 1: General clinical characteristics of patients

Table 1: General clinical characteristics of patients	
Clinical characteristics	Overall, N = 70 ¹
Age (years)	51.5 (46.0, 60.8)
Age group (years)	
0-35	7 (10.0%)
36-49	25 (35.7%)
50+	38 (54.3%)
Tumor size (mm)	17.0 (8.0, 25.0)
Lymph node status	
Negative	37 (55.2%)
Positive	30 (44.8%)
NR ²	3
TNM classification	
T1 N0/1/2 M0	7 (10.3%)
T1 N0 M0	2
T1 N1 M0	4
T1 N2 M0	1
T2 N0/1/2/3 M0	25 (36.8%)
T2 N0 M0	8
T2 N1 M0	12
T2 N2 M0	2
T2 N3 M0	3
T3 N0/1/2/3 M0	24 (35.3%)
T3 N0 M0	2
T3 N1 M0	11
T3 N2 M0	10
T3 N3 M0	1
T4 N0/1/2/3 M0/1	12 (17.6%)
T4 N0 M0	2
T4 N1 M0	5
T4 N1 M1	1
T4 N2 M0	2
T4 N3 M0	2
NR ²	2

¹ Median (IQR); n (%)

² Not reported (NR)

Table 2: Treatment status and tolerability

	Overall, N = 70 ¹
First-line treatment	
Adjuvant chemotherapy	44 (63.8%)
Neoadjuvant chemotherapy	25 (36.2%)
NR ²	1
Adverse events	
No adverse effects	49 (70.0%)
Reported adverse effects	21 (30.0%)
Arthralgia	10
Cardiotoxicidad	1
Cefalea	1
Diarrhea	2
Fatigue	2
Hypertension	1
Myalgia	2
Injection Site Reaction	2
Treatment status	
Completed	97.10%
Suspended	2.90%
Cardiototoxicity	1
Hypertension	1
Intravenous trastuzumab treatment	
No	38 (54.3%)
Yes	32 (45.7%)
Progression status	
No	65 (92.90%)
Yes	5 (7.10%)
Survival status	
Dead	1 (1.43%)
Alive	69 (98.57%)

¹Median (IQR); n (%)

²Not reported (NR)

PO3-17-09

Outcome after the introduction of personalized treatment for axilla in patients with clinically node-negative early breast cancer

Presenting Author(s) and Co-Author(s):

M. Tomiguchi. Kumamoto University Hospital, United States

K. Hidaka. Kumamoto University Hospital, United States

L. Goto-Yamaguchi. Kumamoto University Hospital, United States

A. Kajiwara. Kumamoto University Hospital, United States

K. Nishikido. Kumamoto University Hospital, United States

T. Inao. Kumamoto University Hospital, United States

Y. Yamamoto. Kumamoto University Hospital, United States

Background : After the results of ACOSOG Z0011 and AMAROS trials were reported, axillary treatment has been promoted to de-escalation. For clinically negative cases of axillary lymph node metastasis (cN0), axillary dissection (Ax) has been the standard treatment when sentinel lymph node (SN) metastasis is positive. In our hospital, for patients with cN0, if SN macro metastasis is positive, Ax or irradiation (RT) is selected after sufficient explanation to the patients. Five years have passed since the introduction of treatment selection for the axilla, we examined treatment outcomes retrospectively.

Methods : The subjects were 1376 patients who underwent SN biopsy for primary breast cancer with cN0 at our hospital from October 2004 to December 2018 (median observation period 79 months). Cases who underwent preoperative chemotherapy were excluded. We have introduced the treatment choice system since December 2015, and compared prognosis (local recurrence, distant recurrence and breast cancer specific death) before and after introduction using the log-rank test.

Results : There were 947 cases before introduction of treatment choice system (pre group) and 429 cases after introduction (post group). The median observation period for each group was 91 months and 41 months. The maximum observation period post group was 67 months, then we compared the number of events in patients with observation period less than 67 months in pre group. There was no significant difference between two groups (Pre / Post) in terms of age ($p=0.52$), menopausal status ($p=0.90$), invasion of primary lesion ($p=0.19$), biology and SN metastasis status ($p=0.41$). There were 54 patients (12.6%) in pre group and 135 (14.3%) patients in post group had positive sentinel lymph nodes. In post group, 33 patient (61.1%) were macrometastasis of SN, 28 of whom underwent Ax and 5 underwent RT. Local recurrence was 4 cases (1.7%) in pre group, 9 cases (2.1%) in post group ($p=0.84$), distant recurrence was 13 cases (5.6%) and 5 cases (1.2%) ($p=0.0002$), and breast cancer specific death was 8 cases (0.8%) and 1 case (0.2%) ($p=0.0003$), respectively.

Discussion : There was no significant difference in local recurrence rate within 67 months, but were poor prognosis in pre introduction group for distant metastasis and breast cancer specific survival. In the results of this study, there was no significant difference in local recurrence, but the prognosis for distant recurrence and breast cancer-specific death was poor in the before introduction group. The median observation period in the post introduction group was 47 months, and late recurrence of ER-positive breast cancer occurs later. It is necessary to continue the study by extending period and accumulation cases.

Conclusion : For cN0 cases, if the case is suitable, we introduced the treatment choice system that allows omitting Ax by performing radiotherapy in SN macrometastasis positive patients. After introduction, there was no increase in the relapse rate after introduction in the short term. Appropriate case selection allowed the safety introduction of individualized treatment for axilla.

PO3-17-10

Real-World evidence for Pembrolizumab-based neoadjuvant chemotherapy in early-stage triple negative breast cancer: a single institution experience.

Presenting Author(s) and Co-Author(s):

A. Al-Awadhi. department of Medical Oncology, Tawam hospital - SEHA, United States

M. AIShebli. Department of Internal Medicine, University of Toronto, Canada, United States

L. Wahba. Department of Clinical Pharmacy -Tawam hospital - Abu Dhabi Health Services Company - Al Ain - UAE, United States

T. Younis. Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, United States

Introduction The improved pathologic complete response (pCR) and event-free survival observed in Keynote-522 trial (NCT03036488) led to the adoption of (neo)adjuvant pembrolizumab (pembro)-based chemotherapy (CT) for high-risk early-stage triple-negative breast cancer (eTNBC) in various jurisdictions. However, Real-World Evidence (RWE) for (neo)adjuvant pembro in this setting would further support its ongoing funding and utilization. The aim of this study was to provide RWE for (neo)adjuvant pembro in eTNBC in the United Arab Emirates (UAE), where patients often present with more-advanced disease stages and poorer prognostic profiles compared with North America and Europe. **Method** This is a retrospective cohort study involving all patients treated with pembro-based neoadjuvant chemotherapy (NACT) for eTNBC at a major cancer center (Tawam Hospital) in the UAE between October 2021 and June 2023. Patient characteristics, clinicopathologic features, immune related adverse events (irAE) and disease outcomes were reported by descriptive statistics. An exploratory analysis was also conducted to examine the associations between pCR and HER-2 status (HER2 negative vs HER2 low) as well pCR and treatment interruption (< vs = > 2 weeks). **Results** A total of 41 patients, with a median age of 44 years, were included in this study. All had an ECOG status of 0-1. The clinical and pathological characteristics are provided in Table 1. Pathogenic germline BRCA (gBRCA) mutations were detected in 8 (21%) of the 38 patients who underwent testing, including 6 with gBRCA1 and 2 with gBRCA2), with additional TP53 and SMARC4 detected in one patient each.

Approximately 66% of the patients (n = 27) completed surgery post neoadjuvant pembro+CT, of whom 18 (67%) had breast conserving surgery and 9 (33%) had mastectomy. Of the patients who underwent surgery, 60% (n = 16/27) achieved pCR including 68% (13/19) of the IHC 0+ and 37.5% (3/8) of the HER2 1+ or 2+ ISH negative (p-value = 0.429, Chi Square test).

Of the total population, 16 (40%) did not complete NACT; 1 lost to follow-up, 9 were still on ongoing therapy, 2 discontinued therapy due to toxicity, and 4 developed progressions including 1 locoregional relapse, and 3 metastatic diseases.

Of the 32 patients who completed at least 3 months of pembro-NACT, 14 (34%) reported any grade irAE: skin toxicity (N = 3, 21%), hypothyroidism (N = 8, 57%), Hyperthyroidism (N = 1, 7%), Hepatitis (N = 4, 28.5%), adrenal insufficiency (N = 1, 7%), and pneumonitis (N = 1, 7%). With a median follow up of 4.5 months, pembro was postponed in 4 patients and permanently discontinued in 1 secondary to severe pneumonitis requiring ICU admission. All irARs were graded at I and II, except for 1 grade III dermatitis, and 1 grade III pneumonitis. Interruption of IO was required for irAE in 5 (36%) patients, and steroids were administered in 4 (29%).

pCR was observed in 6 (40%) patients out of 15 who experienced treatment interruption due to IrAE or CT and 10 out of 13 (77%) in those who did not experience treatment interruption ($p = 0.04895$, Chi-square test). Conclusion The pCR rates for Pembro-based NACT in this RWE study, involving patients with an overall higher risk disease, appeared to be consistent with those observed in keynote-522. Interestingly, pCR rates did not seem to differ between HER2 negative and HER2 low groups. However, pCR rates appeared to be lower in patients who experienced treatment interruptions. Approximately half of the patients developed irAE but the majority of the adverse events were of lower grade and did not require treatment interruptions. Overall, the RWE observed in this study supports the ongoing funding and utilization of Pembro-based NACT in eTNBC. Updated data, including the pCR rate and toxicity, will be presented at the meeting once most of the patients have completed surgery.

Table 1: Clinical and Pathological Characteristics of patients (N=41)

		N(%)			N(%)
Median age	44 (25-74)		Clinical N stage	N0	24 (59)
Median BMI	29 (21-41)			N1	9 (22)
Menopausal status	Pre-menopausal	26 (63)		N2	1 (2)
	Post-menopausal	15 (37)		N3	7 (17)
stage	II	21 (51)	HER/neu IHC	0	27 (67)
	III	20 (49)		1	8 (19)
Grade	II	6 (15)		2 (ISH negative)	6 (14)
	III	35 (85)			
Clinical T stage	T1	2 (5)			
	T2	20 (49)			
	T3	11 (27)			
	T4	8 (19)			

PO3-17-11

The Utility of Oncotype DX in Grade 1 Hormone Receptor-Positive Early Breast Cancer: Insights from a Multicentric Real-World Data Study

Presenting Author(s) and Co-Author(s):

R. Colombo Bonadio. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

L. Oliveira. Grupo Oncoclínicas, São Paulo, Brazil, Brazil

D. Batista. 2. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil., Brazil

D. Rosa. Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul, Brazil

A. Katz. Centro de Oncologia - Hospital Sírio-Libanês, São Paulo, Brazil, Brazil

M. Mano. Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil, Brazil

D. Assad-Suzuki. Hospital Sírio-Libanês, Brasília, Brazil, Brazil

D. Argolo. Clion, Grupo Oncoclínicas, Salvador, Brazil, Salvador, Bahia, Brazil

S. Sanches. AC Camargo Cancer Center, São Paulo, Brazil, Brazil

R. Kaliks. Hospital Israelita Albert Einstein, United States

D. Gagliato. Hospital Beneficência Portuguesa, São Paulo, Brazil, Brazil

T. Megid. Centro de Oncologia - Hospital Sírio-Libanês, São Paulo, Brazil, Brazil

D. Musse. Oncologia Dor, United States

T. Correa. Hospital Sirio-Libanês, United States

A. Shimada. Hospital Sirio Libanês, São Paulo , Brazil, Brazil

R. Barroso-Sousa. Dasa Oncology, United States

M. Cesca. AC Camargo Cancer Center, São Paulo, Brazil, Brazil

D. Gaudêncio. Clínica CLION, Grupo Oncoclínicas, Salvador, Brazil, Brazil

L. Moura. Clínica CLION, Grupo Oncoclínicas, Salvador, Brazil, United States

J. Araujo. Hospital Beneficência Portuguesa, São Paulo, Brazil, Sao Paulo, Sao Paulo, Brazil

J. Bines. Instituto Nacional de Câncer (INCA), Brazil

L. Testa. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil

Background: The Oncotype Dx (ODX) genomic risk score (RS) has become an essential tool in clinical practice for guiding adjuvant chemotherapy decisions in early-stage hormone receptor-positive (HR+), HER2-negative breast cancer (BC). Since some of the genes evaluated in the genomic RS tests are proliferation-related, the use of the test is less clear in tumors with low proliferation, such as histologic grade 1 tumors or those with a low Ki67-index. In contrast to common understanding, however, ODX RS is determined more strongly by estrogen-related features and only weakly by proliferation markers. **Methods:** This multicentric real-world data (RWD) study aimed to evaluate the usefulness of (ODX) in patients with grade 1 (G1) HR+, HER2-negative BC. The study population consisted of patients treated between 2009 and 2020 across nine Brazilian cancer centers. Key endpoints included the prevalence of high genomic RS in the histologic grade 1 cohort, recurrence rates based on genomic risk, and invasive disease-free survival (IDFS). **Results:** A total of 651 patients with HR+, HER2-negative BC who underwent Oncotype Dx testing were evaluated. Among 651 patients evaluated, 128 had HG1 tumors, constituting the focus of this analysis. The majority of patients were aged over 50 years (59.4%), had breast carcinoma of non-special type (75.8%), and Ki67 index lower than 20%

(77%). Tumor stage distribution revealed 28.1% T1b, 50% T1c, and 14% T2 cases. Additionally, 74.2% were classified as N0, 9.4% as N1mic, and 16.4% as N1. According to the binary categorization based on Adjuvant! algorithm, 92.2% of patients (n=118) had a low clinical risk. ODX analysis showed that 21.9% had a low RS, 74.2% had an intermediate RS, and only 3.1% had a high RS. Among the few patients with a high genomic RS, only one patient did not receive adjuvant chemotherapy. With a median follow-up of 38.3 months, three patients experienced recurrence, all of whom had an intermediate RS. Among these cases, two patients were younger than 50 years, had low clinical risk, and a genomic RS of 18-24; both had locoregional recurrences. The third patient, aged over 50 years, had high clinical risk, a RS of 12, and had a distant recurrence. The recurrence rates according to Ki67 index were 1.1% for patients with Ki67 index < 20% and 7.1% for those with Ki67 index \geq 20%. Notably, no recurrences were observed in the high genomic risk group. The estimated 5-year IDFS rate was 96.9% (95% CI 88.2% - 99.2%). Conclusion: In the context of G1 BC and low clinical risk, the utility and cost-effectiveness of ODX may be limited. These findings emphasize the importance of carefully assessing clinical risk when selecting patients for genomic RS tests, thereby optimizing resource utilization. Longer follow-up is planned for this RWD cohort.

PO3-17-12

Safety and efficacy of Atezolizumab in combination with nab-Paclitaxel in patients with PD-L1 positive metastatic or locally advanced triple-negative breast cancer: A pan-UK cancer centre experience.

Presenting Author(s) and Co-Author(s):

- J. Waterhouse. The Royal Marsden NHS Foundation Trust, England, United Kingdom
A. Holdich. The Royal Marsden NHS Foundation Trust, United Kingdom
F. Mina. The Royal Marsden NHS Foundation Trust, United Kingdom
M. Obeid. The Royal Marsden NHS Foundation Trust, United Kingdom
K. Joshi. The Royal Marsden NHS Foundation Trust, United Kingdom
S. Barrett. The Beatson West of Scotland Cancer Centre, NHS Greater Glasgow and Clyde, United Kingdom
L. Rajakumar. Kent Oncology Centre - Maidstone, United Kingdom
G. McCormick. Maidstone & Tunbridge Wells NHS Trust, United Kingdom
S. Seymour. The Royal Surrey County Hospital NHS Foundation Trust, United Kingdom
P. Koliou. The Royal Surrey County Hospital NHS Foundation Trust, United Kingdom
R. Sylva. University Hospitals of Leicester NHS Trust, United Kingdom
O. Ayodele. University Hospitals of Leicester NHS Trust, United Kingdom
A. Gautam. Northern Centre for Cancer Care, The Newcastle upon Tyne hospitals NHS Foundation Trust, United Kingdom
J. Smith. Northern Centre for Cancer Care, The Newcastle upon Tyne hospitals NHS Foundation Trust, United Kingdom
J. McKeon. Bristol Haematology and Oncology Centre/ University Hospital Bristol and Weston NHS Foundation Trust, United Kingdom
T. Strawson-Smith. Bristol Haematology and Oncology Centre/ University Hospitals Bristol and Weston NHS Foundation Trust, United Kingdom
R. Douglas. Northern Ireland Cancer Centre/ Belfast City Hospital, United Kingdom
A. Borley. Velindre Cancer Centre, Cardiff, United States
A. Konstantis. Princess Alexandra Hospital NHS Trust & University College London Hospitals Foundation Trust, United States
S. McGrath. The Royal Marsden NHS Foundation Trust, Department of Medicine, Breast Unit, United Kingdom

BACKGROUND Within the United Kingdom (UK), combination chemo-immunotherapy with Atezolizumab and nab-Paclitaxel is National Institute for Health and Care Excellence (NICE) approved as a first line palliative systemic treatment option for patients with advanced triple-negative breast cancer (aTNBC) with programmed death-ligand 1 (PD-L1) expression $\geq 1\%$. Trials demonstrated progression-free survival (PFS) and overall survival (OS) benefits. Treatment-related toxicities may impact on quality of life and result in treatment delay or discontinuation. We conducted a National Service Evaluation (SE) to assess the safety and efficacy in a “real-world” dataset. **METHODS** Data from patients with aTNBC who received Atezolizumab/ nab-Paclitaxel between 9th March 2019 and 2022 across 10 UK Cancer Centres were analysed. All grade 1-4 toxicities were recorded in accordance with Common Terminology

Criteria for Adverse Events (CTCAE) version 5.0 scoring system. Participation was contingent on local approval for this project, and data transferred following receipt of a data sharing agreement. Kaplan-Meier curves for PFS and OS were calculated. RESULTS 129 patients were included in the analysis with a median age of 55 (30-82). 42.6% (n=55) had a PS of 0, 51.2% (n=66) a PS of 1 and 3.9% (n=5) had a PS of 2. Atezolizumab/nab-Paclitaxel was given in the first line setting in most patients (84.5%, n= 109), but in 15.5% (n=20) in the second line setting (privately insured). 21.7% (n=28) of patients presented with de novo metastatic disease, 58.1% (n=75) of patients were post-menopausal and 6.2% (n=8) had a BRCA1 or 2 mutation. 76.7% of patients (n=99) had previous neo-/adjuvant treatment in the non-metastatic setting: 55.8% had prior treatment with a taxane, 51.2% anthracycline, 22.5% platinum, and 66.7% had prior radiotherapy. 83.7% (n= 108) had invasive ductal breast cancer, and 84.5% (n=109) presented with 0-3 number of metastatic sites with 15.5% (n=20) having \geq 4 metastatic sites. Here, the nodal metastatic site dominated in 78.3% of patients. Grade \geq 3 events occurred in 21.7% (n=28) of patients. These were decreased neutrophil count (10.1%, n=13), pyrexia (2.3%, n=3), diarrhoea (1.6%, n=2), hypothyroidism (1.6%, n=2), peripheral neuropathy (1.6%, n=2), anaemia (1.6%, n=2), GGT rise (0.8%, n=1), fatigue (0.8%, n=1), hypophysitis (0.8%, n=1), pneumonitis (0.8%, n=1), nausea (0.8%, n=1), mucositis (0.8%, n=1), platelet count decreased (0.8%, n=1), infections (0.8%, n=1). Increased rates of Grade \geq 3 colitis (2.3%, n=3) and hepatitis (3%, n=2.3) were observed. 20.2% (n=26) of patients required steroids to treat toxicities. Reason for treatment discontinuation included in 58.1% (n=75) disease progression, and 7.8% (n=10) unacceptable toxicity. In 22.5% of patients' treatment was still ongoing at time of data lock. At approximately 12 weeks, 7.8% of patients had a complete and 51.2% a partial response, 10.1% had stable and 22.5% progressive disease and for 8.5% the response was not known as they have not yet reached 12 weeks since treatment start. Median PFS was 5 months and OS was 14 months. CONCLUSIONS The toxicity profile of Atezolizumab/ nab-Paclitaxel was comparable to literature, however, both PFS and OS were shorter. In comparison to the IMpassion130 trial data, patients within this national SE project were less fit and more heavily pre-treated. A higher number of any grade hyperthyroidism and fatigue, and of grade \geq 3 colitis and hepatitis were noticed.

Baseline patient characteristics

TABLE

Baseline patient characteristics	Patients SE Patients (n = 129)	IMpassion130 Patients (n = 188)
Age at baseline* - median (range)	55 (20-82)	53 (20-82)
Age - n (%)		
17-24	47 (36.4)	24 (12.8)
25-34	40 (31.0)	114 (60.3)
35-44	28 (21.7)	63 (33.5)
45-54	8 (6.2)	35 (18.6)
55-64	2 (1.6)	11 (5.9)
65-74	0	1 (0.5)
≥75	2 (1.6)	1 (0.5)
Performance score - n (%)		
0	55 (42.6)	53 (28.2)
1	66 (51.2)	114 (60.3)
2	5 (3.9)	2 (1.1)
Unknown	3 (2.3)	1 (0.5)
Menopausal status - n (%)		
Pre-menopausal	15 (11.6)	10 (5.3)
Post-menopausal	75 (58.1)	127 (67.4)
Menopausal status unknown	9 (6.9)	7 (3.7)
BRCA1 or 2 mutation - n (%)		
BRCA1	2 (1.6)	0
BRCA2	6 (4.7)	0
Unknown	8 (6.2)	0
Previous treatment - n (%)		
None	28 (21.7)	0
One or more	101 (78.3)	188 (100)
Unknown	0	0
Number of metastatic sites - n (%)		
0	13 (10.1)	19 (10.1)
1	43 (33.3)	73 (38.8)
2	32 (24.8)	50 (26.6)
3	22 (17.1)	38 (20.2)
4	10 (7.7)	18 (9.6)
≥5	2 (1.6)	2 (1.1)
Unknown	12 (9.2)	10 (5.3)
Site of metastatic disease - n (%)		
None	28 (21.7)	0
Brain	28 (21.7)	24 (12.8)
Bone	43 (33.3)	100 (53.2)
Colon	13 (10.1)	20 (10.6)
Lung	22 (17.1)	30 (15.9)
Lymph node	10 (7.7)	18 (9.6)
Other	2 (1.6)	2 (1.1)
Unknown	12 (9.2)	10 (5.3)
Number of treatment cycles - median (range)*	9 (1-22)	9 (1-22)
Unknown	0	0
Number of treatment cycles - n (%)		
0-1	13 (10.1)	13 (6.9)
2-3	43 (33.3)	120 (63.5)
4-5	22 (17.1)	36 (19.1)
6-7	10 (7.7)	19 (10.1)
8-9	2 (1.6)	1 (0.5)
≥10	12 (9.2)	18 (9.6)
Unknown	0	0

Abbreviations: ABS, national health service; WHO, world health organization; IC, immunohistochemistry; ECOG, Eastern Cooperative Oncology Group; PS, performance score; BRCA, Breast Cancer gene; SE, adverse event.

*IC1-1 immunohistochemistry positive population

†Median = Cycle 1, Day 1 of Atezolizumab/ nab-Paclitaxel

‡Median with 95% confidence interval (CI) from Day 1 to Day 1 of second line treatment

§Median with 95% confidence interval (CI) from Day 1 to Day 1 of third line treatment

*First line Atezolizumab plus nab-paclitaxel for unresectable, locally advanced or metastatic triple-negative breast cancer - IMpassion130 trial overall survival analysis Esteva, L. A. et al. Annals of Oncology, Volume 32, Issue 9, 993-1000

PO3-18-01

Cirrhosis is associated with worse post-operative survival among patients with breast cancer: a population-based study

Presenting Author(s) and Co-Author(s):

M. Jogendran. Queen's University, United States

J. Flemming. Queen's University, United States

M. Djerboua. Institute for Clinical Evaluative Sciences, United States

S. Merchant. Queen's University, United States

S. Bennett. Queen's University, United States

Background: The relationship between cirrhosis and breast cancer treatment and outcomes has not been specifically explored. We evaluated the association between cirrhosis and surgical outcomes in female patients with breast cancer.

Methods: We performed a retrospective cohort study of female patients undergoing surgery for breast cancer between 2007-2018 using health administrative data from Ontario, Canada. Breast cancer surgeries were captured using Canadian Classification of Health Intervention codes. Patients with cirrhosis were identified using validated coding definitions. Overall and cancer-specific survival from time of surgery to December 2021 was compared between patients with and without cirrhosis using Kaplan-Meier survival analysis. Modified Poisson regression, chi-square and ANOVA were used to assess the association between cirrhosis and 90-day post-operative mortality, post-operative complications, length of hospital stay, intensive care unit (ICU) admission, and post-operative hepatic decompensation within 6 months.

Results: A total of 83,880 females with breast cancer undergoing surgery were identified with 910 (1%) having cirrhosis. The median age at diagnosis was 65 (IQR 57-72) in patients with cirrhosis and 61 (IQR 51-71) in those without ($p < 0.001$). The most common etiology of cirrhosis was non-alcoholic fatty liver disease ($n = 602$, 66%) followed by alcohol-related ($n = 144$, 16%) with $n=27$ (3%) having a history of decompensation within two years prior to surgery. Model for end stage liver disease score (MELD-Na) was available in 24% ($n = 218$), with a median score of 8 (IQR 6 – 11). Patients with cirrhosis had similar breast cancer stage at diagnosis as patients without cirrhosis (47% stage I, 38% stage 2, 11% stage 3, and 0.5% stage 4) with the most common type of surgical procedure being lumpectomy (71%) in both groups. Use of pre-operative chemotherapy was less common in patients with cirrhosis (5.9% vs 7.9%, $p=0.026$). Post-operative radiation and chemotherapy within 6-months after surgery was lower in patients with cirrhosis (56.8% vs 63.7%, $p < 0.001$ and 48.4% vs 52.2%, $p=0.019$, respectively). Patients with cirrhosis had higher 90-day post-operative mortality compared to those without (1.4% vs 0.3%, $p < 0.001$). After adjusting for age, income quintile, and breast cancer surgery, cirrhosis was independently associated with 90-day post-operative mortality (RR, 4.1; 95% CI 2.4-6.8). Patients with cirrhosis had a higher prevalence of incision complications (6.4% vs 4.6%, $p = 0.007$) and blood transfusions (2.9% vs 1.1%, $p < 0.001$), but similar rates of surgical site infections (6.4% vs 5.3%, $p=0.138$) and venous thromboembolism (0.3% vs 0.5%, $p=0.5$). Re-operation was slightly higher in patients without cirrhosis (3.2% vs 4.6%, $p=0.05$). Length of hospital stay was 2 days in patients with cirrhosis and 1.3 days for patients without ($p < 0.001$); ICU admission was more likely in patients with cirrhosis (1.8% vs 0.9%, $p=0.008$); and 18 (2%) patients with cirrhosis developed post-operative hepatic decompensation within 6 months. Survival in patients with cirrhosis was lower than those

without (5-year OS 77% vs 87%, $p < 0.0001$); stage 0/I (83% vs 94%, $p < 0.05$), stage II (75% vs 87%, $p < 0.05$), stage III (62% vs 73%, $p < 0.05$), stage IV (40% vs 40%). Cancer-specific survival was also lower in patients with cirrhosis (5-year CSS 88% vs 91%, $p = 0.017$).

Conclusion: This large population-based study demonstrates that, compared to patients without cirrhosis, patients with cirrhosis are older with similar stage at diagnosis, but are somewhat less likely to receive adjuvant therapies. While they have slightly higher risks of certain post-operative complications and lower overall and cancer-specific survival, their outcomes remain favourable and should be considered for curative-intent therapies.

PO3-18-02

RISK FACTORS FOR DEATH IN ELDERLY PATIENTS WITH BREAST CANCER TREATED IN AN ONCOLOGY REFERENCE HOSPITAL IN THE CITY OF RECIFE, BRAZIL

Presenting Author(s) and Co-Author(s):

A. DE VASCONCELOS. INSTITUTO DE MEDICINA INTEGRAL PROF FERNANDO FIGUEIRA - IMIP, Recife, Pernambuco, Brazil

C. Santos. Instituto D'Or de Pesquisa e Ensino (IDOR), Recife, Brazil, Brazil

J. Telles. Instituto de Medicina Integral Prof. Fernando Figueira ,Iacog, Brazil

M. MELLO. INSTITUTO DE MEDICINA INTEGRAL PROF FERNANDO FIGUEIRA - IMIP, Pernambuco, Brazil

B. LUZ. INSTITUTO DE MEDICINA INTEGRAL PROF FERNANDO FIGUEIRA - IMIP, United States

Background: Breast cancer (BC) is the most common type of cancer among women in the world and in Brazil as well. Age is the most important risk factor for the development of cancer. The treatment of BC in elderly women is particularly challenging, as physiological changes, functional deficits, comorbidities and the use of polypharmacy can alter the risk of toxicity. We conducted this trial to determine the risk factors for deaths in less than 180 days after admission in elderly cancer patients with BC treated at the Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, Brazil, and correlate with specific aspects of this type of cancer, such as type of treatment and immunohistochemical profile. Methods: Prospective cohort, in women aged ≥ 60 years, diagnosed with BC, admitted to the IMIP Oncogeriatric Service. At admission, sociodemographic and clinical variables and 10 tests that make up the CGA (Comprehensive Geriatric Assessment) were evaluated, including Mini Nutritional Assessment Short Form (MNA-SF), Polypharmacy and KPS (Karnofsky Performance Status). The follow-up period was at least six months. Descriptive, bivariate analysis using the Fisher and Chi-square tests, a survival study using the Kaplan-Meier method and univariate analysis were performed, including those with $p < 0.20$ in the multivariate Cox proportional hazards model controlled by Age and Tumor staging. All subjects involved in the research were informed about the objectives of the study and were only included after voluntarily agreeing to participate, signing the informed consent form. Results: The study sample consisted of 326 patients diagnosed with BC in the period from January 2015 to December 2020, all female, with a mean age of 73.46 years ($SD \pm 7.81$). Sociodemographic, clinical and treatment characteristics are described in Table 1. Of the 326 patients, 46 (14,1%) died, and of these, 21 (45,7%) had an infection and 18 (39,1%) required hospitalization. Regarding the domains of the CGA, the characteristics of patients both in the general population and those who died are described in Table 2. After multivariate analysis by Cox regression of clinical variables related to the Comprehensive Geriatric Assessment (CGA) according to death, were identified as a risk factor for death: MNA-SF < 12 (HR = 2,76, IC95%, 1,49-9,48, $p = 0,001$), KPS $\leq 50\%$ (HR = 4,39, IC95%, 2,03-9,48, $p < 0,001$). Conclusions: In order to improve the efficacy and safety of the treatment of elderly women with BC and to improve their quality of life, the instruments of CGA should be performed routinely. In this population, KPS and Mini Nutritional Assessment Short Version (MNA – SF) were identified as important predictors of early death (180 days after admission). Therefore, in elderly patients with BC who are at risk for malnutrition and have low KPS, the treatment should be analyzed with caution, as well as the evaluation for concomitant early palliative care.

Table 1. Sociodemographic, clinical and treatment characteristics of elderly patients treated for BC at IMIP, Recife, 2015-2020.

Variables	Total N = 326 (%)	Death N = 46 (%)	p valor*
Sociodemographic Variables			
Age (Years) Media ± DP	73,46 ±7,81	73,93±8,78	0,867
Female Gender	326 (100)	46 (14,1)	NA
Race (Self- Reported)			0,557
Brown/Black	218 (66,9)	33 (71,7)	
White	100 (30,6)	12 (26,1)	
Yellow/Indigenous	8 (2,5)	1 (2,2)	
Marital Status			0,939
No partner	119 (36,5)	17 (37,0)	
With partner	207 (63,5)	29 (63,0)	
Family Income			0,684
= 2 mínimo wage	218 (66,9)	31 (67,4)	
> 2 mínimo wage	108 (33,1)	15 (32,6)	
Education (years of study)			0,190
= 4	214 (65,6)	35 (76,1)	
> 4	112 (34,4)	11 (23,9)	
Tobacco Use			0,213
Never	199 (61,0)	31 (67,4)	
Current or Ex-smokers	127 (39,0)	15 (32,6)	
Alcohol Use			0,278
Non-alcoholic	303 (92,9)	45 (97,8)	
Current/ Alcoholic	23 (7,1)	1 (2,2)	
IMC (Kg/m²)			0,004
<22	35 (10,7)	11 (23,9)	
22-27	89 (27,3)	14 (30,4)	
>27	202 (62,0)	21 (45,7)	
Subtype Tumoral			0,693
Triple negative	63 (19,3)	16 (34,8)	
Hiperexpression HER2	25 (7,7)	6 (13,0)	
Luminal A e B	230 (70,6)	23 (50,0)	
Especial	4 (1,2)	0 (0,0)	
Not informed	4 (1,2)	1 (2,2)	
Metastatic Disease			0,013
No metastasis	209 (64,1)	21 (45,7)	
Metastasis	117 (35,9)	25 (54,3)	
Clinical Evolution			<0,001
Death	46 (14,1)	—	
Infection	63 (19,3)	21 (45,7)	
Hospitalization	63 (19,3)	18 (39,1)	
Chemotherapy			0,739
Yes	209 (64,1)	32 (69,6)	
No	117 (35,9)	14 (30,4)	
Radiotherapy			1,088
Yes	206 (63,2)	23 (50,0)	
No	120 (36,8)	23 (50,0)	
Surgery			< 0,001
Yes	268 (82,2)	26 (56,5)	
No	58 (17,8)	20 (43,5)	
Endocrine Therapy			< 0,001
Yes	231 (70,9)	19 (41,3)	
No	95 (29,1)	27 (58,7)	
Monoclonal Antibody Drug			0,053
Yes	45 (13,8)	3 (6,5)	
No	281 (86,2)	43 (93,5)	

Table 2. Characteristics of CGA (Comprehensive Geriatric Assessment) of elderly patients treated for BC at IMIP, Recife, 2015-2020.

Comprehensive Geriatric Assessment (CGA)	Total N (%)	Death N (%)		Hazard Ratio	IC95%	P value
		Yes	No			
Charlton Comorbidity Index						
• < 2 comorbities	236 (72,4)	34 (73,9)	202 (72,1)	1		
• = 2 comorbities	90 (27,6)	12 (26,1)	78 (27,9)	0,55	0,26-1,16	0,318
Karnofsky Performance Status (KPS)						
• > 50	308 (94,5)	38 (82,6)	270 (96,4)	1		
• = 50	18 (5,5)	8 (17,4)	10 (3,1)	5,06	1,87-13,67	0,001
Mini Nutritional Assessment Short Version (MNA - SF)						
• Normal (= 12)	225 (69,0)	20 (43,5)	205 (73,2)	1	0,77-4,23	0,374
• Risk of Malnutrition (< 12)	101 (31,0)	26 (56,5)	75 (26,8)	1,80		
Mini Nutritional Assessment (MNA)						
• Normal (= 24)	75 (23,0)	23 (50,0)	52 (18,6)	1		
• Risk of Malnutrition /Malnutrition (< 23,5)	251 (77,0)	23 (50,0)	228 (81,4)	2,54	0,44-1,02	<0,001
Minimal State Examination						
• Media ± SD	1,89 ± 0,99	1,78 ± 0,98	1,91 ± 0,99	1	0,65-1,18	0,364
Geriatric Depression Scale (GDS-15)						
• Normal (= 0)	203 (62,3)	25 (54,3)	178 (63,6)	1	0,49-1,70	0,781
• Medium/Severe Risk (> 4)	123 (37,7)	21 (45,7)	102 (36,4)	0,91		
International Physical Activity Questionnaire (IPAQ)						
• Active	63 (19,3)	4 (8,7)	59 (21,1)	1	0,63-5,31	0,201
• Sedentary/Inactive	263 (80,7)	42 (91,3)	221 (78,9)	1,83		
Teste Timed Up and Go (TUG)						
• Low Risk	205 (62,9)	22 (47,8)	183 (65,4)	1		
• Medium/Elevated Risk	121 (37,1)	24 (52,2)	97 (34,6)	1,32	0,68-2,56	0,400
KATZ Index						
• Independent or Dependent on 1 rule	207 (63,5)	26 (56,5)	181 (64,6)	1		
• Dependent in = 2 rules	119 (36,5)	20 (43,5)	99 (35,4)	0,77	0,38-1,53	0,465
Polipharmacy						
• < 5	256 (78,5)	34 (73,9)	222 (79,3)	1	0,51-2,03	0,951
• = 5	70 (21,5)	12 (26,1)	58 (20,7)	1,02		

PO3-18-03

Preoperative single-dose camrelizumab and/or microwave ablation in women with early-stage breast cancer: A randomized window-of-opportunity trial

Presenting Author(s) and Co-Author(s):

w. zhou. The First Affiliated Hospital with Nanjing Medical University, United States

H. Xie. The First Affiliated Hospital with Nanjing Medical University, United States

q. ding. The First Affiliated Hospital with Nanjing Medical University, United States

S. Wang. Jiangsu Province Hospital, United States

Immune checkpoint blockade (ICB) has shown low response rates for advanced breast cancer, and combinatorial strategies are needed to improve the effect of ICB. As an effective local therapy, microwave ablation (MWA) may be a trigger of antitumor immunity. This window-of-opportunity trial was conducted to determine the safety and feasibility of camrelizumab (anti-PD-1 antibody) combined with MWA in the treatment of early-stage breast cancer preoperatively. The peripheral immune response was also investigated. 60 participants were randomized to receive single-dose camrelizumab alone (n=20), microwave ablation (n=20), or both camrelizumab and microwave ablation (n=20), preoperatively. Camrelizumab and MWA were well tolerated alone and in combination. Different from that in single-dose camrelizumab or MWA group, participants showed stable quantity of blood cells after the combination therapy. After the combination therapy, peripheral CD8+T cells showed enhanced cytotoxic and effect-memory functions. Clonal expansional CD8+T cells showed different functions from emergent clones after the combination therapy, suggesting that the expansional clones may play a vital role in the enhanced biological functions of CD8+T cells. Enhanced interactions between clonal expansional CD8+T cells and monocytes was observed, suggesting monocytes contributed to enhanced functions of clonal expansional CD8+T cells. MHC I related pathways and interferon signaling pathways were activated in monocytes by the combination therapy. In conclusion, camrelizumab combined with MWA was feasible for the treatment of early-stage breast cancer. The peripheral CD8+T cells were activated after the combination therapy, dependent on monocytes with activated MHC I pathways.

PO3-18-04

MBRC-101: a novel antibody-drug conjugate (ADC) targeting the membrane-associated tyrosine kinase receptor EphA5 in breast cancer

Presenting Author(s) and Co-Author(s):

F. Staquicini. MBrace Therapeutics, Inc., United States

F. Tang. Rutgers Cancer Institute of New Jersey and Rutgers New Jersey Medical School, United States

V. de Oliveira. MBrace Therapeutics, Inc., United States

D. Staquicini. Rutgers Cancer Institute of New Jersey and Rutgers New Jersey Medical School, United States

Y. Wu. MBrace Therapeutics, Inc., United States

K. Barnhart. MBrace Therapeutics, Inc., United States

J. Parsons. MBrace Therapeutics, Inc., United States

W. Arap. Rutgers Cancer Institute of New Jersey and Rutgers New Jersey Medical School, United States

I. Chen. MBrace Therapeutics, Inc., United States

R. Pasqualini. Rutgers Cancer Institute of New Jersey and Rutgers New Jersey Medical School, United States

Objectives: ADCs have emerged as a major advance in contemporary medical oncology. The receptor tyrosine kinase (RTK) EphA5 possesses the classical receptor kinase topology with an extracellular-binding domain, a single-pass transmembrane domain, and a cytoplasmic kinase domain. We have previously shown that EphA5 is highly expressed in non-small cell lung cancer and contributes to DNA-damage repair and radiation therapy resistance. Others have reported EphA5 expression in gastric, ovarian, and pancreatic cancers. Here, we investigated the expression of EphA5 in breast cancer (BC) and assessed EphA5 as a potential cancer-specific target using a novel ADC designated MBRC-101. **Methods:** MBRC-101 is composed of a humanized anti-EphA5 IgG1 kappa monoclonal antibody conjugated to the small molecule microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease cleavable valine-citrulline (vc) ThioBridge linker (ThioBridge™-Glu-[Val-Cit-PAB-MMAE] PEG [24u]). MBRC-101 averages a drug-to-antibody ratio (DAR)=4. The specificity profile of the anti-EphA5 monoclonal antibody was characterized using a Membrane Proteome Array (MPA). Receptor-mediated antibody internalization was determined by real-time live-cell analysis; cell killing assays used both live-cell analysis of cell confluence and the CellTiter-Glo® luminescent cell viability assay. Expression of EphA5 in archival human breast tumor tissue sections was evaluated by immunohistochemistry (IHC) using a commercial polyclonal antibody against human EphA5. In vivo efficacy studies used patient-derived xenograft (PDX) models of BC. **Results:** IHC demonstrated robust and selective EphA5 expression in 87% (20 of 23) of triple negative breast cancer (TNBC) and 88% (23 of 26) of hormone receptor-positive (HR+) patient tumors tested. EphA5 expression was not detected in adjacent, non-malignant breast tissue. Antibody-specificity profile testing showed that the anti-EphA5 antibody bound exclusively to EphA5 and did not cross-react with other members of the Eph receptor/ephrin ligand family. Binding of the anti-EphA5 antibody to EphA5 on the cell surface triggered rapid internalization and processing of the EphA5/antibody complex through the endosomal-lysosomal system. Consistently, MBRC-101 was cytotoxic to EphA5-expressing cells and its activity was concentration-dependent and commensurate to the levels of EphA5 on the cell surface. In PDX murine

models of TNBC, once weekly administrations of intravenous (IV) MBRC-101 showed dose-dependent, robust, and reproducible anti-tumor activity in vivo. Partial tumor responses were observed at doses of 2.5 mg/Kg IV and complete and nearly complete tumor responses starting at 5 mg/Kg IV. Doses up to 10 mg/Kg IV were well-tolerated in tumor-bearing mice with no observable weight loss. Pre-clinical safety confirmed MBRC-101 is also well tolerated in rats and in cynomolgus monkeys. **Conclusions:** These results support EphA5 as a new and promising membrane-associated molecular target for the design and development of ADC-based therapies against hormone-positive breast cancer and TNBC and support the conduct of a Phase 1/1b study of MBRC-101 in patients with breast cancer.

PO3-18-05

Pharmacokinetics (PK) of lasofoxifene (LAS) monotherapy and combined with abemaciclib (Abema)

Presenting Author(s) and Co-Author(s):

S. Damodaran. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

P. Plourde. Sermonix Pharmaceuticals, United States

S. Jenkins. Sermonix Pharmaceuticals, United States

P. Mayer. Unaffiliated, United States

D. Portman. Sermonix Pharmaceuticals, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

Introduction: LAS is a selective estrogen receptor modulator (SERM)/tissue-selective estrogen agonist/antagonist studied in women with osteoporosis and vulvar-vaginal atrophy, and most recently, metastatic breast cancer (mBC) with ESR1 mutations. LAS data in healthy postmenopausal women and young men show linear PK and no differences by age or race (Gardner. J Clin Pharmacol 2006;46:52-58; Prakash. Drug Metab Dispos 2008;26:1218-26; Data on file). Also, no PK differences were found between Caucasian and Japanese patients (Jhee. AACR-JCA 2022, abstract A83; Fountaine. J Clin Pharmacol 2006;46:693-99). Here we report select PK data of LAS (5 mg/day) from women with mBC in the ELAINE 1 and ELAINE 2 oncology trials to indirectly investigate possible drug-drug interactions between LAS and Abema.

Methods: Patients with mBC and ESR1 mutations who progressed on endocrine therapy and CDK4/6 inhibitors received LAS 5 mg/day as monotherapy (ELAINE 1) or combined with Abema (provided by Eli Lilly and Co) 150 mg BID (ELAINE 2). Blood was collected prior to daily dosing at weeks 2, 4, 8, and every 4 weeks up to the final visit in ELAINE 1, and visits during the first 8 weeks in ELAINE 2, to determine the plasma trough steady-state concentrations (C_{ss}) of LAS, Abema, and two active Abema metabolites (M2 and M20). LAS was assayed using validated high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS; detection 0.025 to 25.0 ng/mL); levels below the lower limit of quantification (LLOQ) were reported as 0 ng/mL. Abema and its M2 and M20 metabolites were measured by validated Turbo Ion Spray LC/MS/MS (detection 1.00 to 500 ng/mL); values below the LLOQ were reported as < LLOQ ng/mL. Mean trough C_{ss} at each visit were calculated for LAS (ELAINE 1 and 2), and Abema and its M2 and M20 metabolites (ELAINE 2). LAS levels from ELAINE 1 and 2 were compared, while Abema, M2 and M20 plasma levels in ELAINE 2 were compared with previously reported levels. Such indirect comparisons may help determine if Abema altered the metabolism of LAS, or if LAS altered that of Abema, M2, or M20. The relationships of LAS and Abema levels with progression-free survival (PFS) were also explored.

Results: Across all time points for subjects who had PK samples assessed, the LAS mean trough C_{ss} was 33.6 ng/mL (CV%, 39.8) in ELAINE 1 (n=40) and 30.9 ng/mL (CV 50.5%) in ELAINE 2 (n=29); in both studies, LAS concentrations were consistent across visits. LAS levels in ELAINE 2 were similar to those in ELAINE 1 with no evidence of accumulation. Mean (CV%) Abema plasma concentrations at weeks 2, 4, 6 and 8 were 199 (102%), 107 (130%), 82 (271%), and 94.3 (223%) ng/mL, respectively. Minimum and maximums of the mean trough C_{ss}

for LAS, Abema, M2, and M20 are shown in Table 1. No relationships between LAS or Abema levels and antitumor activity measured by PFS were seen (data to be presented).

Conclusion: The steady-state PK of 5 mg LAS in the ELAINE 1 and 2 studies suggest that the addition of abemaciclib to LAS did not result in an obvious or significant LAS-Abema, drug-drug interaction. Abema PK data from ELAINE 2 were consistent with published data (European Medicines Agency, Verzenio). These results support the continued development of LAS alone and combined with Abema for treating ER+/HER2-, ESR1-mutated mBC that progressed on endocrine therapy and CDK4/6 inhibitors.

Table. Mean trough, steady-state concentrations of lasofoxifene and abemaciclib.

Study	Drug/Metabolite	Mean Trough C _{ss} , ng/mL	
		Mean	Range, %CV
ELAINE 1	LAS 5 mg	29.6-37.4	(32-21%)
	LAS 5 mg ^a	29.4-29.6	(33-41%)
ELAINE 2	Abema 150 mg BID ^a	82-199	(102-223%)
	M2 ^a	47-79	(62-118%)
	M20 ^a	72-142	(69-200%)

^aData from patients who received oral LAS (5 mg/day) plus Abema (150 mg BID). Abema, abemaciclib; LAS, lasofoxifene; M2 and M20 are Abema metabolites.

PO3-18-06

First-in-human phase 1A study of RGT-419B, a next generation CDK4 inhibitor, in patients (pts) with hormone receptor positive (HR+) HER2- advanced/metastatic breast cancer (ABC) who progressed on prior CDK4/6 inhibitors (CDK4/6i)

Presenting Author(s) and Co-Author(s):

- S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States
- D. Valacer. David J. Valacer MD Clinical Research Consulting, LLC, United States
- R. Zuniga. New York Cancer and Blood Specialists, Port Jefferson, NY, United States
- H. Yeckes-Rodin. Cleveland Clinic, United States
- C. Perkins. Women's Cancer Research Network, United States
- L. Ge. The Oncology Institute, United States
- L. Yao. Regor Therapeutics Group, United States
- J. Lin. Regor Therapeutics Group, United States
- D. Begley. Regor Therapeutics Group, United States
- F. Sun. Regor Therapeutics Group, United States
- A. Zheng. Regor Therapeutics Group, United States
- J. Han. Regor Therapeutics Group, United States
- Z. Xie. Regor Therapeutics Group, United States
- A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States
- K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

Introduction: RGT-419B is a novel next generation CDK inhibitor. It has high potency against CDK4 with additional activity against CDK2 and selectivity against CDK6 to overcome resistance and reduce hematologic toxicity. In addition to anti-cancer activity in preclinical breast cancer models that are resistant to approved CDK4/6 inhibitors, we report the interim data from the first-in-human, multicenter trial of RGT-419B as a single agent in post-menopausal pts with HR+ HER2- ABC. Methods: Eligible pts received ≥ 2 lines of treatment and progressed on endocrine therapy (ET) and at least 1 line of an FDA approved CDK4/6i. Prior treatments of fulvestrant, other targeted agents and/or chemotherapy were allowed. Dose escalation of RGT-419B as oral (PO) monotherapy was administered in continuous 28-day cycles in 4 cohorts (25, 75, 150 mg QD and 150 mg BID). A standard 3+3 design was employed to determine the maximum tolerated dose (MTD)/recommended dose for expansion (RDE). The primary objective was to assess safety and tolerability. The secondary objectives included pharmacokinetic (PK) assessment and exploratory efficacy. Results: At time of abstract submission, 12 eligible post-menopausal pts with HR+/HER2- ABC received RGT-419B. The median age was 64.8y (range 50-80y). All had prior palbociclib + ET (2 pts had abemaciclib or ribociclib after palbociclib); a majority received fulvestrant (67%) and prior chemotherapy (50%). Across the 4 cohorts (12 pts), the most observed treatment-emergent adverse events (TEAEs; all causality) with RGT-419B were nausea, reduced white blood cell counts (neutrophils and/or lymphocytes) and diarrhea. At data cutoff on June 30th 2023, there have been no CTCAE Grade 3 or higher treatment related AE (TRAEs). No ocular toxicity has been observed. No pts have discontinued treatment due to RGT-419B toxicity. Preliminary PK analyses for RGT-419B showed a dose-dependent increase of exposure at steady state with long half-life. Tumor

assessments (RECIST v1.1) of pts in the first 3 cohorts treated with RGT-419B monotherapy (25-150 mg QD) showed partial responses in 2 pts (7 pts with measurable disease), 28.6% partial response (PR) (RECIST v. 1.1) and clinical benefit rate (CBR) 44%. Updated safety, PK and efficacy data will be presented. Conclusions: RGT-419B, with potent selective CDK4 activity, CDK2 activity and CDK6 selectivity, demonstrated a favorable safety and PK profile in an ongoing phase I study, with no grade 3 or higher TRAEs observed thus far. RGT-419B administered as once daily monotherapy also demonstrated preliminary evidence of efficacy as well. Dose expansions of RGT-419B as a single agent and in combination with ET in pts with HR+/HER2- ABC following prior CDK4/6i progression are planned.

PO3-18-07

Therapeutic Potential of Combining Eltanexor with Tamoxifen to Treat Primary and Metastatic Estrogen Receptor Positive (ER+) Breast Cancers

Presenting Author(s) and Co-Author(s):

V. Jain. Carle-Illinois College of Medicine, University of Illinois Urbana Champaign, Urbana, Illinois, United States

M. Kamdar. School of Molecular and Cellular Biology, University of Illinois Urbana Champaign, United States

H. McGee. School of Molecular and Cellular Biology, University of Illinois Urbana-Champaign, United States

Q. Zuo. Department of Food Science and Human Nutrition, University of Illinois Urbana Champaign, United States

J. Yoo. Department of Food Science and Human Nutrition, University of Illinois Urbana Champaign, United States

Y. Landesman. Hcbiosciences, United States

C. Walker. Karyopharm Therapeutics Inc., United States

Z. Madak-Erdogan. UIUC, United States

Estrogen receptors are key pathway initiators in the aggressive development of more than two-thirds of all breast cancers. Tamoxifen (TAM) is a selective estrogen receptor modulator that disables the ER pathway and inhibits the progression of ER+ breast cancer. Unfortunately, 10-40% of patients with ER+ breast cancer who were treated with TAM experience recurrence and metastasis within 10 years. We have previously identified exportin 1 (XPO1) to be more highly expressed in breast cancers with acquired TAM resistance compared to TAM-sensitive counterparts and showed that a combination treatment of TAM with an XPO1 inhibitor, selinexor, is an effective method of tumor suppression in preclinical models. In this study we investigated the activity of eltanexor, an investigational second generation XPO1 inhibitor with minimal penetration of the blood-brain barrier, to inhibit cancer growth without leading to weight loss. Our results show that mice harboring MCF7-ESR1^{Y537S} xenograft tumors had significantly less ($P < .05$) flank tumor growth when administered a treatment regimen of TAM and eltanexor compared to control mice. In metastatic tumor models, we observed decreased metastatic burden in mice harboring MCF7-ESR1^{D538G} and MCF7-ESR1^{Y537S} tumors when co-administered TAM and eltanexor. We did not observe weight changes in either model. Our findings suggest that eltanexor may be a relevant treatment for further exploration in the context of a TAM combination therapy for treatment of ER+ breast cancer.

PO3-18-08

Rational therapeutic combination of Bromodomain and Extra-Terminal domain (BET) inhibitor and Fibroblast Growth Factor Receptor (FGFR) inhibitor for treatment of invasive lobular carcinoma

Presenting Author(s) and Co-Author(s):

B. Gao. Royal College of Surgeons in Ireland/School of Pharmacy and Biomolecular Sciences, United States

E. Ward. Royal College of Surgeons in Ireland/School of Pharmacy and Biomolecular Sciences, Ireland

A. Blümel. Royal College of Surgeons in Ireland/School of Pharmacy and Biomolecular Sciences, United States

E. Conroy. UCD/Conway Institute, Ireland

R. Moore. Royal College of Surgeons in Ireland/School of Pharmacy and Biomolecular Sciences, United States

G. Cremin. Royal College of Surgeons in Ireland/School of Pharmacy and Biomolecular Sciences, United States

R. Bleach. Royal College of Surgeons in Ireland/Department of Physiology & Medical Physics, United States

K. Haley. Georgetown University/Lombardi Cancer Centre, United States

T. Ní Chonghaile. Royal College of Surgeons in Ireland/Department of Physiology & Medical Physics, United States

A. Lindner. Royal College of Surgeons in Ireland/Department of Physiology & Medical Physics, United States

J. Prehn. Royal College of Surgeons in Ireland/Department of Physiology & Medical Physics, United States

Y. Zhang. Soochow University/College of Pharmaceutical Sciences, United States

I. Cruz. Georgetown University/Lombardi Cancer Centre, United States

L. Hilakivi-Clarke. University of Minnesota, United States

G. Sflomos. ISREC - Swiss Institute for Experimental Cancer Research, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, United States

C. Brisken. ISREC - Swiss Institute for Experimental Cancer Research, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, United States

W. Gallagher. UCD/Conway Institute, Ireland

D. O'Connor. Royal College of Surgeons in Ireland/ School of Pharmacy and Biomolecular Sciences, Ireland

Background: Invasive lobular carcinoma (ILC) is the second most pervasive subtype after invasive ductal carcinoma (IDC), accounting for approximately 10-15% of all breast cancers. It is characterized by loss of E-cadherin expression and non-adherent tumor cells that invade the stroma in a "single-file" pattern. Women with ILC are typically diagnosed at an older age and later stage with ER-positive disease. ILC is more likely to exhibit late recurrence and metastasize to the gastrointestinal tract and urogenital tract compared with IDC. It is routinely

treated with anti-endocrine therapy and chemotherapy, however, while not entirely chemo-refractory, displays a poor response to chemotherapy compared with IDC. As such, options for recurrent disease are limited and there is an urgent need to develop tailored therapy for ILC, especially for those patients that recur. The family of bromodomain and extra-terminal domain (BET) proteins, comprising BRD2/3/4/T, are epigenetic readers that bind to acetylated lysine residues on histones and recruit transcription factors to drive the expression of oncogenes. Previously, we discovered that BRD3 is a marker of poor prognosis in ILC and there is emerging evidence that BET inhibitors (iBET) are effective in diverse types of breast cancer. Here, we investigated the therapeutic potential of iBET in ILC, alone and in combination with FGFR inhibitors. Methods: IC50s for a panel of iBET using two typical ILC cell lines MDA-MB-134VI (MM134) and SUM44PE (SUM44) were determined. RNA-sequencing and Genexplain analysis was applied to reveal transcriptional networks, master regulators and potential resistance mechanisms. BRD3 and FGFR3 were knocked down using siRNA to evaluate their function in ILC cell lines. Furthermore, we utilized ILC cell-derived xenograft (CDX) models in SCID-beige mice established by mammary intraductal (MIND) implantation to evaluate the therapeutic potency of iBET alone or in combination with fibroblast growth factor receptor (FGFR) inhibitor in vivo. Results: We demonstrated that iBET significantly inhibited ILC cell growth in both 2D and 3D culture, with the greatest potency demonstrated by JQ1 and Mivebresib (ABBV-075). RNA-sequencing revealed dysregulated pathways in cell cycle division, DNA damage, apoptosis and MAPK signaling following iBET treatment. Reverse engineering of transcriptional profiles using Genexplain revealed that FGFR3 is a significantly upregulated master regulator (MTR) among 142 MTRs across both cell lines and both iBETs. Upregulation of FGFR3 after iBET treatment was verified at the protein level by Western blotting. We also show that BRD3 and FGFR3 knockdown significantly inhibited cell growth, which supports the key role both play in ILC progression. Further, we analyzed the iBET therapeutic effect when combined with the FGFR inhibitor, erdafitinib, as a strategy to overcome potential resistance due to FGFR upregulation post iBET treatment. This revealed that the combination of iBET and erdafitinib could inhibit ILC cell growth more effectively compared to using either agent alone. Furthermore, our in vivo study showed that JQ1 could inhibit tumor growth in a SUM44-MIND model and alleviate metastasis to peritoneum, bone and ovary compared with the vehicle group. Moreover, we also assessed the combination of mivebresib and erdafitinib in vivo. This revealed that iBET and an FGFR inhibitor work synergistically to decrease tumour burden and metastatic potential in both MM134-MIND and SUM44-MIND models. Conclusion: Our results provide evidence that iBET, either alone or in combination with erdafitinib, is remarkably effective at inhibiting ILC growth, both in vitro and in vivo and represents a rational therapeutic strategy for recurrent ILC patients in the future.

PO3-18-09

OPERA-01: A randomized, open-label, phase 3, study of palazestrant (OP-1250) vs standard-of-care treatment for ER+, HER2- advanced or metastatic breast cancer after endocrine and CDK4/6 inhibitor therapy

Presenting Author(s) and Co-Author(s):

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

M. Bellet- Ezquerro. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain

J. Schroeder. Olema, San Francisco, California, United States

M. Shilkrut. Olema, San Francisco, California, United States

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

Background: In estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC), adding a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor to endocrine therapy (ET) has improved outcomes and is the current standard-of-care treatment in the first-line setting. However, resistance to first-line treatment develops in most patients (pts), which is often attributed to acquired mutations in ESR1. Limited data exist for ET-based treatment options after progression on prior ET and CDK4/6 inhibitors, and most pts will transition to chemotherapy for further treatment. Therefore, there is a significant unmet need for more effective ET in pts with ER-positive, HER2-negative MBC to improve outcomes and delay time to chemotherapy.

Palazestrant (OP-1250) is a small molecule oral complete ER antagonist (CERAN) and selective ER degrader (SERD) that binds the ligand binding domain of ER and completely blocks ER-driven transcriptional activity in both wild-type (ESR1-wt) and mutant (ESR1-mut) forms of ER. In preclinical studies, palazestrant demonstrated better tumor shrinkage in ESR1-wt and ESR1-mut models when compared to fulvestrant; it also showed efficacy in brain metastasis models. In a phase 1/2 monotherapy study in pts with heavily pretreated ER-positive, HER2-negative advanced breast cancer (BC) or MBC (NCT04505826), palazestrant showed a tolerable safety profile, promising antitumor efficacy, and favorable pharmacokinetics (PK) supporting once a day (qd) dosing. The recommended Phase 2 dose of palazestrant is 120 mg qd.

Methods: The OPERA-01 trial is an international, multicenter, randomized, open-label, phase 3 clinical trial comparing the efficacy and safety of palazestrant as a single agent to standard-of-care ET (fulvestrant, anastrozole, letrozole, or exemestane) in pts with ER-positive, HER2-negative advanced BC or MBC that has relapsed or progressed on 1 or 2 prior lines of ET for MBC, which includes a CDK4/6 inhibitor. Eligible pts are women (pre- or post-menopausal) or men who have a confirmed diagnosis of ER-positive, HER2-negative locally advanced evaluable BC or MBC not amenable to curative therapy. ER and HER2 status are determined according to the American Society of Clinical Oncology/College of American Pathologists guidelines. Patients must have Eastern Cooperative Oncology Group performance status 0 or 1. Prior treatments must include 1 or 2 prior lines of ET as monotherapy or in combination with

a CDK4/6 inhibitor for MBC; must have received CDK4/6 inhibitor in combination with ET and have disease progression during or within 28 days of completion of each line of prior treatment for MBC; most recent ET given for ≥ 6 months. Prior chemotherapy in the metastatic setting is not permitted. Patients (N~500) are randomized to palazestrant or standard-of-care ET monotherapy, and are stratified by ESR1 mutation status, prior lines of ET for advanced disease (1 vs 2 lines), and presence or absence of visceral disease. The primary endpoint of progression-free survival will be assessed by blinded independent central review in pts with and without ESR1 mutations in the intent-to-treat population. Secondary endpoints include overall survival, antitumor activity (objective response rate, clinical benefit rate, and duration of response), safety, patient-reported outcomes, and PK in pts with and without ESR1 mutations. The study is planned to be conducted globally.

PO3-18-10

Impact of age and ovarian function suppression (OFS) on endocrine response to short preoperative endocrine therapy (ET): Results from the multicenter WSG-ADAPTcycle trial (n=5,290)

Presenting Author(s) and Co-Author(s):

O. Gluz. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; University Clinics Cologne, Moenchengladbach, Nordrhein-Westfalen, Germany

M. Christgen. Medizinische Hochschule Hannover, Hannover, Niedersachsen, Germany

U. Nitz. West German Study Group and Breast Center Niederrhein, United States

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

M. Braun. Rotkreuzklinikum München, Germany

M. Thill. Agaplesion Markus Krankenhaus, 60431 Frankfurt a.M., Hessen, Germany

R. Wuerstlein. Breast Center, Dept. OB&GYN and CCC Munich, LMU University Hospital, Munich, Germany

P. Wimberger. Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Sachsen, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

C. Schem. Mammazentrum am Krankenhaus Jerusalem, Hamburg, Germany

M. Zaiss. Clinic for Interdisciplinary Oncology & Hematology GbR, Freiburg, Baden-Wuerttemberg, Germany

V. Bjelic-Radusic. Breast Unit, Helios University Clinic, University Witten/Herdecke, Germany

M. Just. Onkologische Schwerpunktpraxis Bielefeld, Bielefeld, Germany

K. Veselinovic. Breast Center, University Hospital Ulm, Department of Women's Health, Ulm, Baden-Wuerttemberg, Germany

M. Vincent. Breast Center, Municipal Hospital Holweide. Cologne, Cologne, Nordrhein-Westfalen, Germany

M. Graeser. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; Department of Gynecology, University Medical Center Hamburg, Moenchengladbach, Nordrhein-Westfalen, Germany

K. Krauss. Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Moenchengladbach, Nordrhein-Westfalen, Germany

O. Hoffmann. University Hospital Essen, Germany

K. Lütke-Heckenkamp. Department of Oncology and Hematology, Niels-Stensen-Kliniken, Georgsmarienhütte, Germany

R. Kates. West German Study Group GmbH, Moenchengladbach, Moenchengladbach, Nordrhein-Westfalen, Germany

C. zu Eulenburg. West German Study Group, Moenchengladbach, Germany; Department of Medical Biometry and Epidemiology, University Medical Center Hamburg, Hamburg, Germany

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

R. Baehner. Precision Oncology, Exact Sciences, Redwood City, California, United States

H. Kreipe. Medical School Hannover, Institute of Pathology, Hannover, Germany; Institute of Neuropathology, United States

N. Harbeck. University of Munich, Munich, Bayern, Germany

Background In HR+/HER2- early breast cancer (EBC), short preoperative endocrine therapy (ET) offers a promising tool for assessment of ET-efficacy based on Ki67-decrease after 2-4 weeks of treatment. Low post-endocrine Ki67 (Ki67_{post}) is associated with good prognosis in several large prospective trials. WSG-ADAPT demonstrated that Ki67_{post} is a promising tool for decision making in cases with uncertain adjuvant chemotherapy indication, e.g., in premenopausal patients (pts.) with N0 and Recurrence Score (RS, Oncotype DX®) RS 16-25 or N1 and RS ≤25. Preliminary results from the phase III ADAPTcycle trial indicated higher efficacy of preoperative ET in premenopausal pts. if ovarian function suppression (OFS) was used together with tamoxifen (TAM) or aromatase inhibitors (AI). In the ADAPTcycle screening population, we are now able to validate these results and investigate the influence of age subgroups, Recurrence Score, and individual biological markers, as well as OFS on ET-response. **Methods** In ADAPTcycle (n=5,290 screened until 06/23 at 84 sites in Germany), N0-1 pts. with RS >25 or N2-3 pts with RS ≤25 and ET-response (Ki67_{post} ≤10%) were randomized to (neo)adjuvant standard chemotherapy (CT) or ribociclib + AI +/- GnRH-analog (n=1,670 randomized). Participation of premenopausal pts. with N1-disease and RS ≤25 or N0 and RS 16-25 was allowed irrespective of ET-response, but randomization recommended only for ET-responders. Use of OFS + TAM or AI for ET response assessment in the preoperative phase was protocol-recommended. This analysis includes all patients with baseline RS and data on ET-response. Ki67-response is defined as Ki67_{post} ≤10% (central pathology assessment) after 2-4 weeks of therapy (OFS-use recommended for 4 weeks). ER-, PR-, and HER2-levels are analyzed by IHC and mRNA. **Results** Results on ET-response according to age and clinicopathological as well as tumor biological characteristics will be presented at the meeting.

So far, ADAPTcycle with >5,000 pts. screened is the largest trial worldwide to look at ET response assessment in pre- and postmenopausal pts. with HR+/HER2- EBC. The results thus have the potential to impact clinical practice. **Contact Information**
oleg.gluz@wsg-online.com

PO3-18-11

A011801 (CompassHER2 RD): Postneoadjuvant T-DM1 + tucatinib/placebo in patients with residual HER2-positive invasive breast cancer

Presenting Author(s) and Co-Author(s):

C. O'Sullivan. Mayo Clinic, Rochester, MN, USA, ROCHESTER, Minnesota, United States

K. Ballman. Weill Cornell Medicine, New York, New York, United States

L. McCall. Duke University, United States

T. Zemla. MAYO CLINIC, United States

A. Weiss. Division of Surgical Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States

M. Mitchell. UT MD Anderson Cancer Center, Houston, Texas, United States

V. Blinder. Memorial Sloan Kettering Cancer Center, United States

N. Tung. Beth Israel Deaconess Medical Center, Boston, United States

W. Irvin. Bon Secours Saint Francis Medical Center Cancer Institute/Southeast Clinical Oncology Research (SCOR), Midlothian, Virginia, United States

M. Lee. University of Maryland Medical Center, United States

S. Kamaraju. Medical College of Wisconsin, Milwaukee, Wisconsin, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

W. Symmans. UT MD Anderson Cancer Center, United States

V. Borges. University of Colorado Anschutz Medical Center, United States

I. Krop. Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, United States

A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

L. Carey. UNC-Lindberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

Background: Patients with HER2+ early breast cancer (EBC) and invasive residual disease (RD) after neoadjuvant therapy (NAT) have a higher risk of relapse than patients who have a pathologic complete response (pCR). Escalation of therapy in patients with RD using post-neoadjuvant T-DM1 has become the new standard of care, leading to improved invasive disease-free survival (iDFS), but patients with estrogen receptor (ER)-negative or nodal RD have suboptimal outcomes, and central nervous system recurrences are a challenge. More effective treatment strategies are urgently needed. Alliance A011801 (CompassHER2 RD) is an escalation trial for patients with high-risk HER2+ RD after neoadjuvant systemic therapy, evaluating the addition of the HER2 selective tyrosine kinase inhibitor (TKI) tucatinib to post-neoadjuvant T-DM1. Methods: Eligibility and Intervention: Patients with high-risk HER2+ RD (i.e., ER-, node-positive, or both) after a predefined course of neoadjuvant HER2-directed treatment are randomized 1:1 to adjuvant T-DM1 + placebo, vs. T-DM1 and tucatinib with adjuvant RT +/- ET. Eligibility criteria include completion of ≥ 6 cycles of NAT, including ≥ 9 weeks of paclitaxel and trastuzumab +/- pertuzumab. All chemotherapy (CT) must be completed preoperatively unless participating in EA1181 (~15-30% will be participants in the CompassHER2 pCR de-escalation companion trial [NCT04266249]; these patients must receive postoperative CT to complete ≥ 6 cycles prior to enrollment on A011801). Patients who received prior HER2-targeted TKIs or antibody-drug conjugates are ineligible. Objectives: The primary objective is to determine if iDFS is improved with addition of tucatinib to T-DM1 in

patients with HER2+ EBC with RD after neoadjuvant systemic therapy; secondary endpoints include overall survival, breast cancer free survival, distant recurrence-free survival, brain metastases-free survival and disease-free survival. Correlative objectives include the association of i) tumor infiltrating lymphocyte (TILs) levels in the primary tumor and RD with iDFS, ii) TILs with tucatinib benefit, iii) iDFS and circulating tumor cells (CTC) at serial timepoints and iv) the magnitude of benefit of tucatinib (iDFS) in patients with/without detectable pretreatment CTCs. Quality of life and pharmacokinetic endpoints are also being evaluated. Statistics: A011801 is a prospective, double-blind, randomized, phase III superiority trial; stratified by i) receipt of postoperative CT (Y/N), ii) hormone receptor-status (+/-), and iii) pathologic lymph node status (+/-). The study targets an absolute difference of 5% in iDFS (control vs. experimental arm 82% & 87%, HR = 0.7), with a two-sided alpha of 0.05 and power of 80%. The sample size is 981; target accrual = 1031 patients; activation and estimated completion dates are 01/6/21 and ~ 01/2028. Accrual as of 7/10/2023: 438 patients. Support: U10CA180821, U10CA180882; Seagen Inc; <https://acknowledgments.alliancefound.org>. ClinicalTrials.gov Identifier: NCT04457596

PO3-18-12

Results from a first-in-human study of DAN-222, a novel high-capacity drug conjugate in metastatic breast cancer as monotherapy and in combination with a PARPi [NCT05261269]

Presenting Author(s) and Co-Author(s):

S. Hurvitz. Fred Hutchinson Cancer Center, Seattle, Washington, United States

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

A. Morikawa. University of Michigan School of Medicine, Ann Arbor, Michigan, United States

H. Soliman. H. Lee Moffitt Cancer Center, Florida, United States

K. Yeung. UC San Diego Health Moores Cancer Center, United States

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

A. Tiersten. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New, New York, United States

W. Razaq. Oklahoma university of health Sciences, Oklahoma City, Oklahoma, United States

K. Foye. Dantari, Inc., United States

T. Hagerty. Dantari, Inc, California, United States

Background: Topoisomerase I inhibitors (Topo I) have been shown to be highly effective across a broad range of tumors including breast cancer. Poly (ADP-ribose) polymerase inhibitors (PARPi) have been shown to be effective in BRCAm breast cancers. The combination of Topo I plus PARPi is known to be synergistic beyond the BRCAm subtype but overlapping myelotoxicities have prohibited successful clinical combinations. DAN-222 is a novel therapeutic HDC (High-capacity drug conjugate) whose payload is the topoisomerase 1 inhibitor camptothecin (CPT). Our previously published preclinical data demonstrates synergy of DAN-222 plus a PARPi regardless of BRCA or HRD status. Furthermore, DAN-222 demonstrates reduced bone marrow exposure enabling clinical combinations. Herein we present data for the first-in-human study of DAN-222 as mono- and combination therapy with a PARPi. The expectation is clinical benefit with this complimentary combination for patients with HRD+ and HRD- tumors, and not restricted to BRCAm, while minimizing overlapping myelotoxicities.

Methods: A phase 1 study of DAN-222 as monotherapy and in combination with niraparib is being conducted in heavily pretreated patients with metastatic breast cancer. The objectives are to evaluate the safety, tolerability, and pharmacokinetics of DAN-222, and initial clinical activity based on RECIST v1.1 criteria to determine the recommended phase 2 dose. PK will be characterized for the total conjugated and the unconjugated CPT. Adults (≥ 18 years) with HER2-negative metastatic breast cancer that progressed on standard therapies were enrolled, without restriction on BRCA or HRD status.

Results: As of June 2023, 30 patients had enrolled in dose escalation of monotherapy (2-16 mg/m²) or combination therapy with niraparib (100 mg). The median age was 61.5 years old (range, 36-75). The median number of prior treatment lines was 6. All patients were PARPi naïve and BRCAwt. In the monotherapy cohorts, the hematological adverse events (AEs) were

neutropenia (28%; grade [Gr] ≥ 3 : 17%), thrombocytopenia (22%; Gr ≥ 3 : 6%) anemia (17%; Gr ≥ 3 : 0%), and lymphopenia (11%; Gr ≥ 3 : 0%), the non-hematologic adverse events Gr ≥ 3 was one case of cystitis. In the combination cohorts, the hematological AEs were anemia (25%; Gr ≥ 3 : 17%), thrombocytopenia (17%; Gr ≥ 3 : 8%), neutropenia (8%; grade Gr ≥ 3 : 8%), and lymphopenia 8%; Gr ≥ 3 : 0%) and there was no Gr ≥ 3 non-hematologic adverse events.

The exposure of DAN-222 was linear and increased in a dose-proportional manner. The mean half-life ranged from 25.2 to 33.5 hours across all cohorts. Clinical activity during dose escalation was demonstrated with stable disease in 28% of patients with monotherapy and 67% of patients with combination therapy across all dose levels.

Conclusions: No DLTs were observed in monotherapy or combination therapy in the dose escalation phase of this study. This study demonstrates the feasibility for DAN-222 to be combined with a PARPi at clinically relevant doses. The reduced myelotoxicity of DAN-222 will also enable combination with other therapies to treat patients with other types of cancer. The promising antitumor activity seen with DAN-222 in combination with PARPi in BRCAwt, supports continued clinical development.

PO3-19-01

A Randomized Controlled Trial of Metastasis-directed Therapy for Oligometastases in Breast Cancer (OLIGAMI trial; JCOG2110)

Presenting Author(s) and Co-Author(s):

T. Ishiba. Tokyo Medical and Dental University, Tokyo, Tokyo, Japan

I. Nishibuchi. Department of Radiation Oncology, Hiroshima University Graduate School of Biomedical & Health Sciences, United States

F. Hara. Breast Medical Oncology, Cancer Institute Hospital of JFCR, United States

K. Sasaki. JCOG Data Center/Operations Office, National Cancer Center Hospital, tyuouku-tukiji, Tokyo, United States

R. Sadate. JCOG Data Center/Operations Office, National Cancer Center Hospital, United States

Y. Sekino. JCOG Data Center/Operations Office, National Cancer Center Hospital, United States

R. Machida. JCOG Data Center/Operations Office, National Cancer Center Hospital, United States

H. Fukuda. JCOG Data Center/Operations Office, National Cancer Center Hospital, United States

T. Kogawa. Department of Advanced Medical Development, Cancer Institute Hospital of JFCR, Tokyo, Japan, United States

T. Fujisawa. Gunma prefectural cancer center, United States

Y. Sagara. Hakuaiikai Sagara Hospital, Kagoshima, Kagoshima, Japan

Y. Naito. National Cancer Center Hospital East, Kashiwa, Chiba, Japan, United States

K. Terata. Akita University Hospital, Department of Breast and Endocrine Surgery, United States

Y. Ozaki. The Cancer Institute Hospital Of JFCR, Koto-ku, Japan

A. Shimomura. Department of Breast and Medical Oncology, National Center For Global Health And Medicine, Tokyo, Japan

T. Sakai. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States

C. Kanbayashi. Department of Breast Oncology, Niigata Cancer Center Hospital, United States

T. Iwatani. Department of Breast and Endocrine Surgery, Okayama University, United States

H. Shigematsu. Department of Breast Surgery and Oncology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Hiroshima, Japan, Kure, Hiroshima, Japan

K. Tamura. Department of Medical Oncology, Shimane University Hospital, Japan

T. Mizowaki. Department of Radiation Oncology & Image-Applied Therapy, Graduate School of Medicine, Kyoto University, United States

M. Yoshimura. Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University, United States

N. Shikama. Department of Radiation Oncology, Juntendo University, United States

T. Shien. Okayama University Hospital, Okayama-city, Okayama, United States

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Background: Oligometastases were initially described as a concept bridging localized disease with widespread distant metastases, but a consensus on its definition has yet to be reached. Recently, the term "metastasis-directed therapy" (MDT) was coined to encompass local therapy for distant metastases, including surgery and radiation therapy (RT), especially stereotactic body radiation therapy (SBRT). Though OLIGO-BC1 and SABR-COMET have indicated the potential benefits of MDT for oligometastases, NRG-BR002 revealed no significant difference in progression-free survival (PFS). As a definitive conclusion to this clinical question has not been reached, there is an increasing demand for phase III trials focusing on breast cancer (BC). We planned the JCOG2110, also called as OLIGAMI trial. Design: OLIGAMI trial is a multi-institutional, two-arm, open-label, randomized controlled phase III trial being conducted with the participation of 50 hospitals belonging to Japan Clinical Oncology Group. After the first registration, all patients will be performed in a 12-week, subtype-specific, systemic therapy consisting of CDK4/6 inhibitors with hormonal therapy for luminal BC, docetaxel with trastuzumab and pertuzumab for HER2-positive BC, chemotherapy with immune checkpoint inhibitors for triple-negative BC expressing PD-L1, and olaparib for cases harboring BRCA mutations. For other triple-negative BC, chemotherapy will be administered. If this 12-week systemic therapy dose not cause any progression or complete response, patients proceed to second registration for randomization; arm A continues same systemic therapy alone, and arm B performs MDT followed by same systemic therapy. The MDT will involve either RT or surgery, and RT will involve mainly SBRT and partly conventional RT. Eligibility criteria: OLIGAMI trial will encompass all subtypes of advanced BC. The key criteria of the first registration are as follows: 1) Histologically diagnosed as invasive BC. Biopsy from oligometastases is desirable but not required. 2) Diagnosed with advanced BC with oligometastases by neck to pelvis enhanced CT, FDG-PET, and brain enhanced MRI. 3) Oligometastases defined as: (i) Maximum diameter of each tumor is 3 cm or less. (ii) Total number of 3 or less. (iii) In case of brain metastasis, maximum diameter is 2 cm or less and asymptomatic. 4) The patient with local recurrence is included. 5) De novo stage IV BC is included. The criteria of secondary registration are as follows: 1) The planned number of courses of systemic therapy has been performed. 2) No progression or new distant metastasis by response evaluation. 3) At least one oligometastases remains. Specific Aims: OLIGAMI trial aims to confirm the superiority of MDT to systemic therapy for oligometastases of BC. The primary endpoint is overall survival (OS) after randomization, while the secondary endpoints include OS after first registration, PFS, progression site (oligometastases vs. non-oligometastases), PFS specifically related to MDT (restricted arm B), proportion of adverse events and serious adverse events, and the non-progression proportion of health-related quality of life. Statistical methods: The sample size was calculated as 268 to detect 12% of 5-year OS difference with one-sided alpha of 0.05, power of 70%, 3 years of accrual, and 5 years of follow up. Therefore, we assumed the planned sample size for second registration for randomization as 270. We set the number of first registration as 340, assuming that there may be some patients with progression or complete response after the systemic therapy for 12 weeks. Present accrual and target accrual: The patient accrual will start in August 2023. Enrolment of 340 patients for first registration is planned over a 3-year accrual period. Contact information: Principal investigator, Toshiyuki Ishiba, MD. Ph.D. ishiba0313@gmail.com

PO3-19-02

White Button Mushroom and Biomarkers of Immune Cell and Inflammatory Responses in Obese Postmenopausal Women at High Risk of Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Dzubnar. City of Hope, United States

L. Yee. City of Hope Comprehensive Cancer Center, United States

S. Chen. Beckman Research Institute of the City of Hope, United States

Background:

White Button Mushroom (WBM), *Agaricus bisporus*, has anti-tumor and anti-inflammatory effects. Oral WBM mitigated the effects of a high fat diet on hepatic steatosis and insulin resistance in ovariectomized mice. A Phase I trial of WBM in men with prostate cancer demonstrated decreased myeloid derived suppressor cells (MDSC) in those with decreased PSA; MDSC have been linked to different cancers, including breast, and conditions of chronic inflammation.

Design:

This is a preliminary evidence trail in postmenopausal, obese women at high risk of breast cancer with a single intervention arm of 14g of WBM taken as 28 tablets daily for 3 months to assess effects on inflammation.

Participants undergo a physical exam, measuring height, weight, and waist circumference, an optional fine needle aspiration (FNA) of breast tissue, a blood draw, a food frequency questionnaire and a 24-hour food recall at baseline and final visits. Participants are contacted monthly for tolerance and adherence.

Blood samples and FNA adipose are used for metabolic measurements and processed for biomarkers of inflammation and immune response. Peripheral blood mononuclear cells (PBMC) will be used for RNA single-cell analysis to assess for immune cell profiles and expression with an interest in evaluating MDSC. Red blood cells will be assessed for fatty acid profiles.

Eligibility:

Postmenopausal, obese (BMI ≥ 30 , Asian ≥ 25) women with high risk for breast cancer who can swallow pills are eligible. Patients are high risk if their relative risk of breast cancer is ≥ 2 times that of the general population; this includes women with a strong family history, a genetic mutation associated with hereditary breast cancer, a high-risk breast histology, Gail model 5-year risk > 1.67 , or a previous history of stage I-II breast cancer.

Participants are excluded for an active malignancy within 5 years, ongoing active or preventative cancer treatment, or lab abnormalities of serum creatinine and total bilirubin > 1.5 the upper limit of normal, hemoglobin of < 9.0 g/dL, platelets of $< 100,000/\text{mm}^3$, or a total white blood cell count of $< 3,500/\text{mm}^3$. Participants cannot be taking mushroom supplements, immunosuppressants, or non-steroidal anti-inflammatories.

Specific Aims:

This study aims to evaluate the effects of WBM on regulating immune response and inflammation in obese women at high risk for breast cancer. Our primary objective is the assessment of PBMC, specifically MDSC immune profiles before and after treatment. Our

secondary objective is to evaluate changes in biomarkers of inflammation, immune cell profiles in breast adipose tissue, BMI, waist circumference, and metabolic biomarkers. Additionally, the study aims to assess tolerability of the WBM dose and effects on diet quality.

Statistical Methods:

26 patients will provide 80% power to detect a change in %MDSC of -0.67, assuming a standard deviation of 1.15, and a 2-sided type I error of 5%. We will have similar power to evaluate changes in other immune subsets, inflammatory markers, metabolic markers, anthropometric measurements, and diet quality.

FNA adipose tissue analysis will be used as a safety signal to evaluate the potential for unwanted inflammation with taking WBM. 13 patients with FNA will provide 80% power to detect a change of 85% of the standard deviation of the difference in the measure of biomarkers such as Interleukin-6 with a 2-sided type I error of 5%. As a safety signal, the signal will be reported without adjustment for multiple comparisons. Any conclusions based on such secondary endpoints will make note of the multiple comparison issue.

Accrual:

The accrual target is 26 evaluable patients with an estimated need to enroll 31. The study has enrolled 27 patients, 14 completed the study and 5 are currently on treatment. 8 participants were removed; 3 never started treatment, 1 was diagnosed with breast cancer, and 4 had other medical issues preventing continuation.

Contact: Jessica Dzubnar, MD: jdzubnar@coh.org

PO3-19-03

Addressing USPSTF 2023 Identified Key Gaps in Knowledge in Breast Cancer Screening through TMIST (ECOG-ACRIN EA1151) or its Ancillary Studies

Presenting Author(s) and Co-Author(s):

E. Pisano. University of Pennsylvania, United States

C. Gatsonis. Dept of Biostatistics, Brown University School of Public Health, United States

M. Schnall. University of Pennsylvania, United States

M. Troester. University of North Carolina at Chapel Hill, United States

E. Cole. American College of Radiology, United States

J. Cormack. Brown University, United States

I. Gareen. Brown University, United States

M. Yaffe. Sunnybrook Health Sciences Centre, United States

L. Collins. Beth Israel Deaconess Medical Center, United States

A. Curtis. Spartanburg Regional Healthcare System, United States

R. Carlos. University of Michigan, United States

K. Miller. Indiana University Simons Comprehensive Cancer Center, Indianapolis, IN, USA, United States

C. Comstock. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background

The United States Preventative Services Task Force in their 2023 recommendations identified areas where more research data is needed to inform future breast cancer screening recommendations. Research areas identified are: improve clinicians and patients understanding and evaluation of dense breast tissue on a screening mammogram, benefits and harms of supplemental screening using ultrasound or MRI for women with dense breasts, health outcomes such as rates of breast cancer diagnosis requiring treatment, rates of advanced breast cancers diagnosed across consecutive screening rounds, and breast cancer-associated morbidity and mortality, causes of increased risk of breast cancer mortality in black women across spectrum of stages and biomarker patterns, understand why black women are more likely to be diagnosed with breast cancers that have biomarker patterns that are indicative of poor health outcomes, assess benefits/harms differences between annual and biennial screening for breast cancer in women overall and if there are differences between black and white women, approaches to reduce the risk of overdiagnosis leading to overtreatment of breast lesions found at screening that may not cause morbidity and mortality, natural history of DCIS, and identify prognostic indicators of breast tumors that are unlikely to affect quality or length of life. **Methods**

The ongoing TMIST study, currently with 88,801 asymptomatic women presenting for screening mammography ages 45-74 enrolled out of 128,905, could contribute to scientific evidence to support the above research areas through existing study aims and planned ancillary studies.

Supplemental Screening with US and MRI: TMIST PreSCRIB will utilize Machine Learning applied to TMIST and All of Us data, including genetics, mammograms, social determinates of health and other data to recommend individualized screening strategies for women. DxMRI is a study where women will get AbMRI at time of Dx work-up. There are plans to use these examinations plus supplemental screening MRIs performed on TMIST subjects in an enriched

reader study to evaluate the role of supplemental screening MRI in moderate risk women.

Rates of breast cancer treatment, consecutive screening, morbidity, and mortality: TMIST's primary outcome is the proportion of women experiencing an advanced breast cancer and needing treatment. TMIST is also collecting information on health care utilization following a cancer diagnosis, including types of treatment given, and costs data from the screening and diagnostic work-up visits, and mortality data for study participants.

Increased risk of breast cancer mortality in black women: TMIST is performing PAM50 plus p53 status, immune profile, DNA repair phenotype, and 21-gene recurrence assay on all breast cancers and a subset of benign tissue. Blood and buccal smears might also help address this issue. Ongoing work, funded by the Susan B. Komen Foundation, focuses on improving Black participation in TMIST Biorepository (currently about 45% participation of the 21% of TMIST US black subjects). Surveys are planned on perceived racism and social determinates of health as part of DxMRI Study.

Screening Frequency: We are developing a collaboration with the UK-based clinical trial PROSPECTS to compare rates of all cancers and advanced cancers for annual, biennial, and 3-year screening.

Overdiagnosis, natural history of DCIS, prognostic indicators of breast tumors not impacting quality of life: PRoGram- will use radiomics, genomics and pathomics to develop a greater understanding of the variability of the non-advanced cancers diagnosed in the TMIST population, including DCIS. It is hoped that this model will provide greater understanding of the risk of poor outcomes for women diagnosed with lower risk cancers, including DCIS.

PO3-19-04

The CROWN STUDY: A multicenter prospective cohort study of cardiovascular outcomes in premenopausal women with hormone receptor positive breast cancer treated with ovarian suppression and an aromatase inhibitor

Presenting Author(s) and Co-Author(s):

S. Dent. Duke University, Durham, North Carolina, United States

E. Douglas. Wake Forest School of Medicine, United States

S. Hatcher. Wake Forest School of Medicine, United States

K. Ansley. Atrium Health Wake Forest Baptist Health, United States

C. Park. Atrium Health Wake Forest Baptist Health, United States

N. O'Connell. Atrium Health Wake Forest Baptist Health, United States

M. Hackney. Virginia Commonwealth University, United States

R. D'Agostino. Atrium Health Wake Forest Baptist Health, United States

R. Bansal. Duke University, Raleigh, North Carolina, United States

R. Avecilla. Center for Onco-Primary Care, Duke University, United States

M. Brown. Center for Onco-Primary Care, Duke University, United States

K. Clayton-Stiglbauer. Center for Onco-Primary care, Duke University, Durham, North Carolina, United States

I. Klem. Duke University Medical Center, United States

J. Jordan. VCU, United States

A. Thomas. Wake Forest Baptist Health, Winston-Salem, North Carolina, United States

Background: Treatment for premenopausal women with high or intermediate risk hormone receptor (HR)+ breast cancer (BC) includes the concurrent use of ovarian function suppression (OFS) and an aromatase inhibitor (AI) to induce near complete estrogen deprivation (NCED). The long-term cardiovascular (CV) sequela for women treated with NCED is unknown. Premature menopause in non-cancer populations is associated with CV disease. The CROWN study (CaRdiac Outcomes With Near complete estrogen deprivation) will use sophisticated imaging assessments of cardiac dysfunction to understand the evolution of CV injury, as well as biomarker and demographic correlates, with the goal of developing tools to assess and mitigate CV risk.

Methods: This is a NIH funded prospective cohort study conducted at 3 regional NCI-supported Cancer Centers (Atrium Health Wake Forest Baptist, Virginia Commonwealth and Duke) that will include premenopausal women, age ≤ 55 , with Stage I-III BC following completion of planned chemotherapy, surgery and radiation with an ECOG 0-1. HR+ BC patients will receive an AI and OFS. Women with HR- BC are included as comparators. CV imaging and biomarkers will be obtained at baseline, 1 year and 2 years (Table 1). These assessments will include serial cardiac magnetic resonance (CMR) and coronary computed tomography angiography (CCTA) imaging as well as laboratory measurements, including exploratory biomarkers. The primary objective is to determine the 24-month difference in stress myocardial blood flow as measured by adenosine CMR imaging in both groups. We will correlate CMR imaging with CCTA to provide complementary detail of coronary plaque changes. The study will also assess the relevance of pre-existing risk factors on study outcomes, including an emphasis on racial disparities, and dynamic change in modifiable and treatment related risk factors.

We plan to enroll 90 women, 67 in the NCED group and 23 in the HR-group, allowing for a 10% drop out rate. There are two primary types of statistical analyses. The first includes testing hypotheses between group (NCED vs HR-) and within group (longitudinal changes within the NCED group). The second analyses, involve developing predictive equations utilizing a stepwise linear regression approach to determine if patient demographics, clinical parameters and serum biomarkers are associated with cardiovascular changes over time. A total of 17 patients are enrolled as of 07/2023. NCT05309655

Study Procedures

Evaluation/Procedure	Baseline	Year 1	Year 2
Vitals	X	X	X
Body measurements: (Height, Weight, BMI, Waist circumference)	X	X	X
Labs/Biomarkers	X	X	X
CMR	X	X	X
CCTA	X		X
EKG	X	X	X
Patient questionnaires	X	X	X

PO3-19-05

Phase III study to evaluate the efficacy and safety of GLSI-100 (GP2 + GM-CSF) in breast cancer patients with residual disease or high-risk PCR after both neo-adjuvant and postoperative adjuvant anti-HER2 therapy, Flamingo-01

Presenting Author(s) and Co-Author(s):

S. Patel. Greenwich LifeSciences, United States

J. Thompson. Greenwich LifeSciences, United States

M. Patel. Greenwich LifeSciences, United States

F. Daugherty. Greenwich LifeSciences, United States

M. Rimawi. Baylor College of Medicine, Houston, Texas, United States

Background: GP2 is a biologic nine amino acid peptide of the HER2/neu protein delivered in combination with Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) that stimulates an immune response targeting HER2/neu expressing cancers, the combination known as GLSI-100. In a prospective, randomized, single-blinded, placebo-controlled, multicenter Phase IIb study, no recurrences were observed in the HER2+ population after 5 years of follow-up, if the patient was treated with GLSI-100, survived, and was followed for more than 6 months ($p = 0.0338$). Immunotherapy elicited a potent response measured by skin tests and immunological assays. Of the 146 patients that have been treated with GLSI-100 over 4 clinical trials, GLSI-100 was well-tolerated and no serious adverse events observed were considered related to the immunotherapy. **Methods:** This Phase III trial is a prospective, randomized, double-blinded, multi-center study. After 1 year of trastuzumab-based therapy, 6 intradermal injections of GLSI-100 or placebo will be administered over the first 6 months and 5 subsequent boosters will be administered over the next 2.5 years for a total of 11 injections over 3 years. The participant duration of the trial will be 3 years treatment plus 1 additional year follow-up for a total of 4 years following the first year of treatment with trastuzumab-based therapy. Patients will be stratified based on residual disease status at surgery, hormone receptor status and region. **Study Size – Interim Analysis:** Approximately 498 patients will be enrolled. To detect a hazard ratio of 0.3 in invasive breast cancer free survival (IBCFS), 28 events will be required. An interim analysis for superiority and futility will be conducted when at least 14 events have occurred. This sample size provides 80% power if the annual rate of events in placebo patients is 2.4% or greater. Up to 100 non-HLA-A*02 subjects will be enrolled in an open-label arm. **Eligibility Criteria:** The patient population is defined by these key eligibility criteria:

1. HER2/neu positive and HLA-A*02
2. Residual disease or High risk pCR (Stage III at presentation) post neo-adjuvant therapy
3. Exclude Stage IV
4. Completed at least 90% of planned trastuzumab-based therapy

Objectives:

1. To determine if GP2 therapy increases IBCFS
2. To assess the safety profile of GP2
3. To monitor immunologic responses to treatment and assess relationship to efficacy and safety

Study Status: The study has been initiated at a number of sites in the US. The study is also expected to be opened in Spain, Germany, and France. **Contact Information:** Greenwich LifeSciences, Inc.

Stafford, TX

Email: Flamingo-01@greenwichlifesciences.com

Website: greenwichlifesciences.com

Funding: This trial is supported by Greenwich LifeSciences.

PO3-19-06

MRD Assay evaluates Recurrence and response via a tumor Informed Assessment: MARIA-Breast Observational Trial

Presenting Author(s) and Co-Author(s):

E. Esplin. Invitae, San Francisco, California, United States

K. Swan. Invitae, United States

L. Ifhar. Invitae, United States

B. Heald. Invitae, United States

S. Nielsen. Invitae, California, United States

D. Pineda-Alvarez. Invitae, United States

W. O'Callaghan. Invitae, United States

R. Daber. Invitae, United States

D. Ross. Onslow Radiation Oncology, Jacksonville, North Carolina, United States

C. Vieira. Columbus Regional Health, Columbus, Indiana, United States

A. Chaudhuri. Washington University School of Medicine, St. Louis, Missouri, United States

W. Korn. Invitae, San Francisco, California, United States

Background: Detectable ctDNA in patients with solid tumors has been associated with disease prognosis pre-treatment, assessing response to therapy in the form of minimal residual disease (MRD), and monitoring for recurrence after curative intent treatment. Utilizing patient-specific genomic mutation profiling of an individual's cancer from a tissue sample, in conjunction with the patient's germline DNA, to create a personalized sequencing panel to analyze for a subset of these genetic mutations from ctDNA in blood is a strategy that has high sensitivity for detecting MRD. Studies have shown that pretreatment levels of ctDNA using this approach are a potential early indicator of disease recurrence after surgery, that ctDNA clearance may be an early predictor of favorable outcomes and has been shown to correlate with pathologic complete response (Forde et al. N Engl J Med. 2022, PMID:35403841), and that this approach has high sensitivity for detecting recurrence for patients in advance of the current standard of care (Abbosh et al. Cancer Res (2020) 80 (16_Supplement): CT023). **Methods:** This is a multi-site, prospective, observational trial in the United States of 200 patients with early stage breast cancer using a patient-specific tumor-informed MRD assay for ctDNA analysis. Participants are asked to provide study specimens prior to initial treatment intervention, after curative intent surgical resection, during adjuvant therapy (as applicable) and pre-recurrence follow-up. ctDNA will be analyzed with an NGS-based, tumor-informed MRD assay that identifies somatic mutations from DNA obtained from the patient's tumor tissue, subtracts germline variants via NGS-based analysis of the patient's germline DNA, and detects a selected set of between 18-50 tumor-specific ctDNA in their blood. All primary tumor specimens will undergo full exome sequencing using the Personalized Cancer Monitoring (PCM) assay. Impact of results of this CLIA-approved MRD assay on clinical decision making will be captured. The primary objective is to assess the ability of MRD to predict post-treatment recurrence. Further objectives are to correlate MRD status with pathologic complete response, determine the lead time to detection of recurrence compared to standard of care, and the association of MRD status with overall survival. Active enrollment started in March, 2022. **Support:** Invitae. **Clinical trial information:** NCT05219734.

PO3-19-07

AC699-001, a first in human Phase 1 trial utilizing a novel estrogen receptor chimeric degrader in patients with advanced or metastatic breast cancer

Presenting Author(s) and Co-Author(s):

M. Patel. Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL, Sarasota, Florida, United States

R. Layman. The University of Texas MD Anderson Cancer Center, United States

J. Nolte Fong. Accutar Biotech, United States

H. Zhang. Accutar Biotech, United States

S. Kim. Accutar Biotech, United States

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

Background

Estrogen receptors (ER) are hormone-regulated transcription factors that play a critical role in breast cancer initiation and proliferation. Modulation of estrogen activity with therapeutics such as tamoxifen and aromatase inhibitors have been the mainstay therapeutic strategy for ER-positive breast cancer. Several ER-directed therapies have been developed to antagonize the oncogenic ER function, including Selective ER Degraders (SERDs) such as fulvestrant which is approved to treat patients with advanced or metastatic breast cancer. However, it requires intramuscular injection and has poor solubility, thereby limiting its administered dose and therefore its efficacy. In addition to SERDs, a newly emerging technology, E3 ligase-engaged chimeric degraders, has been used to induce potent and deeper ER degradation. Empowered by Accutar's proprietary Protein-Protein Interaction Targeting Chimeras (PPI-TAC) platform, AC699 was meticulously designed as a chimeric degrader to target and degrade the protein of interest, ER α . By effectively linking an ER ligand to an E3-ligase recruiting ligand, AC699 brings ER α in proximity to an E3 ligase, thereby inducing subsequent ubiquitination and degradation of ER α . Notably, chimeric ER degraders possess the unique advantage of degrading the ER protein without the inherent risk of activating an ER signal. Moreover, these molecules are not degraded alongside the target protein allowing for their efficient recycling within the cell. This direct mechanism enables chimeric ER degraders to achieve potent ER degradation with increased specificity, thereby potentially providing a higher therapeutic index compared to SERDs. This abstract describes a first-in-human Phase 1 trial of AC699, a novel ER degrader.

Study Description

The AC699-001 Phase 1 dose escalation study will enroll up to 60 patients with locally advanced or metastatic ER-positive, human epidermal growth factor receptor 2-negative, breast cancer. Patients must have progressed on standard treatment including at least two prior endocrine regimens or at least one prior line of therapy if combined with a CDK4/6 inhibitor. Prior chemotherapy is not required but must not exceed three prior cytotoxic regimens. Patients must have at least one measurable lesion or at least one predominantly lytic bone lesion. AC699 is given orally, once daily, with doses ranging from 100 mg to 600 mg in a standard 3+3 dose escalation design. The primary objective is to evaluate the safety and tolerability of AC699 using CTCAE 5.0. Secondary objectives include assessing preliminary anti-tumor activity according to RECIST 1.1 and characterizing the pharmacokinetic profile of single and multiple doses of AC699. Enrollment began in December 2022 with five sites in the United States planned. NCT05654532.

PO3-19-08

A phase 2 randomized pre-operative, window of opportunity trial investigating the effect of elacestrant with/without triptorelin in premenopausal patients with HR+/HER2- breast cancer – SOLTI-2104-PremiÈRe trial.

Presenting Author(s) and Co-Author(s):

M. Bellet- Ezquerra. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain

C. Hernando. Hospital Clínico Universitario de Valencia, Valencia, Spain

P. Tolosa. SOLTI Cancer Research Group, Barcelona, Spain/Medical Oncology Department, Hospital 12 de Octubre, Madrid., Madrid, Madrid, Spain

M. Vidal. Medical Oncology Department, Hospital Clínic of Barcelona ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; SOLTI Breast Cancer Research Group ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Catalonia, Spain

Y. Fernández. Hospital Central de Asturias, Spain, United States

S. González-Santiago. Hospital Universitario San Pedro de Alcántara, Cáceres, Spain

P. Sanchez. Hospital Universitario Virgen de la Arrixaca, Spain

S. De La Cruz. Medical Oncology Department , University Hospital of Navarra., Spain

V. Ortega. Breast Cancer Unit, Hospital Universitari General de Catalunya, United States

X. Gonzalez-Farré. Intituto Oncológico Dr. Rosell, Hospital General de Catalunya, Catalonia, Spain

M. Bergamino. Medical Oncology Department, ICO Badalona, B-ARGO Group, United States

A. Espinosa. SOLTI Cancer Research Group, Catalonia, Spain

T. Pascual. SOLTI Cancer Research Group, Barcelona, Spain /Department of Medical Oncology, Hospital Clínic de Barcelona, Spain / Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

Background. Premenopausal women diagnosed with HR+/HER2- breast cancer (BC) often have a different biology and worse prognosis. The SOFT and TEXT studies demonstrated an increase diseasefree survival (DFS) with ovarian function suppression (OFS) plus tamoxifen or exemestane compared to tamoxifen alone. Of note, high-risk clinicopathologic features, adjuvant chemotherapy, or aged ≤ 35 years correlated with greater OFS benefit. However, adding OFS in this context has intrinsic issues as higher toxicity, which led to treatment discontinuation (20% in SOFT trial), and suboptimal OFS was found in around 25% of patients (pts) with exemestane plus monthly triptorelin (SOFT-EST sub-study). Thus, new effective ET options without OFS are needed for premenopausal patients (pts).

Elacestrant is the first oral, non-steroidal, selective estrogen receptor degrader (SERD) to demonstrate improved efficacy to SOC treatments and specifically compared to fulvestrant in postmenopausal pts with HR+/HER2- metastatic BC at the phase III EMERALD trial. In menopausal patients with HR+/HER2- early BC, the window of opportunity SOLTI-1905 ELIPSE trial (NCT04797728), showed that elacestrant was associated with a 27.3% rate of Complete Cell Cycle Arrest (CCCA) and a statistically significant suppression of Ki-67. Among Luminal A tumors, the CCCA rate was 45% and the average decrease in Ki-67 was 64.6%,

while no CCCA was reported and the suppression of Ki-67 was less pronounced (31.7%) in the Luminal B population. There is still a need for investigating elacestrant without OFS in the premenopausal scenario. We hypothesize that elacestrant as a single agent or in combination with triptorelin is an effective and safe treatment regimen in premenopausal pts with HR+/HER2-negative early BC capable of achieving an equivalent CCCA rate as a surrogate of effectiveness regardless the use of OFS Study design. PREMIERE is a parallel, non-comparative, two-arm, randomized 1:1, open-label, multicenter, exploratory study in premenopausal women with primary operable HR+/HER2-negative BC. The study aims to evaluate the biological effects of elacestrant with or without triptorelin. Participants must have histologically confirmed HR+ ($\geq 10\%$) and HER2- operable early BC stage I to stage IIB >1 cm with a Ki-67 between 10-35%. The primary objective is to assess the ability of each treatment arm to induce CCCA determined by central assessment of Ki-67 ($\% \text{ Ki-67} \leq 2.7\%$). No formal comparison between treatment arms is intended. Secondary objectives include evaluating the biological activity of elacestrant with or without OFS, antiproliferative activity, changes in gene expression including PAM50 subtype changes, and the effect of optimal vs suboptimal suppression on CCCA. Serum E2 and FSH levels will also be evaluated. Safety and tolerability will be assessed based on adverse events and clinical laboratory test results. Pts will undergo screening and randomization, with stratification by PAM50 subtype (Luminal A vs Non-luminal A). Treatment will be elacestrant 400 mg once daily or elacestrant 400 mg once daily plus triptorelin 3.75 mg days +1 and +29 for 30 (+7) days. Surgery or biopsy will be performed after treatment completion, and a post-surgery visit will mark the end of the active follow-up period. Patients will receive SOC treatment after surgery.

48 patients will be recruited in 9 sites within SOLTI Spanish network in 9 months period. This study is financially supported by Menarini-Stemline.

PO3-19-09

SERENA-1: Results from a Phase 1 study (Parts I/J) testing the next-generation oral selective estrogen receptor degrader (SERD) camizestrant (AZD9833) in combination with capivasertib in women with ER+, HER2 advanced breast cancer

Presenting Author(s) and Co-Author(s):

C. Vaklavas. Huntsman Cancer Institute, United States

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

A. Armstrong. The Christie NHS Foundation Trust, United States

I. Moreno. START Madrid-HM Centro Integral Oncológico Clara Campal (CIOCC), Hospital Universitario HM Sanchinarro, Madrid, Spain, Madrid, Spain

C. Twelves. University of Leeds/Leeds Teaching Hospitals Trust, Leeds, United Kingdom, United States

I. Victoria Ruiz. Department of Medical Oncology (Hospital Clinic/IDIBAPs), Spain, United States

B. Bermejo. Hospital Clínico Universitario de Valencia, Valencia, Spain, United States

M. Ajimi. AstraZeneca, United States

T. Brier. AstraZeneca, Cambridge, UK, United States

C. Ciardullo. AstraZeneca, Cambridge, UK, United States

L. Gibbons. AstraZeneca, Cambridge, UK, United States

i. irurzun-Arana. AstraZeneca, Cambridge, United Kingdom

T. Jack. AstraZeneca, Cambridge, UK, United States

T. Klinowska. AstraZeneca, Cambridge, United Kingdom

J. Lindemann. AstraZeneca, Cambridge, United Kingdom

A. Mathewson. Research and Early Development, Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. Morrow. AstraZeneca, Cambridge, United Kingdom

A. Sykes. Research and Early Development, Oncology R&D, AstraZeneca, Cambridge, UK, United States

R. Baird. CRUK Cambridge Centre, University of Cambridge, United Kingdom

Background:

SERENA-1 (NCT03616587) is a Phase 1, multi-part, open-label study of camizestrant in women with ER+/HER2- advanced breast cancer. Data for camizestrant as monotherapy and in combination with palbociclib or abemaciclib have been presented previously.¹⁻³ Here we present data from parts I and J (dose ranging and expansion, respectively), which examined camizestrant in combination with the pan-AKT inhibitor capivasertib.

Methods:

The primary objective was to determine the safety and tolerability of camizestrant 75 mg once daily (QD) in combination with capivasertib 400 mg twice daily (BID; intermittent: 4 days on, 3 days off). Secondary objectives included investigation of anti-tumor response and pharmacokinetics (PK). Participants were women of any menopausal status (pre-menopausal

women received concomitant ovarian function suppression). Prior treatment with an endocrine therapy (ET) in the advanced setting was required with no limit on the number of lines of prior ET. Prior treatment with ≤ 2 lines of chemotherapy in the advanced setting was permitted. Prior treatment with CDK4/6 inhibitors (CDK4/6i) and/or fulvestrant was also permitted.

Results:

As of 21 March 2023, 29 patients had received camizestrant in combination with capivasertib. Patients were heavily pretreated in the advanced setting (48% prior chemotherapy, 90% prior CDK4/6i, 55% prior fulvestrant) and 72% had visceral metastases. The safety and tolerability profile of the combination of camizestrant and capivasertib was broadly consistent with that of each drug individually.^{4,5} In the 29 patients, adverse events considered related to camizestrant and/or capivasertib in >15% of patients (%; n grade 1/n Grade 2/n Grade >3) included diarrhea (66%; 14/2/3), visual effects (62%; all Grade 1), bradycardia (34%; all Grade 1), nausea (34%; 6/4/0), fatigue (21%; 4/2/0) maculopapular rash (17%; 0/3/2) and aspartate aminotransferase increased (17%; 3/0/2). The PK and safety data indicated no clinically relevant drug–drug interactions between camizestrant and capivasertib. The objective response rate was 29.6% (8/27), the clinical benefit rate at 24 weeks was 51.7% (15/29), and median progression–free survival was 8.3 months. Overall, 12 patients had a detectable ESR1 mutation (ESR1m) at baseline (Cycle 1, Day 1) and an evaluable Cycle 2, Day 1 (C2D1) result; of these, ESR1m was reduced by >50% at C2D1 in 91.7% of patients (11/12), including 66.7% (8/12) of patients where ESR1m was cleared.

Conclusions:

Camizestrant 75 mg QD in combination with capivasertib 400 mg BID was well tolerated and associated with encouraging clinical and pharmacodynamic activity. These data support further evaluation of this combination in women with ER+/HER2– advanced breast cancer.

References:

1. Baird R et al. Abstract PS11-05, presented at San Antonio Breast Cancer Symposium, 2020.
2. Oliveira M et al. J Clin Oncol. 2022; 40: Abstract 1032.
3. Turner N et al. Poster P3-07-28, presented at San Antonio Breast Cancer Symposium, 2022.
4. Hamilton E et al. Poster 108, presented at American Society of Clinical Oncology Meeting, 2020.
5. Turner NC et al. N Engl J Med. 2023; 2058–70.

Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

We acknowledge Sandra Heurtaux from InterComm International who provided medical writing support funded by AstraZeneca. Anne Armstrong had not approved the final draft of the abstract at the time of submission.

PO3-19-10

Phase 1b study of EZH1/2 inhibitor valemestostat in combination with trastuzumab deruxtecan in subjects with HER2 low/ultra-low/null metastatic breast cancer

Presenting Author(s) and Co-Author(s):

S. Damodaran. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Iwase. Translational Cancer Research, University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

A. Marx. MD Anderson Cancer Center, United States

J. Willey. The University of Texas MD Anderson Cancer Center, United States

F. Meric-Bernstam. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

C. Barcenas. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. lee. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

N. Ueno. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

Background

Low HER2-expressing breast cancers have traditionally been classified as HER2-negative and treated as TNBC or hormone receptor (HR)-positive. Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate, composed of an anti-HER2 antibody conjugated to topoisomerase I payload, is approved for clinical use in HER2-low (IHC 1+ or IHC 2+ / ISH negative) metastatic breast cancer (MBC). In the DAISY study (NCT04132960), meaningful clinical response was observed with T-DXd in HER2 IHC 0 MBC. Valemestostat is an oral, selective dual inhibitor of enhancer of zeste homolog 1 and 2 (EZH1/2, methyltransferases that specifically methylate histone H3 lysine 27. It is currently approved for patients with relapsed or refractory adult T-cell leukemia/lymphoma in Japan. EZH2-mediated PP2A inactivation has been shown to confer resistance to HER2-targeted therapy. Additionally, valemestostat has been shown to upregulate Schlafen11 (SLFN11), a putative DNA/RNA helicase, that regulates the sensitivity to DNA damaging agents such as topoisomerase I inhibitors. Consequently, this study examines the safety and anti-tumor activity of valemestostat in combination with T-DXd in subjects with HER2 low/ultra-low/null MBC.

Trial Design

This is a single-arm, phase-1b study to evaluate the safety and clinical activity of T-DXd in combination with valemestostat in patients with HER2 low/ultra-low/null MBC. The dosing for T-DXd is 5.4 mg/kg Q3W administered intravenously as indicated for current clinical use.

Valemestostat will be evaluated at three dose levels (100 mg, 150 mg, and 200 mg orally), with starting dose (level 1) at 100 mg QD. The dose-limiting toxicity (DLT) evaluation period will be the first 2 treatment cycles (42 days).

Eligibility criteria

- Pathologically confirmed HER2 low/ultra-low/null breast cancer
- ECOG performance status ≤ 1
- Measurable disease
- Received at least one line of chemo in the metastatic setting
- Progressed and would no longer benefit from endocrine therapy (HR-positive).

- Normal organ and marrow function
- Exclusion: symptomatic brain metastases, interstitial lung disease, cord compression, prior treatment with any anti-HER2 therapy

Specific aims

- To evaluate the safety and determine the maximum tolerated dose (MTD)/recommended dose for expansion (RDE) of valemetostat in combination with T-DXd.
- To evaluate the objective response rate (ORR) of valemetostat at the RDE in combination with T-DXd of valemetostat at the RDE in combination with T-DXd.
- To determine the duration of response (DoR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS) of valemetostat at the RDE in combination with T-DXd.
- To evaluate the pharmacokinetics and pharmacodynamic markers of valemetostat and T-DXd combination.
- To evaluate the immunogenicity of T-DXd when co-administered with valemetostat.

Statistical methods Approximately 12 evaluable patients will be enrolled for the dose-escalation portion based on the Bayesian optimal interval design with a target DLT rate of 25%. Patients enrolled in cohorts of 3. The expansion will be performed at the RDE using the 2-stage Bayesian optimal dose-expansion design. In the first stage, 13 evaluable patients (including those treated at the RDE in the dose-escalation part) will be enrolled. If < 5 patients respond in the first stage, the study will be stopped for futility. If ≥ 5 responses are observed, 13 additional evaluable patients will be enrolled. If 11 or more responses are observed among the total of 26 patients the treatment will be regarded as promising. This two-stage design yields 78% power under the alternative hypothesis of ORR=50% (null ORR = 30%) while controlling the one-sided type I error at 10%. Contact information for people with a specific interest in the trial sdamodaran@mdanderson.org (NCT05633979)

PO3-19-11

CINDERELLA Clinical Trial (NCT05196269): using artificial intelligence-driven healthcare to enhance breast cancer locoregional treatment decisions

Presenting Author(s) and Co-Author(s):

E. Bonci. Breast Unit, Champalimaud Research and Clinical Centre, Champalimaud Foundation (Lisbon, Portugal); Surgical Oncology and Gynecologic Oncology Department, Iuliu Hatieganu University of Medicine and Pharmacy (Cluj-Napoca, Romania), Lisboa, Lisboa, Portugal

O. Kaidar-Person. Breast Cancer Radiation Therapy Unit, Sheba Medical Center (Ramat Gan, Israel); Sackler School of Medicine, Tel-Aviv University (Tel-Aviv, Israel), United States

M. Antunes. Faculdade de Ciências, Universidade de Lisboa (Lisbon, Portugal); CEAUL - Centro de Estatística e Aplicações, Faculdade de Ciências, Universidade de Lisboa (Lisbon, Portugal), United States

O. Ciani. Center for Research on Health and Social Care Management (CERGAS), SDA Bocconi University (Milan, Italy), United States

H. Cruz. Breast Unit, Champalimaud Research and Clinical Centre, Champalimaud Foundation (Lisbon, Portugal), United States

R. Di Micco. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), Italy

O. Gentilini. Breast Surgery Unit, San Raffaele University Hospital, Milan, Italy

N. Rotmensz. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), United States

P. Gouveia. Breast Unit, Champalimaud Research and Clinical Centre, Champalimaud Foundation (Lisbon, Portugal); Faculdade de Medicina da Universidade de Lisboa (Lisbon, Portugal), United States

J. Heil. Department of Obstetrics & Gynecology, Heidelberg University Hospital (Heidelberg, Germany), United States

P. Kabata. Department of Surgical Oncology, Faculty of Medicine, Medical University of Gdańsk (Gdańsk, Poland), United States

N. Freitas. INESC TEC - Institute for Systems and Computer Engineering, Technology and Science (Porto, Portugal); FCUP - Faculty of Sciences, University of Porto (Porto, Portugal), United States

T. Gonçalves. INESC TEC - Institute for Systems and Computer Engineering, Technology and Science (Porto, Portugal); FEUP - Faculty of Engineering, University of Porto (Porto, Portugal), United States

M. Romariz. INESC TEC - Institute for Systems and Computer Engineering, Technology and Science (Porto, Portugal); FCUP - Faculty of Sciences, University of Porto (Porto, Portugal), United States

H. Montenegro. INESC TEC - Institute for Systems and Computer Engineering, Technology and Science (Porto, Portugal); FEUP - Faculty of Engineering, University of Porto (Porto, Portugal), United States

H. Oliveira. INESC TEC - Institute for Systems and Computer Engineering, Technology and Science (Porto, Portugal); FCUP - Faculty of Sciences, University of Porto (Porto, Portugal), United States

J. Cardoso. INESC TEC - Institute for Systems and Computer Engineering, Technology and Science (Porto, Portugal); FEUP - Faculty of Engineering, University of Porto (Porto, Portugal), United States

H. Martins. Breast Unit, Champalimaud Research and Clinical Centre, Champalimaud Foundation (Lisbon, Portugal); ISCTE - Instituto Universitário de Lisboa (Lisbon, Portugal), United States

D. Lopes. Breast Unit, Champalimaud Research and Clinical Centre, Champalimaud Foundation (Lisbon, Portugal), United States

M. Martinho. Breast Unit, Champalimaud Research and Clinical Centre, Champalimaud Foundation (Lisbon, Portugal), United States

L. Borsoi. Center for Research on Health and Social Care Management (CERGAS), SDA Bocconi University (Milan, Italy), United States

E. Listorti. Center for Research on Health and Social Care Management (CERGAS), SDA Bocconi University (Milan, Italy), United States

C. Mavioso. Breast Unit, Champalimaud Research and Clinical Centre, Champalimaud Foundation (Lisbon, Portugal), United States

M. Mika. CANKADO GmbH (Ottobrunn, Germany), United States

A. Pfob. Department of Obstetrics & Gynecology, Heidelberg University Hospital (Heidelberg, Germany), United States

T. Schinköthe. CANKADO GmbH, Digital Health, Alte Landstraße 23, 85521, Ottobrunn, Germany, United States

G. Silva. CEaul - Centro de Estatística e Aplicações, Faculdade de Ciências, Universidade de Lisboa (Lisbon, Portugal); Instituto Superior Técnico, Universidade de Lisboa (Lisbon, Portugal), United States

M. Cardoso. Breast Unit, Champalimaud Research and Clinical Centre, Champalimaud Foundation (Lisbon, Portugal); Faculdade de Medicina da Universidade de Lisboa (Lisbon, Portugal), United States

Background. Breast cancer treatment has improved overall survival rates, with different locoregional approaches offering patients similar locoregional control but variable aesthetic outcomes that may lead to disappointment and poor quality of life (QoL). There are no standardized methods for informing patients of the different therapies prior to intervention, nor validated tools for evaluation of aesthetics and patients' expectations. The CINDERELLA Project is based on years of research and developments of new healthcare technologies by various partners, aimed to provide an artificial intelligence (AI) tool to aid shared decision-making by showing breast cancer patients the predicted aesthetic outcomes of their locoregional treatment. The clinical trial will evaluate the use of this tool within an AI cloud-based platform approach (CINDERELLA App) versus a standard approach. We anticipate that the CINDERELLA App will lead to improved satisfaction, psychosocial well-being and health-related QoL while maintaining the quality of care and providing environmental and economic benefits.

Trial design. CINDERELLA is an international multicentric interventional randomized controlled open-label clinical trial. Using the CINDERELLA App, the AI and Digital Health arm will provide patients with complete information about the proposed types of locoregional treatments and photographs of similar patients previously treated with the same techniques. The Control arm will follow the standard approach of each clinical site. Randomization will be conducted online using the digital health platform CANKADO, ensuring a balanced distribution of participants

between the two groups. CANKADO is the underlying platform through which physicians control the patients' app content and conduct all data collection. Privacy, data protection and ethical principles in AI usage were taken into account.

Eligibility criteria. Patients diagnosed with primary breast cancer without evidence of systemic disease. All patients must sign an informed consent and be able to use a web-based app autonomously or with home-based support.

Specific aims. Primary objective: to assess the levels of agreement among patients' expectations regarding the aesthetic outcome before and 12 months after locoregional treatment. The trial will also evaluate the aesthetic outcome level of agreement between the AI evaluation tool and self-evaluation. Secondary objectives: health-related QoL (EQ-5D-5L and BREAST-Q ICHOM questionnaires) and resource consumption (e.g., time spent in the hospital, out-of-pocket expenses). The questionnaires and photographs will be applied prior to any treatment, at wound healing, at 6 and 12 months following the completion of locoregional therapy.

Statistical methods. Wilcoxon signed rank test will be used to assess the intervention's impact on the agreement level between expectations and obtained results. Weighted Cohen's kappa will be calculated to measure the improvement in classifying aesthetic results with intervention. Statistical tests and/or bootstrap techniques will compare results between arms. A similarity measure will be calculated between self-evaluation and outcome obtained with the AI tool for each participant, and a beta regression model will be used to analyze the intervention's effect. Secondary objectives will be evaluated by scoring questionnaires based on provided guidelines.

Target accrual. The clinical trial, led by Champalimaud Clinical Centre, will enroll a minimum of 515 patients in each arm between July 2023 and January 2025. Recruitment is currently open at five study sites in Germany, Israel, Italy, Poland and Portugal. The clinical trial is still open for further international study sites.

Funding. European Union grant HORIZON-HLTH-2021-DISEASE-04-04 Agreement No. 101057389.

PO3-19-12

Evaluating the impact of ePRO-based follow-up system (Pink Ribbon Diary) on quality of life and treatment adherence in patients with breast cancer receiving CDK4/6 inhibitors: a single center, randomized controlled study (JPRO-B)

Presenting Author(s) and Co-Author(s):

R. Ozeki. Juntendo University school of medicine, Department of breast oncology, United States

H. Shimizu. Juntendo University school of medicine, Department of breast oncology, United States

K. Iijima. Juntendo University school of medicine, Department of breast oncology, United States

M. Okazaki. Juntendo University school of medicine, Department of breast oncology, United States

J. Watanabe. Juntendo University Graduate School of Medicine, Tokyo, Japan

M. Saito. Juntendo University school of medicine, Department of breast oncology, United States

Background: Treatment-related toxicities (TRT) may decrease patient's quality of life (QOL) and may result in a decrease of adherence to the therapy. Cyclin-dependent kinase 4/6 inhibitors (CDK4/6is), such as palbociclib (PAL) and abemaciclib (ABM) improved patients' outcomes with estrogen receptor-positive (ER+) HER2 negative (HER2-) advanced breast cancer (ABC), however, majority of patients who undergo CDK4/6i therapy experience \geq Grade 2 TRTs, such as hematological abnormalities, gastrointestinal disorders or general fatigue. While prompt management of those TRTs is mandatory to prevent patients from discontinuing the therapy, real-time monitoring of TRTs has been warranted.

Recently, efforts have been made to monitor symptoms using electronic patient-reported outcome (ePRO) to detect side effects as early as possible and to provide timely support. However, the efficacy of ePRO in daily clinical practice for those receiving CDK4/6is is still unclear. In addition, the researches in the field of ePRO to date have only focused on drugs administered intravenously in hospitals, where patients' adherence has no clinical importance.

Study design and eligibility criteria: This randomized, open-label, controlled phase 2 trial is designed to assess the efficacy of a new proprietary ePRO system, the Pink Ribbon Diary (PRD), compared with placebo (usual care without the ePRO system) in breast cancer patients with ER+HER2-ABC receiving oral CDK4/6i-based therapy aged \geq 20 years. All eligible patients who complete training on how to use ePRO system are randomly allocated to either arm A using ePRO system or arm B receiving usual care (1:1). Participants in the arm A are required to record medication taken and physical condition every day for 3 months, and report adverse events using PRO-CTCAETM once a week. Patients in the arm B are also asked to answer to questions concerning adverse events using PRO-CTCAETM at monthly hospital visit for 3 months. All participants are asked to respond to the EORTC QLQ-C30 at their monthly visit and a questionnaire survey on adherence before the study and after completion of the study. Participants in the arm A and healthcare providers, will answer the questionnaire about the feeling of using the PRD. Primary endpoint is the change in global health status/QOL (EORTC QLQ-C30) at 3 months from baseline. Secondary endpoints are RDI (relative dose intensity), other domains of EORTC QLQ-C30, number of days missed medication, PDC (proportion of days covered), survey of medication compliance awareness using MMAS-8 (Morisky

Medication Adherence Scale), questionnaire on use of PRD, and comparison between two groups of occurrence of adverse events and incidence of missed medication.

Study objective: To assess the clinical efficacy of PRD in patients with ER+HER2-ABC undergoing CDK4/6i-based therapy.

Statistical methods: For analysis of QOL, the primary endpoint, the differences in global health status/QOL (EORTC QLQ-C30) before and after the study will be compared between the two groups using the t-test.

Present accrual and target accrual: The study was approved by institutional review board in December 2022, and is open for enrollment. The target sample size is 70. The study is ongoing and 22 patients have been accrued to date.

Trial registration numbers: Japan Registry of Clinical Trials (jRCT) jRCT1030220626 (<https://jrct.niph.go.jp/re/reports/detail/30182>).

PO3-20-01

ASTEFANIA: a Phase III study of ado-trastuzumab emtansine plus atezolizumab or placebo as adjuvant therapy in patients with residual invasive breast cancer after neoadjuvant HER2-targeted therapy and chemotherapy

Presenting Author(s) and Co-Author(s):

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

T. Bachelot. Medical Oncology, Centre Léon Bérard, Lyon, France

G. Bianchini. IRCCS Ospedale San Raffaele, Milan, Lombardia, Italy

N. Harbeck. University of Munich, Munich, Bayern, Germany

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

L. Gilham. Patient advocate, Melbourne, VIC, Australia, Australia

T. Boulet. F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States

N. Gochitashvili. Roche Products Limited, Welwyn Garden City, UK, United States

E. Monturus. F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States

C. Lambertini. Oncology Biomarker Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States

B. Nyawira. F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States

A. Knott. Roche Products Limited, Welwyn Garden City, UK, United States

S. Hurvitz. Fred Hutchinson Cancer Center/University of Washington, Los Angeles, California, United States

BACKGROUND

Ado-trastuzumab emtansine (T-DM1) is the standard of care for adjuvant treatment of patients (pts) with HER2-positive early breast cancer (eBC) who have invasive residual disease after preoperative treatment with taxane and HER2-targeted therapy. However, a high unmet need remains in some higher risk subgroups (e.g., inoperable or lymph node-positive, hormone receptor-negative disease) who have 3-year invasive disease-free survival (IDFS) rates of 76%. Exploratory analyses suggest that addition of the programmed death-ligand 1 (PD-L1) inhibitor atezolizumab to T-DM1 results in longer progression-free survival compared with T-DM1 alone in pts with previously treated PD-L1-positive metastatic BC. PD-L1/programmed death-1 inhibitors may have a different effect in eBC, as they result in improved pathologic complete response in early triple-negative BC regardless of PD-L1 status. ASTEFANIA evaluates atezolizumab plus T-DM1 in PD-L1-unselected pts with higher risk residual invasive breast cancer after neoadjuvant treatment.

TRIAL DESIGN

ASTEFANIA is a Phase III, randomized, double-blind, multicenter, study in pts with centrally confirmed HER2-positive eBC with residual invasive disease at surgery after neoadjuvant chemotherapy and HER2-directed treatment including ≥ 9 weeks of taxane and ≥ 9 weeks of trastuzumab. Within 12 weeks of primary surgery, pts are randomized 1:1 to intravenous (IV) T-DM1 3.6 mg/kg every 3 weeks (q3w) plus atezolizumab 1200 mg IV q3w or T-DM1 3.6 mg/kg IV q3w plus placebo IV q3w for 14 cycles. Radiotherapy and/or endocrine therapy is

administered per local standards. Randomization is stratified by clinical stage at presentation, hormone receptor status, preoperative HER2-directed therapy, and PD-L1 status.

ELIGIBILITY CRITERIA

Eligible pts have clinical stage cT4/any N/M0, any cT/N2–3/M0, or cT1–3/N0–1/M0 at presentation. Those with cT1–3/N0–1 disease must have pathologic evidence of residual invasive carcinoma in axillary lymph node(s) at surgery. Pts with cT1mi/T1a/T1b/N0 disease are not eligible.

AIMS

The primary endpoint is IDFS. Secondary endpoints include overall survival, safety, and patient-reported outcomes.

STATISTICAL METHODS

The log-rank test will be used to compare IDFS between the treatment arms, according to the protocol-defined stratification factors. The Cox proportional hazards model, stratified by the protocol-defined stratification factors, will be used to estimate the hazard ratio between the two treatment arms and its 95% confidence intervals.

ACCRUAL

As of Jun 28, 2023, 789 pts of the target of 1,700 have been enrolled.

CONTACT INFORMATION

For more information or to refer a patient, email global.roche.genentech.trials@roche.com or call 1-888-662-6728 (USA only).

Clinicaltrials.gov number NCT04873362.

Originally presented at the ESMO Congress 2021, 202TiP, Peter Schmid et al. – Reused with permission.

Further information is available in Future Oncology 2022; 18:3563–3572. Submitted with permission from Future Medicine & Future Science, part of the Future Science Group.

PO3-20-02

Olaparib front line therapy with endocrine therapy in locally advanced unresectable or in metastatic breast cancer: OFELIA TRIAL

Presenting Author(s) and Co-Author(s):

C. González Núñez. Instituto Nacional de Cancerología, Tlalpan, Distrito Federal, Mexico

P. Cabrera-Galeana. Instituto Nacional de Cancerología, CDMX, Distrito Federal, Mexico

J. Bargalló Rocha. Instituto Nacional de Cancerología (INCAN), Mexico City, Mexico, United States

R. Vazquez-Romo. Instituto Nacional de Cancerología, United States

S. Aguilar-Villanueva. Instituto Nacional de Cancerología, United States

A. Garcilazo. INSTITUTO NACIONAL DE CANCEROLOGIA, United States

A. Velazquez-Martinez. Instituto Nacional de Cancerología, United States

A. Maliachi. Instituto Nacional de Cancerología, United States

R. Rodriguez. Instituto Nacional de Cancerología, United States

INTRODUCTION: Currently, patients with recurrent or metastatic hormone-sensitive breast cancer are treated with endocrine therapy (ET) in combination with cyclin inhibitors, as it has been shown to improve both overall survival and progression-free survival. However, it has been observed that patients with gBRCA1 or gBRCA2 mutations, who receive treatment with endocrine therapy and CDK4/6 inhibitors, have lower OS and lower PFS compared to those without mutations. These findings could be due to the presence of higher cyclin E mRNA levels, which encode the protein that stimulates CDK2 activity provoking a resistance to CDK4/6 inhibitors. Having this said, the use of PARP inhibitors a potential first-line therapeutic option in combination with endocrine therapy could be an option to be re evaluated.

JUSTIFICATION: PARP inhibitors (iPARP) are recommended in international guidelines as second-line palliative treatment and also as adjuvant management in the case of Olaparib. The use of iPARP is approved only as a second-line treatment in HER2 hormone-sensitive breast cancer, according to the results of the EMBRACA and OlympiAD clinical trials. However, these two clinical trials were not designed to evaluate its effectiveness as first-line palliative treatment. Given that patients with gBRCA mutations have lower overall survival when administered cyclin inhibitors (iCDK 4/6) + Endocrine therapy (ET) compared to those without mutations, it is necessary to reevaluate the use of iPARP as first-line palliative treatment in conjunction with ET, with the expectation of achieving a similar objective response rate and progression-free survival.

OBJECTIVE: To Determine the ORR in patients with recurrent or metastatic hormone-sensitive HER2-negative breast cancer managed with PARP inhibitors + Endocrine therapy.

HYPOTHESIS: The use of PARP inhibitors in combination with endocrine therapy will have an objective response rate of 60% or higher in both early stages and advanced disease.

METHODOLOGY: Phase 2 open-label, multicenter clinical trial.

Study Population:

Cohort : All pre- or postmenopausal patients with a diagnosis of recurrent or metastatic hormone-sensitive HER2-negative breast cancer with gBRCA1 and/or gBRCA2 mutation.

Sample: The inclusion of patients will be based on meeting the inclusion criteria.

We plan to achieve an ORR of at least 60% with an acceptable minimum of 40%. Assuming a one-sided alpha level of 0.05 and statistical power of 80%, a two-stage Simon design was used to calculate the required sample size. In the first stage, a minimum of 23 patients is assumed, of which 14 patients need to achieve the desired response rate to proceed to the second stage. In the second stage, an additional 28 patients will be added to obtain a total sample size of 51 patients. The objective response rate will be evaluated using RECIST v1.1 criteria at 8 weeks after initiating treatment, with continued assessment during the first year, followed by assessments every 12 weeks during the second and third year, and then every 24 weeks until progression or toxicity.

EXPECTED RESULTS: PARP inhibitors + Endocrine therapy will have a similar ORR as reported with cyclin inhibitors + Endocrine therapy, as well as a benefit in progression-free survival.

PO3-20-03

First-in-human global study of RLY-2608, a pan-mutant and isoform selective PI3K α inhibitor, as a single agent in patients with advanced solid tumors and in combination with fulvestrant in patients with advanced breast cancer

Presenting Author(s) and Co-Author(s):

- A. Varkaris. Massachusetts General Hospital, Boston, Massachusetts, United States
- K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States
- E. Garralda Cabanas. Vall d'Hebron Instituto de Oncologia, Barcelona, Spain
- L. Sanz. Vall d'Hebron Institute of Oncology, Barcelona, Spain, Spain
- J. Kim. Massachusetts General Hospital, Boston, Massachusetts, United States
- C. Perez. Sarah Cannon Research Institute (Florida Cancer Specialists),, United States
- E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States
- A. Spira. Virginia Cancer Specialists (VCS) Research Institute, Fairfax, VA, United States
- K. Wisinski. University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, United States
- A. Guerrero. Instituto Valenciano de Oncologia, Spain
- J. Henry. Sarah Cannon Research Institute (HealthOne Denver), United States
- J. Rodon Ahnert. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
- G. Tan. Relay Therapeutics, United States
- X. Li. Relay Therapeutics, United States
- D. Hummel. Relay Therapeutics, United States
- T. Hunter. Relay Therapeutics, United States
- A. Timm. Relay Therapeutics, United States
- R. Samadani. Relay Therapeutics, United States
- E. Puente-Poushnejad. Relay Therapeutics, United States
- E. Kwak. Relay Therapeutics, United States
- B. Mar. Relay Therapeutics, United States
- A. Schram. Memorial Sloan Kettering Cancer Center, United States

Background: Oncogenic mutations in PI3K α are common driver events in ER+ breast cancer and other solid tumors. Alpelisib, a non-mutant selective PI3K α inhibitor, is effective in ER+ breast cancer thus validating PI3K α as a therapeutic target. Inhibition of wild-type PI3K α results in toxicity including hyperglycemia which limits tolerability and drug exposure. RLY-2608, a novel, oral allosteric PI3K α inhibitor, is uniquely designed to overcome these limitations via mutant- and isoform-selective PI3K α inhibition for greater target coverage, improved tolerability, and antitumor activity. Initiated in December 2021, ReDiscover is the ongoing, first-in-human study to define the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumor activity of RLY-2608 monotherapy in *PIK3CA*-mutant advanced solid tumor patients (pts) and of RLY-2608 plus fulvestrant in pts with *PIK3CA*-mutant, HR+HER2-BC. At AACR 2023, dose escalation data for RLY-2608 was reported and demonstrated encouraging target inhibition and anti-tumor activity (including partial response),

across PIK3CA genotypes with minimal impact on glucose homeostasis. To date, pts have received RLY-2608 at doses of 100–2000 mg/day, with no reported dose-limiting toxicities; the MTD has not been reached. These proof-of-mechanism data indicate that RLY-2608 is the first allosteric, pan-mutant selective PI3K α inhibitor and that RLY-2608 has broad therapeutic potential in PIK3CA-driven cancers. **Methods:** Enrollment is ongoing in this global, multi-center, dose escalation/expansion study of RLY-2608 as a single agent in adults who have advanced solid tumors and are refractory, intolerant, or have declined standard therapy; and RLY-2608 in combination with fulvestrant in previously treated pts with HR+/HER2– MBC. Eligibility criteria include presence of *PIK3CA* mutation (blood or tumor) per local assessment, ECOG performance status 0–1, evaluable disease per RECIST 1.1 and no prior PI3K inhibitor (except in expansion combination group 2). RLY-2608 is administered on a continuous schedule with 4-week cycles. Adverse events (AEs) per CTCAE v5, PK, biomarkers (pAKT, mutant ctDNAs and insulin pathway markers) and anti-tumor activity are assessed serially. Dose escalation employs a Bayesian Optimal Interval design to identify the MTD and/or the recommended Phase 2 dose (RP2D). Following dose escalation, expansion cohorts will enroll patients with select *PIK3CA*-mutated solid tumors for treatment with RLY-2608 monotherapy and patients with HR+/HER2– MBC for treatment with RLY-2608 and fulvestrant. The primary endpoints are MTD/RP2D and AE profile for single agent and combination; key secondary endpoints are *PIK3CA* genotype in blood and tumor, PK, biomarkers, and overall response rate. ReDiscover (NCT05216432) is enrolling worldwide. For further information, contact clinicaltrials@relaytx.com. **Funding source:** This study is funded by Relay Therapeutics, Cambridge, MA, United States.

PO3-20-04

A first-in-human study of the highly selective PI3K α inhibitor RLY-5836 in patients with advanced breast cancer and other solid tumors

Presenting Author(s) and Co-Author(s):

- A. Varkaris. Massachusetts General Hospital, Boston, Massachusetts, United States
- S. Isakoff. Cancer Center, Massachusetts General Hospital, United States
- C. Perez. Sarah Cannon Research Institute (Florida Cancer Specialists),, United States
- B. O'Neil. 3Community Health Network/MD Anderson Cancer Center, Indianapolis, Illinois, United States
- E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States
- E. Conlin. Relay Therapeutics, United States
- G. Tan. Relay Therapeutics, United States
- X. Li. Relay Therapeutics, United States
- A. Timm. Relay Therapeutics, United States
- R. Samadani. Relay Therapeutics, United States
- E. Puente-Poushnejad. Relay Therapeutics, United States
- E. Kwak. Relay Therapeutics, United States
- B. Mar. Relay Therapeutics, United States
- A. Schram. Memorial Sloan Kettering Cancer Center, United States

Background: Oncogenic activation of PI3K α is a common driver event in solid tumors. Although PI3K α is a validated therapeutic target, there is no approved highly selective inhibitor that targets mutant PI3K α . Alpelisib, a non-selective orthosteric PI3K α inhibitor, is approved in combination with fulvestrant for patients with PIK3CA-mutant, ER+, HER2– advanced breast cancer. Inhibition of wild-type PI3K α causes hyperglycemia, limiting the tolerability, dosing, and efficacy of alpelisib. RLY-5836 is the second allosteric, selective pan-mutant PI3K α inhibitor under clinical investigation. It is molecularly distinct with differentiated pharmaceutical properties compared to RLY-2608. This first-in-human study aims to further explore the tolerability and efficacy of highly selective PIK3CA-mutant inhibition as monotherapy and in combination treatment.

Methods: This multicenter, open-label study is designed to evaluate the safety, maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), pharmacokinetics (PK) and preliminary anti-tumor efficacy of RLY-5836 as a single agent and in various combinations. A Bayesian Optimal Interval design is used for dose escalation, followed by a dose expansion part.

As monotherapy, RLY-5836 will be investigated in pts with advanced solid tumors harboring a PIK3CA mutation (Arm 1) per local assessment (blood and/or tumor). In pts with PIK3CA-mutant, HR+, HER2– advanced or metastatic breast cancer, RLY-5836 combination arms will include anti-estrogen therapy with or without CDK4/6 inhibition: fulvestrant (Arm 2), and fulvestrant + CDK4/6 inhibitor(s) (Arms 3–5).

RLY-5836 is administered orally, continuously in 28-day cycles until disease progression or study discontinuation.

Enrollment criteria include age ≥ 18 years, ECOG PS 0–1, and measurable disease (Arm 1) or evaluable disease (Arms 2–5) per RECIST version 1.1. Participants in the combination arms are required to have received prior treatment with ≥ 1 CDK4/6 inhibitor and ≥ 1 anti-estrogen therapy. Prior treatment with a PI3K α inhibitor is an exclusion criterion for the dose expansion parts of all arms.

Planned overall sample size is ~220 pts (~145 pts for the dose escalation, and ~15 pts in each dose expansion arm). Primary endpoints are the MTD, RP2D and overall safety profile of RLY-5836, either as a single agent or in combination. The MTD will be determined as the dose with a dose-limiting toxicity rate closest to the target toxicity rate (30%) in Cycle 1. Secondary endpoints include PK and efficacy parameters. Statistical analyses will be descriptive.

This study (NCT05759949) is enrolling in the United States. For further information, please contact clinicaltrials@relaytx.com.

Funding source: This study is funded by Relay Therapeutics, Cambridge, MA, United States.

PO3-20-05

Phase II Study of Genomically Guided Radiation Dose Personalization in the Management of Triple Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

K. Ahmed. H. Lee Moffitt Cancer Center, United States
I. Washington. Moffitt Cancer Center, United States
M. Mills. H. Lee Moffitt Cancer Center, United States
M. DeJesus. Moffitt Cancer Center, United States
Y. Kim. Moffitt Cancer Center, United States
R. Nanda. Moffitt Cancer Center, United States
J. Torres-Roca. Moffitt Cancer Center, United States
S. Eschrich. Moffitt Cancer Center, United States
J. De La Iglesia. Moffitt Cancer Center, United States
J. Puskas. Moffitt Cancer Center, United States
M. Rosa. Moffitt Cancer Center, United States
J. Wilson. BayCare, United States
P. Lundgren. BayCare, United States
N. Golesorkhi. BayCare, United States
N. Khakpour. Moffitt Cancer Center, United States
S. Hoover. Moffitt Cancer Center, United States
M. Lee. Moffitt Cancer Center, Tampa, Florida, United States
J. Kiluk. Moffitt Cancer Center, United States
M. Mallory. Moffitt Cancer Center, United States
C. Laronga. Moffitt Cancer Center, United States
L. Kruper. Moffitt Cancer Center, United States
B. Czerniecki. H. Lee Moffitt Cancer Center, United States
R. Diaz. Moffitt Cancer Center, United States

Background: Our group has previously developed the radiosensitivity index (RSI) using a multigene expression model that is directly proportional to tumor radioresistance (high RSI = increased radioresistance). RSI has been previously validated in two datasets of patients with triple negative breast cancer (TNBC). In this study, we will run a selective dose personalization study in TNBC patients undergoing breast conservation therapy (BCT). Based on patients RSI scores, they will either receive a radiation therapy (RT) boost of 10 Gy to the tumor cavity or not. Given our data in two independent datasets, the current study will reveal the feasibility and benefit of selective genomic dose personalization in TNBC following BCT. Trial Design: The study is designed as a prospective, nonrandomized, phase II trial of genomically guided RT in the management of TNBC undergoing BCT. Patients will be allocated to one of two groups based on their RSI determination from fresh frozen tissue collected by biopsy or at the time of BCT. These groups will be Group A, RSI optimized whole breast radiotherapy alone or with a 10 Gy boost or Group B, RSI not optimized whole breast radiotherapy with a boost of 10 Gy to tumor cavity. Patients will receive standard of care chemotherapy, neoadjuvant or adjuvant.

Eligibility: TNBC patients undergoing BCT. Specific Aims: To determine the three-year local control following genomically guided dose personalization in the management of TNBC following BCT. Secondary objectives include determination of overall survival (OS), progression free survival (PFS), and quality of life (QOL) following genomically guided dose personalization. Statistical Methods: The primary hypothesis is the three-year local control rates differ for groups A and B, against the null hypothesis that the two rates are identical. Patients will allocate approximately 78% in group A and 22% in group B and local control rates are expected to be 96% and 75%, respectively. Assuming 80% power and 10% type I error for a log-rank test, 86 patients are needed. An interim analysis will be completed when 4 disease progression events are observed. There will be approximately 43 patients at the time of interim analysis. Patient Accrual: This study is open with 1 patient enrolled at the time of submission. A total of 86 patients will be enrolled. Contact Information: Kamran A. Ahmed MD, Moffitt Cancer Center, email: kamran.ahmed@moffitt.org, Clinical trial information: NCT05115474. Funding: Moffitt and Morton Plant Mease Foundations.

PO3-20-06

TRUDI: A phase II study of neoadjuvant TRastuzumab derUxtecan and Durvalumab for stage III HER2-expressing Inflammatory breast cancer

Presenting Author(s) and Co-Author(s):

P. Tarantino. Breast Oncology Program, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

S. Niman. Dana-Farber Cancer Institute, United States

A. Giordano. Dana Farber Cancer Institute, Harvard University, Boston, MA, United States

F. Nakhlis. Dana-Farber Cancer Institute, United States

J. Bellon. DFCI/BWH, Boston, Massachusetts, United States

W. Woodward. UT MD Anderson Cancer Center, Houston, Texas, United States

A. Nasrazadani. Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Saleem. MD Anderson Cancer Institute, United States

A. Lucci. MD Anderson Cancer Center, Houston, Texas, United States

M. DeMeo. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Ueno. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

V. Valero. Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Bellaire, Texas, United States

M. Regan. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

R. Layman. The University of Texas MD Anderson Cancer Center, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Despite being a rare presentation of breast cancer, inflammatory breast cancer (IBC) is responsible for up to 10% of all breast cancer-related deaths. Most IBCs express HER2, with up to 40% of all IBCs being HER2-positive and 40% being HER2-low. Additionally, IBC more often exhibits PD-L1 expression compared to non-IBC, suggesting a preeminent role for immune evasion in the development and progression of IBC. No systemic treatment approaches have been yet developed specifically for IBC, and standard treatments commonly lead to poor outcomes. Trastuzumab deruxtecan (T-DXd) is an anti-HER2 antibody-drug conjugate currently approved for patients with pretreated HER2-positive and HER2-low metastatic breast cancer. Early-phase data highlighted the safety and potential synergy of combining T-DXd with the immune checkpoint inhibitor durvalumab. The aim of TRUDI is to evaluate the clinical activity and safety of neoadjuvant T-DXd with durvalumab among patients with HER2-expressing IBC. Trial Design: TRUDI is an ongoing, open label, multicenter, two cohort investigator-initiated phase II neoadjuvant trial for patients with stage III HER2-expressing IBC. The trial was activated in May 2023, with enrollment ongoing. Eligible participants are women and men with previously untreated, stage III (T4d, any N) breast cancer, clinically determined to be IBC. Patients will be included in two cohorts, depending on the locally determined HER2 status (with any hormone receptor [HR] status): Cohort 1 (n=36) for patients with HER2-positive disease (HER2 IHC 3+ or 2+/ISH amplified); Cohort 2 (n=27) for patients with HER2-low disease (HER2 IHC 1+ or 2+/ISH not amplified). Patients will receive eight cycles of T-DXd (5.4 mg/kg IV every 21 days) combined with durvalumab (1125 mg IV

every 21 days), followed by modified radical mastectomy and post-mastectomy radiation. Post-surgical systemic treatment will follow local standards. Tumor tissue will be collected at baseline, cycle 1 day 8, and at surgery; blood will be collected at baseline, cycle 4 day 1, cycle 7 day 1 and at surgery; stool will be collected at baseline, after 3-6 weeks of treatment and surgery. The primary endpoint is pathologic complete response (pCR; ypT0/Tis ypN0). Patients in each cohort will be enrolled based upon Simon two-stage designs: in Cohort 1, if $\geq 8/20$ patients with HER2-positive IBC experience pCR then a total of 36 patients will be enrolled. In Cohort 2, if $\geq 1/18$ patients with HER2-low IBC experience pCR then a total of 27 patients will be enrolled. Secondary endpoints include the residual cancer burden at surgery, event free survival, distant progression or distant disease-free survival, as well as safety of the regimen. Exploratory objectives will investigate biomarker analyses on tissue, blood, and microbiome to explore the association of HER2 expression, immune variables, and stool composition on the efficacy of T-DXd with durvalumab among patient with HER2-expressing IBC. To our knowledge, this is the first and only ongoing study testing the combination of an anti-HER2 antibody-drug conjugate with immunotherapy for the neoadjuvant treatment of patients with IBC. Clinical trial information: NCT05795101.

PO3-20-07

Five years and counting: A case of a 47-year-old female with De Novo Metastatic HER2 positive disease on multiple lines of treatment

Presenting Author(s) and Co-Author(s):

S. Unson. St. Luke's Medical Center, Pasig City, National Capital Region, Philippines

R. Li. St. Luke's Medical Center, Quezon, National Capital Region, Philippines

HER2-positive breast cancer refers to a specific subtype of breast cancer characterized by the overexpression or amplification of the human epidermal growth factor receptor 2 (HER2) protein on the surface of cancer cells. The overexpression of HER2 leads to increased signaling pathways that promote cell growth and division, making HER2-positive breast cancer inherently more aggressive compared to other subtypes. The aggressive behaviour of HER2-positive disease may be attributed to its rapid cell growth, high metastatic potential, and increased risk of recurrence. Fortunately, there are targeted therapies that specifically inhibit the HER2 protein. These targeted treatments help to block HER2 signaling, slow down tumor growth, and reduce the risk of recurrence. We report a case 47 year old premenoapausal Filipino female diagnosed with de-novo metastatic HER2-positive breast cancer with liver and lung metastasis in 2018. Advised Pertuzumab Trastuzumab and Taxane therapy but due to financial constraints was amenable only to Trastuzumab and Paclitaxel. During treatment noted symptomatic cardiac decline, hence shifted to Lapatinib & Capecitabine, tolerated well with stable disease for 1 year. Disease then progressed to the contralateral breast, given 6 cycles of Ado Trastuzumab Emtansine with partial response followed by modified radical mastectomy of the right and toilet total mastectomy of the left breast. She was lost to follow up. Her cancer recurred 1 year later as skin lesions on chest wall. She was given 6 cycles of Ado Trastuzumab Emtansine, however still with progression as skin lesions on the chest. Patient was then given 5 cycles of Trastuzumab with Eribulin. Despite treatment, there was progression with symptomatic brain metastasis and further increase in size and number of skin metastasis of the chest wall. Lesions were noted to be ulcerating and bleeding. Hence patient underwent 5 of 5 sessions of Fractionated stereotactic radiation therapy and 10 of 10 sessions of palliative radiotherapy to the chest wall. Patient was then given Pertuzumab & Trastuzumab with note of improvement of chest wall lesions. However, after 7 cycles of treatment, noted progression again as skin metastasis on the chest wall. Hence patient was shifted to Trastuzumab Deruxtecan. At the time of writing, the patient has had a good response with Fam-Trastuzumab Deruxtecan-nxki with partial resolution of her skin metastases on the chest with stable disease of lung and brain target lesions. No bleeding or ulcerations of the lesions and no recurrence of dizziness or imbalance reported. The patient will continue to receive Fam-Trastuzumab Deruxtecan-nxki until disease progression and/or unacceptable toxicity. Here we have a case of patient with extended survival after being fortunate to have received multiple lines of treatment for the disease. In this case we were able to apply the advances of research in HER2-positive breast cancer and see it in the clinical setting. Thus, ultimately translating to extended overall survival for the patient. We see the importance of continuous research on HER2-positive breast cancer disease and how these studies have helped us in overcoming treatment resistance, understanding disease progression, tailoring of therapies to individual patients, optimizing treatment outcomes, developing new therapies, and enhancing the quality of life for patient. Ongoing research continues to explore new therapeutic approaches and strategies to further improve outcomes for individuals with metastatic HER2-positive breast cancer. This is truly an exciting time for cancer research because what used to be a very deadly disease is now becoming something that we are able manage.

PO3-20-08

Case Studies on Detecting Ductal Carcinoma in Situ Using Contrast-Enhanced Spectral Mammography and Predictive Indicators for Underestimation

Presenting Author(s) and Co-Author(s):

M. Song. Asan Medical Center, Seoul, Republic of Korea

H. Shin. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Purpose: To introduce clinical cases of ductal carcinoma in situ (DCIS) underestimation focusing on additional benefits of contrast-enhanced spectral mammography (CESM).

Background: DCIS, a noninvasive breast cancer, is often underestimated during diagnosis. Predicting which cases will upgrade to invasive cancer is crucial. CESM offers superior diagnostic performance compared to mammography and mammography with targeted ultrasound (US). Its low-energy images improve microcalcification conspicuity, enable accurate tumor extent measurement, and provide information on enhancements associated with nonmass microcalcifications. Enhanced areas on CESM can be easily compared with mammographic microcalcifications, for they are obtained during the same session.

Indicators heralding DCIS underestimation

1. Detectability: underestimated DCIS is more likely to be detected on CESM and mammogram than pure DCIS, whereas detection rates do not statistically differ on US and MRI.
2. Lesion type: underestimated DCIS mostly presents as enhancing mass or nonmass lesions on CESM and calcifications on low-energy conventional mammography.
3. Disease extent: on CESM, pure DCIS show smaller tumor extent than the underestimated ones.
4. CESM gray value (CGV) of the lesion on recombined image: the pure DCIS types show lower mean, standard deviation, maximum, and difference values, whereas the underestimated types demonstrate lower minimum values, and vice versa.

Case 1: Screen detected pure DCIS without postsurgical upgrade in an asymptomatic 44-year-old woman. US-guided core biopsy yielded DCIS, intermediate nuclear grade with necrosis. Postsurgical pathology confirmed a 1.5 cm pure ductal carcinoma in situ, intermediate nuclear grade with necrosis.

(A) US shows a 1.3 cm irregular hypoechoic mass in the right breast. (B) Routine mammography demonstrates no definite abnormality in the right breast. (C) CESM shows a 1.2 cm irregular enhancing mass in the upper central portion of right breast and CGV was 2034 AU. (D) Contrast-enhanced MR images show a 2.1 cm irregular enhancing mass in 12 o'clock direction of the right breast.

Case 2: Screen detected DCIS with postsurgical upgrade to microinvasive ductal carcinoma in a 64-year-old woman with nonspecific discomfort in her right breast. US-guided core biopsy yielded DCIS, high nuclear grade with necrosis. Postsurgical pathology confirmed a 2.8 cm sized microinvasive ductal carcinoma, high nuclear grade, histologic grade 3 with necrosis.

(A) US demonstrates a 1.9 cm irregular hypoechoic mass with calcifications in 9 o'clock direction 2.1 cm from the nipple in the right breast. (B) Right magnification view shows a 2.5 cm-extent segmentally distributed fine pleomorphic calcifications in the right breast. (C) CEMM shows a 3 cm irregular enhancing mass with calcifications in the right breast, and CGV was 2045 AU. (D) Contrast-enhanced MR images shows a 2.3 cm irregular enhancing mass in the right breast.

Case 3: Screen detected DCIS with postsurgical upgrade to invasive ductal carcinoma with DCIS in a 47-year-old woman who had a family history of breast cancer. US-guided core biopsy yielded DCIS, intermediate nuclear grade with necrosis. Postsurgical pathology confirmed a 0.2 cm invasive ductal carcinoma with 2.4 cm DCIS.

(A) US demonstrates a 2.3 cm irregular hypoechoic mass in the left breast. (B) Routine mammography shows asymmetry in the upper portion of the left breast. (C) CEMM shows a 3 cm enhancing mass in the left breast, and CGV of the lesion on MLO-recombined image was 2072 AU. (D) Contrast-enhanced MR image shows a 6 cm irregular enhancing mass in the upper portion of the left breast.

Conclusion: CEMM provides added advantages over mammography and breast US in detecting underestimated DCIS, and it is comparable to breast MRI. Key indicators to consider include detectability, enhancing lesion, larger tumor extent, higher mean CGV on CEMM.

PO3-20-09

METACHRONOUS METAPLASTIC BREAST CARCINOMA IN A 55-YEAR-OLD PATIENT WITH SEROUS OVARIAN CARCINOMA

Presenting Author(s) and Co-Author(s):

R. Abella. St. Luke's Medical Center, Quezon City, National Capital Region, Philippines

C. Dy. St. Luke's Medical Center, Quezon City, National Capital Region, Philippines

Metaplastic breast carcinoma is a rare histologic subtype of breast carcinoma, accounting for only 0.2 to 2% of all breast cancers. It is comprised of a heterogeneous histology involving mesenchymal and epithelial components. Metaplastic breast carcinoma usually harbors a triple-negative phenotype, but carries a worse prognosis compared to other breast cancer subtypes. Due to its unique histopathological and molecular characteristics, there has been limited data on the optimal management of metaplastic breast carcinoma. Moreover, the presence of a secondary breast neoplasm in the background of a prior ovarian carcinoma represents a diagnostic and therapeutic challenge. We report a case of a 55-year-old female with a previous history of serous ovarian carcinoma six years ago, who presented with an enlarging right breast mass. Digital mammography showed a right retro-areolar mass, 5.7 x 4.8 x 5.4 cm, BIRADS 4C. Initial biopsy done showed presence of atypical cells in a background of cystic change. The patient underwent modified radical mastectomy with incision biopsy and frozen section. Final histopathologic diagnosis was consistent with metaplastic breast carcinoma, mixed epithelial and mesenchymal type, Nottingham grade 2, with no lymphovascular invasion identified, pT2N0. Tumor was ER negative, PR negative, Her 2 neu negative, with Ki-67 of 10% on immunohistochemistry. She then underwent adjuvant treatment with 6 cycles of paclitaxel and carboplatin. Six years prior, the patient was likewise diagnosed with high-grade serous ovarian carcinoma. She had total abdominal hysterectomy with bilateral salpingo-oophorectomy and adjuvant chemotherapy with 6 cycles of Paclitaxel and Carboplatin was given. She had recurrence in the paraaortic lymph node after 3 years and underwent cytoreductive surgery with excision of nodule and hyperthermic intraperitoneal chemotherapy with cisplatin. Currently, the patient has no evidence of disease in the recent positron emission tomography scan, with normal serum CA-125 level. The current standard of care for metaplastic breast carcinoma follows that of triple-negative breast cancer. However, previous literature has shown that metaplastic breast carcinoma is more chemo-refractory compared to triple-negative breast cancer, with more response seen with taxane-based chemotherapy. Due to poor response rates to neoadjuvant chemotherapy, surgical management for early-stage disease is warranted. Targeting molecular alterations is necessary to improve the prognosis of this subtype. Genomic features of homologous recombination deficiency were also found to be more prevalent in metaplastic breast cancer, thus genomic testing is warranted, especially in the setting of a prior history of ovarian carcinoma.

PO3-20-10

Case Series: Invasive Secretory Carcinoma

Presenting Author(s) and Co-Author(s):

L. Geisel. Orlando Regional Medical Center, United States

H. Venkatesh. Orlando Regional Medical Center, United States

A. Obermiller. Orlando Regional Medical Center, United States

Q. Chu. Orlando Regional Medical Center, United States

J. Gielow. Orlando Regional Medical Center, United States

D. Henry. Orlando Regional Medical Center, United States

Secretory variant invasive ductal carcinoma is not well described in the literature but is defined by its unique histopathology. These tumors stain positive for S100 and are typically triple negative hormonal cancers with an overall good prognosis. There is speculation that secretory carcinoma in adults is more aggressive with a greater likelihood for tumor recurrence. We present two case studies of this rare histopathologic diagnosis. First, a 76-year-old female with a recurrent secretory variant, invasive ductal carcinoma of the left breast. Second, a 68-year-old male who presented with invasive and in situ secretory carcinoma.

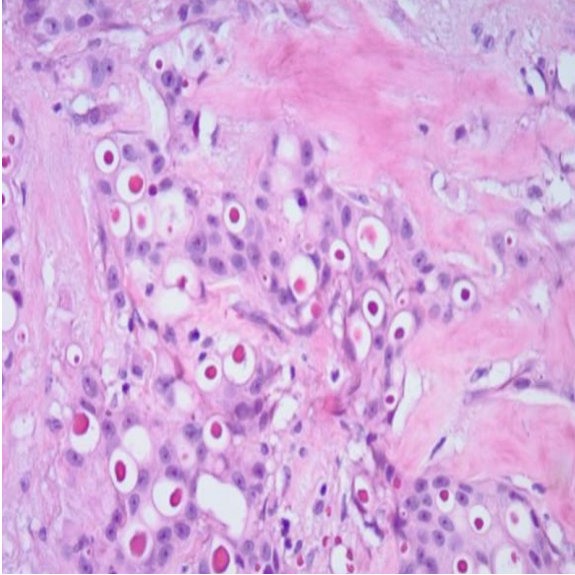
A thorough chart review of all available institutional and outside institution records was performed from initial diagnosis to current treatment. Background information and de-identified patient information was summarized for this case series.

This is a 76-year-old female who presented to her physician in 2011 with a palpable left breast and axillary mass. Her workup demonstrated ER+/PR+/HER2- invasive ductal carcinoma with lobular features of the left breast measuring 2.3 cm, along with a 1.5 cm malignant axillary lymph node. She underwent a left breast lumpectomy with axillary dissection. She underwent adjuvant whole breast radiation, axillary nodal radiation, and was placed on anastrozole therapy for 5 years. Seven years later a recurrence was noted in the superior aspect of the left breast. MRI guided biopsy revealed recurrent left breast cancer with pathology of invasive ductal carcinoma, secretory variant. She elected to undergo lumpectomy alone. Final pathology demonstrated invasive ductal carcinoma, secretory variant, ER negative (0%), PR negative (0%), HER2 negative (0%), pT1bNx. She underwent accelerated adjuvant partial breast radiation. Follow up and surveillance with bilateral breast MRI two years later demonstrated a new left breast mass, found to be triple negative, recurrent secretory variant invasive ductal carcinoma. She underwent definitive treatment with a left skin sparing mastectomy, right sentinel lymph node biopsy, and a latissimus dorsi flap with implant placement. Final pathology demonstrated multifocal recurrent secretory carcinoma, two foci measuring 6 and 11 mm.

Our second patient was a 68-year-old male who initially presented to the clinic for evaluation of a ventral incisional hernia. During his initial assessment, a palpable retro-areolar nodule was noted on physical exam. Subsequent mammography demonstrated a hypoechoic mass with irregular margins measuring 2.8 x 2.3 x 1.7 cm along with increased vascularity and calcifications. An ultrasound guided biopsy demonstrated invasive secretory carcinoma. Initial pathologic testing of the tumor demonstrated ER positive (5%), PR positive (1%), and HER2 negative. The patient was taken to the operating room for a total mastectomy with sentinel lymph node biopsy. His postoperative pathology demonstrated negative margins, and invasive secretory carcinoma with lymph nodes negative for metastatic disease.

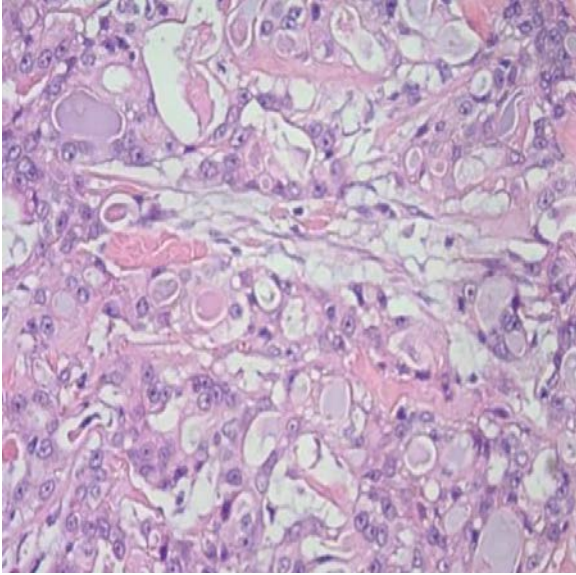
Secretory variant of invasive ductal carcinoma is rare and is determined by its unique immunohistochemical features. We present two cases of secretory carcinoma at our institution. Data suggests that local recurrence is common in patients with secretory breast cancer, occurring in 33-44% of cases. Ki-67 index has been used as a prognostic indicator for metastases and recurrence of disease. Current treatment regimens are diverse; however, surgery is favored as the primary method. This report shows that although indolent, multifocality and recurrence is plausible. Given the limited data on this subset of carcinoma, more investigation is warranted to describe the effectiveness of adjuvant treatment options.

Case 1



Histopathologic examination at 200x shows invasive carcinoma with dense eosinophilic secretory material. By immunohistochemistry, the cells are negative for ER (0%) and PR (0%) with a HER2Neu score of 0, supporting the diagnosis of invasive secretory carcinoma.

Case 2



Histopathologic examination at 200x shows invasive carcinoma with dense eosinophilic secretory material. The tumor cells are positive for CK5/6 (patchy), CD117, ER (focal and weakly), and S100; negative for p63 and calponin, supporting the diagnosis of invasive secretory carcinoma. NTRK3 gene rearrangement was detected on fluorescence in situ hybridization (FISH).

PO3-20-11

Among the < 0.1 percent of breast cancers: A case of adenoid cystic carcinoma

Presenting Author(s) and Co-Author(s):

S. Choi. Rush University Medical Center, United States

S. Keshwani. Rush University Medical Center, United States

A. Madrigrano. Rush University Medical Center, United States

Among the < 0.1 percent of breast cancers: A case of adenoid cystic carcinoma Sera Choi, B.A., Sarah Keshwani, M.D., Andrea Madrigrano, M.D. Introduction: Adenoid cystic carcinoma in the breast (ACCB) is a rare subtype of breast cancer that accounts for < 0.1% of all breast-related malignancies. The majority of ACCB cases in existing literature are comprised of estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor 2 negative, abbreviated as triple-negative breast cancer. Although most triple negative breast cancers are aggressive in nature and prognosis, ACCB is reported to be more indolent with a favorable outcome. This disparity raises the question of whether the treatment approach for ACCB should follow the well-established treatment plan for other triple negative breast cancers given its atypical characteristics. Furthermore, while adenoid cystic carcinoma of the salivary glands is a well-known type of head and neck cancer with established treatment guidelines, there is limited data for recommendations regarding treatment for ACCB. We report a pathologically confirmed case of ACCB and review the existing literature regarding treatment strategy and prognosis. Case: This case is of a 69-year-old female who presented with an abnormal screening mammogram with a core needle biopsy confirming ACCB in the left lower outer quadrant. The patient was asymptomatic with no palpable masses, nipple discharge, or skin changes of the breast. Biopsy revealed adenoid cystic carcinoma grade 2, classic type, with immunohistochemistry confirming estrogen-receptor negative, progesterone-receptor negative, and human epidermal growth factor-receptor negative. After a thorough discussion of the options, the patient elected for breast conserving therapy and sentinel lymph node biopsy. Tumor was resected with negative margins and two out of two lymph nodes were negative for metastasis. The patient was recommended whole breast adjuvant radiation therapy given the large tumor size of 4.8cm. Chemotherapy was not recommended due to data that largely supports local targeted therapy over systemic treatment in patients without metastatic ACCB. The patient is continuing with routine follow-up evaluations. Discussion: Currently, mainstay treatment comprises of surgical resection with lumpectomy or mastectomy, with or without nodal evaluation. Radiation therapy is seen as beneficial in reducing recurrence and prolonging disease-free survival in ACCB. There is ongoing debate regarding the role of chemotherapy in ACCB patients, as triple-negative breast cancers are typically treated with a systemic chemotherapy regimen. However, since ACCB has a more favorable prognosis, the role of chemotherapy remains uncertain. With lack of data on ACCB, treatment modalities should be evaluated on a case-by-case basis. Moreover, considering the scarcity of information concerning this particular subtype of breast cancer, it is advisable to discuss these patients within a multi-disciplinary tumor board setting to ensure patients receive the maximum benefit.

PO3-20-12

A Case Report on the Management of a Patient with Local Breast Cancer, BIA-ALCL and Radiation Induced Metastatic Angiosarcoma: A Multidisciplinary Approach

Presenting Author(s) and Co-Author(s):

L. Varanitskaya. MetroHealth, Cleveland, United States

S. Unlu. Cleveland Clinic Foundation Fairview Hospital, United States

C. Clemow. MetroHealth, Cleveland, United States

A Case Report on the Management of a Patient with Local Breast Cancer, BIA-ALCL and Radiation-Induced Metastatic Angiosarcoma: A Multidisciplinary Approach

Abstract: Breast cancer recurrence presents a complex challenge in clinical practice. We present the case of a 60-year-old female with a history of stage 2A right breast cancer diagnosed on 12/1/2013. The patient underwent bilateral mastectomy and adjuvant chemotherapy, followed by breast reconstruction. The patient subsequently developed asymmetric right breast swelling, which was biopsied and was positive for T lymphocyte markers CD30, CD43, CD45, CD4 and she was diagnosed with anaplastic large cell lymphoma in 12/14/2018, which was thought to be associated with her breast implants. In May 2022, a right chest wall mass was detected, which demonstrated growth and increased vascularity on imaging. A biopsy on 5/5/22 confirmed poorly differentiated carcinoma initially thought to be a secondary intraductal carcinoma of the breast, invading the chest wall by metastasis or direct extension, negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Further workup confirmed this mass to be angiosarcoma, most likely associated with the patient's prior radiation therapy.

The patient was started on neoadjuvant carboplatin/paclitaxel/pembrolizumab on 6/9/2022, and continued with Doxorubicin/Cyclophosphamide and pembrolizumab, which was completed on 11 November 2022. Imaging studies post-treatment showed a slightly smaller mass in the right mastectomy bed, indicating a partial response to treatment. However, a subsequent PET scan revealed a recurrence of breast cancer in the right chest wall. Considering the patient's history of prior radiation therapy and the inability to administer further radiation, the treatment plan was revised. She underwent reconstructive chest wall surgery on 1/4/2023, with complete resection and negative margins. She started on adjuvant pembrolizumab planned for one year, but the patient presented on 3/3/2023 with the growth of a chest wall mass and bleeding, consistent with progression. Liquid Tempus testing was obtained but negative for an actionable target. Options such as hyperthermia, enrollment to clinical trial, and re-irradiation were discussed, and the patient was restarted on weekly paclitaxel on 3/31/2023 due to a previous response. The patient had further local disease progression on 5/26/2023, and this regimen was stopped. The patient is planning to get Tempus testing on tumor tissue and start the next line palliative regimen with either doxorubicin or gentamicin and repeat re-irradiation if no response to these regimens.

This case report highlights the challenges in managing breast cancer therapy-induced adverse conditions with two secondary tumors, both associated with the patient's prior therapy. The importance of a multidisciplinary approach, including medical oncology, surgical oncology, radiation oncology, and sarcoma specialists, is emphasized. The use of molecular testing and consideration of clinical trials may provide additional treatment options. Further research and clinical trials are warranted to optimize the management of recurrent breast cancer with transformation to rare histological subtypes such as angiosarcoma.

PO3-22-02

Concurrent chemotherapy with adjuvant radiation for patients with high-risk locally advanced breast cancer: safety and outcomes

Presenting Author(s) and Co-Author(s):

L. Symonds. University of Washington School of Medicine, United States

S. Swenson. University of Washington, United States

M. Nguyen. University of Washington, United States

D. Hippe. University of Washington, United States

H. Linden. University of Washington, Fred Hutchison Cancer Center, Seattle, Washington, United States

J. Specht. Fred Hutch Cancer Center, University of Washington, Seattle, WA, United States

W. Gwin. University of Washington School of Medicine, United States

J. Kim. University of Washington, Department of Radiation Oncology, United States

Background: Patients with locally advanced breast cancer are at high risk for locoregional and distant recurrence and novel strategies are needed to enhance the efficacy of adjuvant radiation therapy. Selected chemotherapies act synergistically to safely radiosensitize residual disease to radiation therapy and may improve locoregional control when given concurrently. We report our institutional experience using concurrent chemotherapy with adjuvant radiotherapy for high-risk breast cancer patients. **Methods:** We conducted a retrospective study of breast cancer patients treated definitively with chemotherapy, surgery, and concurrent chemo-radiation (chemo-XRT) in the adjuvant setting between May 2006 and April 2019. The decision to combine chemotherapy with adjuvant conventionally fractionated radiation was based on provider discretion regarding patient's risk of recurrence. The primary outcome was risk of locoregional recurrence (LRR). Secondary outcomes included disease free survival (DFS), overall survival (OS), and toxicity. The cumulative incidence of local recurrence was estimated with distant recurrence and death as competing risks. DFS and OS was estimated using the Kaplan-Meier method. **Results:** A total of 42 patients met inclusion criteria; of these 35 (83%) patients were receiving treatment for their initial breast cancer diagnosis and 7 (17%) patients were receiving treatment for a locoregional recurrence. Of the 35 patients treated in the primary setting, the majority had stage III disease (91%). Twenty-nine patients (83%) received neoadjuvant chemotherapy (NAC) all of which had residual disease after NAC and 6 patients (17%) received upfront primary surgery. Overall median total radiation dose was 57 Gy (range 45-68 Gy) with a majority receiving comprehensive regional nodal irradiation (25, 60%). Chemotherapy agents used for chemo-XRT included capecitabine (29, 69%), paclitaxel (8, 19%), and cisplatin (5, 12%). Median follow-up was 5 years after surgery (range: 4 months-16 years). At 5 years, the cumulative risk of LRR was 7% (95% CI: 2-21%). DFS was 47% (95% CI: 34-65%) and OS was 56% (95% CI: 42-74%). Of note, there were multiple exceptional responders, with OS of 51% at 10 years and 45% at 15 years. Chemo-XRT was well tolerated with 7% grade 3 toxicity (dermatitis), no grade 4 toxicity, and no new toxicity signals observed. **Conclusions:** Concurrent chemo-XRT for breast cancer patients with high risk locally advanced disease was safe and well tolerated. Chemo-XRT showed promise as a method to decrease risk of locoregional recurrence: the studied patient population was at very high risk, but only 7% of patients had a locoregional recurrence at 5 years. Further prospective evaluation of concurrent chemo-XRT is needed.

Table 1. Patient characteristics and outcomes (N = 42)

Patient Characteristics	Median (IQR) or No. (%)
Age, years	50 (43 - 56)
Tumor grade	
1	3 (7%)
2	11 (26%)
3	28 (67%)
Tumor receptor status	
HR+, Her2-	26 (62%)
HR+, Her2+	3 (7%)
HR-, Her2+	3 (7%)
Triple negative	10 (24%)
Stage	
IIA	2 (5%)
IIB	1 (2%)
IIIA	10 (24%)
IIIB	6 (14%)
IIIC	16 (38%)
Recurrence	7 (17%)
Complete Pathologic Response after NAC	
Yes	30 (71%)
No	0 (0%)
N/A (Did not receive NAC)	12 (29%)
Adjuvant chemotherapy	
Capecitabine	29 (69%)
Cisplatin	5 (12%)
Paclitaxel	8 (19%)
Outcomes	Estimate (95% CI)
Risk of local recurrence	
5-years	7% (2, 21%)
10-years	10% (4, 26%)
Risk of distant recurrence	
5-years	46% (33, 64%)
10-years	55% (41, 74%)
Disease-free-survival	
5-years	47% (34, 65%)
10-years	35% (22, 54%)
Overall survival	
5-years	56% (42, 74%)
10-years	51% (37, 69%)

PO3-22-03

Effect of Radiation Therapy on Survival Outcomes in Elderly ER/PR Positive AJCC Stage T1 Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

R. Shi. LSU Health Shreveport, Shreveport, Louisiana, United States

G. Burton. LSU Health shreveport, United States

Background: The CALGB 9343 study in 2004 reported that women >70 years of age with pT1NO hormone receptor positive breast cancer received no meaningful benefit from breast irradiation following lumpectomy. The effectiveness of adjuvant radiation therapy in node negative, T1 tumor patients has been limited to institutional experiences with relatively lack of information in population-based studies. In this hospital-based study using National Cancer Data Base (NCDB) from 2004 to 2020, we report on adjuvant radiation therapy (XRT) usage and the survival outcomes in stage IA, IB, IC breast cancer patients who received XRT versus those who did not. Materials and Methods: Patients in the National Cancer Database (NCDB) who were registered between 2004 and 2019 and followed up to the end of 2020 were used in this research. We evaluated a cohort of 126,156 female breast cancer patients of age \geq 70 years with the American Joint Committee on Cancer (AJCC) stage T1A, T1B, and T1C. All patients were ER/PR positive, received hormonal therapy, all patients were either white or black, were either privately or Medicare insured, received hormonal therapy, and patients were receipt of adjuvant chemotherapy or not. Radiation statuses were grouped as no radiation, radiation only and/or radiation with boost. Other adjusted variables included: age, race, Charlson comorbidity index, payer status, income, education, distance traveled, diagnosing/treating facility, location of treatment and treatment delay. SAS for Windows 9.4 was used for all data management and statistical analysis. Multivariate Cox regression was used to assess the effect of the XRT on overall survival while adjusting for other factors. All p-values $<$ 0.05 or 95% Confidence Limits of Hazards Ratio (HR) does not include 1 were considered statistically significant. Results: Among 126,156 female breast cancer patients, the age distribution was 47.87%, 31.72%, and 20.4% for age group of 70-74, 75-79, 80 or older, respectively. Ninety-three percent of patients were white. 89% of patients were Medicare and 11% were privately insured at diagnosis. 21% of patient were with the Charlson Comorbidity index score 1 or above. 10.77%, 34.42% and 54.81% of patients were AJCC Stage T1A, T1B, and T1C respectively. 11.7% of patients received chemotherapy and 57.9% of patients received radiation therapy. 54.38%, 59.59%, and 57.59% of T1a, T1b, and T1c patients received the XRT, respectively. In univariate analysis, the XRT demonstrated a statistically significant increase of 10-year survival by 9.75%, 9.8%, and 12.6% in T1a, T1b, and T1c (all p $<$ 0.0001) patients respectfully.

In multivariate cox regression analysis, age was a predictor of survival outcome with a HR at 1.65, 3.02 for 75-79, and 80 or older as compared to 70-74 years old, respectively. In addition, compared to patients who traveled less than 20 miles, the HR were 0.90 for patients travelled more than 20 miles. AJCC stage was also associated the survival, a HR of 1.05 (95% CI: 1.01-1.186) for T1b, 1.16 (95% CI: 1.11 – 1.21) for T1c as compared for T1a. Adjusting for other factors, the usage of radiation reduced the risk of dying by 25% (HR=0.75, 95% CI: 0.73-0.77) when compared to no radiation therapy.

Conclusion: The current study has demonstrated that more than 54% of these patients received radiation therapy. In univariate analysis, the benefit of adjuvant radiation therapy is more than 9.7% for T1a, T1b, and T1c on 10-year overall survival which is statistically significant.

Adjusting for other factors, patients receiving radiation therapy in these elderly population have a 25% less chance of dying as compared to no radiation therapy regardless of AJCC Stage. A further propensity score matching method would help assess the effectiveness of radiation therapy on these patients' population. A randomized prospective clinical trial would be better to define the precise benefit of adjuvant radiation therapy in this elderly population.

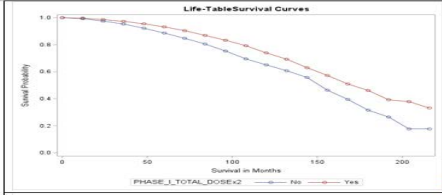
Table 1 Patients Demographic, Social Economic and Clinical Characteristics

Factor Level	Frequency	Percent
Age groups		
70-74	60395	47.87
75-79	40022	31.72
80+	25739	20.44
Race		
White	118212	93.7
Black	7944	6.3
INSURANCE STATUS		
Private	13636	10.81
Medicare	112520	89.19
MED_INC_QUAR_00		
< \$30,000	10288	9.45
\$30,000-\$34,999	18062	16.59
\$35,000-\$45,999	31029	28.49
>= \$46,000	49518	45.47
NO_HSD_QUAR_00		
>= 29%	12686	11.65
20-28.9%	22201	20.39
14-19.9%	27085	24.87
< 14%	46921	43.09
Urban Rural Status		
Metro	102987	83.5
Urban	20345	16.5
Distance Travelled to Care Site		
0-19 Miles	88426	79.05
20+ Miles	23438	20.95
Charlson Deyo Score Index		
0	99273	78.69
>=1	26883	21.31
FACILITY TYPE		
Community Cancer Program	10280	8.15
Comprehensive Community Cancer Program	57440	45.53
Academic/Research Program	30145	23.9
Integrated Network Cancer Program	28291	22.43
FACILITY LOCATION_CD		
New England	8238	6.53
Middle Atlantic	20146	15.97
South Atlantic	28139	22.3
East North Central	24381	19.33
East South Central	7524	5.96
West North Central	10973	8.7
West South Central	7532	5.97
Mountain	5485	4.35
Pacific	13738	10.89
TNM Pathological Tumor		
pT_1A	13389	10.77
pT_1B	43417	34.42
pT_1C	69150	54.81
Chemotherapy		
No	111322	88.24
Yes	14834	11.76
Radiation Therapy		
No	30098	42.07
Yes	68983	57.93
Treatment Start Days from Diagnosis		
0-29 days	69381	55.51
30+ days	55600	44.49

Table 3 Hazard Ratios estimate from Multivariate Cox Regression

Parameter	Hazard Ratio	95% HR Confidence Limits		P-Values
		Lower	Upper	
Age groups				
70-74	1.000			
75-79	1.642	1.693	1.692	<.0001
80+	3.022	2.931	3.115	<.0001
Race				
White	1.000			
Black	1.001	0.950	1.054	0.9784
INSURANCE STATUS				
Private	1.000			
Medicare	1.066	1.024	1.110	0.0021
MED_INC_QUAR_00				
< \$46,000	1.000			
\$30,000-\$34,999	1.135	1.087	1.185	<.0001
\$35,000-\$45,999	1.097	1.060	1.134	<.0001
>= \$30,000	1.182	1.118	1.249	<.0001
NO_HSD_QUAR_00				
< 14%	1.000			
14-19.9%	1.088	1.052	1.126	<.0001
20-28.9%	1.098	1.055	1.142	<.0001
>= 29%	1.073	1.018	1.130	0.0081
Urban Rural Status				
Metro	1.000			
Urban	1.025	0.985	1.066	0.2199
Distance Travelled to Care Site				
0-19 Miles	1.000			
20+ Miles	0.808	0.871	0.939	<.0001
FACILITY TYPE				
Academic/Research Program	1.000			
Community Cancer Program	1.258	1.197	1.323	<.0001
Comprehensive Community Cancer Program	1.168	1.129	1.208	<.0001
Integrated Network Cancer Program	1.126	1.083	1.170	<.0001
FACILITY LOCATION_CD				
New England	1.000			
East North Central	0.956	0.907	1.008	0.0978
East South Central	0.985	0.921	1.054	0.6655
Middle Atlantic	0.890	0.842	0.940	<.0001
Mountain	0.898	0.829	0.972	0.0081
Pacific	0.824	0.777	0.874	<.0001
South Atlantic	0.917	0.870	0.967	0.0014
West North Central	0.930	0.875	0.988	0.019
West South Central	0.828	0.772	0.889	<.0001
TNM Pathological Tumor				
pT_1A	1.000			
pT_1B	1.063	1.006	1.102	0.0268
pT_1C	1.189	1.110	1.211	<.0001
Charlson Deyo Score Index				
0	1.000			
>=1	1.628	1.581	1.670	<.0001
Treatment Start Days from Diagnosis				
0-29 days	1.000			
30+ days	0.938	0.915	0.962	<.0001
Chemotherapy				
No	1.000			
Yes	1.126	1.084	1.169	<.0001
Radiation Therapy				
No	1.000			
Yes	0.753	0.734	0.772	<.0001

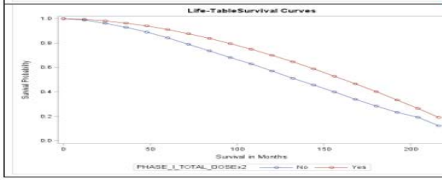
Radiation Effect on Overall Survival of Elderly Breast Cancer Patients by Stage T1A, T1B, T1C



T1A



T1B



T1C

PO3-22-04

PMRT Decision with low prediction of genomic test score in pT3N0M0 luminal breast cancer: Protocol MF22-02: International multicenter real-world data

Presenting Author(s) and Co-Author(s):

A. Soran. UPMC Department of Surgery, Breast Health Working Group International, United States

C. King. University of Pittsburgh, Medical Center Magee-Womens Hospital, Surgical Oncology, Pittsburgh, Pennsylvania, United States

P. Barry. University of Pittsburgh, Medical Center Magee-Womens Hospital, Radiation Oncology, Pittsburgh, Pennsylvania, United States

R. Bhargava. UPMC Magee-Womens Hospital, United States

H. Karanlik. Istanbul University Institute of Oncology, Surgical Oncology, Istanbul, Turkey

M. Gultekin. Hacettepe University, Medical Faculty, Radiation Oncology, Ankara, Turkey

F. Yildiz. Hacettepe University, Medical Faculty, Radiation Oncology, Ankara, Turkey

A. Soyder. Acibadem University, Faculty of Medicine, Department of Surgery, Turkey

B. GOKTEPE. Ege University, Medical Faculty, Department of General Surgery, Izmir, Turkey

K. Senol. Uludag University, Medical Faculty, General Surgery, Bursa, Turkey

C. Guzel. Gazi University, Medical Faculty, Radiation Oncology, Ankara, Turkey

E. Sen Oran. Basaksehir State Hospital, Department of Surgery, Istanbul, Turkey

L. Yeniay. Ege University, Faculty of Medicine, Department of Surgery, Izmir, Turkey

A. Dağ. Mersin University, Faculty of Medicine, Department of Surgery, Turkey

S. Emiroglu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey

D. Trabulus. Bahcesehir University, Department of Surgery, Turkey

A. Coskun. Uludag University, Medical Faculty, Medical Oncology, Bursa, Turkey

N. Cabioglu. Istanbul University, Medical Faculty, General Surgery, Istanbul, Turkey

H. Veliyeva. Azerbaijan Medical University Oncology Clinic, Surgical Oncology, Baki, Azerbaijan

N. Utkan. Kocaeli University, Faculty of Medicine, Department of Surgery, Turkey

B. DEMIRORS. Bursa Yuksek Ihtisas Training and Research Hospital, General Surgery, Bursa, Turkey

E. Sezgin. Breast Health Working Group International, United States

J. Vargo. University of Pittsburgh, Medical Center Magee-Womens Hospital, Radiation Oncology, Pittsburgh, Pennsylvania, United States

Background: In current guidelines, there is no definite recommendation regarding postmastectomy radiation therapy (PMRT) in patients with luminal pT3N0M0 breast cancer (BC). The goal of this study is to determine whether PMRT could be safely omitted for a specific subgroup of those patients. Methods and Materials: There were 202 women from 16 centers with pT3N0M0 hormone receptor (HR) positive, Her2 neu (-) BC who underwent mastectomy, were analyzed retrospectively. None of the patients received neoadjuvant chemotherapy. Three patients were excluded because of positive surgical margins. The patients were divided into two groups, PMRT (+) (n=130) and PMRT (-) (n=69). Groups were compared in terms of overall

survival, loco-regional recurrence rate, and distant metastases regarding Magee score (MS) (< 18 are considered low risk) (<https://path.upmc.edu/onlineTools/mageeequations.html>), menopausal status, axillary surgery, pathology, lymphovascular invasion (LVI), adjuvant chemotherapy, and adjuvant endocrine therapy. Results: The majority of the patients had invasive ductal carcinoma (49%, n=98). There was no significant difference regarding tumor size, axillary surgery, and adjuvant endocrine therapy between the two groups (p=0.82, p=0.28, p=0.12, respectively). LVI was 49% (n=98) and it was greater in PMRT (+) group (25% vs. 10%; p=0.01). PMRT (+) patients received more chemotherapy (66% vs. 30%; p< 0.001), had more grade 3 tumors (28% vs. 9%, p=0.005), and more premenopausal (49% vs. 22%; p=0.0001). At a median follow-up of 51.3 months for the PMRT (-) group and 65.9 months for the PMRT (+) group (p=0.041), 9% (n=6) of patients from the PMRT (-) group and 2% (n=3) from the PMRT (+) group developed locoregional recurrence (LRR) (p=0.047). There was no difference in local recurrence (1% in PMRT (-) group vs. 2% in PMRT (+); p=0.7) and distant recurrence (7% in PMRT (-) group vs. 3% in PMRT (+); p=0.16) between patients who received PMRT and not had PMRT. Further comparison of the LRR in the PMRT (-) and PMRT (+) groups in patients with an MS < 18 did not show a significant difference (3% vs. 4%; p=0.64). However, among patients with a Magee score ≥ 18 , the PMRT (-) group had a higher LRR rate compared to the PMRT (+) group (11% vs. 2%; p=0.01). In patients with an MS ≥ 18 , the administration of PMRT correlates with statistically significantly better LRR-free survival (HR 0.19; 95%CI 0.05 – 0.79; p=0.02). Conclusions: Our findings imply that when considering PMRT for BC with pT3N0M0, HR (+), and Her2 neu (-), clinicians can benefit from a combination of pathological risk factors and recurrence prediction models. Patients with MS < 18 receiving PMRT or not appear to experience a comparable rate of recurrence.

PO3-22-05

Investigating HER2-low tumors from a locoregional perspective- a secondary analysis of a randomized radiotherapy trial

Presenting Author(s) and Co-Author(s):

P. Karlsson. Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, United States

A. Kovács. Department of Clinical Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden, Vastra Gotaland, Sweden

F. Killander. Lund University, Skane Lan, Sweden

E. Niméus. Lund University, Skane Lan, Sweden

E. Holmberg. Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, United States

A. Stenmark Tullberg. University of Gothenburg, Sweden

Background: With the introduction of antibody-drug conjugates directed against HER2, a new subgroup of tumors with low HER2 expression (1+ or 2+ without amplification) has emerged. HER2 signaling has been implicated in radioresistance in mechanistic studies and is an accepted biomarker of immunogenicity. The study aimed to contrast tumors with low HER2 expression versus zero HER2 expression from a prognostic and radiotherapy-predictive locoregional perspective. **Methods:** HER2 status was evaluated using immunohistochemistry and SISH in the randomized radiotherapy (RT) cohort, SweBCG91RT, by a board-certified pathologist. HER2-low status was defined as HER2 IHC 1+ or 2+ without amplification, HER2-zero as 0, and HER2-high as HER2 IHC 3+ or SISH amplified. Tumor-infiltrating lymphocytes were assessed on whole-tissue sections and categorized as low (< 10%) or high (≥ 10%). The endpoint was time to ipsilateral breast tumor recurrence (IBTR) as first event. **Results:** Out of 964 evaluated primary tumors, 433 (44.9%) were classified as HER2-low, 467 (48.4%) as HER2-zero and 64 (6.6%) as HER2-high. TILs levels did not differ between HER2-low and HER2-zero tumors (p=0.33). The hazard ratio for high TILs was 0.79 in HER2-zero tumor (CI 95% 0.43-1.45, p=0.44) and 0.96 in HER2-low tumor (CI 95% 0.56-1.66, p=0.90), and no interaction effect from TILs was observed (p=0.63). The benefit from RT was similar among HER2-low (HR 0.42, CI 95% 0.25-0.72, p=0.001) and HER2-zero tumors (HR 0.31, CI 95% 0.17-0.56, p< 0.001). **Conclusions:** HER2-low tumors do not differ from HER2-zero tumors regarding the benefit from postoperative RT. Unlike high HER2 expression, low expression is not associated with TILs infiltration. HER2-low tumors likely do not represent a biologically distinct subtype from a locoregional aspect.

PO3-22-06

Safety and efficacy of trastuzumab deruxtecan and concomitant radiation therapy in patients with metastatic HER2-positive breast cancer

Presenting Author(s) and Co-Author(s):

L. Visani. Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
C. Becherini. Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
N. Bertini. University of Florence, Florence, Italy
I. Bonaparte. University of Florence, Florence, Italy
L. Burchini. University of Florence, Florence, Italy
C. Orsatti. University of Florence, Florence, Italy
M. Valzano. University of Florence, Florence, Italy
M. Banini. University of Florence, Florence, Italy
V. Salvestrini. Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
E. Scoccimarro. Florence University Hospital, United States
V. Scotti. Florence University Hospital, United States
I. Desideri. Florence University Hospital and Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, United States
G. Francolini. Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
L. Orzalesi. University of Florence, United States
M. Bernini. Florence University Hospital, United States
C. Tommasi. Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
J. Nori. Florence University Hospital, United States
S. Bianchi. University of Florence, United States
I. Meattini. University of Florence, Florence, Toscana, Italy
L. Livi. Florence University Hospital and Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, United States

Background

Trastuzumab deruxtecan (T-DXd) currently represents the standard of care for the treatment of patients with metastatic HER2-positive (HER2+) breast cancer (BC) after disease progression in the first line, which includes taxanes and trastuzumab. This recommendation is based on the results of the DESTINY-Breast03 trial, which demonstrated improved efficacy compared to trastuzumab emtansine (T-DM1). Radiation therapy (RT) is frequently required in the metastatic setting, either for palliative purposes or with ablative intent in cases of oligometastatic or oligoprogressive disease. The aim of our study is to evaluate the safety of using T-DXd and concomitant radiation therapy (RT) in a consecutive series of HER2+ BC patients.

Methods

We conducted a retrospective evaluation of patients diagnosed with metastatic HER2+ BC who initiated treatment with T-DXd between May 2021 and May 2023 at our institution, with or without receiving RT. We collected clinical data pertaining to the diagnosis of metastatic disease, T-DXd treatment, acute toxicities, survival data, and biological characteristics of both the primary tumor and metastases. The primary objective of this study was to assess the

association between RT and any adverse events greater than grade (G) 2.

Results

We retrospectively evaluated data from 30 consecutive patients who were treated with T-DXd, with or without RT. Among these patients, ten received RT either immediately before (within a month) or during T-DXd treatment, while the remaining 20 did not. The median age of the patients was 72 years (range 34-88), and the median follow-up period was 9 months. Thirteen patients received T-DXd as the fourth or subsequent line of systemic anti-HER2 treatment, eight patients received it as the third line, and seven patients received it as the second line. Two patients, who experienced early metastatic disease relapse (< 6 months after completion of adjuvant anti-HER2 therapy), received T-DXd as their first-line treatment. The median prescribed total dose of RT was 34 Gy (range 20-48), with a median number of fractions of 4 (range 2-10). The median equivalent dose in 2 Gy fractions (EQD2) was 64 Gy (range 23.3-104), and the median biologically effective dose (BED) was 76 Gy (range 28-125). The most commonly treated sites were bone (70% of cases), followed by brain (20%) and liver (10%). A chi-square test of independence was conducted to examine the relationship between the administration of RT and the development of toxicity exceeding G2. However, this analysis did not reveal a significant relationship ($p = .27$). Regarding the specific toxicities of interest associated with T-DXd, three cases of grade 3 fatigue were reported in the group that did not receive RT, while one case was observed in the RT group. Overall, only one case of grade 3 nausea was reported, and it occurred in the group that did not receive RT. G2 interstitial lung disease, which led to discontinuation of T-DXd, was observed in one case in the RT group and one case in the no-RT group.

Conclusions

Our initial data is promising regarding the potential safety of this combination, as it indicates that concurrent RT did not lead to an increase in severe acute toxicity. However, larger series of data are required to validate and confirm these findings.

PO3-22-08

Impact of Zip Code-Based Income on Reconstructive Method and Outcomes in Mutation-Positive Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

J. Gupta. Georgetown Univ SOM, United States

S. Sortur. Georgetown Univ SOM, United States

C. Lava. MedStar Georgetown University Hospital, United States

M. Lee. Georgetown University, United States

L. Berger. MedStar Georgetown University Hospital, United States

V. Harish. Georgetown University, United States

D. Spoer. MedStar Georgetown University Hospital, United States

L. Rosal. MedStar Georgetown University Hospital, United States

I. Greenwalt. MedStar Georgetown University Hospital, United States

L. De La Cruz. Medstar Georgetown University Hospital, Department of Breast Surgery, United States

D. Song. Georgetown University, United States

K. Fan. Georgetown University, United States

Background: In the United States, 13% of women develop invasive breast cancer, with certain genetic mutations increasing the risk. Genetic screening is costly and burdensome for patients, particularly those from lower socioeconomic backgrounds. Moreover, lower income (LI) patients face barriers in accessing healthcare and have lower rates of breast reconstruction. This study aims to examine the impact of socioeconomic status, as indicated by ZIP code median income, on the type of breast surgery, reconstructive technique, and perioperative outcomes among mutation-positive (M+) patients.

Methods: A multicenter retrospective cohort study included patients with a genetic predisposition for breast cancer and undergoing breast and reconstructive surgery between January 2016 and October 2022. Patient demographics, history, operative details, and postoperative outcomes were collected. Patient ZIP codes were cross-referenced with the American Community Survey to determine the median household income, which served as a proxy for the patient-specific household income. Four distinct income quartiles were established: quartile 1 (Q1) = \$37,045-\$81,586 ("LI"); quartile 2 (Q2) = \$81,587-\$103,703; quartile 3 (Q3) = \$103,704-\$129,768; and quartile 4 (Q4) = \$129,769-\$213,724.

Results: Among the 170 patients analyzed, 42 (24.7%) were in Q1, 42 (24.7%) in Q2, 44 (25.9%) in Q3, and 42 (24.7%) in Q4. Most patients had BRCA1 (n=73, 42.9%), BRCA2 (n=68, 40.0%), PALB2 (n=11, 6.5%), or CHEK2 (n=8, 64.7%) mutations, and underwent prophylactic mastectomy without evidence of breast cancer (n=119, 70.0%). Mean age and body mass index (BMI) were 41±16 years and 25.0±7.5 kg/m², respectively. There was a significant association between patient race and income (p< 0.0001), such that 30.1% of White patients were in Q4 (vs. 8.3% of Black patients), compared to 38.9% of Black patients in Q1 (vs. 19.0% of White patients). LI was significantly associated with higher BMI (p=0.0083) and obesity rates (p=0.0080). Nipple-sparing mastectomy (NSM) (n=103, 60.6%) was the most frequent surgical approach, followed by skin-sparing mastectomy (SSM) (n=42, 24.7%), simple mastectomy (n=13, 7.6%), lumpectomy (n=4, 2.4%), and radical mastectomy (n=4, 2.4%). Patients in Q3

underwent NSM significantly more often than those in Q1 ($p=0.0080$). Tissue expander ($n=73$, 42.9%) was the most common reconstruction method. 34.7% of patients ($n=59$) experienced postoperative complications. Short-term (< 30 days postoperatively) complications included delayed wound healing ($n=22$, 12.9%), surgical site infection ($n=16$, 9.4%), dehiscence ($n=12$, 7.1%), cellulitis ($n=10$, 5.9%), seroma ($n=9$, 5.3%) and hematoma ($n=9$, 4.7%). Long term (≥ 30 days postoperatively) complications included mastectomy flap necrosis ($n=22$, 12.9%), total reconstructive failure ($n=8$, 4.7%), and red breast syndrome ($n=2$, 1.2%). There was no significant association between income level and incidence of complications ($p > 0.05$). Income level significantly correlated with cancer recurrence, as patients in Q2 ($n=0$, 0.0%) and Q4 ($n=1$, 2.4%) had significantly lower recurrence rates compared to Q1 ($n=6$, 14.3%) ($p=0.0140$). Of the 30.0% of patients with diagnosis of cancer at DOS, 66.7% ($n=34$) of patients had ductal carcinoma in situ (DCIS). Eleven of these patients were in Q1, five in Q2, six in Q3, and twelve in Q4 ($p=0.259$).

Conclusion: LI M+ patients had lower NSM rates than higher income patients, despite similar rates of prophylactic mastectomies, possibly due to perceived costs of increased follow-up care. Moreover, LI patients experienced higher cancer recurrence, despite similar incidences of equivalent cancer subtypes at presentation, likely reflecting differences in post-diagnostic care and morbidity. These findings highlight the need to address financial barriers and ensure equitable access to comprehensive care for M+ patients of all income strata.

PO3-22-09

Implementation of nanoparticle-assisted axillary staging: reduced axillary intervention for patients with node-positive breast cancer following neoadjuvant therapy

Presenting Author(s) and Co-Author(s):

R. Chen. Department of General Surgery, West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

T. He. Department of General Surgery, West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

J. Yang. Department of General Surgery, West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

S. Lu. Department of General Surgery, West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

Y. Wu. West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

C. Wu. Department of Breast Surgery, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, 610041, China, United States

R. Yang. Department of General Surgery, West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

W. Liu. Department of General Surgery, West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

Y. Huang. West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

X. Meng. Department of General Surgery, West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

X. Zhao. Department of General Surgery, West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

Q. Li. Departments of Obstetrics & Gynecology and Pediatrics, West China Second University Hospital, Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, Development and Related Diseases of Women and Children Key Laboratory of Sichuan Province, Sichuan University, Chengdu 610041, China, United States

X. Sun. Chinese Evidence-based Medicine Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

J. Jing. Institutes for Breast Health Medicine, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

J. Chen. Department of General Surgery, West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

Background: Nanoparticle-assisted axillary staging (NAAS), which combines carbon nanoparticles with standard dual-tracer (radioisotope and blue dye) sentinel lymph node biopsy (SLNB), has shown excellent results in patients undergoing neoadjuvant therapy (NAC) for pre-NAC node-positive breast cancer. This pilot study aimed to explore the possible expansion of indications (pre-NAC cN2, and cN3 stages; ycN+ stage) for NAAS, which was the first attempt till now for patients undergoing NAC, and to select specific post-NAC individuals who might be exempt from axillary lymph node dissection (ALND), especially those with relatively low tumor burdens, such as ITCs and micrometastases. **Method:** The medical records of all consecutive patients with breast cancer were prospectively collected from the Breast Center, West China Hospital. Patients with invasive, pre-NAC node-positive breast cancer who underwent NAAS followed by ALND between April 2021 and February 2023 were included. The detection rate (DR), average number of sentinel or NAAS nodes, false negative rate (FNR), negative predictive value (NPV), and NAAS accuracy were assessed. Subgroup analyses according to different pre- and post-NAC cN stages, especially the pre-NAC cN2-3 stages and the post-NAC cN+ stages, which were not the focus of previous studies, were conducted using crosstabs. To screen possible patients who might exempt ALND, we focus on relationships between the status of axillary lymph nodes and the number or tumor burden of NAAS nodes. **Results:** A total of 241 eligible patients were included in the study. There were 153 (63.49%), 40 (16.60%), and 48 (19.92%) patients in pre-NAC cN1, cN2, and cN3 stages, respectively. The post-NAC stages of patients were not restricted, 38.17% (92/241) of them converted to ycN0 stages, while 61.83% (149/241) were still in ycN+ stages. A total of 232 (96.27%) eligible patients successfully underwent NAAS; the DR, NPV, accuracy, and FNR of NAAS were 96.27%, 95.97%, 97.84%, and 4.42%, respectively. Additionally, NAAS showed accuracies of 97.30% and 93.02% and FNRs of 7.14% and 9.09% in patients with pre-NAC cN2 and cN3 breast cancers, respectively. There was no statistical difference among the FNRs of NAAS in the pre-NAC cN1, cN2, and cN3 stages ($p=0.134$). Moreover, NAAS yielded FNRs of 0.00% in the ycN0 population and 6.02% in the ycN+ population, respectively ($p=0.323$). Accuracies reached 100.00% and 96.48% in ycN0 and ycN+ patients, respectively ($p=0.159$). Notably, patients with one NAAS node with ITC or micrometastasis in the entire population showed no further positive disease at ALND. **Conclusion:** NAAS showed excellent and stable performance with a low FNR and high accuracy, indicating valuable application prospects in patients with breast cancer who received NAC. Patients with pre-NAC cN2-3 stages also have a chance to undergo NAAS, and the application of NAAS appears to be feasible regardless of the ycN stage. Especially for ycN0 population, there is no chance for NAAS to miss positive axillary lymph nodes. In addition, patients who had one NAAS node with ITC or micrometastasis might avoid ALND.

Diagnostic performance of nanoparticle-assisted axillary staging in pre-neoadjuvant chemotherapy cN1, cN2 and cN3 patients

Method of lymphatic mapping	Pre-NAC cN1 (N=153)	Pre-NAC cN2 (N=40)	Pre-NAC cN3 (N=48)	p-value
SD-SLNB				
DR (%)	97.38	90.00	72.92	<0.001
Average number of sentinel or NAAS nodes detected (mean±SD)	3.44±1.67	3.49±1.76	2.62±2.39	0.023
FNR (%)	6.35	14.29	15.39	0.260
NPV (%)	95.56	91.67	69.23	0.016
Accuracy (%)	97.32	94.44	88.57	0.044
NAAS				
DR (%)	99.35	92.50	89.58	0.002
Average number of sentinel or NAAS nodes detected (mean±SD)	4.82±1.93	4.53±2.17	3.77±2.29	0.009
FNR (%)	1.52	7.14	9.09	0.134
NPV (%)	98.85	95.83	76.92	0.006
Accuracy (%)	99.34	97.30	93.02	0.032

NAC: neoadjuvant chemotherapy; SD-SLNB: standard dual-tracer sentinel lymph node biopsy; DR: detection rate; NAAS: nanoparticle-assisted axillary staging; SD: standard deviation; FNR: false negative rate; NPV: negative predictive value.

Diagnostic performance of nanoparticle-assisted axillary staging in ycN0 and ycN+ patients

Method of lymphatic mapping	ycN0 (N=92)	ycN+ (N=149)	p-value
SD-SLNB			
DR (%)	95.65	88.59	0.059
Average number of sentinel or NAAS nodes detected (mean±SD)	3.37±1.78	3.23±1.93	0.595
FNR (%)	3.70	11.84	0.448
NPV (%)	98.39	86.15	0.017
Accuracy (%)	98.86	93.18	0.053
NAAS			
DR (%)	97.83	95.30	0.489
Average number of sentinel or NAAS nodes detected (mean±SD)	5.15±2.24	4.20±1.89	<0.001
FNR (%)	0.00	6.02	0.323
NPV (%)	100.00	92.19	0.058
Accuracy (%)	100.00	96.48	0.159

SD-SLNB: standard dual-tracer sentinel lymph node biopsy; DR: detection rate; NAAS: nanoparticle-assisted axillary staging; SD: standard deviation; FNR: false negative rate; NPV: negative predictive value.

Additional axillary disease at axillary lymph node dissection in patients with positive NAAS nodes after neoadjuvant chemotherapy

Positive in NAAS	Additional positive* ALNs				Average number of positive ALNs (mean±SD)
	0 (N=45)	1 (N=15)	2 (N=11)	≥3 (N=37)	
Isolated tumor cell (n=2)	2 (100.00%)	0	0	0	0
1 ITC (n=2)	2 (100.00%)	0	0	0	0
Micrometastasis (n=11)	9 (81.82%)	1 (9.09%)	0	1 (9.09%)	0.55±1.51
1 NAAS node (n=8)	8 (100.00%)	0	0	0	0
2 NAAS nodes (n=3)	1 (33.33%)	1 (33.33%)	0	1 (33.33%)	2.00±2.65
Macrometastasis (n=95)	34 (35.79%)	14 (14.74%)	11 (11.58%)	36 (37.89%)	3.26±5.00
1 NAAS node (n=45)	24 (53.33%)	7 (15.56%)	4 (8.89%)	10 (22.22%)	1.71±3.17
2 NAAS nodes (n=22)	4 (18.18%)	5 (22.73%)	2 (9.09%)	11 (50.00%)	4.09±5.11
3 NAAS nodes (n=13)	2 (15.38%)	0	1 (7.69%)	10 (76.92%)	7.62±8.34
4 NAAS nodes (n=11)	4 (36.36%)	1 (9.09%)	3 (27.27%)	3 (27.27%)	2.73±3.58
≥5 NAAS nodes (n=4)	0	1 (25.00%)	1 (25.00%)	2 (50.00%)	3.50±2.65

*Including isolated tumor cell, micrometastasis and macrometastasis.

NAAS: nanoparticle-assisted axillary staging; ALN: axillary lymph node; SD: standard deviation; ITC: isolated tumor cell.

PO3-22-10

3D-CT mapping with a photo-translucent application using iPad delineates tumor lesions on patient breast skin in breast-conserving surgery: Preliminary results.

Presenting Author(s) and Co-Author(s):

G. Watanabe. Tohoku Medical and Pharmaceutical Medicine, Miyagi, Japan

A. Suzuki. Tohoku Medical and Pharmaceutical Medicine, Japan

Objective: The aim of this study was to evaluate the feasibility and efficacy of a 3D-CT mapping technique with a photo-translucent application using an iPad for tumor localization on the patient's breast skin in breast-conserving surgery (BCS). We also compared the accuracy of tumor localization between conventional methods and 3D-CT mapping.

Methods: Between February and July 2023, 20 female patients with early-stage (0 to 2) breast cancer scheduled for BCS were enrolled in this study. Preoperative enhanced CT scans were performed, and a 3D-CT image was generated by incorporating the patient's skin and manually marking the contrast-enhanced lesion using SYNAPSE VINCENT software. The 3D-CT images, adjusted to individual rotation angles to match the horizontal skin position above the tumor, were imported into an iPad equipped with a photo-translucent application. Using a securely fixed iPad holder, the translucent image was superimposed on the patient's breast, and the enhanced lesion was marked on the skin using a blue pen. Conventional tumor marking was performed based on ultrasound imaging, CT, and MRI findings using a black pen. Photographs were taken to simulate BCS based on the 3D-CT blue marking. All patients underwent BCS with resection margins of 1.5-2 cm from the black marking, and intraoperative frozen section analysis was performed to assess the resection margins.

Results: The majority of patients had hormone receptor-positive breast cancers, and neoadjuvant chemotherapy was administered in three patients (Table1). The extent of tumor involvement assessed by pathological assessment and imaging findings showed the least discrepancy with MRI, with an average error of 4.2 mm. MRI also had the lowest rate of missed tumor detection compared to other imaging modalities. The initial positive margin rate was 20%, and the simulation conducted in this study did not alter that value. Furthermore, the simulation demonstrated more effective excision of the tumor's center compared to conventional surgical methods (Table2).

Conclusion: The use of 3D-CT mapping with a photo-translucent application on an iPad offers a promising approach for accurate tumor localization in BCS. This technique provides a simplified and efficient method, and it can also be applied to cases where lesions have completely disappeared after neoadjuvant chemotherapy.

Table 1. Patient characteristics and pathology		
Age		60 (37-83)
	<50	6
	50-70	17
	>70	7
BMI		22.7 (17.0-34.2)
	Under weight(>18.5)	2
	Normal range (18.5-24.9)	13
	Over weight (<25)	5
Tumor location		
	Upper outer	11
	Upper Inner	5
	Lower inner	1
	Lower outer	3
Stage		
	0	2
	I	15
	IIA	5
	IIB	1
Histology		
	Ductal carcinoma in situ	2
	Invasive ductal carcinoma	17
	Mucinous carcinoma	1
Subtype		
	Luminal A like	12
	Luminal B like	5
	HER2 type	1
	TN	2
Neoadjuvant chemotherapy		
Yes		3 (one pCR, two pPR)
No		17

Table 2. Assessment of tumor spread with each imaging modality and simulation of 3D-CT based surgery				
	Pathological results (n=20)	US findings (n=20)	CT findings (n=20)	MRI findings (n=18)
Tumor spread (mm)	17.7	12.3	12.5	14.7
Invasive size (mm)	12.1			
pathological tumor spread-individual tumor spread (mm)		8.5 (range-7 to 52)	8.1 (range-7 to 50)	4.2 (range-6 to 15)
The proportion of cases with undetectable lesions from the pathological results		7/20 (35%)	5/20 (25.0%)	3/18 (16.7%)
Breast-conserving surgery				
	Pathological mapping	US based conventional surgery	3D-CT based surgery (simulation)	
Intraoperative negative margin rate	16/20 (80%)		16/20 (80%)	
Additional resection rate during surgery	4/20 (20%)			
Pathological margin negative rate	19/20 (95%)*			
The distance between the center of the specimen and the center of the tumor (mm)*		6.2	5.4	
Nearest Margin at first resection (mm)		10.85	11.35	
Longest Margin at first resection (mm)		27.85	27.35	
The proportion of cases in which the surgical extent was determined considering the spread observed on CT or MRI		4/20 (20%)		

* One pCR exhibited degeneration at the site of the specimen, which defined the location of the previous tumor lesion

PO3-22-12

Clinical feasibility of nipple sparing mastectomy (NSM) followed by immediate reconstruction based on direct-to-implant technique

Presenting Author(s) and Co-Author(s):

U. Toh. Kurume University School of Medicine, Dept. Surgery, United States

Y. Takao. Kurume University School of Medicine, Dept. Surgery, Japan

Y. Katagiri. Kurume University School of Medicine, Dept. Surgery, Japan

R. Sugihara. Department of Surgery, Kurume University School of Medicine, Kurume, Fukuoka, Japan

H. Watanabe. Kurume University School of Medicine, Department of Surgery, Japan

[Background] The development of NSM approach combined with immediate implant-based breast reconstruction (IBBR) for patients with early-stage breast cancer (BC) preserve the natural skin envelope including nipple-areolar complex (NAC) to able to immediately reconstruct the breast with a permanent implant and simultaneously omit the skin expansion with a tissue expander. We retrospectively analyzed the clinical results of NSM+IBBR and compared the complication rate, outcome of patients who underwent immediate (one-stage) or delayed (two-stage) IBBR followed by standard TM or NSM.

[Patients and Results] A total of 108 patients who underwent a TM that included SSM or NSM followed by one- or two-stage IBBR between January 2013 and April 2022. 53 patients underwent a total mastectomy (TM) and 32 patients underwent an NSM followed by two-stage IBBR, and 24 patients underwent an NSM followed by one-stage IBBR. The operation times were 236, 247.2, and 321 min, and the mean surgical bleeding was 60.4, 88.8, and 138 ml, respectively. The complications in the three groups included infection (2.7%, 11.1%, and 6.3%), seroma/hematoma (0%, 5.6%, and 6.3%), flap necrosis (2.7%, 11.1%, and 12.5%), and loss of tissue expander or implant (2.7%, 5.6%, and 6.3%), respectively. At the median 62-month follow-up after the NSM + IBBR, one patient was diagnosed with distant lymph node metastases at the 24-month follow-up and one patient had new primary breast cancer within the reconstructed breast at the 38-month follow-up. But no loco-regional recurrence at the NAC or other distant recurrence were detected in the patients undergone regardless TM or NSM + one-stage or two-stage IBBR.

[Summary] Our results suggested that the use of one-stage IBRR tended to increase the operating time and the amount of bleeding compared to two-stage IBRR and the complication rate might be higher in cases in which an NSM is followed by IBBR. Oncological outcome was consistent with the studies showing that loco-regional recurrence is less likely at the NAC regardless of whether the patients underwent one-stage or two-stage IBBR following an NSM.

PO3-23-01

Triple-tracer Technique for Sentinel Lymph Node Biopsy of Breast Cancer after neoadjuvant Chemotherapy using Blue-dye, Radioisotope combined with Real-time Indocyanine green(ICG) Fluorescence Imaging Procedures

Presenting Author(s) and Co-Author(s):

H. Watanabe. Kurume University School of Medicine, Department of Surgery, Japan

Y. Takao. Department of Surgery, Kurume University School of Medicine, United States

Y. Katagiri. Kurume University School of Medicine, Dept. Surgery, Japan

R. Sugihara. Department of Surgery, Kurume University School of Medicine, Kurume, Fukuoka, Japan

U. Toh. Kurume University School of Medicine, Dept. Surgery, United States

Background: For post-neoadjuvant chemotherapy (NAC) patients (pts) with BC, sentinel lymph node biopsy (SNB) was recommended using the dual-tracer mapping technique (radioisotope plus blue dye) or placing a biopsy clip into the positive node at diagnosis and identifying it at the time of surgery due to SN identification rates (IR) were lower and false negative rates (FNR) were greater for pts with local advanced breast cancer (BC) than those of pts with early stage BC in the absence of NAC. Our previous clinical trial has indicated that the real-time ICG fluorescence (RT-ICG) imaging technique could improve the diagnostic sensitivity and detection accuracy for SNB. Methods: Between April 2019 and May 2022, post-NAC SNB were successfully identified in 45 of 52 patients with stage II A to III B (T1-T3, N0-2, M0) who had histologically confirmed breast cancer selected to receive NAC and the standard surgeries were performed after finishing NAC. The SNs were detected by conventional procedures of blue-dye (Indigo carmine) plus ^{99m}Tc radioisotope (dual-tracer) and combined with concurrent RT-ICG technique. Clinical node positive (cN+) was diagnosed by the radiologists using axillary ultrasound, MRI and/or CT scan or assessed by fine needle aspiration cytology (FNAC). The positivity of each single SN by each single tracer (blue dye, ICG, or isotope alone) was counted and identified, respectively. All patients are required to undergo SNB followed by completion axillary lymph node dissection (CND). Then the IR and FNR of each single tracer and their summation (triple tracer) were calculated by comparing the results of the SNB and the histopathology of the resection specimens of CND. Results: Among 45 post-NAC pts, the IR and FNR of each single procedure for SNB was 45.7% and 55.6% when used Indigo Carmine blue, 70.3% and 11.1% when used RI, 82.6% and 0 when used ICG fluorescence, respectively. In contrast, the total calculation of triple tracer showed that IR reached to 100% and FNR was 0, respectively. The IR of triple tracer were 83.9% and 100% for ypN0 and ypN(+) pts after NAC, both FNR were 0%. Conclusion: Our results suggested that the triple tracer technique combining blue dye, ICG, and isotope is effective method for detection of SNs in post-neoadjuvant cN+ BC pts. The IR and FNR of SNB might be improved by this multiple tracer mapping technique, particularly for pts with ypN(+) after NAC. It is considered that the multi-tracer can complement each other for what was not able to be traced and detected by the single tracer with one mapping material, and that result in totally the improvement of identification rate of SNB.

PO3-23-02

Delays in breast cancer surgery during the COVID-19 pandemic: A population-based analysis

Presenting Author(s) and Co-Author(s):

G. Ko. Princess Margaret Cancer Centre – University Health Network, Toronto, ON, Canada, United States

A. Roberts. Odette Cancer Centre – Sunnybrook Health Sciences Centre, Toronto, ON, Canada, United States

Q. Li. ICES, Toronto, ON, Canada, United States

N. Liu. ICES, Toronto, ON, Canada, United States

T. Zhong. Princess Margaret Cancer Centre – University Health Network, Toronto, ON, Canada, United States

E. Amir. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

A. Koch. Radiation Medicine Program, Princess Margaret Cancer Centre – University Health Network, Toronto, ON, Canada, United States

A. Covelli. Sinai Health Systems - Mount Sinai Hospital, Toronto, ON, Canada, United States

V. FREITAS. University of Toronto, Toronto, Ontario, Canada

E. Reel. Princess Margaret Cancer Centre - University Health Network, Toronto, ON, Canada, United States

A. Eskander. Odette Cancer Centre – Sunnybrook Health Sciences Centre, Toronto, ON, Canada, United States

T. Cil. University Health Network / University of Toronto, United States

BACKGROUND: At various times during the COVID-19 pandemic, access to operating room resources were restricted in Ontario, Canada. This resulted in triaging of all non-urgent cases, including breast cancer (BC) surgery. Recent single institution studies have identified treatment delays during the immediate pandemic time period. The objective of this study was to assess the impact of the pandemic on wait times for breast cancer surgery at a population level.

METHODS: We identified patients with a BC diagnosis between January 1, 2018 and November 30, 2021 in Ontario, Canada. Three cohorts were defined based on the following time periods: pre-pandemic (baseline) (January 2018 to 14 March 2020), immediate pandemic (March 15, 2020 to June 13, 2020), and peri-pandemic (June 14, 2020 to November 30, 2021). Time to event analysis was conducted for time to a patient's first BC surgery. A subgroup analysis was conducted for patients who underwent neoadjuvant chemotherapy (NAC).

RESULTS: The study cohort consisted of 36,639 patients with a new diagnosis of BC. Of them 30,862 patients underwent surgery (84.2%) within 18 months after diagnosis. The probability of BC patients undergoing surgery each month from their date of diagnosis was significantly lower (i.e. longer wait times) for patients diagnosed in the immediate and peri-pandemic period compared to patients diagnosed in the pre-pandemic period (log-rank $P < 0.001$). At eight weeks from date of diagnosis, the probability of having had surgery was 65.1% (95% CI: 64.5-65.8%) for patients diagnosed in the pre-pandemic period, 56.1% (95% CI: 53.6-58.6%) for immediate pandemic and 59.0% (95% CI: 58.2-59.8%) for peri-pandemic. Time for 80% of patients to have BC surgery was 5.4 months in the pre-pandemic, 5.9 months in the immediate pandemic, and 6.0 months in the peri-pandemic period. Among patients who received NAC (N=6,121; 16.7% of cohort), the probability of undergoing surgery in each month from the date of diagnosis was similar for patients diagnosed in the pre and peri-pandemic periods, but was

higher (i.e. shorter wait time) for the cohort of patients diagnosed during the immediate pandemic time period (log-rank $P < 0.001$). At six months from date of diagnosis, the probability of surgery for patients who received NAC was 50.7% (95% CI: 48.9-52.5%), 61.6% (95% CI: 56.6-66.6%), and 50.9% (95% CI: 49.0-52.8%) for patients diagnosed in the pre-, immediate, and peri-pandemic periods respectively. Time for 80% NAC patients to have a surgery was 7.2 months in the immediate pandemic period, shorter than the 8.2 months in the pre-pandemic and 8.0 months in the peri-pandemic periods. CONCLUSIONS: In this large population-based study of BC patients in Ontario, we identified a delay in time to surgery in the immediate pandemic period that persisted into the peri-pandemic period. However, among patients receiving NAC there was a shorter wait time during the immediate pandemic and wait times for this group have returned to pre-pandemic levels. This is likely due to surgical prioritization of this group, despite pandemic related resource restrictions. Further research is needed to explore the regional variability and how use of neoadjuvant endocrine therapy interacted with surgical treatment timelines.

PO3-23-03

Radar reflectors for marking of target lymph nodes in patients receiving neoadjuvant chemotherapy for breast cancer – a subgroup analysis of the prospective AXSANA (EUBREAST-03) trial

Presenting Author(s) and Co-Author(s):

M. Banys-Paluchowski. Department of Gynecology and Obstetrics, University of Schleswig-Holstein Campus Lübeck, Lübeck, Germany, United States

S. Hartmann. Department of Gynecology and Obstetrics, University Hospital Rostock, Germany

J. de Boniface. Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, and Department of Surgery, Capio St. Göran's Hospital, Stockholm, Stockholms Lan, Sweden

O. Gentilini. Breast Surgery Unit, San Raffaele University Hospital, Milan, Italy

T. Basali. Department of Gynecology and Obstetrics, Klinikum Esslingen, Esslingen, Germany, United States

E. Stickeler. Klinik für Gynäkologie und Geburtsmedizin, Uniklinik RWTH Aachen, Germany, United States

M. Untch. AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany, Berlin, United States

F. Ruf. University Hospital Schleswig-Holstein Campus Lübeck, Germany, United States

S. Fröhlich. Department of Gynecology and Obstetrics, University Hospital Rostock, Rostock, Germany, United States

M. Thill. Agaplesion Markus Krankenhaus, 60431 Frankfurt a.M., Hessen, Germany

M. Lux. St. Vincenz-Kliniken Paderborn, Germany

F. Peintinger. Univ.Prof. Priv.Doiz. Dr. Florentia Peintinger, Austria

G. Karadeniz Cakmak. Zonguldak Bulent Ecevit University, Department of Surgery, Turkey

I. Rubio. Clínica Universidad de Navarra, Madrid, Spain, United States

M. Kontos. 1st Department of Surgery, Laiko Hospital, National and Kapodistrian University of Athens, Greece

R. Di Micco. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), Italy

D. Murawa. Department of General Surgery and Surgical Oncology, Collegium Medicum, University of Zielona Góra, Poland, Poland

E. Schlichting. Oslo University Hospital, Oslo, Norway

B. Aktas Sezen. European Breast Cancer Research Association of Surgical Trialists (EUBREAST), United States

A. Rody. University Hospital Schleswig-Holstein Campus Lübeck, Germany, United States

D. Langanke. St. Elisabeth KH Leipzig-Brustzentrum, Leipzig, Germany, United States

N. Bündgen. University Hospital Schleswig-Holstein Campus Lübeck, Germany, United States

J. Sanchez-Mendez. La Paz University Hospital/ La Paz Institute for Health Research – IdiPAz / Universidad Autónoma - Madrid (Spain), United States

R. Buss-Steidle. Helios Klinikum Pforzheim, Pforzheim, Germany, United States

C. Mau. Department of Gynecology and Obstetrics, Helios Klinikum Berlin-Buch, Berlin, Germany, United States
N. Buchmann. Department of Gynecology and Obstetrics, Helios Klinikum Berlin-Buch, Berlin, Germany, United States
S. Riemer. St. Joseph Stift Bremen, Bremen, Germany, United States
M. Hansen. University Hospital of North Norway, Tromsø, Norway, United States
N. Ditsch. Department of Gynaecology and Obstetrics, University Hospital Augsburg, Augsburg, Germany
T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany

Background:

Surgical staging procedures of the axilla in breast cancer patients converting from a clinically positive (cN+) to a clinically negative (ycN0) lymph node status during neoadjuvant chemotherapy (NACT) vary across countries and within individual countries. The international prospective AXSANA (EUBREAST-03) study aims at comparatively evaluating long-term outcomes of different staging procedures such as axillary lymph node dissection (ALND), sentinel lymph node biopsy (SLNB), target lymph node biopsy (TLNB) and targeted axillary dissection (TAD). The comparison of marking techniques for the target lymph node (TLN) is a secondary endpoint. In this subgroup analysis, we report on the largest yet prospective cohort of patients receiving a radar reflector for marking of the TLN prior to NACT. Methods:

The AXSANA study is an international prospective cohort study including cN+ patients converting to ycN0 status and treated with different axillary staging techniques according to the standard at their treating institution. The study was initiated by the EUBREAST network and started enrollment in August 2020. Eligible patients have cT1-4c tumors, initially present with axillary lymph node metastasis and receive neoadjuvant chemotherapy. Patients converting to ycN0 status are followed up for 5 years irrespectively of the ypN status. In the present subgroup analysis, only patients with a TLN marked by a radar reflector were included. We prospectively examined the retrieval rate of radar reflectors and the identification rate of the TLN (defined as unequivocal removal of the lymph node, i.e., the presence of lymphatic tissue in the TLN specimen and/or pathological confirmation of post-NACT changes typical for metastatic lymph nodes responding to treatment). Results:

A TLN was marked using a radar reflector in 74 patients prior to NACT. The median age was 52 years (range: 32-77). The most common subtype was no special type in 68 (92%) patients and invasive lobular cancer in 7 (7%) patients. Most patients (n = 44, 59%) had one suspicious node at time of diagnosis, followed by two (n = 15, 20%), three (n = 10, 14%) or ≥ four suspicious nodes (n = 5, 5%). Only one TLN was marked in 73 (99%) patients and two nodes were marked in one patient (1%). Fifteen patients (20%) had a MRI between marker placement and surgery. In 4 out of 15 cases (27%), MRI artifacts were described. However, the assessment of MRI was limited due to artifacts only in one out of these four patients (25%). Out of the 74 patients with radar reflector marked TLN, 45 (61%) had undergone final surgery at the time of analysis and 29 (39%) are still under NACT. 36 out of 45 patients (80%) who received final surgery converted to ycN0. Most patients had undergone a TAD (n = 41, 91%), followed by TLNB in 7% (n = 3) and upfront ALND in 2% of cases (n = 1). All radar reflectors were successfully removed. In 44 out of 45 patients (98%) the TLN was unequivocally identified and removed. In one patient the tissue specimen containing radar reflector consisted of fat tissue and no lymphatic tissue was identifiable, so it remains unclear whether the TLN was excised, or the reflector might have dislocated. 29 patients (65%) had converted to ypN0 status.

Conclusion:

To the best of our knowledge this is the largest prospective series of patients receiving a radar reflector for the marking of TLN prior to NACT for breast cancer. The removal rate of the marker

and the detection rate of the target node were very high. Our data demonstrate that radar reflectors are a reliable tool for marking of target lymph nodes before neoadjuvant treatment.

PO3-23-04

Patient-reported outcomes and complication profiles of implant-based breast reconstruction in patients with postmastectomy radiation therapy

Presenting Author(s) and Co-Author(s):

J. Liu. Hangzhou First People's Hospital, United States

C. Chen. Hangzhou First People's Hospital, United States

H. Chen. Hangzhou First People's Hospital, United States

A. Xiang. Prof., United States

R. Zheng. Hangzhou First People's Hospital, United States

S. Hu. Hangzhou First People's Hospital, United States

J. Guo. Hangzhou First People's Hospital, United States

L. Qu. Hangzhou First People's Hospital, United States

J. Zhou. Hangzhou First People's Hospital, United States

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Objective: This study aims to investigate the patient-reported outcomes (PROs) and complications of distinct implant-based breast reconstruction (IBBR) modality for patients with postmastectomy radiation therapy (PMRT).

Methods: A retrospective review was conducted on breast cancer patients with stage II-III disease who performed IBBR following with PMRT between September 2016 and April 2022. The patients were categorized into two matched groups: (1) patients receiving prepectoral breast reconstruction (PBR) or subpectoral breast reconstruction (SBR) followed by PMRT; (2) patients undergoing PMRT with the tissue expander (PMRT-TE) or permanent implant (PMRT-PI) groups. PROs were measured with BREAST-Q questionnaire. Early and late complications were recorded and analysed.

Results: A total of 55 eligible patients were recruited. For PROs, patients underwent PBR reported significantly higher Satisfaction with Breasts scores ($P = 0.003$) compared with SBR group, and PMRT-TE group presented higher Satisfaction with Breasts ($P = 0.001$) but lower Physical Well-being ($P = 0.029$) scores compared with PMRT-PI group. Moreover, Patients in SBR cohort had a higher risk of capsular contracture (Baker grade III or IV) (20.5% vs 6.3%) and implant dislocation (48.7% vs 12.5%) than patients in PBR cohort. Patients in PMRT-PI group had a slightly higher rate of capsular contracture (Baker grade III or IV) than PMRT-TE group (20.8% vs 12.9%).

Conclusions: PBR was associated with lower rates of late complications, especially for implant dislocation, and higher Satisfaction with Breasts scores compared to SBR. In addition, compared to PMRT-TE with PMRT-PI, patients in PMRT-TE cohort reported superior patient-reported outcomes of Satisfaction with Breasts.

Table 1. Patient and Tumor Characteristics of 55 Patients Stratified with Prepectoral/Subpectoral and PMRT-TE/PMRT-PI Reconstructive Procedure.

Table 1. Patient and Tumor Characteristics of 55 Patients Stratified with Prepectoral/Subpectoral and PMRT-TE/PMRT-PI Reconstructive Procedure.

	All (N=55)	PBR (N=16)	SBR (N=39)	P value	PMRT-TE (N=31)	PMRT-PI (N=24)	P value
Age (years)	38.7 ± 7.8	37.3 ± 8.7	39.2 ± 7.5	0.419	38.0 ± 6.9	39.5 ± 8.9	0.485
BMI (kg/m ²)	21.6 ± 8.0	23.1 ± 3.0	21.1 ± 2.6	0.017	21.5 ± 2.5	21.8 ± 3.2	0.406
Grade				0.496			0.671
I+II	27	9 (56.3)	18 (46.2)		16 (51.6)	11 (45.8)	
III	28	7 (43.8)	21 (53.8)		15 (48.4)	13 (54.2)	
ER				1.000			0.542
positive	39	11 (68.8)	28 (71.8)		23 (74.2)	16 (66.7)	
negative	16	5 (31.3)	11 (28.2)		8 (25.8)	8 (33.3)	
PR				0.466			0.472
positive	35	9 (56.3)	26 (66.7)		21 (67.7)	14 (58.3)	
negative	20	7 (43.8)	13 (33.3)		10 (32.3)	10 (41.7)	
HER2				0.750			0.404
positive	17	4 (25.0)	13 (33.3)		11 (35.5)	6 (25.0)	
negative	38	12 (75.0)	26 (66.7)		20 (64.5)	18 (75.0)	
Ki-67				0.303			0.960
≤30	30	7 (43.8)	23 (59.0)		17 (54.8)	13 (54.2)	
> 30	25	9 (56.3)	16 (41.0)		14 (45.2)	11 (45.8)	
Stage				0.665			0.620
II	30	8 (50.0)	22 (56.4)		16 (51.6)	14 (58.3)	
III	25	8 (50.0)	17 (43.6)		15 (48.4)	10 (41.7)	
NAC				0.002			0.009
Yes	27	13 (81.3)	14 (35.9)		20 (64.5)	7 (29.2)	
No	28	3 (18.8)	25 (64.1)		11 (35.5)	17 (70.8)	
Surgery				0.227			0.419
NSM	31	7 (43.8)	24 (61.5)		16 (51.6)	15 (62.5)	
SSM+SRM	24	9 (56.3)	15 (38.5)		15 (48.4)	9 (37.5)	

Abbreviations: PBR, prepectoral breast reconstruction; SBR, subpectoral breast reconstruction; PMRT-TE, postmastectomy radiotherapy delivered to the tissue expander; PMRT-PI, postmastectomy radiotherapy delivered to the permanent implant; BMI, body mass index; NAC, neoadjuvant chemotherapy; NSM, nipple-sparing mastectomy; SSM, skin-sparing mastectomy; SRM, skin-reducing mastectomy.

Table 1. Patient and Tumor Characteristics of 55 Patients Stratified with Prepectoral/Subpectoral and PMRT-TE/PMRT-PI Reconstructive Procedure.

Table 2. Patient-Reported BREAST-Q Scores

Table 2. Patient-Reported BREAST-Q Scores

	PBR (N=16)	SBR (N=32)	P value	PMRT-TE (N=28)	PMRT-PI (N=20)	P value
Satisfaction with Breasts			0.003			0.001
Mean ± SD	72.3 ± 17.0	56.8 ± 16.5		68.8 ± 18.3	52.4 ± 12.7	
Median (IQR)	69.0 (58.3-87.8)	54.0 (44.3-67.0)		67.0 (54.3-74.5)	53.0 (42.0-58.8)	
Physical Well-being			0.495			0.029
Mean ± SD	40.8 ± 16.8	44.2 ± 16.1		38.7 ± 16.7	49.2 ± 13.7	
Median (IQR)	45.0 (25.0-55.0)	45.0 (32.0-60.0)		38.0 (24.0-53.8)	55.0 (40.0-60.0)	
Psychosocial Well-being			0.082			0.057
Mean ± SD	81.9 ± 17.4	70.9 ± 19.7		79.0 ± 19.6	68.5 ± 18.0	
Median (IQR)	85.0 (63.8-100.0)	67.5 (58.5-91.5)		81.5 (62.5-100)	65.0 (54.8-86.0)	
Sexual Well-being			0.354			0.159
Mean ± SD	60.1 ± 17.6	54.3 ± 21.4		59.8 ± 23.4	51.4 ± 13.9	
Median (IQR)	62.5 (40.0-70.0)	51.5 (43.0-66.0)		60.5 (43.8-73.0)	50.0 (40.0-61.3)	

Abbreviations: PBR, prepectoral breast reconstruction; SBR, subpectoral breast reconstruction; PMRT-TE, postmastectomy radiotherapy delivered to the tissue expander; PMRT-PI, postmastectomy radiotherapy delivered to the permanent implant. SD, Standard Deviation; IQR, InterQuartile Range.

Table 2. Patient-Reported BREAST-Q Scores

Table 3. Association of Reconstruction Techniques with Late Complications.

Table 3. Association of Reconstruction Techniques with Late Complications.						
	PBR (N=16)	SBR (N=39)	<i>P</i> value	PMRT-TE (N=31)	PMRT-PI (N=24)	<i>P</i> value
Capsular contracture			0.258			0.482
Yes	1 (6.3)	8 (20.5)		4 (12.9)	5 (20.8)	
No	15 (93.8)	31 (79.5)		27 (87.1)	19 (79.2)	
Implant dislocation			0.012			0.927
Yes	2 (12.5)	19 (48.7)		12 (38.7)	9 (37.5)	
No	14 (87.5)	20 (51.3)		19 (61.3)	15 (62.5)	
Rippling			0.414			0.718
Yes	1 (6.3)	7 (17.9)		4 (12.9)	4 (16.7)	
No	15 (93.8)	32 (82.1)		27 (87.1)	20 (83.3)	

Abbreviations: PBR, prepectoral breast reconstruction; SBR, subpectoral breast reconstruction; PMRT-TE, postmastectomy radiotherapy delivered to the tissue expander; PMRT-PI, postmastectomy radiotherapy delivered to the permanent implant.

Table 3. Association of Reconstruction Techniques with Late Complications.

PO3-23-05

Capsular contracture after post-mastectomy radiotherapy in the patients undergoing implant-based breast reconstruction: impact of implant positioning and two-stage surgery

Presenting Author(s) and Co-Author(s):

S. Moon. Gangnam Severance Hospital, South Korea

K. min. Gangnam Severance Hospital, United States

J. Eom. Gangnam Severance Hospital, United States

Y. Kook. Gangnam Severance Hospital, South Korea

S. Baek. Gangnam Severance Hospital, South Korea

J. Kim. Gangnam Severance Hospital, South Korea

M. Kim. Gangnam Severance Hospital, Seoul, Seoul-t'ukpyolsi, Republic of Korea

S. Lee. Gangnam Severance Hospital, South Korea

I. Yun. Gangnam Severance Hospital, United States

T. Roh. Gangnam Severance Hospital, United States

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Y. Kim. Gangnam Severance Hospital, United States

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Background Capsular contracture is a significant concern in patients undergoing post-mastectomy radiotherapy (PMRT) following implant-based breast reconstruction. It negatively impacts cosmetic outcomes and can have a profound effect on the individual's quality of life. Our study aimed to explore whether the degree of capsular contracture varies based on the placement of the inserted implant and the type of operation (one- or two-staged). **Patients and Methods** This retrospective study was conducted at a single center, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea. Our study included patients who underwent PMRT following total mastectomy and implant-based breast reconstruction surgery between January 2017 and September 2022. To assess the degree of capsular contracture, we evaluated the presence of capsular contracture, particularly severe capsular contracture classified as Baker grade 3 or higher, as well as implant migration. The implants were placed either in the pre-or sub-pectoral position, and the surgical approach employed was either direct-to-implant (DTI) or two-staged operation. **Results** A total of 195 patients were included in the study, with 83 (42.6%) patients in the pre-pectoral group and 112 (57.4%) patients in the sub-pectoral group. In addition, 116 underwent a two-stage operation, while 79 underwent DTI surgery. There was a significant difference in the occurrence of capsular contracture based on the implant placement, with 16 patients (19.3%) in the pre-pectoral group and 46 patients (41.1%) in the sub-pectoral group experiencing this complication (OR 4.142 [1.973-8.698]). Furthermore, the severity of capsular contracture differed significantly between the two groups, with 5 patients (6.0%) in the pre-pectoral group and 16 patients (14.3%) in the sub-pectoral group affected (OR 3.434 [1.153-10.227]). The incidence of capsular contracture was lower in the two-stage operation group compared to the DTI group

(28 [23.9%] vs 34 [38.6%]; OR 3.064 [1.528-6.141]), and the severity of capsular contracture was also reduced (9 [7.7%] vs 12 [14.5%]; OR 2.854 [1.092-7.455]). There were no significant differences in other complications such as seroma and infection. In addition, sub-pectoral placement was identified as a significant risk factor for implant upward migration (OR 2.531 [95% CI, 1.263-5.071]).

Conclusions Our findings suggest that pre-pectoral reconstruction and the two-stage operation are beneficial for patients who may undergo PMRT based on their initial nodal stage. These approaches can help reduce the incidence of capsular contracture and abnormal implant migration following radiation, leading to improved aesthetic outcomes and greater patient satisfaction.

PO3-23-06

Short-term clinical and patient-reported outcomes of oncoplastic breast conserving surgery and mastectomy with and without immediate breast reconstruction: The UK ANTHEM multicentre prospective cohort study

Presenting Author(s) and Co-Author(s):

C. Davies. Bristol Medical School, United States
L. Johnson. Bristol Medical School, United States
C. Conefrey. Bristol Medical School, United States
N. Mills. Bristol Medical School, United States
P. Fairbrother. Independent Cancer Patients' Voice (ICPV), United States
C. Holcombe. Liverpool University Hospital NHS Foundation Trust, United States
L. Whisker. Nottingham Breast Unit, United States
W. Hollingworth. Bristol Medical School, United States
J. Skillman. Coventry and Warwickshire NHS Trust, United States
P. White. University of West of England, United States
D. MacMillan. Nottingham Breast Unit, United States
C. Comins. University Hospitals Bristol and Weston NHS Foundation Trust, United States
S. Potter. Bristol Medical School, United States

Background: Oncoplastic breast conserving surgery (OPBCS) may allow women with early breast cancer to avoid mastectomy leading to fewer complications and better quality of life. High quality comparative evidence, however, is lacking. The UK ANTHEM study (ISRCTN18238549) aimed to explore the feasibility of undertaking a large-scale multicentre study comparing the clinical and patient reported outcomes (PROs) of OPBCS as an alternative to mastectomy +/- immediate breast reconstruction (IBR) in women offered both options.

Methods: Women aged 18 and over with invasive breast cancer or DCIS not suitable for standard breast conserving surgery, who were offered OPBCS as an alternative to mastectomy +/- IBR were eligible to participate in the study. Demographic, operative, oncological data were collected and the numbers of women experiencing complications at 3 months following surgery compared by procedure type.

Participants completed the validated BREAST-Q at baseline and 3 months post-operatively. Questionnaires were scored according to the developers' instructions and scores compared across timepoints by procedure group. Analysis of covariance, adjusting for baseline scores was used to explore factors influencing patient-reported outcomes after surgery.

Results: 361 women from 32 UK centres participated in the study. When offered both options, the majority (n=284, 78.7%) elected to undergo OPBCS with either a therapeutic mammoplasty (TM) (n=207, 57.3%) or a chest wall perforator flap (CWPF) (n=77, 21.3%). The remaining 77 (21.3%) women chose mastectomy with (n=40, 11.1%) or without IBR (n=37, 10.3%). Women having mastectomy + IBR were significantly younger than those choosing other procedure types (p=0.002) and those choosing TM had higher BMIs (P=0.008), but there were no other differences between the groups.

By 3 months post-operatively, 23.0% (n=83) women had experienced at least one complication, but there were no differences between the groups ($p=0.50$).

The BREAST-Q was completed by 329 (91.1%) and 282 (78.1%) women at baseline and 3 months respectively. Although their scores were initially the lowest, women undergoing TMs reported clinically meaningful and statistically significant increases in 'Satisfaction with Breasts' (baseline 53.7 [95% confidence interval [CI] 50.4-57.0] to 3 months 68.9 [95% CI 65.5-72.2], $p<0.001$) and 'Psychosocial Well-being' scores (baseline 62.1 [95% CI 59.2-65.0] to 3 months 70.4 [95% CI 66.9-73.8] $p<0.001$) from baseline to 3 months. Women having CWPF and mastectomy +/- IBR did not report any significant changes in either 'Satisfaction with Breasts' or 'Psychosocial Well-being' scores over time. 'Physical Well-being' scores significantly decreased from baseline to three months in all treatment groups ($p<0.001$) but were lowest after mastectomy only (56.5 [95% CI 47.4-65.5]) and highest in the TM group (68.6 [95% CI 65.9-71.3], $p<0.001$). 'Sexual Well-being' decreased in all groups except for women having mastectomy + IBR.

Adjusting for baseline, women undergoing OPBCS with TM (13.2, 95% CI 4.2-22.2, $p<0.001$) or CWPF (11.4, 1.6-21.2, $p=0.02$) reported significantly higher 'Satisfaction with Breasts' scores at 3 months than those undergoing mastectomy. Receipt of IBR did not appear to lead to significantly higher scores compared with mastectomy alone (6.47, 95% CI -6.19 to 19.12, $p=0.32$). Women undergoing TM reported significantly higher 'Psychosocial' and 'Physical well-being' at 3 months compared with those having other procedure types. Experiencing a post-operative complication resulted in significant decreases in all BREAST-Q domains.

Conclusions: When offered OPBCS as an alternative to mastectomy, most women choose breast conservation. This option is safe and appears to be associated with improved short-term PROs, particularly in the TM group. Further work is needed to establish the long-term outcomes of these techniques to support informed decision-making.

PO3-23-07

Evaluation of the role of axillary ultrasound to estimate axillary nodal burden to guide de-escalation of upfront axillary surgery in node positive early breast cancer patients.

Presenting Author(s) and Co-Author(s):

N. Garg. Guy's & St. Thomas' NHS Foundation Trust, United States

M. Thorat. Guy's & St. Thomas' NHS Foundation Trust, United States

H. Hamed. Guy's & St. Thomas' NHS Foundation Trust, United States

A. Kothari. Guy's & St Thomas NHS Foundation Trust, Kings College, London, United Kingdom, United States

Background: Axillary surgery is now routinely de-escalated in clinically node negative breast cancer patients with limited axillary nodal burden (up to 2 involved sentinel nodes) based on the results of ACOSOG-Z0011 and AMAROS trials. However, patients with proven axillary metastasis following on ultrasound (AUS) guided core needle biopsy (CNB), undergoing primary surgery are still subjected to an axillary lymph node dissection (ALND) irrespective of the magnitude of the axillary nodal burden. If we could predict axillary nodal burden with a low false negative rate (FNR) for the presence of extensive axillary nodal involvement, we can then hypothesize that axillary surgery could be safely de-escalated in this cohort of patients. We investigated whether pre-operative AUS suggesting limited axillary burden is sensitive enough to rule out gross axillary disease burden. Methods: A single institution retrospective study. We undertook an electronic chart review of all T1 to T3 patients undergoing upfront ALND with either mastectomy or breast conserving surgery between January 2019 and June 2023. Patients with palpable axillary nodes, locally advanced breast cancer or a completion ALND after positive sentinel lymph node biopsy (SLNB) were excluded from the study. Clinical and pathological characteristics associated with nodal burden of disease were evaluated. Limited axillary burden was defined as < 2 involved nodes with ≥ 3 taken as gross nodal burden for primary analyses. Sensitivity analyses were carried out with limited axillary burden defined as < 3 involved nodes (N1) and ≥ 4 (N2) taken as gross nodal burden. Subgroup analyses in T1 or T2 tumors were carried out as well. The probabilities of discordant events, defined as limited burden on AUS-CNB but gross burden on final histopathology evaluation (HPE), assuming 10% FNR, were estimated using inverse cumulative binomial distribution function. Results: Data on the exact number of suspicious nodes on AUS were missing for 2 patients, therefore, the final study cohort included 39 patients. The correlation between AUS nodal burden and that on HPE was moderate (Spearman's $\rho = 0.48$; $p = 0.0018$). The sensitivity and specificity of AUS in identifying gross nodal burden were 61% and 81% respectively. Observation of 9 discordant events in 22 patients with low burden on AUS ruled out an FNR of < 10% with 99.99% certainty. The sensitivity and specificity in T1/T2 subgroup were 60% and 75% respectively. The sensitivity analyses classifying N1 as limited and N2 as gross axillary burden showed the sensitivity and specificity of 35% and 82% respectively and an FNR of < 10% was ruled out with 99.996% certainty. Conclusion: Pre-operative AUS alone lacks the sensitivity and specificity to accurately predict the true axillary nodal burden to safely guide de-escalation of axillary surgery. AUS followed by targeted axillary dissection (TAD) in conjunction with a dual technique SLNB may provide the desired sensitivity and specificity to guide de-escalation of axillary surgery. A prospective evaluation of this approach is merited. Given the limited number of patients that could be enrolled in such prospective study from individual institutions, an international collaborative effort is needed to address this important research question.

PO3-23-08

Cancer and immune cells evolutionary trajectories under treatment with the aromatase inhibitor letrozole and the CDK4/6 inhibitor ribociclib.

Presenting Author(s) and Co-Author(s):

M. Fongård. Oslo University Hospital, United States

L. Schmiester. University of Oslo, Oslo Centre for Biostatistics and Epidemiology (OCBE), University of Oslo, Norway, Norway

S. Ghannoum. Oslo University Hospital, United States

M. Bjørnstad. Oslo University Hospital, United States

T. Bosnjak. Novartis, United States

S. Kleivbo. Novartis, Norway

K. Selsås. Department of Breast and Endocrine Surgery, Akershus University Hospital, Oslo, Norway, Norway

S. Geisler. Dept. of oncology, Akershus University Hospital, Lørenskog, Akershus, Norway

K. Fjermeros. Akershus university hospital, Norway

S. Bhargava. Department of Oncology, Akershus University Hospital, Oslo, Norway, United States

M. Seyedzadeh. Akershus University Hospital, United States

U. Buvarp. Akershus University Hospital, United States

A. Vuoriluoto. Akershus University Hospital, United States

N. Nguyen. Department of Medical Genetics, Oslo University Hospital, Oslo, Norway, United States

T. Lüders. Akershus University Hospital, United States

D. Lambrechts. Laboratory of Translational Genetics, VIB Center for Cancer Biology, KU Leuven, Leuven, United States

M. Lyngra. Akershus University Hospital, United States

A. Frigessi. University of Oslo, Oslo Centre for Biostatistics and Epidemiology (OCBE), University of Oslo, Norway, Norway

V. Kristensen. Oslo University Hospital, United States

J. Geisler. University of Oslo, Norway, Lorenskog, Norway

X. Tekpli. Oslo University Hospital, United States

Cancer and immune cells evolutionary trajectories under treatment with the aromatase inhibitor letrozole and the CDK4/6 inhibitor ribociclib.

Marie Fongaard¹, Leonard Schmiester², Salim Ghannoum¹, Pål Marius Bjørnstad¹, Tatjana Bosnjak³, Signe Meltzer Kleivbo³, Knut Selsås⁴, Stephanie Beate Geisler⁵, Kamilla Fjermeros⁵, Sameer Bhargava⁵, Manouchehr Seyedzadeh⁶, Unn-Cathrin Buvarp⁵, Aino Katri Rosenskiold⁵, Nam Thi Nguyen⁵, Torben Lüders⁷, Diether Lambrechts⁸, Marianne Lyngra⁹, Arnoldo Frigessi², Vessela Kristensen^{1,10}, Jürgen Geisler^{5,10,*}, Xavier Tekpli^{1,*} 1) Department of Medical Genetics, Oslo University Hospital, Oslo, Norway 2) University of Oslo, Oslo Centre for

Biostatistics and Epidemiology (OCBE), University of Oslo, Norway 3) Novartis, Medical Affairs, Oslo, Norway 4) Department of Breast and Endocrine Surgery, Akershus University Hospital, Oslo, Norway 5) Department of Oncology, Akershus University Hospital, Oslo, Norway 6) Department of Radiology, Akershus University Hospital, Oslo, Norway 7) Department of Clinical Molecular Biology (EPIGEN), Akershus University Hospital, Oslo, Norway 8) Laboratory for Translational Genetics, Department of Human Genetics, KU Leuven, Leuven, Belgium 9) Department of Pathology, Akershus University Hospital, Oslo, Norway 10) University of Oslo, Institute of Clinical Medicine, Faculty of Medicine, Oslo, Norway< * Jointly supervised the work, shared corresponding authors

Background The recent introduction of CDK4/6 inhibitors is regarded as a major improvement in the field of breast cancer therapy. A growing body of evidence suggests that CDK4/6 inhibitors may impact on the recruitment of immune cells within the tumor microenvironment during therapy. Further, CDK4/6 inhibitors may potentially contribute to the extinction or survival of specific cancer cell clones through evolutionary pressure exerted on breast tumors.

Clinical trial The NEOLETRIB-study is a multicenter, single-arm, open-label phase II clinical trial. Patients with locally advanced, LUM-A/LUM-B breast cancer, characterized by cT3-cT4 tumors and/or cN2-3 lymph node involvement, receive ribociclib (600 mg daily, 21 days on and 7 days off) in combination with letrozole (2.5 mg daily) for a duration of 6 months in the neoadjuvant setting. Patients with large cT2 tumors are also allowed to participate.

Aim of the study Using single-cell analyses at different time points of treatment, we aim at studying the evolutionary trajectories of cancer and immune cells in 30 patients participating in the NEOLETRIB-trial.

Methods Tumor biopsies taken before treatment (baseline) and during treatment (day 21 of ribociclib cycles 1 and 6, respectively), underwent single-cell RNA (scRNA), T cell receptor (TCR), and B cell receptor (BCR) sequencing. The sequencing data was first processed using cellRanger and Seurat .

Results Initial clustering of the scRNA enabled the identification of the main cell types in breast tumors, which included T/NK cells, B cells, epithelial cells, cancer-associated fibroblasts, myeloid cells and endothelial cells.

Focusing on epithelial cells, we were distinguished cancer cells from normal epithelial cells using the InferCNV algorithm. Further, by estimating the copy number events, we determined the genetic background of clones resistant or sensitive to combination therapies for each patient, revealing the dynamics of tumor heterogeneity evolution during treatment.

Additionally, we examined CD4, CD8 and NK cell types, identified different cell states within these cell types and inferred pseudotime and immune cell type differentiation trajectories.

ConclusionsWe identified the cell types present in tumor biopsies from the NEOLETRIB trial. We characterized the effects of therapies on the evolution of cancer and immune cells and gain insights into the factors influencing sensitivity and resistance to the combination of letrozole and ribociclib.

PO3-23-09

ESR1 mutations drive resistance to CDK4/6 inhibitors in ER+ Breast Cancer.

Presenting Author(s) and Co-Author(s):

M. Chica-Parrado. University of Texas Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, United States

C. Lin. University of Texas Southwestern Simmons Comprehensive Cancer Center, United States

E. Jaeger. Tempus Labs, Inc., United States

M. Harris. Tempus Labs, Inc., United States

L. Guo. UT Southwestern Medical Center, United States

E. Bikorimana. UT Southwestern Medical Center, United States

F. Napolitano. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

C. Chao. Tempus Labs, United States

A. Hanker. UT Southwestern Medical Center, Dallas, Texas, United States

C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

Mutations in ESR1 (the gene encoding the estrogen receptor, ER α) are major drivers of resistance to antiestrogen therapy in ER+ breast cancer. However, it remains unclear whether ESR1 mutations also drive resistance to CDK4/6 inhibitors (CDK4/6i). We analyzed de-identified next generation sequencing (NGS) data of tumor tissue DNA (n=1,820) and circulating tumor (ct) DNA (n=2,138) from patients with ER+/HER2- metastatic breast cancer. NGS of tumor tissue DNA and ctDNA previously had been performed using the Tempus xT tumor assay (595-648 genes) and Tempus xF liquid biopsy (105-523 genes), respectively. Patients were stratified into treated (xT:1,070; xF:1,885) or untreated (xT:750; xF:253) with CDK4/6i prior to biopsy, and untreated patients were restricted to those biopsied within 30 days of metastatic diagnosis. ESR1 was the only gene for which mutations were significantly enriched in patients who received CDK4/6i vs. those who did not in both xT (32% vs. 4.8%, $q < 0.001$) and xF (29% vs. 9.5%, $q < 0.001$) cohorts.

To determine whether ESR1 mutations drive resistance to CDK4/6i, we used MCF-7 cells carrying ESR1 wild-type (WT), Y537S, or D538G 'hotspot' knock-in mutations to assess cell proliferation upon treatment with the CDK4/6i palbociclib. Cells harboring the Y537S and D538G mutations displayed a 3-fold increase in the IC₅₀ of palbociclib single agent compared to ESR1^{WT} cells. When treated with palbociclib + fulvestrant or palbociclib + estrogen-free medium (mimicking estrogen suppression in patients treated with aromatase inhibitors), cells harboring the Y537S and D538G mutations displayed an 11.2 to 46.9-fold increase in the IC₅₀ of palbociclib. Treatment with palbociclib arrested growth of MCF-7 ESR1^{WT} xenografts established in ovariectomized nude mice whereas MCF-7 ESR1^{Y537S} and MCF-7 ESR1^{D538G} tumors continued to grow. These results suggest that ESR1 mutations enable cell proliferation and tumor growth in the presence of CDK4/6i and the combination of CDK4/6i + antiestrogens.

Next, we performed RNA-seq to investigate the mechanisms underlying ESR1 mutation-mediated resistance to CDK4/6i. Gene set enrichment analysis (GSEA) of the RNA-seq data

showed significant upregulation of cell cycle-related Hallmark gene signatures such as E2F targets, G2/M checkpoints, and mitotic spindle in ESR1^{Y537S} vs. ESR1^{WT} and ESR1^{D538G} vs. ESR1^{WT} MCF-7 cells upon treatment with palbociclib. Upregulation of these gene signatures in ESR1-mutant vs. WT cells was also observed upon treatment with palbociclib + fulvestrant and palbociclib in estrogen-free media, suggesting that ESR1 mutations hamper the inhibitory effects of CDK4/6i alone or in combination with antiestrogens on cell cycle progression. Additionally, RNA-seq analysis showed that cells expressing either the Y537S or D538G mutation had elevated basal gene signatures (METABRIC_basal, TCGA_basal, and Huper_basal) compared to ESR1^{WT} cells, consistent with previous studies suggesting that ESR1 mutations promote a luminal-to-basal subtype switch in ER+ breast cancers. We are currently investigating whether this lineage reprogramming underlies resistance to CDK4/6i in ESR1-mutant cells. In addition, we will validate our findings by analyzing the tumor tissue transcriptome from the patients included in this study.

Conclusions: ESR1 mutations are enriched following treatment with CDK4/6i in a cohort of 3,958 patients with ER+/HER2- metastatic breast cancer. Mutations in ESR1 in ER+ breast cancer cells directly promote resistance to CDK4/6i alone or CDK4/6i + antiestrogens in vitro and in vivo.

PO3-23-10

Continued treatment with CDK4/6 inhibitors slow tumor progression by extending G1-phase duration in drug resistant populations.

Presenting Author(s) and Co-Author(s):

J. Armand. Columbia University Medical Center, New York, New York, United States

S. Kim. Columbia University Medical Center, New York, New York, United States

H. Yang. Columbia University Medical Center, New York, New York, United States

CDK4/6 inhibitors (CDK4/6i) have significantly improved the prognosis of patients with metastatic hormone receptor-positive breast cancer. However, the development of drug resistance leads to the discontinuation of CDK4/6i treatment. The potential benefits of maintaining CDK4/6i treatment in the context of resistance and their underlying molecular mechanisms remain elusive. Here we show that despite tumor progression, continued treatment with CDK4/6i notably extends the G1 phase in drug-resistant cells, thereby slowing their growth. Our single-cell data reveal that the duration of the G1 phase in these resistant cells is approximately tripled under continuous CDK4/6i treatment compared to conditions with CDK4/6i withdrawal, while the durations of the S and G2 phases remain comparable. The maintenance of CDK4/6i induces an alternative inactivation of the retinoblastoma (Rb) protein in drug-resistant cells through its post-translational degradation. However, this alternative form of Rb inactivation is ineffective and thus induces slow activation kinetics of E2F transcription factors, significantly delaying G1 progression. The beneficial effect of maintaining CDK4/6i treatment was further validated in breast cancer xenograft models. Furthermore, our findings suggest that given the spectrum of various CDK4/6i, switching between different CDK4/6i types after the emergence of drug resistance may further delay tumor progression. This study provides new mechanistic insights into the maintenance of CDK4/6i treatment despite the development of drug resistance.

PO3-23-11

Multomics analysis of ER+ breast cancer with matched primaries, lymph node metastases and recurrent cancers on adjuvant endocrine therapy

Presenting Author(s) and Co-Author(s):

C. Martinez-Perez. The University of Edinburgh, Edinburgh, Scotland, United Kingdom

C. Kay. The University of Edinburgh, United States

R. Swan. NHS Lothian, Edinburgh, Northern Ireland, United Kingdom

L. Renshaw. NHS Lothian, Edinburgh, Scotland, United Kingdom

J. Dixon. The University of Edinburgh / Edinburgh Breast Unit, United States

A. Turnbull. The University of Edinburgh, United States

Background: 80% of all breast cancers (BCs) are ER-positive (ER+). A significant number develop endocrine therapy resistance (ETR). Clones develop in lymph nodes (LNs) which differ from the primary and these are implicated in ETR. A multomics analysis of primary ER+ breast cancers, matched LN metastasis (LN+), if present, and matched recurrences (primary, nodal or distant) has been performed. **Patients and Methods:** The patients included are: Cohort A: 95 patients with matched primary and recurrent ER+ BC on different endocrine therapies. 35% had involved LNs at diagnosis. Recurrences: local in 59/95, concurrent local and nodal in 33/95, LN-only in 3/95. Median time to recurrence 4.5 years. Cohort B: 18 patients with ER+ LN+ BC who developed multiple recurrences (local and/or nodal, >3 consecutive recurrences/patient) on different lines of sequential endocrine therapy. Cohort C: 7 patients with ER+ breast cancer with multiple involved LNs treated with 3-6 months of neoadjuvant ET before surgery. Biopsies of primary and matched LNs performed at diagnosis and throughout treatment (3-4 timepoints/patient). Clinical response by serial ultrasound. Primary and LN samples (mean 12 samples/patient) were analysed together with normal DNA. Targeted RNAseq and DNA exome sequencing and whole-genome expression analysis was performed. Somatic mutations and copy number alterations (CNA) were determined, and differential gene expression analysis was performed. Validation of pathways implicated in ETR was by spatial NanoString GeoMx. All patients have long term follow-up. **Results:** Cohort A: A mean of 6 potential driver mutations identified by DNA sequencing in each primary BC (range 1-16). Most commonly mutated genes were PIK3CA, TP53, ERBB4, MAP3K1 and ERBB3. Multiple aberrations and a highly diverse mutational landscape were observed in all recurrences. In the majority of recurrences significant changes in variant allele frequency (VAF) were identified across several ETR-implicated genes and in over 50% new gains/losses were identified. Most frequently, losses were seen in ERBB3, ARID1A, HRAS and FOXA1 with gains in CDH1, NF1, PIK3CA, ESR1, TBX3 and GATA3 in recurrences vs primaries. Transcriptomic analysis revealed differentially expressed pathways including ER, HER2, GATA3, AKT, RAS and p63 signalling. Integrated analysis revealed several driver mutations with corresponding changes in upstream pathway activity. 33 patients had concurrent local and nodal recurrences and 52% had similar somatic mutation profiles in both with only minor variance in VAF. In 48%, 1 or more new potential driver mutations was identified in axillary nodes compared to recurrent primary cancers with losses in AKT1, CDH1 and TP53 being most common. Multomics profiling of Cohorts B and C is complete and analysis underway. **Discussion:** This multomics study is the largest cohort to-date of matched early and recurrent ER+/HER2- cancers. It sheds new light on the complex somatic and transcriptomic changes in local and nodal recurrent disease. The mechanisms of ETR are diverse and underlying mechanisms and clinically meaningful biomarkers including potentially actionable mutations and targets have been identified. Cohort

C will uniquely capture and compare clonal evolution of breast cancer in primary and multiple matched lymph during neoadjuvant ET.

PO3-24-01

Mapping inter- and intra-tumor heterogeneity in Ductal Carcinoma in situ and invasive breast cancer using integrative multi-omic profiling

Presenting Author(s) and Co-Author(s):

H. Kaplan. Swedish Cancer Institute, United States

A. Dowdell. Earle A Chiles Research Institute, Providence Cancer Center, Portland, Oregon, United States

R. Ben Shimoli. Earle A Chiles Research Institute, Providence Cancer Center, Portland, Oregon, United States

A. Crabtree. Earle A Chiles Research Institute, Providence Cancer Center, Portland, Oregon, United States

A. Berry. Syapse, San Francisco, California, United States

F. Robinson. Earle A Chiles Research Institute, Providence Cancer Center, Portland, Oregon, United States

C. Carney. Paul G Allen Research Center, Swedish Cancer Institute, Seattle, Washington, United States

C. Bifulco. Earle A Chiles Research Institute, Providence Cancer Center, Portland, Oregon, United States

B. Piening. Earle A Chiles Research Institute, Providence Cancer Center, Portland, Oregon, United States

Background: Molecular profiling of ductal carcinoma in situ (DCIS) has shown some prognostic utility in the clinic. However, there is still an incomplete understanding of the diversity of molecular mechanisms by which DCIS progresses to invasive breast cancer (IBC). Here, we utilize integrative multi-omic profiling of co-occurring DCIS and IBC in humans as a model for mapping the relationship between tumor mutations, global gene expression and morphological changes in DCIS and IBC. **Methods:** We performed targeted panel DNA sequencing (Tempus xT), whole transcriptome profiling and hyperplex immunofluorescence (Lunaphore COMET) on a cohort of 39 pairs of co-occurring DCIS and IBC lesions. We performed an integrative analysis of the above multi-modal data to uncover similar and dissimilar molecular trajectories in DCIS/IBC pairs. DAVID, KEGG and Reactome databases were utilized to analyze differential pathway activity between DCIS and IBC lesions. **Results:** IBC samples significantly overexpressed pathways associated with cycling cells and proliferation. For DCIS, many of the enriched pathways were related to CYP enzymes and xenobiotic metabolism. We also assessed enrichment of specific transcription factor binding sites (TFBS) with the associated differentially expressed genes. The top site enriched in IBC was a promoter regulatory element of unknown function (M120 motif KRCTCNNNNMANAGC) as well as sites regulated by heat shock transcription factor 4 (HSF4). Top TFBS enriched in DCIS included MEF2, HMEF2, AR and CEBPE. The top pathways associated with IBC using DAVID were related to extracellular matrix (ECM) organization and regulation. Interestingly, the top pathways associated with DCIS also included several pathways associated with ECM organization. On Reactome pathways diagrams for ECM formation distinct components of ECM formation and organization were enriched in IBC vs DCIS lesions, with invadopodia formation components and proteoglycans specifically enriched in IBC and integrin/laminin signaling enriched in DCIS. Among the 39 cases profiled, we observed distinct patterns of DCIS/IBC pairs with highly similar mutational profiles indicative of derivation from a shared progenitor as well as pairs with

little-to-no molecular concordance that likely arose independently. Even within mutationally similar DCIS/IBC pairs there were different degrees of gene expression concordance. We subdivided mutationally similar pairs into two groups based on gene expression similarity (Euclidean Distance) and identified 115 genes that differed between these groups ($q < 0.05$), with the dissimilar DCIS lesions hallmarked by upregulation of a variety of pathways related to B-cell function, complement cascade and cell cycle progression. Specific mutations also were related to conserved transcriptional programs in these lesions, with MCL-1 amplified tumors showing a common gene expression signature of 357 altered genes ($q < 0.05$) with key differences in extracellular matrix organization and adaptive immune response pathways. Dissimilarly, tumors with CKS1B copy number alterations associated with 627 differentially expressed genes ($q < 0.05$) with the top targets related to endothelial function and angiogenesis. **Conclusions:** Integrative multi-modal analysis helps us better understand tumor progression at multiple levels of biomolecular dysregulation and shows the complex interplay among genome alterations, gene expression reprogramming and tissue morphology. Such approaches may yield future biomarker signatures that better encapsulate the diverse mechanisms by which DCIS lesions evolve.

PO3-24-02

Molecular characterization and therapeutic approach for VISTA+ triple-negative breast cancers

Presenting Author(s) and Co-Author(s):

Y. Zhao. UT Southwestern Medical Center, United States

F. Charles. UT Southwestern Medical Center, United States

A. Lipchik. UT Southwestern Medical Center, United States

Y. Peng. UT Southwestern Medical Center, United States

J. Ford. Stanford Cancer Institute, Stanford University School of Medicine, Stanford CA, Stanford, California, United States

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

S. Zhang. UT Southwestern Medical Center, United States

A. Kurian. Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California, United States

M. Snyder. Stanford University, United States

J. Gruber. University of Texas Southwestern Medical Center, United States

Introduction: Current FDA-approved immunotherapeutics for triple-negative breast cancer are only available for a subset of patients, highlighting the need to develop improved immune-targeting strategies. VISTA (V-domain Ig suppressor of T cell activation) is a single-pass transmembrane immune checkpoint receptor that is an emerging clinical target for cancer immunotherapy. It is expressed widely on lymphoid and myeloid cells in healthy individuals, is commonly expressed on cells of the tumor microenvironment and can be abnormally upregulated on tumor cells in a wide variety of tumors. Although VISTA confers quiescence to naïve T cells, molecular mechanisms responsible for this effect remain unclear. Also, the effects of VISTA expression on tumor cells remains poorly defined. **Methods:** Multi-omic profiling was performed in human breast cancer cells lines to determine immune regulatory genes controlled by growth factor stimulation. Human triple-negative breast cancer tumor specimens (N=248) were examined by immunohistochemistry for expression of VISTA, PDL1, PD1 and FoxP3. VISTA expression was engineered into human and mouse triple-negative breast cancer cell lines and growth metrics were characterized in vitro and in immunocompetent (syngeneic) and immunodeficient (xenograft) mouse tumor models. Membrane receptor trafficking and localization of EGFR was performed in human TNBC cells lines expressing VISTA and VISTA mutants. Proximity biotinylation identified protein partners that interacted with VISTA's intracellular domain. Deletion mutagenesis was performed to identify motifs required for biochemical interactions between VISTA and clathrin adaptor proteins. Clathrin adapter localization was examined in WT and VISTA knock-out cell lines. Cytokine response, clathrin adaptor localization and tumor growth kinetics were measured in TNBC cell lines expressing VISTA or VISTA mutants. **Results:** A class of human triple-negative breast cancers were identified with high VISTA expression, low tumor infiltrating lymphocytes and low proliferative index (8-20% of all TNBCs). Tumor models demonstrated that enforced expression of VISTA in tumor cells caused growth suppression, even in the absence of an immune system. This effect was mapped to the cytoplasmic domain of VISTA, which lacks defined signaling domains. Through biochemical approaches, the clathrin-adaptor molecules NUMB and GULP1 were found in complex with a VISTA intracellular NPGF motif. This motif sequestered NUMB at early endosomes, resulting in diminished NUMB recycling for EGFR

endocytosis, thereby causing growth suppression. VISTA impaired NUMB recycling by blocking Rab11 effector complex formation. VISTA NPGF mutations did not disrupt cytokine secretion in mixed lymphocyte assays. VISTA-targeted antibodies did not disrupt NUMB sequestration. VISTA+ tumors were selectively sensitive to VISTA-blocking antibodies. **Conclusions:** VISTA+ TNBC have distinct features including slower proliferative index and increased sensitivity to VISTA-blocking antibodies. This work identifies mechanisms by which VISTA enforces a quiescent cellular state by sequestering clathrin adapter proteins away from sites of endocytosis in cancer cells. This is the first description of intracellular molecular mechanisms controlled by VISTA's intracellular tail. It may inform features of the VISTA-dependent immune checkpoint that could be exploited to improve anti-tumor immunity.

PO3-24-03

Cisplatin synergizes immune checkpoint blocking through RNFT1 mediated PD-L1 recycling in Triple Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Chu. Nanjing Medical University, United States

Y. Zhang. Nanjing Medical University, United States

Y. Hua. The First Affiliated Hospital of Nanjing Medical University, United States

J. Gong. Nanjing Medical University, United States

J. Mei. The First Affiliated Hospital of Nanjing Medical University, United States

Z. Fu. Nanjing Medical University, United States

Y. Yin. The First Affiliated Hospital of Nanjing Medical University, United States

Since chemotherapy showed synergies with PD-1/PD-L1 blockage therapy in solid tumors, the efficacy in triple negative breast cancer (TNBC) varies greatly and only a subset of patients achieves durable responses. To increase their clinical efficacy, it is important to explore the underlying mechanisms of immune checkpoint ligand PD-L1. Here, we found cisplatin influenced the controlled intracellular transport of PDL1 by inducing the RNFT1-mediated endoplasmic reticulum autophagy. Overexpression of RNFT1 increases the endocytosis-recycling rate of the plasm membrane PD-L1, which is regulated by K63-polyubiquitination and endoplasmic reticulum autophagy degradation of PD-L1, thereby having negative impact on antitumor immunotherapy, such as reduced effective drug concentration and avoiding immune surveillance. Genetically or pharmacologically modulating RNFT1-induced K63 polyubiquitination blocks endocytosis of PD-L1, consequently enhances the antitumor response to PD-L1 blockade. Thus, our results suggest that cisplatin treatment is involved in RNFT1-induced K63 polyubiquitination of PD-L1 endocytosis-recycling pathway that governs immune response, and blocking RNFT1 might enhance the efficacy of PD-1/PD-L1 blockade. These studies have high application and translational potential in triple-negative breast cancer.

PO3-24-04

Altered epigenetic modifications and genome architecture reshape lipid metabolism during secondary trastuzumab resistance formation of HER2-positive breast cancer

Presenting Author(s) and Co-Author(s):

N. Duan. The First Affiliated Hospital of Nanjing Medical University, United States

Y. Hua. The First Affiliated Hospital of Nanjing Medical University, United States

Y. Yin. The First Affiliated Hospital of Nanjing Medical University, United States

Title

Altered epigenetic modifications and genome architecture reshape lipid metabolism during secondary trastuzumab resistance formation of HER2-positive breast cancer

Background

Secondary trastuzumab resistance seriously affects the treatment of HER2-positive breast cancer. Although studies have demonstrated several key cellular properties that are closely accompanied with trastuzumab resistance formation, we still have poor knowledge on the genetic and epigenetic variations that promote such transformation. Here we suggested that the epigenetic modification changes on histone H3 together with altered chromatin architecture promote lipid metabolism reprogramming during secondary trastuzumab formation.

Materials and methods

Induced secondary trastuzumab-resistant SKBR3_HR cell line together with the original trastuzumab-sensitive SKBR3 cell line were applied in this study. Total RNA was collected for transcriptome analysis. Anti-H3K4me3 and K27me3 antibodies were chosen for CUT&Tag sequencing library preparation. Total genome DNA was prepared for Micro-C sequencing library preparation. Activity score of metabolism pathway was calculated as relative gene expression value averaged over all genes in this pathway in certain cell types.

Results

Upregulation of arachidonic acid metabolism and downregulation of unsaturated fatty acid synthesis, which are mainly characterized by the activation of PTGS1 and PTGES genes and the repression of FASN and SCD genes, respectively, were observed during the formation of secondary trastuzumab resistance from SKBR3 cell to SKBR3_HR cells.

Variations of H3k4me3 instead of H3k27me3 regulate the expression of these 4 genes. The accumulation of H3k4me3 was detected at the promoters of PTGS1 and PTGES genes while they were removed from the promoters of FASN and SCD genes in SKBR3_HR cells.

More intra-chromosomal interactions were constituted during resistance formation. In detail, 4626 and 4394 topological associated domains, 3125 and 5824 DNA loops were founded in SKBR3 and SKBR3_HR cells, respectively. Furthermore, the lost and gained DNA loops between SCD and PTGS1 genes and distant genome regions may indicate the weaken and strengthen interactions with transcriptional regulators located there.

Conclusions

During trastuzumab resistance formation, altered histone modifications as well as higher genome structure could regulate the expression of key genes in lipid metabolism pathways,

which may further affect cell properties and interactions with cells in tumor microenvironment.

PO3-24-05

Cysteine metabolism related ferroptosis sensitivity in trastuzumab resistant HER2 positive breast cancer

Presenting Author(s) and Co-Author(s):

Y. Yin. The First Affiliated Hospital of Nanjing Medical University, United States

Y. Hua. The First Affiliated Hospital of Nanjing Medical University, United States

N. Duan. The First Affiliated Hospital of Nanjing Medical University, United States

C. Sun. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

F. Yang. Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, United States

Background Trastuzumab has shown great effectiveness in HER2 positive breast cancer treatment, but about 50% patients would undergo resistance during or after treatment. Although previous research has suggested several potential reasons for trastuzumab resistance, the metabolic reprogramming during resistance formation remains largely unclear. Here we identified aberrant ferroptosis associated cysteine metabolism in trastuzumab resistant HER2 positive breast cancer, which might become a novel target for overcoming resistance. Methods Trastuzumab sensitive HER2 positive breast cancer cell SKBR3 and resistant JIMT1 were obtained for transcriptomics, proteomics, metabolomics and epigenomics analysis. Gene silencing was mediated by siRNAs. CUT&Tag was applied to compare H3K4me3 and H3K27me3 binding regions. DNA methylation levels and different methylated regions were evaluated by WGBS-seq. CRISPRi with dCas9-DNMT3A was applied to regulate specific DNA methylation in CpG islands. Lipid ROS was measured by flow cytometry with BODIPY-C11. Results Joint analyses of transcriptomics and proteomics according to ferroptosis pathways revealed downregulated glutathione metabolism, glutamate transmembrane and homocysteine metabolism processes, as well as upregulated fatty acid metabolism and iron metabolism pathways in JIMT1. Metabolomics verified that JIMT1 increased cysteine metabolism and decreased glutathione metabolism. SLC7A11 expression and GSH/GSSG ratio were increased in JIMT1, while no difference was observed in free cysteine. JIMT1 featured significant higher UGC codon usage bias and increased cysteinyl-tRNA synthetase. The abundance of H3K4me3 other than H3K27me3 in SLC7A11 promoter region was found increased in JIMT1, and the 5-mC level of CpG islands in SLC7A11 promoter region was shown decreased. Using dCas9-DNMT3A, the methylation of SLC7A11 promoter was enhanced and SLC7A11 expression was reduced in JIMT1. Inhibition of SLC7A11 by siRNAs, CRISPRi or Erastin all indicated a higher ferroptosis sensitivity in JIMT1. Conclusion Trastuzumab resistant HER2 positive breast cancer features aberrant cysteine metabolism resulting from altered H3K4me3 modification and DNA methylation in SLC7A11 promoter region. This might provide novel targets for further anti-HER2 treatment.

PO3-24-06

Integrative genomic and CRISPR screen analysis identifies synthetic viability interactions in BRCA1/2 cancers

Presenting Author(s) and Co-Author(s):

Y. Zhu. Memorial Sloan Kettering Cancer Center, New York, New York, United States

X. Pei. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

A. Novaj. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

J. Setton. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

F. Derakhshan. Department of Pathology and Cell Biology, Columbia University, United States

P. Selenica. Memorial Sloan Kettering Cancer Center, United States

N. McDermott. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

S. Sinha. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

A. Khan. MSKCC, United States

S. Powell. MSKCC, United States

J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States

N. Riaz. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

Background Pathogenic BRCA1 and BRCA2 (BRCA1/2) germline mutations contribute to hereditary breast cancer and are linked with increased risk of other cancers. Paradoxically, bi-allelic inactivation of BRCA1/2 (bBRCA1/2) is embryonically lethal. Although TP53 loss can at least in part mitigate the deleterious impact of Brca1 deficiency in mice, this is insufficient in human cells to compensate for decreased proliferative capacity. What other compensatory mechanisms facilitate oncogenesis remains unclear. **Methods** We performed an integrative analysis of cancer genomes from bBRCA1/2 tumors and CRISPR/Cas9 screens from cellular models to identify novel gene candidates that facilitate synthetic viability. First, we analyzed cancer genomes from ovarian and breast cancer derived from TCGA and identified genomic loci, which were enriched for recurrent copy number alterations (CNAs) in bBRCA1/2 tumors. We subsequently identified genes from these CNA loci that had corresponding changes in gene expression. Then, we used high-throughput genome-wide CRISPR/Cas9 knockout screens in BRCA1/2^{-/-} cell lines (BRCA1^{-/-} in RPE1 cells, BRCA2^{-/-} in DLD1 cells) to identify which of these genes increased cell proliferation in vitro. Lastly, we experimentally validated these synthetic viable interactions using an orthogonal MCF12a system to evaluate changes in colony formation with a clonogenic cell survival assay. **Results** In human cancer genomes, we identified that bBRCA1/2 tumors harbored recurrent large-scale genetic deletions significantly more frequent than histologically matched control tumors. We identified 148 cytobands (23 distinct genomic loci) frequently deleted in bBRCA1/2 ovarian cancers (N=92), and 90 cytobands (15 distinct genomic loci) in bBRCA1/2 ER+ breast cancers (N=30). Subsequent computational analysis of gene expression data identified transcriptionally decreased genes in the frequently deleted loci. Cross-referencing with CRISPR/Cas9 screens in BRCA1/2^{-/-} cells,

we ultimately identified 277 and 218 genes that were altered in human tumors and putatively enhanced viability in BRCA1/2-null models but not in isogenic wild-type cell lines in BRCA1 and BRCA2 models, respectively. We subsequently selected 17 genes that either increased viability in BRCA1, BRCA2, or both contexts for experimental validation. Of these, about 40% (7 of 17) were experimentally validated (RIC8A, GNA12, ATMIN, IPO7, ATXN2, KDM1A, and NUP98) and had evidence of synthetic viability in this cellular context. Interestingly, RIC8A and GNA12 interact with each other, are both involved in G protein-coupled signaling pathway, and are synthetically viable with both BRCA1^{-/-} and BRCA2^{-/-} cells. In a re-analysis of a recently published genomic dataset on metastatic breast cancer, we found that homologous recombination deficient tumors developed additional loss of function mutations in RIC8A in the metastatic setting. **Conclusions** This study provides insights into the oncogenesis of BRCA1/2 malignancies and describes a high-throughput framework to identify synthetic viability interactions and causal driver genes affected by large-scale CNAs in human cancers.

PO3-24-07

The role of Hepatitis A Virus Cellular Receptor 1 (HAVCR1) in breast cancer and the impact on penetration of blood brain barrier

Presenting Author(s) and Co-Author(s):

X. CAO. 1.Cardiff University School of Medicine;2.Tianjin Medical University;3. Shandong Cancer Hospital and Institute., United States

B. Cong. 1.Cardiff University School of Medicine;2.Shandong Cancer Hospital and Institute., United States

W. Jiang. Cardiff University, United States

T. Martin. Cardiff University, Cardiff, United States

Background: Hepatitis A Virus Cellular Receptor 1 (HAVCR1) is associated with the biological behaviour of several cancers, and has been shown to regulate junctional complexes. However, its role in breast cancer remains unexplored. This study aimed to investigate the effects of HAVCR1 on human breast cancer. Methods: We explored the UALCAN web portal, which is linked to the TCGA database, to determine the expression of HAVCR1 in breast cancer and the Kaplan-Meier plotter to evaluate the correlation with the survival of the patients. HAVCR1 siRNA was used to knock down the HAVCR1 expression in MCF-7 and MDA-MB-231 cell lines. In vitro cell growth, wounding healing, and electric cell impedance sensing (ECIS for assessing cellular proliferation, migration and adhesion) assays were used. Transepithelial resistance (TEER) and paracellular permeability (PCP) were assessed to determine changes in the barrier function of human breast cancer cells. The expression of HAVCR1 and prospective interactive binding molecules of HAVCR1 protein was assessed using quantitative polymerase chain reaction (qPCR). Cellular response to docetaxel was evaluated and shown (IC₅₀). The invasiveness of breast cancer cells through the human cerebral microvessel endothelial cells (hCMEC/D3) cell layers was measured using an in vitro transwell cell invasion assay. Results: HAVCR1 gene expression levels were significantly lower ($P < 0.001$) in breast cancer tissue compared with normal tissues. Patients with high expression of HAVCR1 had a significantly better relapse-free survival than low expression ($P < 0.001$). There was no significant difference in overall survival (OS) between the HAVCR1 high and the low expression groups ($P = 0.22$). However, in subgroup analysis, high HAVCR1 expression was associated with better OS in luminal A ($P = 0.04$). Knockdown (KD) HAVCR1 in breast cancer cells influence cell function by enhanced adhesion, proliferation, and migration compared to wild type (WT) cell lines. It was noted that loss of HAVCR1 rendered both MCF-7 and MDA-MB-231 cells resistant to docetaxel (IC₅₀ for WT and HAVCR1 KD respectively being 0.86nM vs 1.75nM for MCF-7 and 1.35nM vs 15.48nM for MDA-MB-231). HAVCR1 KD increase adhesion to hCMEC/D3 cells (53.14±8.23 vs ±99.37±8.97 for MCF-7, $P < 0.001$; 109.5±97.56 vs 147.1±96.63 for MDA-MB-231, $P = 0.228$, WT and HAVCR1 KD). In the cerebral endothelial cell invasion assay, we found that HAVCR1 KD resulted in a significantly increased invasion of the breast cancer cells through the endothelium (19.27±8.74 vs 33.58±16.81 for MDA-MB-231, $P = 0.0114$, WT and HAVCR1 KD). For the barrier function, the knockdown led to a decrease in TEER and an increase in PCP when compared with WT cells in both cell lines. HAVCR1 KD cells showed decreased barrier function, together with reduced expression of Claudin-1/8/10, occludin, MarvelD3, Tricellulin and ZO1. Conclusions: HAVCR1 is a potential biomarker for breast cancer prognosis. HAVCR1 influences the integrity of barrier function by influence the gene expression of tight junction in breast cancer, and influence the penetration to blood brain barrier. Together, it suggests that HAVCR1 may be a potential therapeutic target in breast cancer.

PO3-24-08

Establishment of a selective culture method for breast cancer stem cells derived from patient tissue and a subgroup analysis of cancer stem cells

Presenting Author(s) and Co-Author(s):

S. Sueoka. Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, United States

T. Kadoya. Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, United States

K. Azusa. Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, United States

S. Sasada. Hiroshima University, United States

A. Emi. Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, United States

M. Okada. Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, United States

Y. Kobayashi. Department of Pharmacology, Asahikawa Medical University, United States

K. Nakayama. Department of Pharmacology, Asahikawa Medical University, United States

Purpose

Cancer stem cells are considered to cause recurrence and metastasis due to their resistance to drug and radiation therapy. Breast cancer stem cells are therefore the true target for the treatment of breast cancer. In this study, we established a method to selectively culture breast cancer stem cells from patient-derived breast cancer tissue, and we analyzed their characteristics using immunostaining to identify gene expression.

Method

Breast cancer tissues from ER+, HER2- and drug-naive patients were fragmented and cultured using low-adherent plates (spheroid culture). We investigated the stemness of the breast cancer cells obtained by the spheroid culture by immunostaining the breast cancer stem cell markers and examining their proliferation and differentiation in a mouse transplantation model. The diversity of the cells was further examined by means of the expression of the EMT markers and genetic analysis.

Results

In 48 cases, the proportion of CD44+/CD24- breast cancer cells increased from 13.8% to 61.6% in the spheroid culture. In addition, even small numbers of cells obtained by the spheroid culture were transplanted into mice, and the transplanted cells subsequently differentiated in the mice, demonstrating their stemness. ER expression was negatively changed in 52.1% of cases, and the expression of EMT markers, Twist, Snail, and Vimentin, was increased from 43.8% to 75.0%, 12.9% to 58.1%, and 7.71% to 37.7%, respectively. A DNA microarray with 14 cases showed that breast cancer stem cells obtained from ER+ and HER2- breast cancer tissue were classified into two groups.

Conclusion

We demonstrated that breast cancer stem cells were selectively cultured from patient-derived breast cancer tissue in a spheroid culture. Furthermore, breast cancer stem cells have different

characteristics from breast cancer cells in primary tumors and are diverse at an EMT level, and in genetic analyses.

Expression of primary tumors and spheroids

		primary tumors	spheroids
CD44+/CD24-	(mean ± SD)(%)	13.8 ± 10.6	61.6 ± 33.8
ER	(Allred total score)		
0-2		0 (0)	25 (52.1)
3-5		0 (0)	11 (22.9)
6-8		48 (100)	12 (25.0)
PgR	(Allred total score)		
0-2		6 (12.5)	33 (68.8)
3-5		11 (22.9)	7 (14.6)
6-8		31 (64.6)	8 (16.7)
Twist1+	(mean ± SD)(%)	43.8 ± 13.8	75.0 ± 18.1
Snail+	(mean ± SD)(%)	12.9 ± 12.2	58.1 ± 20.1
Vimentin+	(mean ± SD)(%)	7.71 ± 9.63	37.7 ± 13.4

PO3-24-09

May ESR1 mutant breast cancer cells influence fibroblast phenotype?

Presenting Author(s) and Co-Author(s):

L. Gelsomino. University of Calabria, Italy

A. Caruso. University of Calabria, United States

R. Malivindi. University of Calabria, Italy

A. Leonetti. University of Calabria, United States

E. Tasan. University of Calabria, United States

S. Panza. University of Calabria, United States

G. Naimo. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

I. BARONE. Department of Pharmacy and Health and Nutritional Sciences, Centro Sanitario, University of Calabria, United States

C. GIORDANO. Department of Pharmacy and Health and Nutritional Sciences, Centro Sanitario, University of Calabria, United States

D. Bonofiglio. University of Calabria, United States

L. Mauro. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

G. Gu. Baylor College of Medicine, United States

S. Fuqua. Baylor College of Medicine, United States

S. CATALANO. Department of Pharmacy and Health and Nutritional Sciences, Centro Sanitario, University of Calabria, United States

S. Andò. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

May ESR1 mutant breast cancer cells influence fibroblast phenotype? Gelsomino L^{1,2}, Caruso A¹, Malivindi R¹, Leonetti AE¹, Tasan E¹, Panza S¹, Naimo GD¹, Barone I^{1,2}, Giordano C^{1,2}, Bonofiglio D^{1,2}, Mauro L¹, Gu G³, Fuqua SAW³, Catalano S^{1,2}, Andò S^{1,2} ¹Department of Pharmacy and Health and Nutritional Sciences, University of Calabria, Rende, Italy. ²Centro Sanitario, University of Calabria, Via P. Bucci, Rende, Italy. ³Lester & Sue Smith Breast Center, Baylor College of Medicine, Houston, TX, USA. For almost 50 years, it has been postulated that carcinogenesis relies on the intrinsic genetic abnormalities of tumor cells, but in the last decades, it has been reported that their functional interactions with the tumor microenvironment (TME) might affect therapy response and contribute to the disease progression. Based on these observations, the aim of the present study was to investigate the functional interactions between one of the essential components of TME, the fibroblasts, and breast cancer (BC) cells, expressing mutations in the hormone-binding domain (HBD) of the gene encoding for the estrogen receptor alpha (ESR1). Thus, we employed estrogen receptor-positive MCF-7 BC cells CRISPR engineered to express the Y537S-HBD mutation. Y537S is the most commonly detected mutation harbored in HBD-ESR1 and is a major contributor to endocrine therapy resistance and poor clinical outcome in BC. We collected conditioned media (CM) from BC cells and fibroblasts isolated from primary human tissues (normal fibroblasts, NFs, and cancer-associated fibroblasts, CAFs) in order to assess in vitro co-culture systems that can mimic the

complex in vivo TME. It was interesting to observe that CAFs displayed a significant increase in their proliferation and migration when exposed to CM of mutant BC cells with respect to the parental ones. These latter findings fit with the immunofluorescence analysis showing a more evident formation of actin stress fibers. However, proteomic analysis demonstrated, in the same circumstances, more significant changes in NFs than in CAFs. Among the up-regulated proteins revealed by NFs upon Y537S-CM exposure, most of them overlap the up-regulated proteins featuring the intrinsic phenotype of CAFs, mainly involved in the cellular ultrastructural organization (i.e. cytoskeleton, focal adhesion, vesicle, and organelle) as evidenced by Metacore functional analysis. On the other side, we demonstrated that mutant clones showed more aggressive behavior in terms of proliferation, growth, migration, and invasion, compared to the parental counterpart upon exposure to the CM-derived from NFs and CAFs. This led us to further investigate the intrinsic properties of the mutated clones through their genomic and proteomic profiles that evidenced, by using Metacore software, an enrichment of insulin-like growth factor 1 receptor (IGF1R) pathway. The relevance of the latter datum was confirmed by the higher content of the IGF-1 ligand found in the secretome of mutant cells. Thus, the short autocrine loop maintaining IGF1/IGF1R signaling activation in mutant clones might reasonably play an important role in mediating the autocrine and paracrine effects between mutant cells and fibroblasts. For instance, the pharmacological blockade of IGF1R signaling interfered with the reciprocal interactions between fibroblasts and BC cells that sustained tumor growth and progression as evidenced in both “in vitro” and “in vivo” experiments. In conclusion, our study addressed the IGF1R pathway as a potential druggable target helpful to disconnect mutant breast cancer cell-fibroblast crosstalk that potentiates breast tumor growth and progression.

PO3-24-10

Losartan enhances the radiosensitivity of triple-negative breast cancer by reshaping the tumor immune microenvironment

Presenting Author(s) and Co-Author(s):

C. Liu. Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China, United States

X. Wang. Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China, United States

Z. Xia. Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China, United States

Y. Ma. Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China, United States

Y. Zhao. Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China, United States

Triple-negative breast cancer (TNBC) represents the most aggressive subtype of breast cancer, and the therapeutic options available for TNBC are limited. In addition to surgery and chemotherapy, radiotherapy (RT) is a primary treatment modality for TNBC. However, radio-resistance poses significant challenges to TNBC treatment. Prior research has shown that losartan, an angiotensin receptor blocker, can improve vessel perfusion and drug delivery, thereby enhancing the efficacy of chemotherapy or radiotherapy in cancer. However, in our study, we found that losartan could enhance the radiosensitivity of TNBC in immunocompetent mice model, but not in immunodeficient mice model and TNBC cells. It suggested that losartan might enhance the radiosensitivity of TNBC in an immune system dependent way. Previous studies had noted that tumor immune microenvironment (TIME) played an important role in radio-resistance. Therefore, we focused on the TIME in our further study. For immune cells, it had reported that the recruitment and activation of immunosuppressive cells such as M2 phenotype tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), could lead to the establishment of and immunosuppressive TIME and decreased the radiosensitivity. In this study, we found losartan facilitated the polarization of TAMs towards the M1 phenotype, and impeded the immunosuppressive function of MDSCs after RT in 4T1 TNBC mice model. Additionally, losartan also caused a significant increase of CD8⁺ T lymphocytes in the TIME, and also markedly enhanced the activity of infiltrated T cell. When the CD8⁺ T cells were eliminated by anti-CD8 α antibody, the radiosensitization effect of losartan was significantly decreased. Therefore, T-cell mediated tumor suppression is essential for the radiosensitization caused by losartan in TNBC. For immune factors, we found that TNBC exhibited an increase in the expression of programmed death-ligand (PD-L1) and indoleamine-2,3-dioxygenase (IDO) upon exposure to irradiation, and the combination of losartan resulted in a significant reduction in their expression in vitro and in vivo. At the same time, the 4T1 TNBC transplantation tumors were significantly inhibited by losartan combined with PD-1 inhibitor after RT, which indicated that losartan might amplify the efficacy of radio-immunotherapy. Collectively, these findings suggest that losartan could reshape the TIME of TNBC through regulating immune cells (TAMs, MDSCs and CD8⁺ T cells) and immune factors (PD-L1 and IDO), which result in the enhancement of radiosensitivity of TNBC. In our investigation, losartan was innovatively found to increase the radiosensitivity of TNBC by reshaping the TIME rather than on the tumor stroma. As one of the most commonly prescribed drugs for hypertension, the safety and affordability of losartan have been extensively confirmed. In the future, losartan combined with radiotherapy might be a promising strategy for TNBC treatment.

PO3-24-11

Impact of Circulating Extracellular Vesicles derived from Obese Women on Pro-Tumor Functions of Stromal Fibroblasts in Breast Cancer

Presenting Author(s) and Co-Author(s):

I. BARONE. Department of Pharmacy and Health and Nutritional Sciences, Centro Sanitario, University of Calabria, United States

P. DEL CONSOLE. Department of Pharmacy and Health and Nutritional Sciences, University of Calabria, United States

F. ACCATTATIS. Department of Pharmacy and Health and Nutritional Sciences, University of Calabria, United States

L. GELSOMINO. Department of Pharmacy and Health and Nutritional Sciences, University of Calabria, United States

G. AUGIMERI. Department of Pharmacy and Health and Nutritional Sciences, University of Calabria, United States

E. AVOLIO. Dept. of Biology, Ecology and Earth Science Dept. (DiBEST), University of Calabria, United States

S. Andò. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

D. BONOFILIO. Department of Pharmacy and Health and Nutritional Sciences, Centro Sanitario, University of Calabria, United States

C. GIORDANO. Department of Pharmacy and Health and Nutritional Sciences, Centro Sanitario, University of Calabria, United States

S. CATALANO. Department of Pharmacy and Health and Nutritional Sciences, Centro Sanitario, University of Calabria, United States

The incidence of obesity has risen sharply worldwide, and growing evidence shows its impact on several malignancies, including breast cancer (BC). Excessive adiposity and high body mass index (BMI) significantly affect BC incidence, prognosis, and therapeutic response of patients. Indeed, obese women exhibit larger tumor size, lymph node involvement, metastatic spread, and poorer survival outcomes. Preclinical and clinical studies indicated that the obese setting provides local and systemic modifications that may stimulate BC progression and influence tumor microenvironment, particularly composed of stromal fibroblasts (SF). The mechanisms behind this interplay are likely to be multifactorial and may involve important adipocyte-derived mediators, such as adipokines and growth factors. Aside from these soluble factors, extracellular vesicles (EVs), nanoscale lipid-bilayer enclosed vesicles released by a variety of cells, are emerging as powerful regulators of cell-to-cell communication able to promote BC initiation, growth, metastatic dissemination and drug resistance. However, the potential impact of obesity-derived EVs in affecting tumor-stimulatory features of SF has not been yet investigated.

To this aim, circulating EVs were isolated from the serum of women categorized as normal weight (NW; $18 < \text{BMI} < 24.9 \text{ Kg/m}^2$) and overweight/obese (OW/Ob; $\text{BMI} > 25 \text{ Kg/m}^2$). Immortalised human mammary control fibroblasts (CF), their cancer-associated counterparts (exp-CAFs), and human CAFs, isolated from biopsies of primary BC, were used as experimental models for stromal fibroblasts. Human MCF-7 and T47D BC cells were employed as experimental cell models for mammary carcinoma in co-culture experiments.

Circulating EVs were successfully extracted from the serum of NW and OW/Ob women, and characterized by their shapes, size and protein markers. Transmission Electron Microscopy (TEM), and Nanoparticle Tracking Analysis (NTA) showed that EVs in the isolated fractions were oval or bowl-shaped with a size range between 50-200 nm. In accordance with the Minimal Information for Studies of Extracellular Vesicles (MISEV) 2018, enrichment of the EV markers TSG101, CD81, and CD63 were all detected in the EV isolated fractions. Interestingly, elevated levels of circulating EVs were detected in OW/Ob women compared to NW subjects. Treatment of CF with OW/Ob-EVs resulted in an increased cell motility, invasiveness, contractility along with an up-regulation of CF markers. BC cells cocultured with conditioned medium (CM) derived from OW/Ob-EV-treated CF exhibited higher anchorage-independent growth and migratory capacity than BC cells cocultured with CM derived from NW-EV-treated CF. Moreover, OW/Ob-EVs enhanced tumor-stimulatory activities of exp-CAFs and CAFs, further highlighting how obese-related EVs may have the potential to modulate fibroblast phenotype in BC. Finally, cytokine arrays revealed that treatment of CF with OW/Ob EVs was associated with an enhanced release of Fibroblast Growth Factor 19 and Cystatin C, factors that are closely related to BC growth and development.

In conclusion, our data provide first evidence for the functional importance of EVs isolated from obese women in impacting tumor-stroma cross-talk and drive BC progression. Since obesity and its pathophysiological sequelae are on the rise, this new knowledge may help to identify specific biomarkers and innovative targets (i.e. FGF-19, and Cystatin C) that may allow a personalized management of patients affected by BC and obesity.

PO3-24-12

CRIPTO-regulated extracellular vesicles mediate heterotypic cellular crosstalk in triple negative breast cancers

Presenting Author(s) and Co-Author(s):

D. Freeman. Huntsman Cancer Institute, United States

B. Spike. Huntsman Cancer Institute, United States

B. Gates. Huntsman Cancer Institute, United States

Tumor progression involves the dynamic interaction between various cell types within the tumor microenvironment. Fibroblasts, which normally participate in wound healing, exhibit reciprocal communication with breast cancer cells that contributes to tumor cell plasticity and heterogeneity. Gaining insights into the molecular mechanisms underlying cell-to-cell communication, which drive cellular plasticity and play a pivotal role in breast cancer progression and metastasis, has the potential to unlock novel avenues for targeted therapeutic interventions.

The small GPI-adaptor protein CRIPTO is a key player in this context. CRIPTO orchestrates the activity of TGF- β and growth factor-like signaling pathways that activate c-Src/MEK/AKT. CRIPTO is expressed during mammary development, wound healing, and breast cancer but is largely undetectable in homeostatic tissue, making it a promising therapeutic target. Our previous studies have demonstrated that the activity of CRIPTO is contingent upon cellular stress, with pronounced influence within pro-fibrotic, hypoxic domains of tumors. Importantly, we have shown that inhibition of CRIPTO using the soluble recombinant protein antagonist A4Fc effectively impedes the progression of triple negative breast cancer (TNBC) in murine xenograft models. Building upon these findings, we have been dissecting CRIPTO's role in coordinating fibroblast activation and cell-state reprogramming in TNBC. Notably, we have found that inhibition of CRIPTO with A4Fc suppresses cancer associated fibroblast (CAF) activation and collagen remodeling in vivo. And, by modeling tumor cell: fibroblast crosstalk using in vitro organoid co-cultures, we have demonstrated CRIPTO expression in tumor cells is necessary for extracellular vesicle (EV) uptake by fibroblasts, their SMAD pathway activation and their priming for reciprocal signaling back to tumor cells to for transcriptional reprogramming and cellular invasion.

The significance of these findings lies in their potential to pave the way for the development of new therapies specifically targeting crucial tumor cell: fibroblast crosstalk mechanisms at primary and metastatic sites. Plasticity targeting therapies are urgently needed in the treatment of TNBC and other malignancies, and hold great promise for improving patient outcomes.

PO3-25-01

CTLA4 expression profiles and their association with clinical outcomes of breast cancer

Presenting Author(s) and Co-Author(s):

W. Noh. Konkuk University Medical Center, United States

Y. Yoo. Konkuk University Medical Center, United States

K. Park. Konkuk University Medical Center, United States

S. Nam. Konkuk University Medical Center, United States

S. Lim. Konkuk University Medical Center, United States

The cytotoxic T-lymphocyte-associated protein 4 (CTLA4) is involved in the progression of various cancers, but its biological roles in breast cancer (BRCA) remain unclear. Therefore, we performed a systematic multiomic analysis to expound on the prognostic value and underlying mechanism of CTLA4 in BRCA. First, the expression of CTLA4 in pan-cancer was evaluated using the platforms of OncoPrint. Afterward, the web-based bioinformatics platforms of GEPIA and UCLAN were used to compare the expression of CTLA4 in breast cancer and normal tissues. Next, we assessed the relationship between CTLA4 mRNA expression and prognosis in breast cancer patients using the PrognScan Database, Kaplan-Meier Plotter, and R2: Kaplan-Meier Scanner. Additionally, the correlation between CTLA4 expression and immune cell infiltration in breast cancer and functional enrichment analysis of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways was performed to elucidate the potential biological functions of CTLA4. Finally, we used the STRINGdb and cytoHubba plugin Cytoscape to create a PPI network and identify known and predicted structural essentials for CTLA4 functions and the top five hub genes. CTLA4 was highly expressed in BRCA tumor tissue compared to normal tissue ($p < 0.01$). The CTLA4 mRNA levels in BRCA based on breast cancer subtypes of luminal, Human epidermal growth factor receptor 2 (HER-2), and Triple-negative breast cancer (TNBC) were considerably higher than in normal tissues ($p < 0.001$). However, the overexpression of CTLA4 was associated with a better prognosis in BRCA ($P < 0.001$), and was correlated with clinicopathological characteristics including age, T-stage, estrogen receptors (ER), progesterone receptors (PR), and PAM50 ($P < 0.01$). The infiltration of multiple immune cells was associated with increased CTLA4 expression in BRCA ($P < 0.001$). CTLA4 was highly enriched in antigen binding, immunoglobulin complexes, lymphocyte-mediated immunity, and cytokine-cytokine receptor interaction. This study provides suggestive evidence of the prognostic role of CTLA4 in breast cancer, which may be a therapeutic target for breast cancer. Furthermore, CTLA4 may influence breast cancer prognosis through antigen binding, immunoglobulin complexes, lymphocyte-mediated immunity, and cytokine-cytokine receptor interaction. These findings help us understand how CTLA4 plays a role in breast cancer and set the stage for more research.

PO3-25-02

Circadian Rhythm Disruption Accelerates Aggressive Mammary Tumorigenesis by Altering Tumor Microenvironment

Presenting Author(s) and Co-Author(s):

O. Ogunlusi. Texas A&M University, College Station, Texas, United States

M. Sarkar. Texas A&M University, United States

T. Nguyen. Texas A&M University, United States

D. Boland. Texas A&M University, United States

J. Cai. Texas A&M University, United States

A. Chakrabarti. Texas A&M University, United States

B. Mallick. Texas A&M University, Texas, United States

A. Keene. Texas A&M University, United States

T. Roy Sarkar. Texas A&M University, College Station, Texas, United States

Circadian Rhythm Disruption Accelerates Aggressive Mammary Tumorigenesis by Altering Tumor Microenvironment

Ogunlusi Ogunlusi¹, Mrinmoy Sarkar¹, Tristan Nguyen¹, Devon Boland², James Cai³, Arhit Chakrabarti⁴, Bani Mallick⁴, Alex Keene¹, Tapasree Roy Sarkar¹

1. Texas A&M University, Department of Biology, College Station, TX. 2. Texas A&M Institute of Genomic Science & Society, College Station, TX. 3. Texas A&M University, Veterinary Integrated Bioscience, College Station, TX. 4. Texas A&M University, Department of Statistics, College Station, TX.

\Breast cancer is the most common cancer in women worldwide, leading to over 650,000 deaths worldwide. The circadian rhythm is a 24-hour biological rhythm that controls most cellular, hormonal, and behavioral processes in living organisms, which is why perturbation of these rhythms is linked to several devastating diseases such as cardiovascular diseases, diabetes, and cancer. In the mammary gland, circadian clocks regulate the rhythmic expression of numerous genes. Circadian rhythm disruption (CRD), which has been termed a "carcinogen" by the International Agency for Research in Cancer, is caused by different factors, one of them being shift work. Several epidemiological studies have revealed that women who work night shifts are predisposed to breast cancer. The aim of this study is to investigate the effect of circadian rhythm disruption on aggressive mammary tumorigenesis. To do this, we used genetically engineered mouse models of mammary tumors (HER2-tumor and triple-negative breast tumor, or TNBC). Chronic jetlag, which mimics shift work in mice and is known to cause CRD, was introduced in one group of mice by perturbing the normal light and dark cycles with an 8-hour advance every three days. Wheel-running, which is represented by an actogram, was used to confirm the circadian disruption in the CRD mice. CRD was found to accelerate tumor initiation with a significant increase in weight in the CRD group of mice. CRD enhanced tumor burden significantly compared to LD mice. Our results also showed high metastatic foci in the lungs of CRD mice compared to LD mice. A flow cytometry study showed a higher cancer stem cell population in CRD tumors. Mammosphere assays with tumor-derived cells showed that CRD increased the number and size of the mammospheres compared to the control tumors. The tumor cells were analyzed using single-cell RNA sequencing, which showed that CRD

alters the tumor microenvironment by developing more immunosuppressive and "cold" tumors. The tumor-derived organoids (tumoroid) showed resistance to chemotherapeutics. Finally, bioinformatics analysis using single-cell RNA seq data from human breast tumors (TNBC, ER/PR, and HER2) showed that the malignant cells in TNBC tumors had a significantly higher circadian rhythm disrupted score (CRD score) compared to ER/PR tumors. Taken together, our data showed how circadian rhythm disruption affects TNBC tumorigenesis and drug response by altering the tumor microenvironment.

Keywords: Breast cancer, circadian rhythm disruption, tumor microenvironment.

PO3-25-03

Can intratumoral microRNA-125a levels be a prognostic biomarker of a ER-positive breast cancer patients ?

Presenting Author(s) and Co-Author(s):

Y. Tokumaru. Breast Surgery, Gifu University Hospital, United States

M. Oshi. Yokohama City University Hospital, Yokohama, Kanagawa, Japan

M. Okawa. Gifu University School of Medicine, Japan

S. Ando. Gifu University School of Medicine, Japan

Y. Niwa. Gifu University School of Medicine, Japan

R. Mori. Gifu University School of Medicine, United States

K. Takabe. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

M. Futamura. Department of Breast Surgery, Gifu University Hospital, Japan

Background: MicroRNA-125a (miR-125a) has been shown to function as tumor suppressive miRNA by pre-clinical in vitro studies. However, to the best of our knowledge, there has been no study that investigated the clinical relevance of miR-125a in breast cancer patients. We hypothesized that miR-125a expression in breast cancer associate with its aggressiveness and can be a prognostic biomarker.

Material and Methods: Non-tumorigenic epithelial cell line, MCF-10A and breast cancer cell lines, MCF-7, T47D, and MDA-MB231, were used to analyze the expression levels of miR-125a as well as cell viability. The data of 2042 patients were extracted from publicly available databases, The Molecular Taxonomy of Breast Cancer International Consortium (METABRIC), The Cancer Genome Atlas (TCGA), and GSE57897. These databases included clinicopathological and survival data as well as transcriptome data. The survival analysis, gene set enrichment analysis (GSEA) were conducted comparing miR-125a high expressing and low expressing tumors, divided by the median cutoff. The association between the miR-125a expression and tumor immune microenvironment was assessed by xCell.

Results: The expression levels of miR-125a were suppressed in breast cancer cell lines, MCF-7, T47D, and MDA-MB231 compared with MCF-10A. This was concordant with human samples. The expression levels of miR-125a were lower in tumors compared with normal breast tissues in both TCGA and GSE57897 cohorts. These results were in agreement with the notion that it is a tumor suppressive miRNA ($p < 0.001$ and $p < 0.001$, respectively). ER-positive/HER2-negative (ER+/HER2-) showed the highest miR-125a expression among the subtypes in TCGA ($p < 0.001$). MiR-125a expression was not associated with cancer staging in any of the subtypes in neither TCGA nor METABRIC cohorts. To our surprise, high miR-125a tumors demonstrated worse disease free survival (DFS), disease specific survival (DSS), and overall survival (OS) compared with low expressing in ER+/HER2- breast cancer patients ($p=0.008$, $p=0.005$, and $p=0.037$) which was not the case for the other subtypes in METABRIC cohort. Interestingly, miR-125a expression was associated with Nottingham histological grade only in ER+/HER2- among the subtypes ($p < 0.001$). Also, high miR-125a tumors significantly demonstrated higher expression of MKI67, one of the most commonly used parameters for cell proliferation, correlated with miR-125a expression in ER+/HER2- ($p=0.02$), but not in other subtypes. Furthermore, high miR-125a tumors enriched four out of five cell proliferation-related gene sets in Hallmark collection, such as E2F Targets, G2M Checkpoint, Mitotic Spindle, and MYC Targets V2 in ER+/HER2- subtype, but not in TNBC. This was also the case in immune-related

gene sets; interferon-alpha response and interferon-gamma response that enriched to high miR-125a tumors in ER+/HER2-, but not in TNBC. Anti-tumor immune cells, CD8 cells, T-helper type 1 cells, and M1 macrophages, were all elevated in high miR-125a tumors in ER+ /HER2-subtype (all $p < 0.03$), but none in TNBC. Also, pro-cancerous immune cell such as T-helper type 2 cells were similarly highly infiltrated with high miR-125a tumors only in ER+ /HER2-subtype ($p=0.026$). Given its association with the survival outcome, we cannot help but speculate that miR-125a expression is parallel with highly proliferative ER+/HER2- breast cancer, but its tumor suppressive effect is not enough to improve survival outcome.

Conclusion: High miR-125a levels in tumors were associated with aggressive biology and worse survival, thus it can be a candidate for a prognostic biomarker in ER+/HER2- patients.

PO3-25-04

Variation in expression of various subsets of T Lymphocytes with different modalities of treatment in patients of breast cancer

Presenting Author(s) and Co-Author(s):

G. Puri. AIIMS, New Delhi, New Delhi, Delhi, India

K. Kataria. Aiims New Delhi, United States

A. SRIVASTAVA. Subharti Institute of Cancer Management and Research, MEERUT, Uttar Pradesh, India

S. Deo. All India Institute of Medical Science, New Delhi, New Delhi, Delhi, India

A. Rizwan. AIIMS, New Delhi, Delhi, India

S. Hussain. ICMR, United States

K. Sharma. AIIMS, New Delhi, New Delhi, Delhi, India

P. Ranjan. AIIMS New Delhi, United States

A. Dhar. AIIMS, New Delhi, New Delhi, Delhi, India

Introduction:

Effective anti- tumor response in breast cancer requires CD4+ and CD8+ T cells. There is paucity of knowledge about dynamic and functional alterations of these subsets.

Methodology:

This prospective cohort study was conducted with objective to determine the expression of different subtypes of T cells: T- Regulatory cells(FOXP3CD25) , T helper cells (CD4) , Cytotoxic T cell (CD8) in peripheral blood before and after chemotherapy and surgery, and in the tumor tissue.

Results:

A total of 90 subjects were recruited with 60 cases (30 NACT, 30 surgery) and 30 controls. The mean TLC was 6918 cells/ul, 6480 cells/ul in surgery and NACT respectively. Tumor size negatively correlated with CD4 and CD8 cells but positively with Treg. TLC and CD4 counts were significantly higher with axillary metastasis. CD4 counts increased from 39.49% in pre-62.14% post-surgery ($p < 0.05$). CD8 and Treg witnessed a downfall. After NACT even though TLC reduced the ALC increased from a mean value of 1481 cells/ul to 1640 cells/ul ($p < 0.05$). CD4 cells increased with a fall of CD8 T cells and Treg cells remained same. Subgroup analysis showed rise in Treg with complete or partial response to NACT ($r=0.8$, $p < 0.05$). Tissue FOXP3 expression was higher in the tumor and decreased with age over 45 years.

Conclusion:

In conclusion, the T-cell subgroups in breast cancer patients undergo dynamic, significant changes during surgery and chemotherapy. Monitoring T lymphocytes may provide useful information for the evaluation of the immune system and prognosis of patients.

PO3-25-05

Eribulin Induces Chromosomal Instability and Enhances cGAS Expression in the Nucleus of Triple-Negative Breast Cancer.

Presenting Author(s) and Co-Author(s):

H. Yamada. Japan/ Chiba University/ Breast surgery, United States

M. Takada. Japan/ Chiba University/ Breast surgery, Japan

A. Suzuki. University of Wisconsin Carbone Cancer Center, United States

Y. Muhan. Chiba University, Japan

T. Nagashima. Japan/ Chiba University/ Breast surgery, United States

H. Fujimoto. Japan/ Chiba University/ Breast surgery, United States

J. Sakakibara. Chiba University, United States

M. Kasuya. Japan/ Chiba University/ Breast surgery, United States

T. Kawate. Tokyo Medical University, United States

D. Miura. Japan/ Akasaka Miura clinic, United States

M. Suzuki. Japan/ National Hospital Organization Chiba Medical Center, United States

M. Miyashita. Japan/ Konan medical center, United States

K. Narui. Yokohama City University Medical Center, United States

Y. Hasegawa. Hachinohe City Hospital, Hachinohe, Aomori, Japan

T. Ishikawa. Tokyo Medical University, United States

M. Otsuka. Chiba University, United States

Background: Eribulin (ERI), a microtubule polymerization inhibitor, is approved for locally advanced or metastatic breast cancer. However, its effects on drug-naïve cancers are not well understood. In EMBRACE trial, ERI improves overall survival (OS) of the patients with metastatic breast cancer. This result might suggest that ERI could be involved in the immune system. In particular, there are a few reports on the effects of ERI on the innate immune system. This study aimed to investigate how ERI influences the innate immune system, focusing on the cyclic-GMP-AMP synthase (cGAS), a DNA sensor that triggers the production of type-I interferons. Methods: Clinical samples from the JONIE-3 trial were analyzed using immunohistochemistry (IHC). 121 patients were assigned to 2 different neoadjuvant chemotherapy (NAC) groups receive ERI (Group E) or paclitaxel (Group P) followed by FEC. The patients of both groups were performed biopsy before and after chemotherapy. We performed IHC on 56 samples and examined for association with pathological complete response (pCR), which was defined as no invasive residual tumor tissue in the breast.

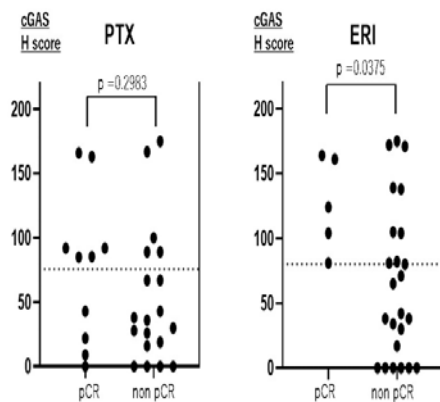
Additionally, 5 different cell lines were established to evaluate the acute and chronic effects of ERI treatment.

The cell lines were as follows: no treatment (control), PTX for short time (PTX short), PTX for long time (PTX long), ERI for short time (ERI short) and ERI for long time (ERI long).

We evaluated the acute effects of short-term dosing, while the chronic effects of long-term dosing, which mimic resistance to treatment. Protein expression of the cGAS-STING pathway was examined, along with cGAS and IFN β expression levels and their impact on cell division in

the above cell lines. Then at the cellular level, each cell lines were evaluated for differences in cGAS and IFN β expression and their effects on cell division. The differences in cGAS expression between cytoplasmic and nuclear fractions were verified by the cell fractuation assay. In addition, mitotic abnormalities and cell proliferation were also assessed. Results: In the clinical trial, ERI did not significantly differ from paclitaxel in terms of pathological complete response (pCR). However, high cGAS expression in Group E (ERI) correlated with increased pCR rates, while no such correlation was observed in Group P (PTX) (Figure). Additionally, High IFN β expression in Group E also correlated with increased pCR rates, differed from Group P . In vitro, ERI upregulated cGAS, STING, pIRF3, and IFN β protein expression compared to PTX. Notably, ERI induced elevated cGAS expression in the nucleus, as confirmed by immunofluorescence and cell fracturation assays. Additionally, PTX and ERI differed in their ability to cause mitotic abnormalities. PTX induced more micronuclei cells than ERI, on the other hand ERI induced more micronuclei cells and mitotic slippage. These results were also verified by live cell imaging. Finally, the knockdown of cGAS resulted in accelerated cell proliferation. Conclusion: ERI promoted chromosomal instability, leading to increased cGAS expression, particularly in the nucleus. These findings contribute to our understanding of ERI's effects on the innate immune response in triple-negative breast cancer, potentially paving the way for improved therapeutic strategies.

The differences in intensity scores between GroupP and GroupE in the immunostaining of cGAS



High cGAS expression in Group E correlated with increased pCR rates ($p=0.0375$), while no such correlation was observed in Group P ($p=0.2983$).

PO3-25-06

Expression of CD28, Fas, PD1, and CTLA4 molecules on cellular immune response in the blood peripheral of patients with locally advanced triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

M. Salgado. Hospital de Câncer de Pernambuco - HCP, Recife, Brazil, Pernambuco, Brazil

F. Soares. International Research Center, A.C. Camargo Cancer Center, São Paulo - SP, United States

D. Viana. Hospital de Cancer de Pernambuco - HCP, Recife, Brazil, Pernambuco, Brazil

A. Salgado. Hospital de Cancer de Pernambuco - HCP, Recife-Brazil, Recife, Pernambuco, Brazil

C. Vasconcelos. Hospital de Cancer de Pernambuco - HCP, Recife, Brazil, Recife, Pernambuco, Brazil

C. Anunciação. Hospital de Cancer de Pernambuco- HCP, Recife, Brazil, Recife, Pernambuco, Brazil

E. Salgado. Hospital de Cancer de Pernambuco, HCP, Recife, Brazil, Recife, Pernambuco, Brazil

L. Torres. Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, Brazil; Hospital de Cancer de Pernambuco (HCP), Recife, Brazil; Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil, Recife, Pernambuco, Brazil

Background: Locally advanced triple-negative breast cancer (TNBC) represents a public health problem in Brazil; its standard treatment consists of neoadjuvant chemotherapy followed by surgical and radiotherapy, with highly variable success rates are depended on access to appropriate cancer treatment, and the type of pathological response. In the last decade, the immune system's role in breast cancer has gained space by demonstrating the favorable impact of lymphocyte tumor infiltrate (TILs) and gene expression of the immune response, especially in tumors with high proliferation rates and negative estrogen receptors. The cellular immune response is regulated by co-stimulatory and co-inhibitory proteins such as CD28, Fas, PD1, and CTLA4 molecules. **Methods:** This was a longitudinal study with follow-up performed between 2015 and 2017. The study was conducted at the Hospital de Cancer de Pernambuco and Translational Research Laboratory of the Instituto de Medicina Integral Prof. Fernando Figueira (IMIP). Thirty women (18 to 60 years) diagnosed with locally advanced TNBC submitted to neoadjuvant chemotherapy (NAC), and 30 healthy women as a control group were included. The co-stimulatory and co-inhibitory proteins analyses were performed in the peripheral blood of TNBC women before (Pre-NAC) and after NAC (Post-NAC) **Results:** High levels of CD28+CD3+ T, CD28+CD4+ T, PD1+CD3+ T, and CTLA4+CD3+ T cells in the pathological complete response (pCR) and non-pCR groups compared to the control group ($p < 0.05$). High levels of Fas+CD4+T cells and PD1+CD8+T cells in the non-pCR compared to the pCR group ($p < 0.05$). In the paired analysis, significant differences were observed in CD3+T and CD4+T levels with CD28, Fas, and PD1 expression between pre- and post-NAC. **Conclusion:** Fas+CD4+T and PD1+CD8+T levels in peripheral blood in TNBC are associated with pCR, suggesting potential predictive biomarkers of NAC response. Preliminary results allow us to infer that neoadjuvant chemotherapy modulates the cellular immune response in TNBC women.

PO3-25-07

Characterization of tertiary lymphoid structures and its association with response to immune checkpoint inhibitors in triple negative breast cancer using spatial transcriptomics

Presenting Author(s) and Co-Author(s):

X. Wang. Institut Jules Bordet, Belgium

D. Venet. Institut Jules Bordet, Belgium

F. Lifrange. Department of Pathology, University Hospital Center of Liege, Liege, Belgium, Belgium

D. Larsimont. Institut Jules Bordet, Belgium

M. Rediti. 9 Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B), Université Libre de Bruxelles (ULB), Brussels, Belgium., Belgium

L. Stenbeck. SciLifeLab, United States

F. Dupont. Institut Jules Bordet, United States

G. Rouas. Institut Jules Bordet, Belgium

A. Joaquin Garcia. Institut Jules Bordet, United States

D. Gacquer. Institut Jules Bordet, United States

L. Craciun. Institut Jules Bordet, Belgium

L. Buisseret. Institut Jules Bordet, Belgium

N. Bhalla. SciLifeLab, United States

Y. Masarapu. SciLifeLab, United States

K. Thrane. SciLifeLab, United States

E. Gracia Villacampa. SciLifeLab, United States

L. Franzén. SciLifeLab, United States

S. Saarenpää. SciLifeLab, United States

L. Kvastad. SciLifeLab, United States

J. Lundeberg. Science for Life Laboratory, Division of Gene Technology, Sweden

F. Rothé. Institut Jules Bordet, Belgium

C. Sotiriou. Institut Jules Bordet, United States

Background Tertiary lymphoid structures (TLS) are ectopic lymphoid organs playing a role in adaptive antitumor immune response. They were shown to be associated with favorable outcome and appears to be a promising biomarker for response to immune checkpoint inhibitors (ICI). Yet, there is no consensus for their detection and quantification. Here we aimed to derive a specific TLS signature using high resolution spatial transcriptomics data from a large series of triple negative breast cancer (TNBC) samples and to assess its clinical relevance including response to ICI. Methods Spatial transcriptomics (ST) was performed on a series of 94 early-stage TNBC surgical samples with detailed clinicopathological and outcome data. TLS and tumor infiltrating lymphocytes (TILs) were scored using hematoxylin and eosin and double immunohistochemistry (CD3/CD20) stained slides by a dedicated breast pathologist. Regression based on morphological annotations and deconvolution methods estimated the

fraction of gene expression related to TLS in each ST spot allowing to derive specific TLS signature. Its prognostic and predictive value of response to ICI was assessed using publicly available breast cancer (METABRIC, SCAN-B, and I-SPY2) and other tumor type datasets treated with ICI (Bareche et al. Ann Oncol, 2022) from bulk gene expression data. Results Deconvolution of the TLS compartments using the ST gene expression data showed that TLS are enriched in all B cell subsets, CD4+ (central) memory and naïve T cells, as well as mast cells. A functional analysis showed an enrichment of 'vascular endothelial cell proliferation', 'mitotic G2/M transition checkpoint', 'V/D/J recombination' and 'regulation of cell chemotaxis to fibroblast growth factor' suggesting that TLS aggregates are associated with angiogenesis, immune cell proliferation, adaptative humoral response and tissue remodeling. A comparison of gene expression data between TLS and non-aggregated TILs led to the development of a specific TLS gene signature comprising B and T cell-specific genes, immunoglobulin genes as well as genes associated with TLS initiation. Its projection on tumor slides overlapped with the regions annotated as TLS by the pathologist, demonstrating its specificity for TLS detection. As expected, the highest levels of the TLS signature were observed in the immunomodulatory TNBC molecular subtype and fully inflamed tumors, whereas the lowest levels were observed in the mesenchymal molecular subtype and immune desert tumors ($p < 0.05$). Of note, high levels of the TLS signature were associated with better prognosis in TNBC patients from METABRIC ($p = 6.5 \cdot 10^{-5}$) and SCAN-B datasets ($p = 1.6 \cdot 10^{-3}$) as well as with higher pathological complete response rates in all breast cancer patients treated with neoadjuvant pembrolizumab in the I-SPY2 study ($p = 0.026$). Similar results were found in other tumor types treated with immunotherapy in the metastatic setting including metastatic melanoma, pancreatic and bladder cancers (PFS, $p = 6 \cdot 10^{-6}$). Of interest, the TLS signature outperformed the predictive value of other immune-related signatures including TILs suggesting a key role of TLS in obtaining a sustainable, adaptive antitumor immune response in the vicinity of the tumor area. Conclusion By leveraging the potential of spatial transcriptomics, we have successfully developed a unique TLS gene signature that demonstrates a strong correlation with the response to ICI in breast cancer and various other tumor types. This TLS gene signature outperforms other immune biomarkers, underscoring the pivotal role of TLS in eliciting a robust antitumor immune response. The universality of this TLS signature makes it a potent biomarker capable of identifying patients who would benefit from immunotherapy, pending further validation.

PO3-25-08

Artificial Intelligence-based screening of small molecule inhibitors of phosphoenolpyruvate carboxykinase 2 (PCK2), a novel cancer therapeutic target

Presenting Author(s) and Co-Author(s):

A. Rios Hoyo. Yale School of Medicine, United States

N. Shan. Yale Cancer Center, United States

H. Lin. Yale Cancer Center, Yale School of Medicine, United States

G. Espinoza Campos. Yale University, United States

M. Ahmed. Atomwise, United States

S. Umlauf. Yale Center for Molecular Discovery, United States

R. Cardone. Yale School of Medicine, United States

Y. Surovtseva. Yale Center for Molecular Discovery, United States

V. Gunasekharan. Yale University, United States

L. pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

Background: Metabolic rewiring is a hallmark of cancer that is often mediated by alterations in metabolic isozyme expression. Isozymes that are overexpressed in cancer and catalyze rate limiting steps in key metabolic processes are potential therapeutic targets. We previously identified phosphoenolpyruvate carboxykinase 2 (PCK2) as cancer dominant isoform, required for maintaining high metabolic activity and proliferation of lung, prostate, and breast cancer (BC) cells in vitro and in vivo. No PCK2 specific small molecule inhibitors exist.

Methods: mRNA expression levels were assessed in the TCGA data. PCK2 MISSION shRNAs (Millipore) were used to knock-down expression of PCK2 in BC cells. Alterations in metabolic flux caused by PCK2 down-regulation were examined via ¹³C-labeling and mass spectrometry using a SCIEX 5500 QTRAP and SelexION instrument for mobility separation of metabolites. The AtomNet™ (Atomwise Inc.) deep convolutional neural network structure-based drug design software was used to identify candidate small molecule PCK2 inhibitors which were tested in PCK1 and PCK2 in vitro enzyme activity assays. The lead compound was assessed for drug-like properties by QickPropV4.0.001w, and its growth inhibitory activity was tested in MDA-MB-321 and BT-549 cells.

Results: Analysis of mRNA levels in TNBC samples revealed a significant decrease in PCK1 expression compared to normal tissues, while PCK2 expression remained elevated or even increased. Quantification of mRNA levels in TNBC cell lines confirmed the higher expression of PCK2 compared to PCK1. To assess functional significance of PCK2 expression, we downregulated PCK2 using shRNA constructs in TNBC cell lines. Western blot analysis confirmed efficient knockdown of PCK2 protein without affecting PCK1 expression. Clonogenic assays demonstrated that PCK2-depleted BT-549 and MDA-MB-231 cells exhibited impaired proliferation, with reduced colony number and size compared to control cells. Metabolic analysis of PCK2-depleted TNBC cells demonstrated decreased levels of glycolytic and TCA intermediates and reduced flux through pyruvate carboxylase, indicating altered metabolic pathways upon PCK2 depletion. To identify potential inhibitors of PCK2, virtual screening was conducted using compound structures. We used a PCK2 protein structure homology model and designated the 3-mercaptopycolinic acid-binding site of the PCK1 structure as the site of interest to perform virtual drug screening of 7 million diverse compounds. The first screen yielded 86

structures to be tested in vitro, of which 5 demonstrated > 16% PCK2 inhibition. The top hit ($IC_{50}=2.4\mu M$) was used to refine a second round of in silico screen that yielded 87 second-round candidates that were assessed for PCK2 inhibition in vitro. 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate emerged as the lead compound. QickProp predicted favorable absorption, distribution, metabolism, and excretion properties, but relatively low cell permeability (apparent Caco-2 and MDCK2 cell permeabilities 18 nm/sec and 8 nm/sec, respectively). The specificity of 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate was tested in PCK1 and PCK2 enzymatic assays and revealed IC_{50} of 500nM on PCK1 and an IC_{50} of 3 nM on PCK2. We next tested the cell growth inhibitory effect of 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate on parental MDA-MB-231 and BT-549 cells and their PCK2 knockdown clones. Cell growth and viability significantly decreased in the MDA-MD-231 and BT-549 parental cells (the IC_{50} for MDA-MB-231 was 173 μM) and in shRNA non-targeting control cells, but not in the PCK2 depleted clones, demonstrating PCK2-dependent inhibitory effect.

Conclusion: We identified 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate as a high affinity selective PCK2 enzyme inhibitor. This compound also has significant growth inhibitory activity in BC cell lines in vitro and represents a novel therapeutic lead compound.

PO3-25-09

OKI-219, a PI3K α H1047R-mutant-selective inhibitor demonstrates efficacy as a single agent and drives combination responses with standard of care therapies in pre-clinical PI3K α H1047R mutant breast cancer models.

Presenting Author(s) and Co-Author(s):

M. Taylor. OnKure Inc., United States
Q. Zhao. OnKure Inc., United States
D. Mareska. OnKure Inc., United States
M. Hoh. OnKure Inc., United States
Y. Izrayelit. OnKure Inc., United States
K. Litwiler. OnKure Inc., United States
M. Boys. OnKure Inc., United States
R. Woessner. OnKure Inc., United States
D. Walker. OnKure Inc., United States
J. Winkler. OnKure Inc., United States
J. Diamond. OnKure Inc., United States

Mutations in PI3K α lead to constitutive activation of the PI3K/AKT/mTOR pathway and are highly prevalent in cancer. PI3K α H1047R is the most common amino acid substitution mutation and represents approximately one-third of all PI3K α mutations, with 15% of breast cancers having a PI3K α H1047R mutation. In breast cancer, PI3K α H1047R mutations are associated with resistance to targeted therapies, including HER2- and estrogen receptor (ER)- targeted agents. Although targeting PI3K α in cancer is a therapeutically proven strategy, with the currently approved drug alpelisib showing clinical efficacy alone or in combination with other therapies, treatment with non-mutant selective PI3K α inhibitors such as alpelisib is associated with significant toxicities such as hyperglycemia, due to on-target inhibition of the wild-type enzyme. This often leads to dose modification or discontinuation. Therefore, there is a significant need to develop new PI3K α -targeted therapies that can avoid or minimize on-target toxicity and improve the safety and clinical benefit for patients. OKI-219 is an orally bioavailable, PI3K α H1047R mutant-selective inhibitor, with ~100-fold cellular selectivity for the H1047R mutation over wild-type. OKI-219 demonstrates selectivity across a panel of 412 kinases, with no other kinases showing >30% inhibition at 1 μ M. In vitro, OKI-219 drives decreased phosphorylated AKT (pAKT) and decreased proliferation specifically in PI3K α H1047R mutant cell lines across several tumor types, including breast cancer. In vivo, as a monotherapy, OKI-219 demonstrates dose dependent antitumor activity in multiple human tumor xenograft models, including the H1047R mutant breast cancer CDX models T47D and HCC1954 and several PDX models, with regression rates up to 100% at doses that show no sign of the metabolic dysfunction (increased glucose or insulin) associated with wild-type protein inhibition. The in vivo antitumor activity correlates with pathway inhibition, measured by decreased pAKT in tumors. Moreover, OKI-219 dosed in combination with the selective estrogen receptor degraders (SERDs) fulvestrant, elacestrant or camizestrant showed significant combination benefit leading to tumor regressions of up to 100% in the ER+ H1047R mutant breast cancer model xxT47D, at doses where no regressions were observed with single agent treatment. Dosing OKI-219 in combination with HER2-inhibitors, such as tucatinib, led to tumor regressions in the ER-HER2+ and H1047R mutant breast cancer CDX model HCC1954, also at doses where no regressions were observed with single agent treatment. These data

indicate that OKI-219 offers improved efficacy and a wider therapeutic window compared to non-mutant selective PI3K α inhibitors. OKI-219 is advancing into clinical trials.

PO3-25-10

Selective and Effective Targeting of Triple-Negative Breast Cancer by CMPD1: Inhibition of MAP kinase-activated protein kinase 2 and Microtubule Dynamics

Presenting Author(s) and Co-Author(s):

M. TAKADA. Chiba University, United States

Y. CHEN. University of Wisconsin–Madison, United States

Y. Muhan. Chiba University, Japan

H. Yamada. Japan/ Chiba University/ Breast surgery, United States

J. Sakakibara. Chiba University, United States

H. Fujimoto. Chiba University, United States

T. Nagashima. Chiba University, United States

M. Otsuka. Chiba University, United States

M. Takaku. Chiba University, United States

A. Suzuki. Chiba University, United States

Background:

Microtubule-targeting agents (MTAs) have been widely utilized in cancer treatment, but the development of novel MTAs has faced limitations. CMPD1, a highly selective inhibitor of MAP kinase-activated protein kinase 2 (MK2) with dual functions as a microtubule inhibitor, shows promise as a targeted therapy for triple-negative breast cancer (TNBC). This study aimed to investigate the effects of CMPD1, targeting MK2 and acting as a microtubule inhibitor, on cell cycle progression, microtubule dynamics, and TNBC-related processes.

Methods:

CMPD1 was evaluated in non-transformed retinal pigment epithelial cells (RPE1) and TNBC cell lines, including MDA-MB-231 and MDA-MB-468 cells. Time-lapse microscopy and immunofluorescence staining were employed to observe the effects of CMPD1 on mitotic progression, cellular morphology, activation of the spindle assembly checkpoint (SAC), and microtubule dynamics. Anchorage-independent growth assays and in vivo studies using a TNBC xenograft model were performed to assess the impact of CMPD1 on colony formation, tumor growth, and metastasis.

Results:

CMPD1 treatment induced prometaphase arrest and mitotic slippage in both non-transformed and TNBC cells. This arrest was associated with SAC activation, evidenced by increased levels of Mad1 at kinetochores. CMPD1 exhibited robust microtubule depolymerization, primarily targeting microtubule plus-ends and inhibiting microtubule polymerization in vitro. Furthermore, CMPD1 disrupted the organization of the microtubule network in interphase cells and perturbed the mitotic spindle during mitosis.

Additionally, CMPD1 treatment resulted in the formation of cytoplasmic protrusions, membrane deformations, and dynamic movement of clustered mitotic chromosomes. These morphological alterations were indicative of the impact of CMPD1 on cellular structures and processes during mitosis.

Notably, CMPD1 demonstrated significant efficacy in inhibiting anchorage-independent growth

in TNBC cells, highlighting its potential as an anti-TNBC agent. In the TNBC xenograft model, CMPD1 exhibited superior anti-tumor activity compared to the standard chemotherapeutic agent Taxol. Tumor growth was markedly suppressed, and the formation of metastatic lesions was significantly reduced upon CMPD1 treatment.

Furthermore, CMPD1 treatment effectively inhibited TNBC cell migration and invasion, likely through its modulation of microtubule dynamics. The disruption of microtubule dynamics by CMPD1 impaired the ability of TNBC cells to migrate and invade surrounding tissues, which are crucial processes in cancer metastasis.

Importantly, CMPD1 showed high selectivity for TNBC cells, exerting minimal cytotoxic effects on normal cells, and could be efficiently washed out. This selectivity and washout ability enhance its potential as a targeted therapeutic agent for TNBC treatment.

Conclusions:

CMPD1, a highly selective MK2 inhibitor and microtubule inhibitor, exerts profound effects on cell cycle progression, microtubule dynamics, and TNBC-related processes. It induces prometaphase arrest, mitotic slippage, and microtubule depolymerization, resulting in altered cellular morphology. CMPD1 displays high selectivity for TNBC cells, while sparing normal cells and allowing efficient washout, making it a promising therapeutic agent for TNBC treatment. Its inhibition of anchorage-independent growth, suppression of tumor growth in vivo, and ability to impair TNBC cell migration and invasion further underscore its potential as a targeted anti-TNBC therapy.

PO3-25-11

Unprecedented responses to neoadjuvant sequential administration of Tocilizumab followed by cisplatin/docetaxel for locally advanced triple negative breast cancer patients

Presenting Author(s) and Co-Author(s):

T. Al-Tweigeri. KFSHRC, Saudi Arabia

N. Alraouji. KFSHRC, United States

A. Tulbah. King Faisal Specialist Hospital & Research Center, United States

S. Akhtar. KFSHRC, United States

M. Alzahrani. KFSHRC, United States

S. Najjar. KFSHRC, United States

D. Ajarim. King Faisal Specialist Hospital and Research Center, Saudi Arabia

K. Suleman. KFSHRC, United States

A. Al Sayed. KFSHRC, United States

A. Aboussekhra. KFSHRC, United States

Background: Triple negative breast cancer (TNBC) remains a challenge for clinicians due to its aggressive behavior and scarcity of effective treatment. Interleukin 6 (IL-6) is well known to contribute to poor therapeutic gain, tumor relapse and aggressive tumor growth. Here we have explored targeting the IL-6 signaling pathway by Tocilizumab (Actemra) as a new potential therapeutic approach for the treatment of TNBC. Methods: The study population includes thirty (30) patients with (T2-T4, N0-3) stage (IIB-III) TNBC treated uniformly with Tocilizumab followed with cisplatin/docetaxel according to a traditional 3+3 design using a sentinel patient at each cohort. Eligible patients received Tocilizumab on day 1 followed by cisplatin/docetaxel on day 2 every 4 weeks for a total of six cycles. The primary end points were pathological complete response in breast and axilla (pCR) (ypT0/ypN0) and assessment for tolerability/toxicities profiles. Additionally, the status of the BRCA1 and BRCA2 genes was determined in all patients. Results: Eligible patients who were enrolled in this phase I/II trial had a median age of 42 years, with 63% premenopausal and 67% had nodal involvement at base line. The median tumor size was 45 mm (range 25-150 mm), stage III A/B 26% and stage IIIC 50%. Germline BRCA1/2 mutations represented 27%. The overall pCR and (RCB class 0+1) were 66% and 69%, respectively. Interestingly, pCR reached 81% in axilla, and 100% in patients with tumors bearing BRCA1/2 mutations. Interestingly, tocilizumab affected the blood level of several pro-carcinogenic cytokines. Conclusions: To our knowledge this novel therapeutic strategy is the first to report the inhibition of a cytokine signaling (a new class of biological therapy) in combination with chemotherapy for the intricate and hard-to-treat TNBC patients with unprecedented responses and acceptable tolerability/toxicities, which merits further investigation. Pending Patents: US Patent Application No. 18/122,839 European Patent Application No. 23 162 694.6

PO3-25-12

Tigecycline-Induced Metabolic Reprogramming and Cytokine Modulation Suppress the Characteristics of Breast Cancer Cells

Presenting Author(s) and Co-Author(s):

H. Yu. Department of Breast and Thyroid Surgery, The First Affiliated Hospital of Chongqing Medical University, CHONGQING, China (People's Republic)

L. Tang. Department of Breast and Thyroid Surgery, The First Affiliated Hospital of Chongqing Medical University, United States

S. Liu. Chongqing Medical University, United States

Objective: Patients with advanced breast cancer are prone to recurrence and metastasis. Hence, there is still a need to find new potential drugs or adjuvants to improve prognosis. The Warburg effect, which is highly dependent on glycolysis, has been found to be present in the energy metabolism of tumors, including breast cancer. The effect also promotes the production of cytokines, to adapt the inflammatory microenvironment of tumor. However, drugs targeting Warburg effect and inflammatory environment are rarely reported in the treatment of breast cancer.

Tigecycline (Tige) is a commonly used glycylicycline antibiotic. Previous research has indicated it impede mitochondrial oxidative phosphorylation (OXPHOS) in various solid tumors. Based on the team's previous research, our study aimed to investigate whether Tige could inhibit breast cancer development by interfering with the Warburg effect and the inflammatory environment.

Methods: MB231, MB468 and MCF7, T47D, which represent triple-negative and estrogen receptor positive breast cancers, were treated with Tige at different concentrations for different periods of time. CCK8, colony formation and sphere formation assays were used to evaluate the effects on proliferation and tumor stemness in vitro, respectively. The effects on migration and invasion were evaluated by wound healing assay and Transwell. RNA sequencing was used to explore the genes altered and analyze the pathways involved. After labeling with probes, the changes of reactive oxygen species (ROS) were detected by fluorescence microscope, microplate reader, and flow cytometry. Cell cycle and apoptosis were detected by flow cytometry. Liquid cytokine chip was used to analyze the secretion of cytokines. Electron microscopy was performed to observe the changes in mitochondrial morphology. RT-PCR was used to detect the expression of rate-limiting enzymes in glycolysis pathway. Glucose consumption, lactate and pyruvate production were measured using glucose, lactate and pyruvate detection kits, respectively. Western blot was used to detect the changes of respiratory chain protein complex and other related pathway proteins in OXPHOS.

Results: Four breast cancer cells showed a significant decrease in cell proliferation, invasion and migratory ability after Tige treatment. Sphere-forming assays also showed that Tige had an effect on the stemness of breast cancer. RNA-sequencing showed that glycolysis, cell cycle, and immune-related pathways were inhibited after Tige treatment, and ROS production analysis revealed a decrease in ROS production. Flow cytometry also revealed that the cell cycle was arrested in S phase without significant apoptosis. Cytokine liquid chip analysis showed that the secretion of many cytokines, mainly interleukin (such as IL-1B), was inhibited after Tige intervention. RT-PCR results showed that the expression of several rate-limiting enzymes of the glycolytic pathway decreased. Glucose, lactate and pyruvate assay results showed that Tige reduced glucose uptake and lactate, pyruvate production. Electron microscopy results revealed that mitochondria in Tige treated cells showed significant

contractures. WB results also showed a decrease in the expression of OXPHOS-related proteins. However, due to the heterogeneity of the four breast cancer cells, the degree of change in these capacities was not entirely consistent.

Conclusions: Tige not only inhibits mitochondrial OXPHOS, but also inhibits the glycolysis pathway, which results in the inhibition of glucose uptake and the production of pyruvate and lactate. The secretion of early pro-inflammatory cytokines also affected. Therefore, this study suggests that Tige may change the glucose metabolism and energy metabolism, and also change the inflammatory environment of breast tumors, which provides new evidence for the anti-tumor effect of Tige in breast cancer.

PO3-26-01

Preclinical in vitro and in vivo characterization of a novel, wild-type-sparing, PI3K α H1047R mutant-selective inhibitor

Presenting Author(s) and Co-Author(s):

A. Smith. Cogent Biosciences, United States
B. Arwood-Levine. Cogent Biosciences, United States
A. Born. Cogent Biosciences, United States
R. Brizendine. Cogent Biosciences, United States
P. Chatterjee. Cogent Biosciences, United States
M. Chicarelli. Cogent Biosciences, United States
M. Conner. Cogent Biosciences, United States
B. Fell. Cogent Biosciences, United States
J. Fulton. Cogent Biosciences, United States
A. Guarnieri. Cogent Biosciences, United States
R. Jalluri. Cogent Biosciences, United States
H. Knox. Cogent Biosciences, United States
K. Koch. Cogent Biosciences, United States
D. Krischlunas. Cogent Biosciences, United States
V. Kumar. Cogent Biosciences, United States
C. McHugh. Cogent Biosciences, United States
B. Mclean. Cogent Biosciences, United States
K. Nassar. Cogent Biosciences, United States
B. Newhouse. Cogent Biosciences, United States
R. Rieger. Cogent Biosciences, United States
J. Robinson. Cogent Biosciences, United States
M. Rodriguez. Cogent Biosciences, United States
L. Salituro. Cogent Biosciences, United States
L. Stunkard. Cogent Biosciences, United States
F. Sullivan. Cogent Biosciences, United States
R. Turton. Cogent Biosciences, United States
S. Winski. Cogent Biosciences, United States
Y. Zhou. Cogent Biosciences, United States

The PI3K pathway is a key cell cycle regulating pathway that has an established role in tumor growth and development. Specifically, the H1047R and helical domain mutations E542K/E545K of the p110 α subunit of PI3K are known activating mutations that are targeted by inhibitors under clinical investigation as well as by approved drugs. PI3K α mutations are prevalent in patients with breast, colorectal, lung, endometrial, and numerous other cancers. The approved PI3K α inhibitor, alpelisib, shows promise for this targeted class with improvements in progression-free survival in HR+/Her2- breast cancer in combination with fulvestrant. However, tolerability concerns such as hyperglycemia, gastrointestinal issues, and skin reactions have

emerged related to on-target inhibition of wild type PI3K α . These issues likely limit dose administration leading to exposure which is suboptimal for maximal efficacy and creates an opportunity to identify an inhibitor with an improved tolerability profile that targets oncogenic mutations while sparing wild type PI3K α . Herein, we present preclinical in vitro and in vivo activity of a novel, wild type sparing PI3K α inhibitor which is potent against the oncogenic H1047R mutation.

PO3-26-02

Identification of a novel, brain penetrant, EGFR sparing, ErbB2 inhibitor with activity against oncogenic ErbB2 mutations

Presenting Author(s) and Co-Author(s):

M. Chicarelli. Cogent Biosciences, United States
B. Arwood-Levine. Cogent Biosciences, United States
T. Bettendorf. Cogent Biosciences, United States
K. Bouhana. Cogent Biosciences, United States
R. Brizendine. Cogent Biosciences, United States
L. Cable. Cogent Biosciences, United States
M. Crow. Cogent Biosciences, United States
B. Fell. Cogent Biosciences, United States
J. Fischer. Cogent Biosciences, United States
J. Fulton. Cogent Biosciences, United States
A. Guarnieri. Cogent Biosciences, United States
M. Hillman. Cogent Biosciences, United States
R. Jalluri. Cogent Biosciences, United States
D. Krischlunas. Cogent Biosciences, United States
K. Koch. Cogent Biosciences, United States
V. Kumar. Cogent Biosciences, United States
C. Malinky. Cogent Biosciences, United States
R. Rieger. Cogent Biosciences, United States
J. Robinson. Cogent Biosciences, United States
L. Stunkard. Cogent Biosciences, United States
F. Sullivan. Cogent Biosciences, United States
R. Turton. Cogent Biosciences, United States
L. Vine. Cogent Biosciences, United States
S. Winski. Cogent Biosciences, United States
Y. Zhou. Cogent Biosciences, United States

Alterations in ErbB2 have an established role as oncogenic drivers in many solid tumors, including gastric and breast cancer. While ErbB2 amplification is well recognized, activating ErbB2 mutations including exon 20 YVMA insertions, S310F/Y, L755S, V777L, and V842I, have emerged as mutually exclusive oncogenic drivers. ErbB2 mutations are present in ~3-4% of breast cancers and are now recognized as known mechanisms of acquired resistance to ErbB2 targeted therapies. These alterations can also be found in metastatic breast cancer that has advanced to the brain, a major clinical challenge with few therapeutic options. Unfortunately, many approved ErbB2 inhibitors are limited in their utility due to the inhibition of wild type EGFR resulting in severe rash and diarrhea. Herein, we describe preclinical data on a brain penetrant, wild type EGFR sparing, ErbB2 inhibitor with activity against prevalent mutations including exon 20 YVMA insertions.

PO3-26-04

Discovery of novel inhibitors of the epigenetic regulatory KAT6A histone acetyl transferase and their anti-tumor activity in breast cancer cells

Presenting Author(s) and Co-Author(s):

L. Holsinger. Isosterix Inc., San Diego, California, United States

R. Rai. Isosterix, United States

R. Nagawade. Discovery Chemistry, Sai Life Sciences, India

B. Pal. Discovery Chemistry, Sai Life Sciences, India

S. Pawar. Discovery Chemistry, Sai Life Sciences, India

P. Singh. Biology, Sai Life Sciences, India

K. Putta. Biology, Sai Life Sciences, India

M. Jaleel. Biology, Sai Life Sciences, India

T. Bostrom. Pelago Bioscience AB, Sweden

J. Karen. Pelago Bioscience AB, Sweden

Q. Huang. Frontage Laboratories, California, United States

A. Hannah. Isosterix Inc, California, United States

KAT6A is a histone acetyltransferase (HAT) which directs chromatin structural rearrangement and subsequent changes in gene transcription through acetylation of histones, primarily specific lysine residues on histone H3. KAT6A is modified in cancer, including genomic amplification, overexpression, mutation, as well as genetic rearrangement resulting in the production of fusion proteins. Dysregulation of this MYST family member and its acetyl transferase activity is known to drive gene expression and tumorigenic progression in cancers. An inhibitor of KAT6A and related MYST family member KAT6B has entered phase 1 clinical trials with durable partial responses seen in a variety of tumor types, including estrogen-receptor positive (ER+) breast cancer previously treated with a CDK4/6 inhibitor (Sommerhalder, ASCO2023). Evidence of dose dependent pharmacodynamics (H3K23Ac inhibition) was observed in peripheral blood mononuclear cells and paired tumor biopsies.

Isosterix has developed 2 distinct series of KAT6A selective inhibitors which engage in the active site of KAT6A in the acetyl CoA substrate binding pocket and inhibit histone acetylation activity. The kinetics of target enzyme binding and inhibition will be discussed for both series of inhibitors. These compounds have been characterized for potency and cellular activity in a variety of assays. Both series of compounds inhibit KAT6A-mediated histone acetylation with single digit nM potency in a biochemical assay as well as significant potency in the breast cancer tumor cell line ZR-75-1, inhibiting H3K23 acetylation. Using a thermal shift assay (CETSA) and mass spectrometry-based protein quantitation, direct target engagement of KAT6A within cells has been shown. These compounds reduce cell viability of a number of breast cancer cell lines with 10 days of compound administration confirming the dependence of these tumor cell lines on KAT6A acetyl transferase activity for proliferation and cell cycle progression.

Compound	Kat6A Biochemical IC ₅₀ (μM)	ZR-75-1 H3K23 Acetylation EC ₅₀ (μM)	Mouse PK (p.o.)		Mouse PK (i.v.)	Inhibitor class
			%F	T _{1/2} (h)	Cl (mL/min/kg)	
SL-IST-001	0.007	0.01	100	5.2	0.47	Series 1
SL-IST-002	0.007	0.005	100	6	0.48	Series 2

Compounds are orally bioavailable with excellent pharmacokinetic (PK) properties in mice including half-lives >5 hours with oral administration. Finally, Isosterix inhibitors demonstrated anti-tumor efficacy with oral administration in a ZR-75-1 mouse xenograft tumor model. Inhibitors against this novel epigenetic target demonstrate the potential for efficacy in ER+ breast cancer as well as other tumor indications through suppression of KAT6A-directed transcriptional induction and chromatin remodeling.

Compound	Kat6A Biochemical IC ₅₀ (μM)	ZR-75-1 H3K23 Acetylation EC ₅₀ (μM)	Mouse PK (p.o.)		Mouse PK (i.v.)	Inhibitor class
			%F	T _{1/2} (h)	Cl (mL/min/kg)	
SL-IST-001	0.007	0.01	100	5.2	0.47	Series 1
SL-IST-002	0.007	0.005	100	6	0.48	Series 2

PO3-26-06

A self-replicating RNA Precision Immunotherapeutic for Overcoming Resistance to Endocrine Therapy in Estrogen Receptor Positive Breast Cancer (ER+BC)

Presenting Author(s) and Co-Author(s):

Z. Goldberg. Replicate Bioscience, San Diego, California, United States

C. Maine. Replicate Bioscience, United States

G. Dailey. Duke University Medical Center, United States

C. Domingo. Replicate Bioscience, United States

G. Picarda. Replicate Bioscience, United States

H. Little. Replicate Bioscience, United States

A. Chou. Replicate Bioscience, United States

J. Sparks. Replicate Bioscience, United States

D. Spasova. Replicate Bioscience, United States

S. Miyake-Stoner. Replicate Bioscience, United States

Z. Hartman. Duke Medical Center, United States

C. Rabiola. Duke University Medical Center, United States

E. Crosby. Duke University, United States

H. Lysterly. Duke University, United States

N. Wang. Replicate Bioscience, United States

P. Aliahmad. Replicate Bioscience, United States

Advanced or metastatic ER+HER2- breast cancer (ER+BC) is an incurable disease. Standard 1L therapy (SOC) utilizes endocrine blockade with a nonsteroidal aromatase inhibitor (NSAI) combined with a CDK4/6 inhibitor (CDK4/6i). While most patients respond and disease remains controlled for over 2 years (mPFS ~25-28 months), virtually all patients progress over time, requiring more toxic therapies with decreasing periods of disease control. Prolonging the time that the tumor remains under endocrine control is therefore of significant medical value. The most common molecular drivers of endocrine resistance are well characterized and include mutations in ESR1 and bypass mechanisms in select signaling pathways. RBI-1000 is a self-replicating RNA (srRNA) precision immunotherapeutic to generate robust immunity directed against acquired resistance mutations that develop in ER+ BC in response to endocrine blockade by NSAI. RBI-1000 includes 6 on-target mutations within the estrogen receptor ligand binding domain, and bypass mutations either in the form of activating mutations in PI3K kinase or amplifications of HER2/HER3. Precision immunotherapy (PIO), combined with SOC targeted therapy, educates the patient's immune system to eliminate tumor cells that express acquired resistance mutations. Thus, the tumor is in a lose-lose situation where it is either eliminated by the targeted therapy, or if it develops acquired resistance mutations to the targeted therapy, it is killed by the PIO. Specifically for endocrine resistance, RBI-1000 PIO offers an attractive therapeutic approach to prevent/delay endocrine resistance specifically, by generating an effective immune response against those tumor cells that express the resistance-associated molecules that arise while on NSAI+CDK4/6i. The ability to encode multiple targets in a single therapeutic srRNA molecule, alongside the prolonged expression of srRNA in host cells (>49 days) creates a versatile and powerful cancer drug development platform. srRNA precision immunotherapeutics are delivered intramuscularly (i.e. a jab in the non-dominant deltoid) and

generate an effective immune response via the same pathways and mechanisms as a traditional vaccine. We have demonstrated that this srRNA encapsulated in a lipid nanoparticle primes polyfunctional CD4 and CD8 T cells and antibody responses, leading to tumor growth inhibition and improved survival in a mouse model expressing the targeted acquired resistance mutations. Priming of T cells against acquired mutations is also confirmed in human HLA-transgenic mice. The immune cell-mediated elimination of clones expressing the acquired resistance mutations is predicted to prolong endocrine control of ER+BC, in an analogous manner to small molecule or monoclonal antibody targeted therapies, but with a more favorable dosing and adverse event profile due to precise immunologic targeting and no DDI. RBI-1000 is anticipated to enter clinical studies in the first half of 2024.

PO3-26-07

Epigenetic approaches to deliver a targeted radiotherapy for triple negative breast cancer

Presenting Author(s) and Co-Author(s):

K. Brookes. University of Birmingham, Birmingham, United Kingdom

M. Read. University of Birmingham, Birmingham, United Kingdom

S. Wani. Cedars-Sinai Medical Center, United States

S. Jhiang. The Ohio State University, United States

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

M. Ringel. The Ohio State University, United States

C. McCabe. University of Birmingham, United States

M. Campbell. Cedars-Sinai Medical Center, Los Angeles, California, United States

The sodium iodide symporter (NIS, encoded by SLC5A5) is the sole transporter of iodide, and successfully exploited in thyroid cancer to uptake radioiodide (RAI). NIS is essentially undetected in normal mammary epithelial cells but elevated during lactation, and has a heterogeneous expression profile in breast cancer (BRCA), as evidenced by TCGA cohort and also in a ~120 sample TMA we have profiled. Furthermore, pre-clinical studies support an epigenetic mechanisms that involves Retinoic Acid Receptor alpha (RARa) to regulate SLC5A5 expression. Therefore, we have applied an orthogonal approach to both elucidate and target mechanisms that control NIS expression and function to deliver a therapeutic strategy that targets this transporter as a novel radiotherapy in BRCA.

To understand the epigenetic control of expression we segregated samples in the TCGA-BRCA cohort into lower and upper quartile SLC5A5 expression and identified ~600 significant differentially expressed of genes (DEG). Interestingly, restricting analyses to either triple negative (TN) or tumors from African American (AA) patients doubled the number of DEGs. These DEGs were significantly associated with several transcription factors including LHX3, a pituitary development transcription factor regulated by thyroid signaling. The most significantly altered ~70 DEGs significantly clustered tumors by genomic ancestry and ERBB2/HER2 IHC status.

The DEGs also supported a footprint of RARa signaling include PRAME, a known RARa co-repressor associated with histone deacetylase, and reflects the finding that NIS expression is highly responsive to SAHA treatment. To investigate if PRAME expression suppresses RARa regulation of SLC5A5 we have established a panel of BRCA cell lines (AU565, SKB3 SUM52 and MDA-MB-231) stably transfected with either CRISPR-VP64 (activator) and CRISPR-KRAB (repressor) to modulate PRAME and measure the epigenomic impact, the expression of SLC5A5 and the ability to transport RAI.

In parallel we have applied a drug screen approach that targets non-canonical approaches to govern NIS expression, for example by targeting valosin-containing protein (VCP) that induces NIS proteolysis. In the first instance we have developed a therapeutic strategy to target NIS by inhibiting VCP. Specifically, we are screening a range of VCP inhibitors in combination with the HDAC inhibitor SAHA or the transcriptional potentiator, disulfiram metabolite Cu(DDC)₂ in BRCA cell lines by testing the ability to augment RAI uptake. Remarkably, in MDA MB 231

cells, $\text{Cu}(\text{DDC})_2$ combined with the VCP inhibitor CB5339, resulted in a significant additive increase in RAI uptake and a prominent decrease in cell proliferation and survival.

These studies combined with future murine and PDX testing of CRISPR-edited tumors and drug exposures will develop a comprehensive analyses of the mechanisms that control SLC5A5 expression across breast cancer cell types, how this can be most effectively targeted to restore NIS expression, and exploited to promote RAI as a novel targeted BRCA radiotherapy.

PO3-26-08

Genetic modification of tumor associated macrophages using CRISPR lipid nanoparticle platform altered tumor microenvironment and induced cancer cell elimination

Presenting Author(s) and Co-Author(s):

F. Leonard. Houston Methodist Research Institute, Texas, United States

T. Galbraith. Houston Methodist Research Institute, United States

N. Abdelfattah. Houston Methodist Research Institute, United States

A. Ziemys. Houston Methodist Research Institute, United States

C. Hashimoto. Houston Methodist Research Institute, United States

H. Cook. Houston Methodist Research Institute, United States

Y. Xu. Houston Methodist Research Institute, United States

S. Chen. Houston Methodist Research Institute, United States

R. Rosato. Houston Methodist, United States

K. Yun. Houston Methodist Research Institute, United States

More than half of patients with stage IV breast cancer will eventually develop liver metastasis. Due to their nature, liver metastases are hard to treat, and the five-year survival rate for stage IV breast cancer is very low (~11%). In the recent years, vital roles macrophages play in cancer progression and immune evasion have become increasingly clear, making them an appealing target for therapeutic intervention. As one of the most abundant cell populations recruited to the tumor microenvironment, tumor-associated macrophages (TAM) are typically immunosuppressive Arg1⁺ M2-like macrophages, which support cancer growth, metastasis progression, and drug resistance. Numerous studies, including from our laboratory, have shown that reversal of the macrophage phenotype to the classical inflammatory CD80+ M1-like macrophages is very promising for cancer eradication. In this study, we used CRISPR loaded into lipid nanoparticles (CRISPR-LNP) to modulate macrophage polarization in breast cancer metastasis in vivo.

We hypothesize that CRISPR-mediated gene editing through lipid nanoparticle (LNP) delivery of CRISPR enzyme and target gRNA (CRISPR-LNP) is a highly effective and safe approach.

Using our CRISPR-LNP platform, we screened multiple genes with significant roles in macrophage polarization and found that targeting the RICTOR gene alone enabled reprogramming of pro-tumorigenic M2 TAMs to anti-tumorigenic M1 phenotype in vitro and in vivo. We administered the CRISPR-LNP targeting RICTOR (CRISPR-RIC-LNP) on a syngeneic liver metastasis mouse model via intravenous injection. Single dose studies were conducted to determine biodistribution, treatment efficacy, and shift in immune landscape of the tumor after treatment via immunofluorescence staining, Imaging Mass Cytometry, and single cell RNA sequencing. A spatial map was built using digital pathology analysis for investigation of the interactions amongst immune and tumor cells within the tumor immune microenvironment.

In 4T1 breast cancer liver metastatic model, we observed that CRISPR-RIC-LNP treatment: (i) accumulated in the liver metastases lesions in vivo 24 hours after injection. ~0.5% of total injected dose, which corresponds to ~75% of fluorescence from the whole body at 24h time point was confined only in the metastatic regions; (ii) led to modest increase of macrophage number, and (iii) significant shift of macrophage phenotype from immunosuppressive, pro-

tumorigenic Arg1⁺, CD206⁺ macrophages to inflammatory, anti-tumor CD80⁺ phenotype (from ~5 to ~9% of total cell in the tumor lesions) 24 hours after injection; (iv) reduced the cancer cell number by almost 80%; and (v) dramatically reduced exhausted T-cell and regulatory T-cell population, as determined by single cell RNA sequencing analysis. We plan to validate our preliminary finding with flow cytometry analysis of metastatic lesions, and evaluate the efficacy of CRISPR-RIC-LNP as single and in combinatorial therapies in survival studies.

These data showed that reprogramming macrophages from cancer-supporting to cancer-eliminating phenotype is a promising tool to suppress cancer cell growth and increase the presence of cytotoxic CD8⁺ T-cells. We propose that this approach can be efficiently used as single therapy or as combination with immune checkpoint inhibitors to obtain synergistic effects and efficiently eradicate cancer cells. We will assess the safety, optimize the accumulation in TME, and devise methods to limit exposure to healthy cells. In the future, we also aim to expand scope of our candidate therapy as therapeutics for other types of breast cancer metastases.

PO3-26-09

A novel class of RNR inhibitors that induces genomic instability and breast cancer cell death without inducing overt toxicities.

Presenting Author(s) and Co-Author(s):

T. Baker. Case Western Reserve University, United States

K. Weber-Bonk. Cleveland Clinic, United States

W. Huang. Case Western Reserve University, United States

D. Taylor. Case Western Reserve University, United States

R. Keri. Cleveland Clinic, United States

Despite the development of screening techniques and therapies, nearly 30% of breast cancers progress to Stage IV metastatic disease. These advanced cancers are highly proliferative, engaging in ongoing DNA synthesis that requires ribonucleotide reductase (RNR), the rate-limiting enzyme for dNTP synthesis. RRM2, the small subunit of RNR, activates the enzyme, increases deoxynucleotide pools, and is overexpressed in many cancers, including breast cancer. Thus, RNR is an established therapeutic target in advanced breast cancer. Currently, gemcitabine is the only FDA-approved RNR inhibitor used to treat Stage IV disease. As a nucleoside analog, gemcitabine also causes severe dose-limiting toxicities (i.e. myelosuppression and hepatotoxicity) due to off-target DNA replication termination. We hypothesize that a novel, non-nucleoside, RNR inhibitor may overcome these limitations. To address this, we developed TMU27a, a derivative of naphthyl salicylic acyl hydrazone (NSAH), which was identified in an *in silico* screen for its high-affinity binding to the RNR catalytic site. To measure direct interactions between TMU27a and purified RNR protein, we used surface plasmon resonance, revealing on-target, tight binding ($K_d = 150$ nM). Unbiased docking and molecular dynamics simulations (using lowest energy calculations) predicted the binding site of TMU27a to be the catalytic site of RNR, where it is stabilized through extensive interactions formed with conserved residues. Preliminary docking predictions also indicate multiple clash sites between TMU27a and the DNA polymerase lambda nucleotide pocket even in the lowest energy pose (unlike gemcitabine), suggesting that TMU27a inhibits RNR activity through a novel mechanism without significant off-target binding to other nucleotide binding proteins that contribute to toxicity. Demonstrating on-target inhibition, TMU27a reduces dATP levels and induces S and G2/M-phase stalling, leading to significant DNA damage and chromosomal instability. This excessive genomic damage causes growth repression, apoptosis, and senescence in several triple negative breast cancer (TNBC) cell lines. In xenograft mouse models of TNBC, TMU27a fully suppressed tumor growth without impacting mouse weight, suggesting strong drug efficacy in the absence of overt toxicity. Moreover, while short-term exposure to gemcitabine suppresses red and white blood cell populations, TMU27a does not. Together, these data indicate that TMU27a and its potential analogs are novel, non-toxic RNR inhibitors that overcome the limitations of gemcitabine for treating breast cancer. We are currently investigating how and where TMU27a binds human RNR using cryo-electron microscopy with the goal of generating a novel class of RNR inhibitors through structure-based drug design, improving binding affinity and selectivity.

PO3-26-10

Small molecule inhibitor of PELP1 exhibit cytotoxic effects on breast cancer cells by blocking ribosome biogenesis

Presenting Author(s) and Co-Author(s):

X. Yang. UT Health San Antonio, United States
K. Nassar. UT Health San Antonio, United States
U. Pratap. UT Health San Antonio, United States
R. Gopalam. UT Health San Antonio, United States
B. Ebrahimi. UT Health San Antonio, United States
D. Panneerdoss. UT Health San Antonio, United States
X. Li. UT Health San Antonio, United States
Y. Yuan. UT Health San Antonio, United States
D. Zhou. UT Health San Antonio, United States
G. Sareddy. UT Health San Antonio, United States
R. Tekmal. UT Health San Antonio, United States
M. Rao. Greehey Children's Cancer Research Institute, United States
S. Viswanadhapalli. UT Health San Antonio, Texas, United States
R. Vadlamudi. UT Health San Antonio, San Antonio, Texas, United States

Introduction: Breast cancer (BC) is the second-leading cause of cancer-related deaths in women. Despite responsive to endocrine therapy, a sizeable portion of estrogen receptor positive (ER⁺) BC goes on to develop therapy-resistant breast cancer (TR-BC). Furthermore, triple-negative breast cancer (TNBC) has a more aggressive clinical course with fewer targeted therapeutic options. The development of more effective therapies for TR-BC or TNBC represent an unmet need. Excessive ribosome biogenesis has recently been linked to BC progression, and resistance to therapy. Oncogene PELP1, which is required for ribosome biogenesis, is frequently dysregulated in BC and serves as a prognostic factor for poor BC survival and therapy resistance. We recently identified SMIP34 as a PELP1 small molecule inhibitor of its kind and it is effective against both TR-BC and TNBC. The objective of this study is to determine the mechanisms by which SMIP34 exhibit cytotoxic effects on BC cells.

Methods: We have used multiple ER⁺, therapy resistant and TNBC models in cell viability, and apoptosis assays. Modelling studies were done based on Cryo-EM structure of the WDR18/PELP1 Rix1 complex (PDB code 7UWF). Biochemical assays include immune precipitation, reporter assays, GST pulldown, and Western Blotting. SMIP34 effect on protein synthesis was measured by using Western blot of puromycin treated total lysates for puromycinylated protein content. SMIP34 effect on protein synthesis assessed using Cayman's Protein Synthesis Assay Kit. Ribosome biogenesis in SMIP34 treated cells was monitored using confocal microscopy using rpS6 antibody.

Results: In in vitro cell based assays, SMIP34 was highly effective in reducing the cell viability, reducing colony formation and inducing apoptosis of ER⁺, endocrine therapy resistant, and TNBC model cells. PELP1 homodimer has recently been predicated to act as the core of the WDR18/PELP1 assembly. Our biochemical assay results suggest that SMIP34 binds to the

same region involved in the PELP1 homodimerization and disrupts the formation of PELP1 homodimer and subsequently blocks the formation of WDR18/PELP1 Rix1 complex. Modeling studies predicted that altering the conformation of PELP1 aa 696-720 loop by SMIP34 binding may influence the conformation of the following C-terminal region, which may disturb the interaction of other PELP1 partners such as SENP3 and TEX10. Accordingly, the results from immunoprecipitation experiments demonstrated decreased association of Rix1 complex proteins WDR18, TEX10, and SENP3 with PELP1 under conditions of SMIP34 treatment. Further, Western blotting analysis confirmed that SMIP34 treatment decreased levels of PELP1 and its complex proteins, such as WDR18, TEX10, LAS1L, and SENP3. SMIP34 significantly reduced ribosomal biogenesis in a dose dependent manner. Additionally, puromycin labelling experiments confirmed a dose dependent decrease in new protein synthesis upon SMIP34 administration. Data from the DepMap database analysis revealed that PELP1 is required for cancer cell survival. Additionally, analysis of TCGA breast cancer datasets revealed that PELP1 expression is positively correlated with WDR18, TEX10, LAS1L, and SENP3. In in vivo xenograft assays and ex vivo explant assays using tumor tissue, SMIP34 strongly inhibited the growth of ER⁺, endocrine treatment resistant, and TNBC model cells.

Conclusion: These findings provide solid evidence that the Rix1 complex, which is required for ribosomes production, is disturbed by SMIP34 binding to PELP1. SMIP34 represents a new therapeutic for the treatment of both ER⁺ and TNBC breast cancer. Supported by VA grant 1 I01 BX004545-01A1.

PO3-26-11

Enhancing endoplasmic reticulum stress for treating endocrine therapy resistant breast cancers driven by mutant estrogen receptors

Presenting Author(s) and Co-Author(s):

S. Viswanadhapalli. UT Health San Antonio, Texas, United States

K. Parra. UT Southwestern, United States

T. Lee. UT Dallas, United States

R. Gopalam. UT Health San Antonio, United States

K. Kassees. UT Dallas, United States

T. Reese. UT Southwestern, United States

G. Sharma. UT Southwestern, United States

X. Liu. UT Southwest, United States

X. Yang. UT Health San Antonio, United States

C. Chen. UT Dallas, United States

C. Roggero. UT Southwestern, United States

L. Chen. UT Southwestern, United States

S. Bhattacharya. UT Health San Antonio, United States

U. Pratap. UT Health San Antonio, United States

R. Hayward. EтираRX, United States

S. Gargosky. EтираRX, United States

J. Ahn. UT Dallas, United States

G. Raj. UT Southwest, United States

R. Vadlamudi. UT Health San Antonio, San Antonio, Texas, United States

Background: Estrogen receptor alpha (ER α) mutations are common (30-40%) in metastatic endocrine therapy-resistant breast cancers (ETR-BC), enable resistance to endocrine therapies and are the molecular drivers of ETR-BC. We had previously shown that an oligobenzamide, ERX-41, could enhance endoplasmic reticulum stress in ETR-BCs driven by mutant (MT) ER α , resulting in cancer cell death in vitro and in vivo. To enable clinical translation of ERX-41, we performed lead optimization, followed by preclinical and IND-enabling studies. Methods: Over 2000 oligo-benzamides were designed, synthesized and tested in multiple BC models including those that express WT-ER α (MCF7, and ZR75) and BC models with acquired resistance (MCF7-Tam, and MCF7-LTLT) and engineered models that express MT-ER α (MCF7-ER α -D538G, MCF7-ER α -Y537S, ZR75-ER α -D538G, ZR75-ER α -Y537S). For our lead compound, mechanistic validation studies were performed using CRISPR LIPA mutants, RT-qPCR and Western blotting. Explants, organoids, cell line-(CDX) and patient-derived (PDX) xenografts were used to test the ex vivo and in vivo effectiveness of our lead compound as a monotherapy and in combination with abemaciclib. Results: Testing of >2000 synthesized oligo-benzamides identified a lead compound, ERX-315, that had broad and potent activity (IC₅₀ between 20-100 nM) against both WT and MT (mutant) ER α -driven BC cells in in vitro assays. CRISPR KO of LIPA (which encodes lysosomal acid lipase (LAL) in BC cells abrogated cytotoxic response to ERX-315, validating LIPA as the molecular target of ERX-315. Ultrastructural and molecular studies confirm that ERX-315 induces significant endoplasmic

reticulum stress, leading to a shutdown of de novo protein synthesis and apoptotic cell death in BC. Importantly, ERX-315 does not induce endoplasmic reticulum stress or cell death in normal cells and is non-toxic in animal models. We have shown that this capacity of ERX-315 to induce endoplasmic reticulum stress is unique among drugs targeting ER α , including selective ER α modulators and degraders, such as GDC-0180, AZD-9496 and fulvestrant. ERX-315 has potent anti-proliferative activity against MT-ER α -driven BC, as seen in genetically modified cell lines both grown as monolayer or spheroids in vitro, patient derived explants (PDEs) ex vivo and cell line derived (CDX) and patient-derived (PDX) xenografts in vivo. The combination of ERX-315 and CDK4/6 inhibitor abemaciclib was synergistic in decreasing the proliferation of both endocrine therapy-sensitive and endocrine therapy-resistant BC cells, in vitro, in xenograft models in vivo, and in primary patient-derived explants ex vivo. We are currently optimizing both the synthesis of ERX-315 using GMP process for kilogram scale production and validated methods for pharmacokinetic studies. We have developed formulations for both intravenous and oral administration with favorable pharmacokinetic parameters and proven utility of the formulated ERX-315 against CDX and PDX tumors in vivo. Toxicity studies in dogs and rodents have demonstrated >8-fold therapeutic to toxicity window. A phase I clinical trial is planned to be open to enrollment by Q1 2024. Conclusions: We have identified a lead compound ERX-315, which represents a novel class of agent that induce catastrophic levels of ER stress resulting in cancer cell death and that can effectively work against multiple forms of ETR-BC, including those driven by MT-ER α . Preclinical studies, GMP manufacturing, formulation and IND-enabling studies are being completed in time for the commencement of the phase I clinical trial by Q1 2024.

PO3-26-12

Targeting Lipocalin-2 in HER2+ Inflammatory Breast Cancer Using Herceptin-Conjugated Liposomes

Presenting Author(s) and Co-Author(s):

M. Flores-Colón. University of Puerto Rico, Medical Sciences Campus, Puerto Rico, United States

P. Vivas-Rivera. University of Puerto Rico, Río Piedras Campus, United States

P. Vivas-Mejía. Universidad de Puerto Rico, United States

Inflammatory breast cancer (IBC) is a rare and aggressive subtype of BC that accounts for 1 to 5% of all types of BC. Due to its inflammatory characteristics and the absence of a palpable mass, IBC is usually confounded with a mastitis. Unfortunately, once properly diagnosed, IBC has already metastasized. A high portion of IBC tumors overexpress human epidermal growth factor receptor 2 (HER2). These IBC patients (HER2+) are treated with Trastuzumab, a monoclonal antibody. However, many IBCs become resistant to this therapy. Thus, there is not an optimal treatment against this horrendous disease. One potential target against IBC is Lipocalin-2 (LCN2), a secreted protein involved in iron homeostasis, immune responses, transport of siderophores, and epithelial cell differentiation. In many aggressive tumors, high levels of LCN2 have been associated with increased cancer cell motility, proliferation, angiogenesis, invasion, and metastasis. LCN2 is aberrantly abundant in IBCs compared with non-IBC patients and cell lines. This information indicates that LCN2 could be a target for IBC therapy. Our research team showed that small interference RNAs (siRNAs) targeting LCN2 effectively reduced the cell proliferation and invasion ability of IBC cells. To systemically deliver siRNA specifically to HER2+ IBC cells, we prepared Herceptin-conjugated liposome loaded with siRNA against LCN2. Trastuzumab conjugated liposomes were characterized by using dynamic light scattering to measure the size distribution and the zeta potential. Our formulation displayed sizes of 18.3 and 73.7 nm which could correspond to free DSPE-PEG-(2000) trastuzumab and the trastuzumab-liposome, respectively. To determine the optimal timepoint of liposome internalization into IBC cell lines, we incubated HER2+ IBC3 cells with liposomes for different time-points. Optimal internalization was observed at 24 and 48-hr. To further understand the downstream effectors of LCN2 in IBC cells, we performed RNAseq in siRNA-mediated LCN2 knockdown cells. Further bioinformatics with the RNAseq data, revealed 138 dysregulated genes following LCN2 knockdown as compared with a negative control (NC) siRNA. Particularly, increased STAT1 levels has been associated with distant metastasis and poor clinical prognosis in cancer. In our study, STAT1 levels decreased after LCN2 silencing. Ingenuity Pathway Analysis (IPA) showed 25 canonical pathways altered in the LCN2 knockdown cells as compared with the NC-siRNA. These results indicate that LCN2 activate molecular pathways involved in cell proliferation, invasion and metastasis in IBC cells.

PO3-27-01

Prediction of pathological complete response to neoadjuvant treatment in loco-regional advanced breast cancer by using advanced PET/CT metabolic parameters.

Presenting Author(s) and Co-Author(s):

M. Shamy. Rambam Health Care Campus, Radiotherapy Institute, United States

O. Kagna. Rambam Health Care Campus, Nuclear Medicine Institute, Technion-Israel institute of Technology, The Ruth and Bruce Rappaport Faculty of Medicine, United States

Z. Keidar. Rambam Health Care Campus, Nuclear Medicine Institute, Technion- Israel institute of Technology, The Ruth and Bruce Rappaport Faculty of Medicine, United States

T. Palchan-Hazan. Rambam Health Care Campus, Nuclear Medicine Institute, United States

S. Billan. Rambam Health Care Campus, Radiotherapy Institute, Technion- Israel institute of Technology, The Ruth and Bruce Rappaport Faculty of Medicine, United States

R. Abdah-Bortnyak. Rambam Health Care Campus, Radiotherapy Institute, Technion- Israel institute of Technology, The Ruth and Bruce Rappaport Faculty of Medicine, United States

Prediction of pathological complete response to neoadjuvant treatment in loco-regional advanced breast cancer by using advanced PET/CT metabolic parameters. Abstract:

Background: The standard treatment for locally advanced breast cancer (LABC) is neoadjuvant systemic therapy followed by surgery. The usefulness of FDG PET/CT for evaluating the treatment efficacy in breast cancer is well established; however, the role of quantitative functional PET/CT parameters, such as the metabolic tumor volume (MTV) and total lesion glycolysis (TLG), remains inconclusive. The aim of this study was to determine the correlation between quantitative functional parameters derived from PET/CT in LABC patients at staging and the response to neoadjuvant therapy. **Methods:** Seventy-eight consecutive patients (aged 25-82 y) with confirmed LABC (stages II-III) who underwent PET/CT as a part of their staging assessment and received neoadjuvant therapy followed by surgery were retrospectively included in this study. All patients underwent an FDG PET/CT at staging; and values of SUV max, SUV mean, MTV, and TLG were determined from the PET/CT studies.

The patients were divided into two groups, based on the completeness of histopathologic response to neoadjuvant therapy, both in the primary tumor and axillary lymph nodes. Clinical, imaging and demographic data were collected from patient's medical record. **Results:** A complete pathologic response (pCR) was achieved in 33/78 (42%) patients. Among patients with ER/PR positive, Her2-neu negative tumors, in 23/27 (85%) patients only partial pathologic response was reached; 91% of patients with ER/PR negative, Her2-neu positive and 43% of Triple-negative patients had complete pathological? response. For the primary breast tumor response, a higher SUV max, 10.7 ± 5.34 for pCR vs. 7.24 ± 4.62 for non-pCR group was measured, p -value=0.003; threshold value of 6.625. A higher SUV mean in the primary tumor resulted in a significantly higher rate of pCR, 5.95 ± 2.36 vs 4.4 ± 2.16 , $p=0.004$, with a threshold value of 5.795.

Neither MTV, not TLG were predictive parameters of the primary tumor response. For lymph nodes response, SUV max and SUV mean had no role in the prediction of pCR. Statistically significant difference however, was found between pCR and non-pCR in MTV values in the involved lymph nodes, with a median $=2.13 \text{ cm}^3$ [0-7.85] in pCR group vs 5.43 cm^3 [3.11-15.3] in non-pCR, $p=0.01$ (threshold value 2.375) as well as in TLG measurements, with a median of 4.64 [0-19.8] vs. 12.7 [3.21-23.1], $p=0.047$, (25-75 IQR). **Conclusion:** Primary breast tumor SUV max/mean values have a significant correlation with the treatment response and threshold values were found.

Low MTV and TLG measurements in lymph nodes may predict pCR. Neither MTV nor TLG had were found to have a significant role in the prediction of the primary tumor response.

PO3-27-02

A novel PTK6 PROTAC degrader induces apoptosis of drug resistant breast cancer cells

Presenting Author(s) and Co-Author(s):

C. Martinez. Icahn School of Medicine at Mount Sinai, United States

Y. Xiong. Icahn School of Medicine at Mount Sinai, United States

A. Bartkowski. Icahn School of Medicine at Mount Sinai, United States

J. Byerly. University of Pennsylvania, United States

J. Jin. Icahn School of Medicine at Mount Sinai, United States

H. Irie. Icahn School of Medicine at Mount Sinai, United States

Background. PTK6/Brk, a non-receptor tyrosine kinase, is an oncogenic driver for several tumor types, including breast, prostate, liver, and pancreatic cancers. PTK6 is expressed in all breast cancer subtypes and higher levels of expression are associated with worse patient outcomes. The optimal approach to targeting PTK6 for therapeutic benefit has not been established. Although several inhibitors of PTK6 kinase activity have been developed, none have thus far been successfully translated to clinical trials. This may be in part due to kinase activity-independent functions of PTK6, for which there is growing evidence, that are not effectively targeted by traditional small molecule kinase inhibitors. Downregulation of PTK6 using shRNA inhibits growth, invasion/migration, survival and metastasis of breast cancer cells, including those that are resistant to standard therapies. PTK6 kinase inhibitor treatment phenocopies effects of PTK6 downregulation with respect to some, but not all PTK6-driven oncogenic activities. Moreover, growth of PTK6 CRISPR-targeted cells can be rescued either with wild type or catalytically inactive PTK6, supporting kinase activity-independent activities of PTK6 in regulating growth and viability of breast cancer cells. Therefore, PROTAC degraders may be a better way to chemically target and downregulate PTK6 expression in cancer, thereby phenocopying the effects of PTK6 shRNA. **Methods.** We developed a first-in-class PTK6 degrader using PROTAC (proteolysis-targeting chimeric) technology to target PTK6 expression in breast cancer cells of diverse subtypes. Degradation controls were also synthesized to assess specificity of MS105's effects. **Results.** PTK6 degrader, but not degradation controls, potently downregulates PTK6 expression in multiple breast cancer cell types. Proteomic and kinome profiling confirm the specificity of our PTK6 degrader. PTK6 PROTAC degrader inhibits viability and induces apoptosis of PTK6-expressing breast cancer cells, whereas treatment with parent kinase inhibitor or degradation controls that do not engage PTK6 or E3 ligase have minimal effect. Treatment with PTK6 degrader, but not kinase inhibitor or degradation controls, induces expression of pro-apoptotic Bim, phenocopying the effects observed with PTK6 shRNA. In contrast, PTK6 degrader and kinase inhibitor are comparably effective in inhibiting cell migration, supporting the differential kinase dependency of PTK6-dependent oncogenic functions. Therefore, our PTK6 PROTAC degrader effectively inhibits both kinase-dependent and independent oncogenic activities of PTK6. Our studies support the development of PTK6 PROTAC degraders as a preferred approach to clinically targeting PTK6 in cancer.

PO3-27-03

PROMISE Study: Pre-Operatory MRI is not Effective. A Systematic review of impact of magnetic resonance imaging on surgery-decision and clinical outcomes in women with breast cancer.

Presenting Author(s) and Co-Author(s):

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

A. Amorim. Perola Byington Hospital, United States

E. Mateus. Grupo Oncoclinicas SP, United States

F. Bagnoli. Grupo Oncoclinicas SP, United States

F. Zerwes. PUC-RS, United States

F. Pimentel Cavalcante. Hospital Geral Fortaleza (HGF), United States

G. Novita. Hospital Albert Einstein, United States

L. Mori. Grupo Oncoclinicas SP, United States

M. Madeira. Hospital Albert Einstein, United States

M. Diogenes. HOSPITAL PEROLA BYINGTON, SÃO PAULO, Sao Paulo, Brazil

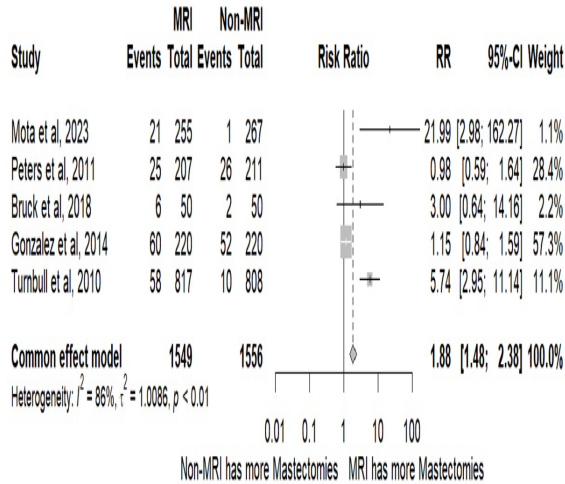
M. ANTONINI. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, Sao Paulo, Sao Paulo, Brazil

L. OKUMURA. UNIVERSITY OF YORK, United States

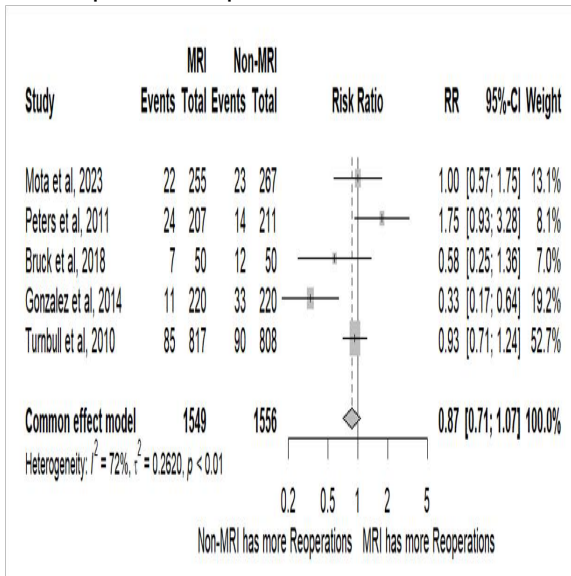
Background: The use of magnetic resonance imaging (MRI) in patients with breast cancer before surgery has been a subject of ongoing debate and discussion. The role of MRI as a preoperative tool to guide surgical decision-making remains controversial. Some studies suggest that MRI may improve the detection of additional tumors or assess the extent of disease, while others discuss that it may lead to increased false-positive findings and unnecessary interventions. The potential benefits and potential harms of incorporating MRI into the preoperative assessment of breast cancer patients continue to be topics of research and clinical interest. Clarifying the impact of preoperative MRI on surgical outcomes is crucial to inform evidence-based practices and optimize patient care. Until present, there is no pooled analyses from randomized clinical trials perspective of the clinical impact regarding the routine use of MRI. **Objectives:** This study aims to conduct metanalysis of randomized controlled trials (RCT) to investigate the association between preoperative MRI and surgical outcomes in women with newly diagnosed invasive breast cancer, providing evidence-based recommendations for clinical practice. **Methods:** A comprehensive search of electronic databases including PubMed, Medline, Embase, Ovid, Cochrane Library, and Web of Science was conducted by three independent researchers from inception to May 2023. The inclusion and exclusion criteria were based on Cochrane's principles. Relevant data from eligible studies were extracted. A systematic evaluation and meta-analysis were performed using the fixed-effects model to estimate the pooled risk ratio (RR) and 95% CI. **Results:** Out of 21 studies found, 6 were RCTs and 15 observational comparative studies. The results showed that in RCT preoperative MRI significantly reduce the rate of immediate breast conservative surgery (RR=0.94, 95%CI 0.91~0.96, I²=0%) and increase the mastectomy rate (RR=1.88, 95%CI 1.48~2.38, I²=86%). There wasn't any change in reoperations rates (RR=0,87, 95%CI 0.71~1.07, I²=72%). Only 1 trial reported data on survival, showing no difference between groups. **Conclusion:** From RCT standpoint, the evidence suggests that preoperative MRI for newly diagnosed invasive breast cancer may not be beneficial to the patients by increasing rate

of mastectomy with no survival benefit and that should be considered when offering as a routine practice to patients with breast cancer before surgery.

Forest plot of mastectomy as an outcome



Forest plot of re-operation as an outcome



PO3-27-05

Racioethnic and Ancestral Differences in Risk of Cardiometabolic Conditions and Cardiovascular Disease in Women Treated for Breast Cancer: the Pathways Heart Study

Presenting Author(s) and Co-Author(s):

S. Yao. Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

H. Sheng. Roswell Park Comprehensive Cancer Center, United States

P. Fiorica. Roswell Park Comprehensive Cancer Center, United States

R. Cheng. University of Washington, United States

L. Mendicino. Roswell Park Comprehensive Cancer Center, United States

A. Omilian. Roswell Park Comprehensive Cancer Center, United States

Q. Zhu. Roswell Park Comprehensive Cancer Center, United States

J. Roh. Division of Research, Kaiser Permanente Northern California, United States

C. Laurant. Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States

V. Lee. Kaiser Permanente Division of Research, United States

I. Ergas. Division of Research, Kaiser Permanente Northern California, United States

C. Iribarren. Kaiser Permanente Division of Research, United States

J. Rana. Kaiser Permanente Division of Research, United States

M. Nguyen-Huynh. Kaiser Permanente Division of Research, United States

E. Rillamas-Sun. Fred Hutch Cancer Center, United States

D. Hershman. Columbia University, New York, New York, United States

C. Ambrosone. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

L. Kushi. Kaiser Permanente Northern California, United States

H. Greenlee. Fred Hutch Cancer Center, United States

M. Kwan. Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States

Background: Despite the established literature of racioethnic disparities in cardiovascular disease (CVD) in the general population, few studies have examined such differences in women after BC treatment, who are at higher risk due to cardiotoxic cancer treatment. Moreover, few prior studies have considered genetic similarity among the participants in the analyses, which can be objectively inferred to delineate the ancestral background of an individual. **Methods:** The Pathways Heart Study was established to investigate the incidence of cardiometabolic risk factors and CVD events in women with a history of BC at Kaiser Permanente Northern California (KPNC). The main study endpoints for this analysis were cardiometabolic risk factors (hypertension, diabetes, and dyslipidemia) and CVD events, identified by ICD and CPT codes from EHR. Prevalent conditions were identified within 3 years prior to the date of BC diagnosis, and incident conditions were from the date of BC diagnosis to December 31, 2021. Ethnicity was self-reported and classified as non-Hispanic White (NHW), non-Hispanic Black (NHB), Asian, Hispanic, other, or unknown. Global genetic ancestry was estimated to capture the proportion of continental ancestries genetically similar to the reference populations in Africa, Americas, Asia, and Europe from the 1000 Genome Project and Human

Genome Diversity Project (HGDP), which, with the current lack of universally accepted labeling, are herein referred to as African, Native American, Asian, and European ancestry, respectively. Multivariable logistic and Cox proportional hazards regression models with all-cause mortality considered as competing risk were used to analyze the associations of race and ethnicity and genetic similarity with prevalent and incident cardiometabolic risk factors and CVD events. Results: Of the 4,071 women with BC in this analysis, 2,713 (66.6%) self-reported as NHW, 305 (7.5%) as NHB, 512 (12.6) as Asian, 447 (11.0%) as Hispanic, and 94 (2.3%) as other or unknown. NHB, Asian, and Hispanic women were more like to have prevalent diabetes than NHW women, the pattern of which persisted after BC diagnosis. Adjusted OR (95% CI) of risk of incident diabetes was 1.74 (1.21-2.49) for NHB, 3.63 (2.59-5.08) for Asian, and 2.19 (1.58-3.04) for Hispanic women, as compared to NHW. Analysis of genetic similarity revealed results consistent with self-reported race and ethnicity (sHR [95% CI] per 25% increment of African ancestry 1.19 [1.07-1.34], Asian ancestry 1.57 [1.44-1.72], and Native American ancestry 1.60 [1.29-2.00]), in comparison to European ancestry. For CVD risk, NHB women were more like to develop any prevalent and incident CVD than NHW women, particularly for ischemic heart disease (incident risk sHR=1.80 [1.10-2.94]). Genetic similarity analyses also showed higher risk of ischemic heart disease associated with African ancestry (incident risk per 25% increment, sHR=1.23 [1.06-1.43]). In contrast, Hispanic women were at lower risk of any incident CVD, serious CVD, arrhythmia, heart failure or cardiomyopathy, and ischemic heart disease. Similarly, lower risk of these CVD conditions was associated with Native American ancestry. Conclusions: Compared with women who self-reported as NHW, those self-reported as NHB, Asian, and Hispanic were at higher risk of diabetes prior to BC diagnosis and the elevated risk persisted after BC diagnosis. Moreover, Black women had higher risk of prevalent and incident CVD, whereas Hispanic women had lower risk of CVD, the latter of which might be related to the admixture of Native American ancestry. To our knowledge, this is the largest multi-ethnic study of disparities in CVD health in women post BC treatment, demonstrating corroborating findings between self-reported race and ethnicity and genetic similarity. The results highlight disparities in cardiometabolic risk factors and CVD among BC survivors that may warrant more research and clinical attentions.

PO3-27-06

Investigating The Association Between Exercise and Quality of Life Among Breast Cancer Survivors in The Black Women's Health Study

Presenting Author(s) and Co-Author(s):

N. Burse. University of North Carolina at Chapel Hill, United States

C. Wiesen. University of North Carolina at Chapel Hill, United States

T. Schwartz. University of North Carolina at Chapel Hill, United States

S. Kneipp. University of North Carolina at Chapel Hill, United States

A. Leak Bryant. University of North Carolina at Chapel Hill, United States

Background: Black breast cancer survivors (BCS) experience suboptimal quality of life (QoL) compared to White BCS. QoL is a multi-dimensional concept focused on different aspects of wellbeing. Exercise (a subset of physical activity) has been shown to improve QoL in cancer survivors. However, there is limited evidence on the benefits of exercise in relation to QoL among Black BCS and warrants further investigation. **Purpose:** To examine the association between exercise intensity (e.g., moderate activity) and multiple domains of QoL (e.g., physical wellbeing) among BCS in the Black Women's Health Study (BWHS). **Methods:** The BWHS is the largest prospective cohort study following 59,000 Black women in the United States since 1995. Self-reported questionnaires are distributed every two years to obtain current health information, including lifestyle factors and disease occurrence. The 2019 survey data, completed by 3,608 Black BCS, were used to address the primary aim. Of the 3,608 Black BCS, 1,085 females were eligible to participate in this cross-sectional study. The primary predictors were moderate and vigorous exercise intensity. The outcomes (physical, mental, functional, social functioning, and financial wellbeing) were categorized as excellent, very good or good, and fair or poor health. The covariates were marital status, occupation, education, age, body mass index, time since diagnosis, breast cancer stage, and general health. Adjusted multinomial logistic regressions were performed to estimate the odds ratios and 95% confidence intervals for the associations with each predictor. Multiple imputation was used to address missing data. **Results:** At baseline, the majority of the BCS were 64 years or younger (99%), premenopausal (69%), employed (95%), and had more than a high school degree (86%). About 50% of the participants were married or living as married. There were significant and positive associations between exercise intensity and QoL ($p < .05$). Compared to BCS who reported little or no exercise (< 60 minutes/week), those who reported at least 60 minutes/week of vigorous exercise had greater odds of experiencing excellent QoL including financial wellbeing (OR=1.70, 95% CI: 1.08-2.67), functional wellbeing (OR=3.64, 95% CI: 1.56-8.49), social functioning (OR=4.56, 95% CI: 2.42-8.60), and physical wellbeing (OR=4.26, 95% CI: 2.12-8.52). Similarly, BCS who engaged in at least 150 minutes of moderate exercise/week had increased odds of reporting excellent social functioning (OR=2.59, 95% CI: 1.41-4.76) and functional wellbeing (OR=4.40, 95% CI: 1.89-10.24) than those who engaged in less than 150 minutes/week of moderate exercise. **Conclusions:** Black BCS who engage in certain durations (e.g., 150 minutes/week) and exercise intensities (e.g., moderate activity) tend to have better QoL. These findings may help to build upon the relevance of exercise in the context of supportive care for racial and ethnic minority cancer survivors and encourage healthcare professionals to assess the frequency, intensity, time, and type of exercise during routine or follow-up care. Future longitudinal studies are needed to examine the proposed associations among Black BCS and to compare the current study findings.

PO3-27-07

Age at diagnosis and the food environment are associated with postdiagnosis weight gain among Black American breast cancer survivors in Maryland

Presenting Author(s) and Co-Author(s):

A. Connor. Johns Hopkins Bloomberg School of Public Health, MD and Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, MD, United States

K. Ho. Johns Hopkins Bloomberg School of Public Health, United States

K. Dibble. Dana-Farber Cancer Institute, United States

K. Visvanathan. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, MD and Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States

Background: Weight management is now included in the American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines due to its clinical impact on breast cancer (BC) survivorship outcomes. While numerous individual-level risk factors for weight gain after BC diagnosis have been identified, such as younger age at diagnosis, cancer stage, and cancer treatments (chemotherapy), there are limited data on the impact of neighborhood-level factors associated with weight change postdiagnosis among Black BC survivors. Methods: Utilizing social media recruitment strategies and survivor networks, we recruited 100 Black female BC survivors to complete an online survey, including demographic, clinical characteristics, and lifestyle factors, between January 5, 2022, and August 18, 2022. To capture the food environment, we utilized the 2023 Food Environment Index County Health Rankings, which accounts for access to healthy foods due to proximity and income (considering the distance an individual lives from a grocery store or supermarket, locations for health food purchases in most communities, and the inability to access healthy food because of cost barriers). The index ranges from 0 (worst) to 10 (best). Our outcome of postdiagnosis weight gain was calculated as percent weight change from time at diagnosis to time of survey, calculated as $([\text{weight at survey} - \text{weight at diagnosis}] / \text{weight at diagnosis}) \times 100$. Participants were grouped into mutually exclusive categories of stable weight (within $\pm 3\%$) or weight loss ($\leq -3\%$) compared to weight gain ($\geq 3\%$). Adjusted odds ratios (aORs) and 95% confidence intervals (CI) were calculated for the associations between clinical factors, county-level food environment index, and postdiagnosis weight gain. Results: The average ages at time of survey and at primary BC diagnosis were 58.6 years (standard deviation [SD]= 10.1) and 49.1 years (SD=10.2), respectively. Most women (70%) were diagnosed with invasive BC and only 22% were currently undergoing treatment at the time of the survey. While only 7% reported being obese at the time of BC diagnosis, 54% reported being obese at the time of survey which was on average 9 years post-BC diagnosis; and while 61 women had weight loss or stable weight, 34 women experienced weight gain postdiagnosis. Among the 95 women included in multivariable models who reported weight and height measurements for calculating weight change, women ≥ 50 years of age at BC diagnosis (versus < 50 years) were 3.43 times more likely to gain weight after diagnosis (95% CI 1.13-11.50). Women living in counties with a Food Environment Index ≥ 8.8 (median cut-point compared to < 8.8) were significantly less likely to experience weight gain (aOR 0.11; 95% CI 0.01-0.90). Stage and BC treatments were not significantly associated with weight gain. Conclusions: Our study findings demonstrate the importance of evaluating the food environment during BC survivorship and longitudinal monitoring of weight postdiagnosis to mitigate weight gain among Black BC survivors. Our findings will be used to inform a larger prospective study and future interventions among this population.

PO3-27-08

Geographic Distribution and Accessibility of Clinical Trials for Advanced-Stage Breast Cancer in the United States: A Focus on Rural and Minority Health Disparities

Presenting Author(s) and Co-Author(s):

E. Westergard. Gunderson Health System, La Crosse, Wisconsin, United States

A. Swenson. Medical College of Wisconsin, United States

Z. Schroeder. University of Kansas School of Medicine, United States

W. Swenson. Lakewood Health System, United States

Background: Our research examines the geographical distribution and accessibility of clinical trials for metastatic breast cancer patients in the U.S., spotlighting the challenges faced by rural communities and minority groups. Prior research indicated nearly half of these patients would have to commute over an hour to reach a trial site. [1] Our study provides a refreshed perspective on this issue, offering a more comprehensive analysis. **Methods:** Utilizing the ClinicalTrials.gov portal, we identified active interventional clinical trials for metastatic breast cancer patients as of November 25, 2022. We obtained distinct zip codes linked to these trials and, using 2020 census data, estimated the proportion of the U.S. populace residing within specific distances from these sites. Our analysis encompassed ethnicity, and other socio-economic parameters. Using GIS software, we also developed illustrative maps to visually represent the U.S. clinical trial accessibility landscape. **Results:** The majority of Americans diagnosed with metastatic breast cancer have clinical trials within their reach. A significant 81.8% of the U.S. populace resides within a 30-mile radius of a relevant clinical trial site. However, there is significant variation among ethnic groups, especially among American Indians, where 56.5% live within 30 miles of a clinical trial site. **Conclusions:** While a commendable 81.8% of the U.S. population resides within 30 miles of a metastatic breast cancer clinical trial site, our data underscores the uneven geographical spread of these trials. Our findings underscore the need for strategic initiatives to ensure clinical trials are within reach for every individual, irrespective of their location or background. **Reference:** 1. Galsky MD, Stensland KD, McBride RB, Latif A, Moshier E, Oh WK, Wisnivesky J. Geographic accessibility to clinical trials for advanced cancer in the United States. *JAMA Intern Med.* 2015 Feb;175(2):293-5. PMID: 25437434.

The U.S. Population living within 30-, 60-, and 120-miles of an open clinical trial site for patients with metastatic breast cancer.

	Total			Household			Total
	Population	Male	Female	Age 65+	Income <\$25k	Income <\$50k	Households
Population	329,821,023	162,362,645	167,458,378.78	53,029,706.00	23,205,170	48,759,100	123,559,074
<30 miles	81.8%	81.6%	82.0%	79.2%	75.0%	76.6%	81.5%
<60 miles	93.3%	93.2%	93.3%	92.4%	89.5%	90.8%	93.1%
<120 miles	98.1%	98.1%	98.1%	97.9%	96.1%	97.1%	98.2%
	Black	American Indian	Asian	Hawaiian	2+ Races	Hispanic Origin	White
Population	41,595,181	2,893,348	18,426,259	611,548	17,180,559	62,573,187	231,912,323
<30 miles	84.5%	66.5%	95.0%	84.9%	84.1%	82.2%	80.0%
<60 miles	94.8%	78.4%	98.5%	93.0%	93.0%	88.8%	92.7%
<120 miles	98.9%	92.1%	99.7%	99.0%	97.2%	93.7%	98.2%

Map of 30-, 60-, and 120-mile buffers from clinical trial sites open to patients with metastatic breast cancer.



PO3-27-09

A Multidisciplinary Telehealth Approach to Breast Cancer Prevention in a Veteran Population

Presenting Author(s) and Co-Author(s):

H. Shang. Baylor College of Medicine, United States

S. Ansari. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

S. Dhar. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

M. Irranejadparizi. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

S. Edwards. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

J. Honkomp. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

M. Siehr. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

B. Aiena. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

M. Nikityn. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

D. Bearden. Michael E. DeBakey VA Medical Center, United States

D. Menefee. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

S. Bushan. Michael E. DeBakey VA Medical Center, Baylor College of Medicine, United States

INTRODUCTION An estimated 13% of women will be diagnosed with breast cancer at some point in their lifetime. There are non-modifiable and modifiable risk factors including family history, genetics, obesity, and estrogen exposure. Interventions that reduce breast cancer risk and/or mortality include screening, chemoprevention, and lifestyle modification. A recent national survey shows that there are significant gaps in providing breast cancer prevention care for female Veterans. We describe the creation of a multi-disciplinary telehealth clinic aimed at reducing breast cancer risk in a high-risk female Veteran population. **METHODS** The breast cancer prevention clinic (BCPC) team consists of a medical oncologist, geneticist, genetic counselor, dietician, psychologist, and nurse navigator. High risk women are identified through a combination of screening questionnaires at annual mammography and genetics or primary care provider (PCP) evaluation, then referred to the clinic. Criteria for referral include age ≥ 35 , Gail 5 year risk $\geq 1.7\%$, Tyrer-Cuzick 10 year risk $\geq 5\%$, or history of thoracic radiation. At the BCPC telehealth visit, the medical oncologist makes individualized recommendations about chemoprevention by discussing the risks and possible complications of therapy. Use of screening magnetic resonance imaging (MRI) is also recommended to women with lifetime Tyrer-Cuzick score $> 20\%$. Within the same visit, patients meet with a dietician to discuss nutrition modification, and a psychologist to address psychosocial barriers to lifestyle change. Those who start chemoprevention attend a 3 month follow-up with a nurse navigator to discuss tolerability and side effects. Subsequently, the patient's PCP becomes responsible for management of chemoprevention and annual breast MRI. **RESULTS** Between January and December 2022, 33 patients were seen in BCPC. Patients had an average age of 52 years (range 42-70), Gail 5-year score of 2.53%, Tyrer-Cuzick 10-year score of 6.65%, and Tyrer-Cuzick lifetime score of 21.5%.

Thirteen patients (39.4%) started chemoprevention, the majority of which were selective estrogen receptor modulators (SERM). Nine reported starting the medication at the 3 month

follow-up appointment. The most reported side effect was hot flashes in 67%, although only the majority had mild symptoms. Three reported weight gain and one reported vaginal dryness. None reported worsening arthralgia or fatigue. Despite the low incidence of severe symptoms, only 3 continued to fill the medication at the time of chart review in August 2023.

Twenty (60.6%) patients did not initiate chemoprevention. Four (20%) did not qualify due to cardiovascular or thrombotic risk factors, and three (15%) did not qualify due to concurrent use of hormone replacement therapy. Two (10%) elected not to start chemoprevention because they were planning for risk reducing mastectomies. Eleven (55%) did not initiate chemoprevention due to patient preferences and concern for side effects.

Twenty-eight patients were recommended to obtain breast MRI in addition to mammogram for yearly screening. At time of chart review, 15 had at least one screening breast MRI ordered by PCP after BCPC visit, with 10 MRIs performed. **CONCLUSIONS** The unique interdisciplinary model of our breast cancer prevention clinic allows for a comprehensive and personalized evaluation for high-risk female Veterans on interventions to reduce their breast cancer risk. However, the current model does not ensure long-term compliance with these interventions. Studies have shown that more frequent/short-term follow up may improve compliance with endocrine therapies. Future directions include clinic expansion and providing additional follow-up with the multidisciplinary team to promote continued adherence to BCPC interventions.

PO3-27-10

Financial Stress and Care Disruption in Breast Cancer: A Ten-Year National Health Interview Survey Analysis

Presenting Author(s) and Co-Author(s):

M. Doyle. Massachusetts General Hospital, United States

E. Quinn. Massachusetts General Hospital, United States

S. Bell. University of Michigan, United States

B. Wekwerth. Massachusetts General Hospital, United States

R. Carlos. University of Michigan, United States

Background: Financial stress is an adverse event of BC. Increased availability of oral targeted therapy (OTT) is hypothesized to add to this burden. We assess financial stress at the population level as a function of availability of OTT. Design: We used 2013-2022 NHIS adult BC population data. Financial stress markers were care disruption, food insecurity and percent home ownership. Care disruption was defined as at least 1 event of skipping or taking less medication or delayed filling or unable to afford prescriptions. Available oral therapy Florida Blue July 2023 was cross-referenced with the NCI targeted therapy list for breast cancer as of July 2023. Initial FDA approval date for breast cancer for OTT determined the number of available OTT by survey year. We conducted a time-adjusted logistic regression to account of external effects such as COVID and adjusted for sociodemographics. Results: In a population of over 30 million respondents with BC, care disruption affected < 10%; food insecurity, < 1.3%, >83% reported home ownership. The number of available OTT did not affect outcomes. Survey year was associated with reduced care disruption (adjusted OR 0.82, 95% CI 0.68–0.99). Self-reported Black race affected home ownership (aOR 0.57, 95% CI 0.43-0.77) and any care disruption (a2.11, 95% CI 1.38-3.24). Non-White patients more likely reported food insecurity (aOR 5.56, 95% CI 2.58-12.01). Income < 200% of poverty level negatively affected outcomes. Stroke (aOR 1.97, 95% CI 1.09-3.55) and heart attack (aOR 2.10, 95% CI 1.11–4) history increased likelihood of care disruption. Conclusion: Available number of OTT did not influence financial stress in a BC population. Adverse sociodemographics and comorbidities correlated with care disruption. Our study was limited by absence of actual OTT use; further assessment at the individual level is needed.

Outcomes

Table 2: Outcomes		Population: Adult Female Patients With Breast Cancer		
	Home Owner yes/no [Logistic regression; aOR (95% CI)]	Any Care Disruption yes/no [Logistic regression; aOR (95% CI)]	Number of Care Disruption Instances (0-4) [Logistic regression with aggregated data; aOR (95% CI)]	Food Insecurity yes/no [Logistic regression; aOR (95% CI)]
Covariates				
Survey year	0.99 (0.87-1.12)	0.82 (0.68-0.99)	0.86 (0.7-1.04)	0.88 (0.52-1.48)
Total number of breast cancer drugs	1.03 (0.9-1.17)	1.2 (0.98-1.46)	1.12 (0.92-1.36)	1.18 (0.67-2.06)
Clinical Variables				
Comorbid Conditions				
Hypertension	0.95 (0.76-1.17)	1.31 (0.94-1.83)	1.18 (0.8-1.72)	3.16 (1.25-7.98)
Coronary heart disease	0.76 (0.53-1.08)	1.64 (1.01-2.66)	1.22 (0.7-2.14)	Comorbid conditions omitted due to small event counts
Angina	1.03 (0.66-1.59)	0.99 (0.52-1.9)	1.2 (0.62-2.3)	
Heart attack	1.04 (0.67-1.6)	1.73 (0.96-3.11)	2.10 (1.11-4)	
Stroke	0.89 (0.6-1.31)	1.25 (0.73-2.14)	1.97 (1.09-3.55)	
Sociodemographic Characteristics				
Age (years)				
18-30	Ref.	Ref.	Ref.	Ref.
31-66	0.94 (0.19-4.6)	0.73 (0.11-4.86)	0.42 (0.06-2.91)	0.1 (0.01-1.3)
67 and older	1.02 (0.21-5.09)	0.26 (0.04-1.74)	0.14 (0.02-0.97)	0.02 (0.001-0.26)
Ethnicity				
Hispanic/Spanish/Latino	0.56 (0.37-0.85)	0.88 (0.5-1.57)	0.86 (0.42-1.79)	Omitted due to small event counts
Non-Hispanic/Spanish/Latino	Ref.	Ref.	Ref.	
Race				
White only	Ref.	Ref.	Ref.	Ref.
Black/African-American only	0.57 (0.43-0.77)	1.69 (1.07-2.67)	1.27 (0.8-2.01)	5.56 (2.58-12.01)
Asian only	0.69 (0.42-1.13)	0.49 (0.19-1.3)	0.62 (0.21-1.78)	Race indicator dichotomized to White/non-White due to small event counts by race
AIAN only	0.75 (0.17-3.26)	1.36 (0.36-5.2)	1.5 (0.39-5.81)	
Other	0.49 (0.25-0.95)	2.92 (1.36-6.26)	3.34 (1.38-8.1)	
Income				
<100% poverty level	0.11 (0.08-0.16)	2.11 (1.38-3.24)	2.33 (1.45-3.74)	Omitted due to small event counts
100-<200% poverty level	0.35 (0.28-0.44)	1.65 (1.13-2.4)	1.68 (1.11-2.55)	
200% and above poverty level	Ref.	Ref.	Ref.	

PO3-27-11

Exploring Associations among Breast Cancer Survivor Empowerment, Peer Support, and Patient Navigation: Implications for Community-Based Care Planning

Presenting Author(s) and Co-Author(s):

M. Sleiman Jr. Lombardi Comprehensive Cancer Center, United States

M. Yockel. Lombardi Comprehensive Cancer Center, United States

A. Fleischmann. Sharsheret, United States

M. Liu. Lombardi Comprehensive Cancer Center, United States

O. Young. Lombardi Comprehensive Cancer Center, United States

S. Arumani. Lombardi Comprehensive Cancer Center, United States

K. Tercyak. Lombardi Comprehensive Cancer Center, United States

Background: Women surviving with breast cancer (BC) may utilize peer support and patient navigation to augment their medical care--potentially leading to greater patient empowerment. However, the quality of support and navigation services vary widely among community-based organizations (CBOs) delivering such care, and often due to patients' psychosocial status and program-specific determinants: outcome studies could inform care planning. **Method:** We analyzed secondary data from N=733 BC survivors participating in a CBO's annual evaluation of its patient navigation program, assessing patients' emotional distress, perceived navigation quality, care satisfaction, peer support, and empowerment. Bivariate associations explored program factors associated with these attributes; those significantly associated were retained in a multivariable model of patient empowerment. **Results:** Overall, patient empowerment was high as most BC survivors felt more informed (66.4%) and confident (71.2%) in managing their own care. Quality of navigation was also very high (91%) because it was: helpful (92.7%), informative (92.6%), timely (92.2%), effective (88.7%), supportive (91.3%), reliable (91.5%), and recommendable to others (93.9%). Regarding satisfaction, BC survivors felt helped (91.6%), understood (92.0%), and supported by abundant resources (92.8%) and programs (91.2%). Peer support, in particular, was offered to >25% of patients and 85.1% reportedly engaged with their assigned peer supporter. Regarding quality of life, 25.3% were in fair/poor health and 25.6% endorsed frequent mental distress--with an average of 8.3 physically unhealthy days, 8.16 mentally unhealthy days, and 6.71 activity-limited days. Interestingly, disparities in patient engagement were observed as a function of their quality of life: lowest among those with more frequent mental distress ($t=-2.13$, $p<.05$), mentally unhealthy days ($r=-.083$, $p<.05$), and activity-limited days ($r=-.058$, $p<.05$). These burdens may have influenced survivors' perceptions of their own empowerment--especially among those without peer support program engagement ($t=3.77$, $p<.001$), who downgraded the quality of the navigation services they received ($t=.60$, $p<.01$), and were least satisfied with their supportive care ($t=.57$, $p<.01$). In a multivariable model of empowerment controlling for frequent mental distress ($B=-.318$, $SE=.144$, $p<.05$), both care satisfaction ($B=.194$, $SE=.019$, $p<.001$) and speaking with a peer supporter ($B=.610$, $SE=.151$, $p<.005$) were positively associated with empowerment. Specifically, those who spoke with a peer and who rated their care satisfaction higher felt more empowered. **Conclusion:** The CBO's patient navigation model among >700 respondents was strong and helped BC survivors feel more empowered to manage their health needs. The majority of BC survivors were better informed and in control of their futures. Where disparities existed were among those with the lowest CBO satisfaction and who had frequent mental distress. Outreach may strengthen navigation and the delivery of peer support for those with

the poorest mental health in order to better empower their BC survivorship.

PO3-27-12

Dexamethasone is necessary for preventing acute emesis induced by anthracycline/cyclophosphamide chemotherapy (HELEN-009) : a multicenter, randomized, open-labeled phase 3 trial

Presenting Author(s) and Co-Author(s):

X. Chen. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

J. Dechuang. Henan cancer hospital, United States

C. Zhang. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

X. Sun. Affiliated Cancer Hospital of Zhengzhou University, United States

Z. Lu. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

L. Li. Affiliated Cancer Hospital of Zhengzhou University, China (People's Republic)

J. Qiao. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

C. Wang. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

M. Yan. Henan Cancer Hospital, Henan, China

Y. Feng. Department of Breast Surgery, Xinxiang Central Hospital, Xinxiang, China, United States

Y. Wei. Anyang Cancer Hospital, United States

Z. Liu. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

Background

Olanzapine, in combination with NK1 receptor antagonist (RA), 5-hydroxytryptamine-3 (5-HT3) RA, and dexamethasone, is now the standard approach to prevent chemotherapy-induced nausea and vomiting (CINV). In this study, we assessed the preventive effect of removing dexamethasone from the quadruple standard antiemetic regimen on CINV caused by anthracycline/cyclophosphamide chemotherapy. Methods

The HELEN-009 was a multicenter, randomized, open-labeled phase 3 trial to evaluate the efficacy of NK1RA,5-HT3RA and Olanzapine triplet-combination antiemetic therapy done in 3 hospitals in China. Key inclusion criteria were patients with early breast cancer who were scheduled to be treated with epirubicin plus cyclophosphamide chemotherapy for the first time, age between 18 and 75 years, and with Eastern Cooperative Oncology Group performance status of 0–1. Eligible patients were randomly assigned (1:1) to receive either fosaprepitant, tropisetron, dexamethasone and olanzapine (quadruple group) or fosaprepitant, tropisetron and olanzapine without dexamethasone (triple group). Patients were randomly assigned to interventions by use of a web entry system and the minimization method with a random component, with age as factors of allocation adjustment. The primary endpoint was the proportion of patients who achieved a complete response, defined as absence of vomiting and no use of rescue medications in the overall phase (days 1–5) after starting chemotherapy. All randomly assigned patients who satisfied eligibility criteria received epirubicin plus cyclophosphamide chemotherapy were included in efficacy analysis. All patients who received any treatment in this study were assessed for safety. This study is registered at Clinical Trials Registry, number NCT05242874. Findings

Between January 2022 and July 2023, 439 patients with breast cancer were enrolled in the study, with 218 participants randomly assigned to quadruple group and 221 participants assigned to triple group. All eligible patients were observed 120 h after epirubicin plus cyclophosphamide chemotherapy initiation. One patient in the quadruple group withdrew consent. One patient in the quadruple group and one in triple group discontinued treatment on day 1 and was excluded from the efficacy analysis. In the overall phase, the proportion of patients who achieved a complete response was 180 (83.3% [95% CI 78.3–88.3] of 216 patients in the quadruple group and 137 (62.4% [55.8–68.7] of 220 patients in the triple group ($p < 0.0001$). No grade 3 or higher treatment-related adverse events occurred in either of the groups. Interpretation

Dexamethasone remains essential in preventing acute emesis in patients receiving epirubicin plus cyclophosphamide chemotherapy.

Proportion of patients in the efficacy analysis set achieving a complete response

	Group A: Control arm (n=216)	Group B: Experimental arm (n=220)	P _{interaction} *
Complete response			
Day 1	212(98.1%)	216(98.2%)	1.000
Day 2	180(83.3%)	137(62.3%)	< 0.001
Day 3	195(90.2%)	158(71.8%)	< 0.001
Day 4	207(95.8%)	192(87.3%)	< 0.001
Day 5	207(95.8%)	205(93.2%)	0.225
Complete control			
Day 1	213(98.6%)	217(98.6%)	1.000
Day 2	184(85.2%)	145(65.9%)	< 0.001
Day 3	207(95.8%)	182(82.7%)	< 0.001
Day 4	213(98.6%)	204(92.7%)	0.004
Day 5	214(99.1%)	216(98.2%)	0.685
Total control			
Day 1	207(95.8%)	211(95.9%)	1.000
Day 2	128(59.2%)	58(26.3%)	< 0.001
Day 3	131(60.6%)	64(29.1%)	< 0.001
Day 4	147(68.0%)	96(43.6%)	< 0.001
Day 5	164(75.9%)	123(55.9%)	< 0.001

Treatment-related adverse events with an incidence $\geq 2\%$

	Group A: Control arm (n=216)			Group B: Experimental arm (n=220)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Somnolence	21(9.7%)	0	0	28(12.7%)	0	0
Constipation	7(3.2%)	1(< 1%)	0	9(4.1%)	0	0
Hiccups	6(2.8%)	0	0	16(7.3%)	0	0
Insomnia	18(8.3%)	0	0	7(3.2%)	1(< 1%)	1(< 1%)
Dizziness	36(16.7%)	1(< 1%)	0	30(13.6%)	0	0
Dry mouth	199(92.1%)	1(< 1%)	0	201(91.3%)	0	0
Malaise	0	0	0	2(< 1%)	0	0
Dyspepsia	17(7.9%)	0	0	21(9.5%)	0	0
Acneiform						
Rash	0	0	0	0	0	0
Eczema	0	0	0	0	0	0
Mycotic Stomatitis	0	0	0	0	0	0
Hyperglycemia	1(< 1%)	4	0	1(< 1%)	6	1(< 1%)
Hypertension	13(6%)	0	1(< 1%)	17(7.7%)	1(< 1%)	0

PO3-28-01

More Than a Diagnosis: An Untold Story of Quality of Life

Presenting Author(s) and Co-Author(s):

S. Tinianov. Advocates for Collaborative Education, Santa Cruz, California, United States

K. Shanahan. Metavivor Research and Support, United States

C. Thomsen. Zero Breast Cancer, United States

G. Mason. IBC Research Foundation, United States

L. Carfang. Surviving Breast Cancer, United States

J. Hayashi. Breast Cancer Hawaii, United States

L. Hutcheson. Lobular Breast Cancer Alliance Inc., Massachusetts, United States

Background Advocates for Collaborative Education, a global coalition of patient, community, research, and policy advocates, initiated an anonymous, online survey to assess Quality of Life (QoL) impacts of cancer diagnosis and treatment to inform research, clinical care, and the broader cancer community. Identifying what matters most to individuals can potentially guide improvements in supportive care to effectively address QoL impacts. **Methods** A six-section, 93 question survey was co-created by patients, survivors, and advocates. Co-creation was instrumental in determining categories, specific questions, and measurement scales used to assess severity and impact of QoL challenges. Beyond demographic, treatment, and cancer diagnosis data, co-creation participants identified seventeen (17) treatment-related side effects. Survey questions asked about these side effects, their perceived severity, how well informed they felt about possibilities of experiencing these side effects, supportive care access, side effects of supportive care therapies, and personal preferences for receiving cancer-related information. Recruitment efforts for this online survey were conducted through advocacy groups and social media platforms. **Results** Across a wide range of demographic subsets, including age, race, stage of cancer, and treatment modalities, 334 respondents with a history of breast cancer reported a decline in QoL scores pre cancer vs post cancer according to the co-created measurement tool. Physical and emotional well-being emerged as top priorities for most respondents, 47.9% and 27.5% respectively. Of 17 listed side effects, respondents cited fatigue (49%), muscle/joint pain (36%), and emotional distress (35%) as primary concerns, with sexual dysfunction and cognitive impairment ranking prominently. Forty-six percent reported severe (frequent & highly disruptive) to very severe (constant & severely impacting quality of life) emotional distress, but only 55% of those felt informed or well informed about the possibility of emotional distress. Among respondents, only 41% received a plan to address emotional distress. Many felt unprepared for physical side effects as well. While 54% of individuals experienced diarrhea or fecal incontinence as a treatment side effect, 22% of affected individuals did not feel informed about the possibility of such side effects. Survey findings also highlight consequences of treatments to manage side effects. For example, 37% of respondents were prescribed treatment to address diarrhea and 100% of these patients reported additional side effects stemming from this supportive care including nausea, constipation, and fatigue. Detailed results for all categories as well as stratification by subsets of age, race, metastatic vs. early stage, treatment type, and others will be available for presentation and publication. **Conclusion** This study sheds light on an underexplored area of cancer research. Management of treatment side effects is integral to supportive care, yet supportive medications can introduce a cascade of their own side effects, exacerbating the overall burden on patients. Information and education are critical to bridge the gap. The collaboration with patients and survivors in developing this survey represents a pivotal step in

determining areas that demand attention for improving QoL and offers valuable insights aimed at enhancing the well-being of individuals affected by cancer and additional research will pursue collaborative solutions.

Demographic and High Level QoL Responses from MTAD (Breast)

MTAD (Breast)			
Category	Response	Count	Percentage
Response	1/5 correct	284	1
	1	13	0.038
	2	127	0.218
	3	45	0.195
	4	83	0.278
	OK	4	0.012
Current Age	18-28	5	0
	27-34	5	0.018
	35-44	98	0.124
	45-54	94	0.387
	55-64	115	0.364
Current Tx Status	85+	58	0.177
	Not on Tx (with 95 days)	3	0.009
	Active Tx	26	0.387
	Maintenance Tx	71	0.213
	Not on Tx (71 ended with 0 yrs)	36	0.198
	Long Term survivor (57 yrs post active Tx)	51	0.159
Race	Hispanic/Latino	142	0.425
	AAP	31	0.093
	Black/African	48	0.146
	White	14	0.042
	Other	236	0.707
	Native American	5	0
Ethnicity	Prefer not to share	5	0.015
	Hispanic	28	0.078
	Non-Hispanic	351	0.887
	Prefer not to share	5	0.015

Demographic and High Level QoL Responses from MTAD (Breast)

	Select Top 3		Select Top 10	
	count	percent	count	percent
Cardiac (Heart) Issues	28	0.087	4	0.012
Cognitive Impairment (Doubles Thinking/forgetfulness)	94	0.287	20	0.075
Constipation	26	0.082	1	0.003
Coughing	7	0.023	1	0.003
Dermatitis / Facial Acne/eczema	54	0.163	20	0.060
Dizziness	11	0.031	1	0.003
Emotional distress	123	0.368	47	0.141
Fatigue	174	0.504	63	0.188
Financial distress	65	0.195	22	0.066
Muscle Joint Pain	126	0.384	41	0.120
Nausea and vomiting	34	0.107	6	0.018
Pain/Neuropathy	62	0.203	20	0.058
Sexual dysfunction	94	0.287	17	0.051
Serious distress	11	0.031	0	0.000
Vision Issues	13	0.037	2	0.006
Weight Changes	62	0.201	23	0.068
Other	27	0.077	14	0.042

Detailed data on perceived severity, impact to QoL, perceived preparation for, and relevant supportive care is available for each side effect

PO3-28-02

BODY-IMAGE DISTRESS IN BREAST CANCER SURVIVORS AND THEIR EVALUATION OF MEDICAL TATTOOING FOLLOWING SURGERY

Presenting Author(s) and Co-Author(s):

M. Proctor. University of Central Florida, United States

J. Cassisi. University of Central Florida, United States

A review of the literature reveals a high incidence of body-image distress among breast cancer survivors who have undergone surgery, which is a natural response to the significant changes in their appearance. Reconstructive surgery, utilizing implants or flaps, may be employed to restore breast size and shape. Medical tattooing can recreate the nipple-areola complex and decorative appliques can conceal scars and skin color variations. Both reconstructive surgery and medical tattoos are associated with patient-reported satisfaction, yet further research is necessary to understand their combined impact on body-image distress. To investigate this, a survey was distributed among national breast cancer support groups and advocacy organizations, yielding 207 responses from individuals meeting the study's criteria. The participants were categorized into two groups: those who received post-surgical medical tattoos (n = 61) and those who did not (n = 146). The study also examined how participants evaluated the cosmetic and decision satisfaction of patients who made various surgical and cosmetic intervention choices. This was accomplished by having participants rate images of patients who had received three types of intervention: mastectomy and reconstruction only, mastectomy and medical tattooing only, and mastectomy, reconstruction, and medical tattooing. Using linear regression and multilevel modeling that controlled for demographic and clinical factors associated with body-image distress, the findings demonstrated that participants with medical tattoos reported significantly lower levels of body-image distress, depressive symptoms, and perceived stress compared to those without medical tattoos. Furthermore, participants rated images of patients who underwent both reconstruction and medical tattooing post-mastectomy as having significantly higher cosmetic and decision satisfaction ratings than images of patients who received reconstruction or medical tattooing alone. This research expands on our understanding of body-image distress in survivors as a multidimensional construct and may serve to indicate potential means for intervention. Enhancing our understanding of how breast cancer treatment and surgery affects survivors' body-image distress may aid healthcare professionals in offering additional psychoeducation and recommendations. Furthermore, presenting information about medical tattooing as a complementary cosmetic option early in the treatment process allows patients the opportunity to consider it within the context of their overall treatment plan.

Linear regression results using BIBCQ as the outcome variable and medical tattoo group as the predictor variable with covariates included.

Variable	B	SE B	β	t	p
<i>Main Effect</i>					
Medical Tattoo Group	-0.30	0.09	-.19	-3.26	.001
<i>Covariates</i>					
Age	-0.002	0.01	-.03	-0.52	.60
Surgery Type	0.15	0.06	.13	2.45	.02
Disease Stage	0.001	0.001	.01	0.26	.80
Time Since Surgery	0.001	0.001	.01	0.16	.88
PHQ9	0.04	0.01	.35	4.65	.001
PSS	0.03	0.01	.33	4.47	.001

Note. PHQ9 = Patient Health Questionnaire-9. PSS = Perceived Stress Scale.

PO3-28-03

Mitigating Financial Toxicity Through Individualized Education

Presenting Author(s) and Co-Author(s):

J. Doran. Triage Cancer, United States

M. Bryant. Triage Cancer, United States

Background Triage Cancer® offers a free Legal & Financial Navigation Program (LFN) that supports individuals coping with cancer, their caregivers, and health care providers as they navigate the legal and practical matters that arise after a diagnosis. Without access to the proper resources, individuals impacted by cancer may suffer the financial burden of a diagnosis – or financial toxicity, as coined by researchers at Duke. Financial toxicity has proven to have a negative impact on quality of life and mental and physical health of individuals coping with cancer. The LFN provides individuals impacted by a diagnosis with the accurate information and resources needed to help mitigate financial toxicity. The LFN addresses the gap in education around cancer-related legal issues to improve the overall health of individuals coping with cancer. This tailored education is particularly important for providers, as there is a significant lack of training around cancer-related legal issues. Consequently, health care providers are often not equipped to answer their patient's complex questions about cancer-related legal issues, including health insurance, disability insurance, and employment. The LFN provides personalized education on relevant laws and actionable steps to navigate the situation, which improves the provider's ability to support their patients and the patients' ability to self-advocate. **Methods** To start the process, individuals complete a brief intake form online and schedule a call with the staff. During the call, the staff provides education around relevant laws and practical options to manage the situation. The efficacy of the program is measured through voluntary survey response. Callers receive a follow-up email with a one question survey within a day of the initial call. After three weeks, the caller also receives a detailed survey. **Results** In 2022, Triage Cancer® provided direct consultation to 1,289 callers; 384 with breast cancer. For those callers, the most common topics included: employment, disability insurance, and health insurance. Survey data indicates that after speaking with staff, 93% felt better prepared with regard to their options and 94% agreed that they had actionable next steps. **Conclusion** The LFN provides tailored education around cancer-related legal issues in order to improve the quality of life of individuals coping with cancer. The LFN provides accurate information on relevant laws and actionable steps to help individuals make informed decisions to mitigate financial toxicity.

PO3-28-04

Ganglioside-Monosialic Acid for Prevention of Peripheral Neuropathy Induced by nab-Paclitaxel in Breast Cancer Patients (HELEN-004): A Randomized, Double-Blind, Phase II Trial

Presenting Author(s) and Co-Author(s):

Z. Lu. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

D. Jiao. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

J. Qiao. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

H. Zhang. Department of Breast & Thyroid Surgery, Nanyang center Hospital, United States

H. Dai. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

X. Sun. Affiliated Cancer Hospital of Zhengzhou University, United States

M. Yan. Henan Cancer Hospital, Henan, China

Y. Zhou. Department of Breast Surgery, Xinxiang Central Hospital, United States

L. Li. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

C. Wang. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, United States

X. Chen. Department of Breast Disease, Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, United States

Z. Liu. Department of Breast Disease, Henan Breast Cancer Center. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, United States

Introduction Chemotherapy-induced peripheral neuropathy (CIPN) is a dose limiting adverse effect of nab-paclitaxel. Ganglioside-Monosialic Acid (GM1) is an abundant glycosphingolipid in neuronal membranes and studies have shown its potential in preventing CIPN as a neuroprotective factor. This study was conducted to evaluate the effect of GM1 in preventing CIPN induced by nab-paclitaxel in breast cancer patients. **Methods** This study was a randomized, double-blind, placebo-controlled phase II trial conducted at three hospitals in China (NCT04222790). Female patients 18 to 75 years with early-stage breast cancer who were scheduled to receive nab-paclitaxel containing chemotherapy were randomly assigned to receive GM1 or placebo. Nab- paclitaxel was given 125-150 mg/m² once per week for 12 cycles or 260 mg/m² once every 3 weeks for four cycles. GM1 or placebo started one day before chemotherapy and was given once per day for 3 days (day -1, day 1, and day 2). The primary outcome was peripheral neuropathy evaluated by the Functional Assessment of Cancer Treatment Neurotoxicity (FACT-Ntx) subscale at 2 weeks after four cycles of chemotherapy. Other endpoints included peripheral neuropathy evaluated by CTCAE version 4.0, Functional Assessment of Cancer Therapy – General (FACT-G) scores and Functional Assessment of Cancer Therapy – Taxane (FACT-Taxane) scores at 2 weeks after four cycles of chemotherapy. Adverse events were evaluated by CTCAE version 4.0. Additional long-term assessments were performed at 3 months, 6 months, and 1 year after the completion of chemotherapy. All assessments were performed by trained physicians. **Results** 159 patients

were enrolled from April 2020 to June 2021, with 79 patients assigned to the GM1 group and 80 patients to the placebo group. Eight patients in the GM1 group and eight patients in the placebo group did not complete the endpoint assessments. In total, 71 patients in GM1 group and 72 in placebo group were evaluated. Baseline characteristics were generally well balanced between groups. After four cycles of Nab-paclitaxel containing chemotherapy, Patients in the GM1 group reported similar mean FACT-Ntx subscale 36.1 (35.1-37.0) with patients in the placebo group 36.4 (35.3-37.3). Compared with baseline, the mean FACT-Ntx score at two weeks after four cycles of chemotherapy decreased by 7.9 in the GM1 group ($p < 0.001$) and 7.6 in the placebo group ($p < 0.001$). The difference between GM1 group and placebo group was not statistically significant ($P=0.703$). No difference was observed in secondary outcomes except that GM1 group showed lower FACT G scores (61.0, 95% CI, 58.1-63.9) than the control group (67.0, 95% CI, 63.2-70.8) at two weeks after four cycles of chemotherapy, the difference was statistically significant ($P=0.014$). The main results of primary and secondary outcomes were summarized in Table 1. Random assignment was stratified by age (< 60 or ≥ 60) and BMI (< 24 or ≥ 24). Subgroup analysis was performed for patients in different age and BMI groups. Overall, patients above 60 years old showed lower FACT-Ntx score at than patients under 60 (34.1 and 36.5, respectively. $P=0.056$). Overweight patients (BMI ≥ 24) showed similar FACT-Ntx score with patients with BMI smaller than 24 (36.8 and 35.7, respectively. $P=0.095$). The FACT-Ntx score was not significantly different between the GM1 and placebo group in different age and BMI subgroups. The most common adverse events, including myalgia-arthralgia, nausea, vomit, and diarrhea, were evaluated according to CTCAE version 4.0. Incidence and severity of adverse events were not statistically significantly different between the two groups. **Conclusion** GM1 did not prevent peripheral neuropathy induced by nab-paclitaxel in breast cancer patients. The effect of GM1 in preventing CIPN is still inconclusive and further studies are needed. Caution in recommending GM1 to prevent CIPN is clearly warranted.

Table 1. FACT-Ntx subscale, CTCAE version 4.0, FACT-Taxane and FACT G at 2 weeks after four cycles chemotherapy.

	GM1 group (n=71)	Placebo group (n=72)	p
FACT-Ntx^a subscale, mean (95% CI)			
baseline	44	44	
After four cycles	36.1 (35.1-37.0)	36.4 (35.3-37.3)	0.703
CTCAE4.0^b, No. (%)			
0	6 (8.5)	9 (1.3)	
1	41 (57.8)	44 (61.1)	
2	19 (26.7)	18 (25.0)	0.985
3	5 (7.0)	1 (1.4)	
4	0 (0)	0 (0)	
FACT-Taxane^c, mean (95% CI)			
After four cycles	55.4 (54.4-56.4)	55.5 (54.3-56.7)	0.912
FACT G^d, mean (95% CI)			
After four cycles	61.0 (58.1-63.9)	67.0 (63.2-70.8)	0.014

- a. FACT-Ntx: Functional Assessment of Cancer Treatment- Neurotoxicity;
- b. CTCAE4.0: Common Terminology Criteria for Adverse Events;
- c. FACT-Taxane: Functional Assessment of Cancer Treatment – Taxane;
- d. FACT G: Functional Assessment of Cancer Treatment- General.

PO3-28-05

Therapeutic Plasmapheresis as a Symptomatic Treatment for Paclitaxel-Associated Peripheral Polyneuropathy

Presenting Author(s) and Co-Author(s):

S. Abdugafforov. Clinic RZD-Medicine Moscow, Tashkent, Toshkent Shahri, Uzbekistan

V. Vorotnikov. "The Clinical hospital "RZD-Medicine" in Moscow, United States

A. Soynov. Clinic RZD-Medicine Moscow, United States

T. Mchedlidze. Clinic RZD-Medicine Moscow, United States

I. Kopytich. "The Clinical hospital "RZD-Medicine" in Moscow, United States

S. Kim. Saint-Petersburg State Pediatric Medical University, United States

Relevance: Paclitaxel-associated peripheral polyneuropathy (PIPNe) is one of the most common side effects that develop during treatment with drugs of the taxane group. In the treatment of early breast cancer with paclitaxel 80 mg/m² weekly, 12 injections, PIPNe develops in 90% of patients of varying severity. The main symptoms are pain and numbness in the arms and legs, which is associated with the accumulation of paclitaxel in the ganglia of the spinal cord, as well as increased expression in the ganglia of the spinal cord of chemokines and cytokines, such as IL-1 β , IL-8 and TNF- α , as well as CXCR4, RAGE, CXCL1, CXCL12, CX3CL1 and C3. We hypothesized that the severity of PIPNe symptoms can be reduced by lowering the concentration of chemokines and cytokines in the blood by performing plasmapheresis sessions. Research methods: An open prospective study was carried out, the protocol of which was approved by the ethical committee. The study included 30 patients (100% women) aged 30 to 60 years (mean age 45 years) who developed PIPNe during paclitaxel therapy 80 mg/m², weekly, 12 injections. The severity of PIPNe symptoms was assessed using a "visual analogue scale" (VAS). The results of the VAS evaluation varied from 6 to 8 points. Patients underwent 5 courses of membrane plasmapheresis with exfusion of 400-500 ml of plasma per session (20 ml per 1 kg of body weight), plasma loss was compensated with saline. Repeated procedures were performed once every two months for 6 months. Results: 30 patients underwent 15 procedures of therapeutic plasmapheresis within 6 months. In 21 patients (70%) there was a pronounced decrease in PIPNe symptoms (VAS - 2-3 points), in 3 patients (10%) a moderate decrease in symptoms (VAS -5-6 points), in 6 (20%) no effect of plasmapheresis (VAS - 7-8 points). Approximately 15% of procedures were associated with adverse events, the most common of which were vasovagal reactions; 20% of patients had at least one adverse event. Conclusions: Given the subjective reduction in the severity of PIPNe symptoms during courses of therapeutic plasmapheresis in more than 70% of cases, therapeutic plasmapheresis can be used as a symptomatic therapy for PIPNe, however, taking into account the subjective assessment of the results by patients, there may be a risk of developing cognitive errors. Therefore, this method of therapy requires more thorough study.

PO3-28-06

YAP1 expression is a good prognostic marker of hormone receptor-positive HER2-negative breast cancer: clinicopathologic analysis using the 21-gene recurrent score

Presenting Author(s) and Co-Author(s):

I. Park. Gangnam Severance Hospital, Yonsei University, College of Medicine, United States

Y. Lee. Gangnam Severance Hospital, Yonsei University, College of Medicine, United States

J. Kim. Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Y. Cha. Gangnam Severance Hospital, Yonsei University, College of Medicine, United States

Background: YAP1 is a downstream transcription factor of Hippo pathway and considered an oncogene in numerous solid cancers. Oncotype Dx (ODX) test is a multigene test for patients with hormone receptor-positive, HER2-negative (HR+HER2-) breast cancer that provides a risk score (RS), a high RS means high-risk. In this study, we investigated the relation between YAP1 expression and RS in patients with HR+HER2- breast cancer and validated the clinical impact of YAP1 on breast cancer using public datasets. Methods: This retrospective study included 401 patients who received curative-purpose resection of HR+HER2- breast cancer and underwent ODX test between May 2014 and April 2020 at Gangnam Severance Hospital in Seoul, Korea. YAP1 nuclear localization was evaluated using immunohistochemical staining, and clinicopathological parameters including RS were analyzed. Clinical outcome was validated using YAP1 mRNA expression in TCGA-BRCA and METABRIC datasets. Results: High-YAP1 expression was significantly correlated with low ODX RS (OR [odds ratio] 0.373, 95% CI [confidence interval] 0.198-0.703, $p=0.002$). High expression of YAP1 mRNA correlated with superior clinical outcomes, particularly in patients with ER-positive breast cancer ($p < 0.0001$, overall survival [OS] in METABRIC; $p=0.00085$, recurrent-free survival [RFS] in METABRIC; $p=0.040$, disease-free survival [DFS] in TCGA-BRCA). With different ESR1 mRNA expression thresholds and highly expressed YAP1, patients in the upper 80-, 60-, or 40 percentiles of ESR1 expression levels consistently demonstrated superior OS and RFS in METABRIC as well as DFS in TCGA-BRCA. Conclusion: YAP1 could serve as a prognostic marker as well as a therapeutic target in patients with HR+HER2- breast cancer.

PO3-28-08

Triple Hormone Receptor Signatures as Novel Prognostic Markers in Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Omar. Weill Cornell Medicine, NEW YORK, New York, United States

C. Harrell. Virginia Commonwealth University, United States

R. Tamimi. Weill Cornell Medicine, New York, NY, USA, United States

L. Marchionni. Weill Cornell Medicine, United States

T. Ince. Weill Cornell Medicine, United States

Background Tumor phenotype across various cancers, including breast cancer, is predominantly shaped by a synergy between genomic alterations and the cell-of-origin from which the tumor emerges. These elements collectively influence crucial aspects like tumor aggressiveness, treatment response, and patient prognosis. While existing research highlights that the cell-of-origin often leaves a lasting imprint on the molecular architecture of tumors, leveraging this information for actionable clinical insights has proven challenging. Specifically, in the realm of breast cancer, utilizing cellular ancestry signatures could be a key factor in tailoring effective therapeutic strategies and improving patient outcomes. Methods In this study, we developed a unique signature anchored in the expression levels of triple hormone receptors (THR)—namely androgen (AR), estrogen (ER), and vitamin D (VDR)—in normal breast cells. Building on this, we formulated two distinct mRNA markers, THR-50 and THR-70, aimed at categorizing breast tumors based on their THR expression profiles. These markers were rigorously validated across 65 independent breast cancer studies, involving a total of 6,679 patients, utilizing Kaplan-Meier survival curves, Cox proportional hazards models, and unsupervised clustering analyses. Results Our findings indicate that both THR-50 and THR-70 are robustly associated with overall survival and recurrence-free survival in breast cancer patients across all datasets evaluated. Importantly, these THR signatures demonstrate broad applicability across various breast cancer subtypes, grades, and treatment phases—unlike conventional prognostic markers that tend to be subtype-specific. Additionally, the THR signatures have revealed four unique patient clusters with divergent survival outcomes, three of which are ER-positive and one ER-negative. When augmented with an immune-based signature (i20), THR-70 identifies a specific ER-negative breast cancer subgroup with a highly favorable prognosis, comparable to ER-positive subtypes, as well as another ER-negative subgroup characterized by exceedingly poor survival outcomes. Conclusion The THR-based cellular ancestry signatures open a new avenue in understanding the intricacies of breast cancer biology. These signatures offer a robust and stable framework for developing other prognostic markers, thus providing an enhanced stratification of existing breast cancer categories as well as creating new classifications.

PO3-28-09

Does Diffusely Infiltrating Lobular Carcinoma of the Breast Arise from Epithelial-Mesenchymal Hybrid Cells?

Presenting Author(s) and Co-Author(s):

A. Voros. University of Szeged, Department of Pathology, United States

L. Tabar. Falun Central Hospital, United States

R. Bozo. University of Szeged, Department of Dermatology, United States

O. Olah. University of Szeged, Department of Pathology, United States

K. Ormandi. University of Szeged, Department of Radiology, United States

Z. Vereb. University of Szeged, Department of Radiology, United States

I. Nemeth. University of Szeged, Department of Dermatology, United States

P. B. Dean. University of Turku, Department of Diagnostic Radiology, United States

O. Puchkova. Il'inskaya Hospital, Department of Breast Imaging, United States

M. Yen. Taipei Medical University, College of Oral Medicine, United States

L. Chen. Taipei Medical University, College of Oral Medicine, United States

Classic diffusely infiltrating lobular carcinoma has imaging features divergent from the breast cancers originating from the terminal ductal lobular units and from the major lactiferous ducts. Although the term “invasive lobular carcinoma” implies a site of origin within the breast lobular epithelium, we were unable to find evidence supporting this assumption. Exceptional excess of fibrous connective tissue and the unique cell architecture combined with the aberrant features at breast imaging suggest that this breast malignancy has not originated from cells lining the breast ducts and lobules. The only remaining relevant component of the fibroglandular tissue is the mesenchyme. The cells freshly isolated and cultured from diffusely infiltrating lobular carcinoma cases contained epithelial–mesenchymal hybrid cells with both epithelial and mesenchymal properties. The radiologic and histopathologic features of the tumours and expression of the mesenchymal stem cell positive markers CD73, CD90, and CD105 all suggest development in the direction of mesenchymal transition. These hybrid cells have tumour-initiating potential and have been shown to have poor prognosis and resistance to therapy targeted for malignancies of breast epithelial origin. Our work emphasizes the need for new approaches to the diagnosis and therapy of this highly fatal breast cancer subtype.

PO3-28-10

MRI Radiomic phenotypes derived from the ECOG-ACRIN E4112 Trial to assess high-risk ductal carcinoma in situ

Presenting Author(s) and Co-Author(s):

K. Slavkova. University of Pennsylvania, United States

R. Kang. Brown University, United States

V. Belenky. University of Pennsylvania, United States

A. Kazerouni. University of Washington, United States

D. Biswas. University of Washington, United States

H. Horng. University of Pennsylvania, United States

R. Chitalia. University of Pennsylvania, United States

M. Hirano. University of Washington, United States

J. Xiao. University of Washington, United States

R. Corsetti. Tulane University, United States

S. Javid. Fred Hutchinson Cancer Center, United States

D. Spell. Mary Bird Perkins Cancer Center, United States

A. Wolff. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States

J. Sparano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

S. Khan. Northwestern University, Chicago, Illinois, United States

C. Comstock. Memorial Sloan Kettering Cancer Center, New York, New York, United States

J. Romanoff. Brown University - ECOG-ACRIN Biostatistics Center, Providence, Rhode Island, United States

J. Steingrimsson. Brown University, United States

C. Gatsonis. Dept of Biostatistics, Brown University School of Public Health, United States

C. Lehman. Massachusetts General Hospital, United States

S. Partridge. University of Washington, United States

D. Kontos. University of Pennsylvania, Department of Radiology, Philadelphia, Pennsylvania, United States

H. Rahbar. University of Washington, United States

INTRODUCTION Ductal carcinoma in situ (DCIS) is a non-lethal pre-invasive breast cancer that can co-exist with invasive disease. Dynamic contrast-enhanced (DCE) MRI is sensitive for the detection of high-grade DCIS and invasive cancer while Oncotype DCIS Score is a 12-gene assay that can assess recurrence risk. In practice, it is difficult to distinguish low- from high-risk DCIS, which leads to overtreatment for up to half of women diagnosed with DCIS. We hypothesize that radiomic phenotypes of DCIS derived from DCE-MRI data may serve as prognostic markers to improve risk stratification by capturing disease heterogeneity. Here we evaluate the ability of these phenotypes to predict DCIS Score and upstaging of DCIS to invasive disease on wide local excision in a multicenter trial. **METHODS** Data: DCE-MRI data from the ECOG-ACRIN E4112 trial were retrospectively analyzed. Primary analysis focused on

participants with data on disease upstaging (N=295), with secondary analysis in a subset (N=174) of participants with DCIS Scores (dichotomized as >55 and ≤55) and pure DCIS. Clinical information included patient demographics, lesion morphology on MRI, background parenchymal enhancement, DCIS grade, central necrosis, and hormone receptor status. **Data analysis:** Radiologist-drawn lesion segmentations and publicly available software, CaPTk, were used to compute 64 radiomic features from first post-contrast images for each participant. Radiomic phenotypes were identified using hierarchical clustering on the extracted features. A Chi-square test was used to evaluate the association between radiomic phenotypes and each outcome. The likelihood ratio test was used to compare two logistic regression models: 1) clinical model using only clinical information as predictors and 2) clinical+phenotypes model using clinical information and phenotype assignment as predictors. Each model was used for the prediction of upstaging to invasive disease and DCIS score. Model performance was evaluated as the 10-fold cross-validated area under the receiver operator characteristic curve (AUC). A $p < 0.05$ was considered significant. **RESULTS** A total of 45 (15%) cases upstaged to invasive disease. Two radiomic phenotypes were identified: Phenotype 1 indicated greater lesion signal heterogeneity, while Phenotype 2 indicated lower heterogeneity. Radiomic phenotype was strongly associated with disease upstaging ($p=0.0034$) – with a higher rate of upstaging for Phenotype 1 – but not with DCIS score ($p=0.1174$, Table 1). For predicting disease upstaging, the clinical+phenotypes model yielded a higher AUC=0.72 and a significantly better fit to the data ($p=0.0022$) compared to the clinical model parameterized by clinical information alone (AUC=0.69). For predicting DCIS Score, the clinical+phenotypes model (AUC=0.77) showed similar performance compared to the clinical model (AUC=0.76) and no significant improvement in fit to the data ($p=0.2920$). **CONCLUSION** Radiomic phenotypes capturing disease heterogeneity show promise as prognostic predictors for predicting disease upstaging in DCIS compared to clinical information alone and may enable more efficient disease management. We observed that phenotypes did not have independent predictive outcome for DCIS score, suggesting that MRI and DCIS Score offer independent information and could be combined in future models to better predict disease recurrence or progression. Clinical applications of radiomic phenotypes may improve risk stratification and potentially result in decreased overtreatment of women diagnosed with DCIS.

Table 1: Association between radiomic phenotypes and DCIS outcomes using a Chi square test.

Table 1: Association between radiomic phenotypes and DCIS outcomes using a Chi square test.			
Upstage to invasive cancer	Radiomic Phenotype 1 (n=104)	Radiomic Phenotype 2 (n=191)	p-value
Yes	25 (24%)	20 (10.5%)	0.0034
No	79 (76%)	171 (89.5%)	
DCIS Score	Radiomic Phenotype 1 (n=66)	Radiomic Phenotype 2 (n=108)	p-value
Low/Intermediate (<=55)	42 (36.4%)	82 (75.9%)	0.1174
High (>55)	24 (63.6%)	26 (24.1%)	

PO3-28-11

Potassium channel activity unveils breast cancer vulnerability

Presenting Author(s) and Co-Author(s):

S. Gentile. Medical University of South Carolina, Charleston, South Carolina, United States

Decades of studies on ion channels have vastly demonstrated the critical functions of these proteins in many physiological and pathological conditions and have provided for an extraordinary pharmacopeia of useful compounds, often with selective actions and minimal side effects. Nevertheless, the function of ion channels in controlling cancer biology is still unknown and underexplored. Our research demonstrates that breast cancer downregulates expression of specific potassium channels (e.g., Kv11.1, KCa3.1) independently of their molecular characterization (ER+, HERB2+ and TNBC). Furthermore, breast cancer patients expressing high protein level of each of these channels presents a better overall survival when compared with patients with low expression. These data indicate that potassium channels can be prognostic factors and that high activity of these protein affects tumor growth. Therefore we wanted to understand the therapeutic benefits of pharmacological targeting specific potassium channels in breast cancer. We discovered that stimulation of the Kv11.1 with specific and selective activator molecules produced a significant growth arrest in a variety of experimental systems including in vitro, in vivo and ex vivo (e.g. Patient-derived organoids) systems. Studying the biochemical pathways that underline these events we discovered that Kv11.1 agonists affects different hallmarks of cancer including metabolism, growth and metastasis signaling without producing significant side effects. For example, use of Kv11.1 agonists produced a strong suppression of oncogene protein function including c-Myc while increasing oncosuppressors such as p21 and p16. These events associated with activation of a senescent phenotype. Furthermore, stimulation of Kv11.1 channel reversed the epithelial-to-mesenchymal transition by inhibiting the WNT signaling and reduced spreading of a TNBC by arresting the metastatic process. . Furthermore, Kv11.1 activation produced a Ca²⁺-dependent mitochondria damage where the antioxidant transcription factor NRF2 played a fundamental role in determining resistance to death. Therefore, we conclude that targeting the Kv11.1 potassium channel in breast cancer can be considered a new, effective and safe targeting strategy for breast cancer.

PO3-28-12

Targeting the K_{Ca}3.1 potassium channel arrests ER⁺ breast cancer growth and re-sensitizes to drug resistance.

Presenting Author(s) and Co-Author(s):

D. Delisi. Medical University of South Carolina, United States

M. Cetin. Medical University of South Carolina, United States

O. Saatci. Medical University of South Carolina, United States

O. Sahin. Medical University of South Carolina, United States

S. Gentile. Medical University of South Carolina, Charleston, South Carolina, United States

Standard of care for breast cancer (BC) treatment including Selective-Estrogen Receptor (ER)-modulators and/or degraders (SERM; tamoxifen, SERD; Fulvestrant) or cyclin-dependent kinases CDK4 and CDK6 (palbociclib) can be effective therapeutic strategies. However, drug toxicity and/or drug resistance severely limit these approaches and patients succumb to the disease. Therefore, there is an urge to develop new therapeutic strategies against ER⁺-BC. Ion channels are general pharmacological targets however, little is known about the role of this class of proteins in cancer biology. We discovered that expression of the K_{Ca}3.1 potassium ion channel is downregulated in ER⁺-BC. Also, patients expressing high level of K_{Ca}3.1 present a better overall survival (OS) and relapse free survival when compared with patients with low expression. Thus, these data indicate that K_{Ca}3.1 is a prognostic factor in ER⁺-BC and that high activity of this channel plays a fundamental role in an oncosuppressor signature. Our central hypothesis is that pharmacological targeting K_{Ca}3.1 with activator molecules arrests growth of ER⁺-BC. We discovered that ER⁺-BC patient-derived organoids (PDO) and cell lines treated with K_{Ca}3.1 agonists including the FDA approved Chlorzoxazone, (CZX) arrests significantly inhibit tumor growth. Activation of K_{Ca}3.1 arrested the cell cycle in the G₀/G₁ phase by activating a senescent-like phenotype. Furthermore, our studies on the biochemical signaling that underlines this event demonstrated that increased expression level of K_{Ca}3.1 protein associated with lower expression level of ER α in a cell cycle phase-dependent manner. Furthermore, use of K_{Ca}3.1 activator produced a proteasomal-dependent ER α degradation. To better characterize the therapeutic benefit of targeting the K_{Ca}3.1, we assessed the effects of CZX on developed several tamoxifen and/or palbociclib resistant cell lines and PDO models. We found that the combination of CZX strongly potentiated the lethal effects of both tamoxifen and palbociclib in the relative resistant models. We conclude that pharmacological targeting K_{Ca}3.1 potassium channel in ER⁺-BC can be considered a novel, safe and efficacious therapeutic strategy.

PO3-29-01

Defining the molecular-genetic mechanism of CDK4/6 inhibition therapy induced senescence to identify biomarkers and determine how senescence contributes to patient outcomes.

Presenting Author(s) and Co-Author(s):

M. Benitez. Memorial Sloan Kettering Cancer Center, New York, New York, United States

R. Kudo. Memorial Sloan Kettering Cancer Center, Koto-City, Tokyo, Japan

C. Gleason. Memorial Sloan Kettering Cancer Center, New York, New York, United States

S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

A. Koff. Department of Molecular Biology, Memorial Sloan Kettering Cancer Center, United States

In the context of ER+ breast cancers the CDK4/6i have had extraordinary success extending the duration of median PFS, and in some cases, OS, particularly in combination with hormone antagonists. Still there are several individuals who do not have good clinical responses or can only maintain these for a short period of time and then resistance manifests. One challenge to improving patient outcomes by combining CDK4/6i with other modalities is our incomplete understanding of how they induce these beneficial outcomes at the cellular and molecular level. For example, while a few mutations associated with resistance prevent induction of cell cycle exit by the drug, simply inducing cell cycle exit does not explain the positive activity of CDK4/6i. Additional mechanisms such as drug induced enhancement of MHC class I antigen presentation on the surface of treated cancer cells to non-cancer cell autonomous effects on the development of T_{regs} may also contribute. CDK4/6i can also induce cellular senescence in cancer cell lines in vitro and in mouse models of cancer. Senescence is a cell fate transformation whereby the cell 'differentiates' into a stably-arrested, inflammation-provoking cell fate through a largely poorly understood developmental pathway. However, identification of stably arrested and inflammation provoking cells, particularly in human biopsies, has been a pernicious challenge. This might be overcome by identifying the molecular and genetic basis of how senescent cells arise from non-cycling quiescent cells, and two developmental studies, one, carried out in dedifferentiated liposarcoma cell lines treated with CDK4/6i and another during DNA damage induced senescence in primary fibroblasts have begun to do this. These showed that the canonical markers used in the laboratory, such as the accumulation of the CDK inhibitor p16Ink4a or the accumulation of senescence associated beta-galactosidase positive cells, arise well before cells underwent stable arrest. Furthermore, it is now universally acknowledged that the idiosyncratic heterogeneous nature of the expression of the various cytokines and growth factors that are part of the senescence-associated secretory program, precludes the use of transcripts and proteins culled from lists of gene products associated with senescence in other systems. Thus, the limited analysis of therapy induced senescence in breast cancer cell lines has prevented the evaluation of how this biology, induced by CDK4/6i, might contribute to disease management. We had pioneered the approach to identify late-appearing necessary regulators that control the fate transition from reversible to stable arrest in dedifferentiated liposarcoma. This insight was then used to identify senescent cells in patients and address the contribution that senescence makes over time. In this presentation we will describe similar but as of yet unpublished work describing the detailed temporal molecular genetic analysis of CDK4/6i therapy induced senescence in ER+ breast cancer cell lines, and discuss how we have nominated highly specific late markers of cellular senescence for application in a number of archival and ongoing clinical trials to determine (1) whether therapy induced senescence contributes to disease management and (2) how its contributions change

over time. Such insights will further inform patient care and also drive research in model organisms to unravel the complex role that senescence plays in breast cancer development and therapy.

PO3-29-02

Single Nucleotide Polymorphisms (SNPs) in Inflammatory Pathways Associated with Body Mass Index (BMI) and Breast Cancer (BC) Risk: A Scoping Review

Presenting Author(s) and Co-Author(s):

E. Quinn. Massachusetts General Hospital, United States

B. Wekwerth. Massachusetts General Hospital, United States

M. Doyle. Massachusetts General Hospital, United States

R. Carlos. Massachusetts General Hospital, United States

Background: BMI is a risk for BC, with inflammation as a possible link. We conducted a scoping review assessing SNPs in inflammatory pathways posited to modify BC risk by BMI. Design: We followed PRISMA guidelines for scoping reviews. Pubmed, Medline and OVID databases were interrogated for publications between 1/2000-12/2023 using search terms “breast cancer” AND [BMI OR “body mass index” OR elevated BMI OR obesity] AND [SNP OR “single nucleotide polymorphism” OR polymorphism OR mutation] AND [inflammation OR cytokines OR IL-1 OR IL-2 OR IL-4 OR IL-6 OR IL-8 OR IL-10 OR IL-12 OR TNF-A or TGFB OR CRP]. A single reviewer assessed 67 unique publications and determined that 17 met inclusion criteria as a case control or cohort study. Two reviewers extracted the following data: demographics, SNP, number of cases and controls by BMI. Disagreements were resolved by consensus with a third reviewer. High BMI was defined by each study using accepted levels within their population: ≥ 25 (United States, Mexico) or ≥ 22 (Korea). Unadjusted odds ratios (OR) for BC risk were calculated by SNP stratified by BMI. Results: Data were extractable from 5 studies, all case controls. We requested patient level data for 12 studies from the corresponding author, without response. When stratified by BMI, we detected heterogenous effects of SNPs on BC risk (Table 1, only significant or trending correlations presented). With high BMI, IL-1 β -31 TT (OR 2.19, 0.86-5.59) and GC/CC (OR 0.81, 0.68-0.97) correlated with BC risk ($p < 0.05$). With normal BMI, STAT3 rs1026916 GA (OR 0.78, 0.62-0.96) and JAK2 rs1536800 TT (OR 1.93, 1.07-3.48) correlated with BC risk. Additional SNPs trended to correlate with BC risk ($0.05 < p < 0.10$) by BMI. Conclusion: The association of inflammatory SNPs and BC risk is complex and can be both protective and predisposing to BC risk, with BMI modifying SNP risk. Future research can assess SNPs and

BC risk in more diverse populations.

Table: Unadjusted ORs. *p<0.05; †0.05 p 0.10

Auth of	Year	Coun by Ethnicity	Sam ple size	Gene	SNP	Allele / Geno type	High BMI			Normal BMI		
							OR	Lowe r 95% CI	Uppere r 95% CI	OR	Lowe r 95% CI	Uppere r 95% CI
Lee et al.	2008	Korea - Korea	1108	IL-1RN	--	non-2allele						
Eras et al.	2019	Turkey, not defined	414	IL-1β-31	--	CT						
Eras et al.			414		--	TT	2.19	0.86	5.59			
Slattery et al.	2008	South western (SW) US, White	5162	IL-6	rs180 0795	GC/C C	0.61*	0.68	0.97	0.62*	0.67	1.00
Slattery et al.			5162		rs180 0795	GC/C C						
Slattery et al.	2014	USCA enico White, Hispanic Ameri can, India n, Mexican	4708	JAK1	rs491 6005	TC						
Slattery et al.			4708		rs491 6005	CC				1.64*	0.98	3.45
Slattery et al.			4708		rs310 211	AG						
Slattery et al.			4708		rs310 211	GG						
Slattery et al.			4708		rs225 6298	CT						
Slattery et al.			4708		rs225 6298	TT						
Slattery et al.			4708	JAK2	rs705 7491 5	GA						
Slattery et al.			4708		rs705 7491 5	AA						
Slattery et al.			4708		rs704 3371	AT						
Slattery et al.			4708		rs704 3371	TT	1.29*	0.98	1.69			
Slattery et al.			4708		rs153 6800	CT						
Slattery et al.			4708		rs153 6800	TT	0.71*	0.45	1.10	1.93*	1.07	3.46
Slattery et al.			4708		rs378 0361	AC						
Slattery et al.			4708		rs378 0361	CC						
Slattery et al.			4708	STAT 3	rs806 9545	AG						
Slattery et al.			4708		rs806 9545	GG						
Slattery et al.			4708		rs650 3695	TC						
Slattery et al.			4708		rs650 3695	CC						
Slattery et al.			4708		rs125 4991 3	TC						
Slattery et al.			4708		rs125 4991 3	CC						
Slattery et al.			4708		rs102 6916	GAA A				0.78*	0.62	0.96
Slattery et al.			4719	TRAF 2	rs278 4075	GAA A						
Slattery et al.			4720		rs702 7245	GAA A				1.28*	1.00	1.65
Slattery et al.			4721		rs908 831	AG						
Slattery et al.			4721		rs908 831	GG						

PO3-29-03

An Emerging Class of ER mutations Enhances ER Dimerization and Promotes ER Activity

Presenting Author(s) and Co-Author(s):

S. Irani. Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA, United States

W. Tan. Texas A&M University, United States

Q. Li. Memorial Sloan-Kettering Cancer Center/Rutgers University, United States

W. Toy. MSKCC, United States

C. Jones. MSKCC, United States

M. Gadiya. MSKCC, United States

A. Marra. Memorial Sloan Kettering Cancer Center, United States

J. Katzenellenbogen. University of Illinois Urbana-Champaign, United States

K. Carlson. University of Illinois (Urbana, Champagne), United States

B. Katzenellenbogen. University of Illinois Urbana-Champaign, United States

Y. Shen. Texas A&M University, United States

S. Chandralapaty. Memorial Sloan Cancer Center, New York, New York, United States

Physiological activation of estrogen receptor alpha (ER α) requires the binding of estradiol (E2) to the ligand binding domain (LBD) of the receptor. This interaction triggers a repositioning of helix 12 (H12), facilitating the recruitment of coactivator proteins to the unoccupied coactivator binding groove. However, in the context of breast cancer, point mutations of ER α at H12 lead to its repositioning and self-activation in the absence of E2.

Through MSK clinical sequencing breast cancer cohort (MSK-IMPACT), we assayed 8302 samples of ER+ breast cancer patients and identified 649 mutations within the LBD of ER α . 471 of these mutations (73%) were located at H11-H12 loops (D538, Y537, L536), while the remaining 27% were located near the dimer interface of ER α (V422, G442, F461, S463P, L469). Through in vitro biochemical and cell assays, we identified that these mutations promote dimer formation and hormone-independent transcriptional activity. Tumors expressing these mutations exhibited significantly accelerated growth compared to their wild-type controls. Unlike Y537S, cells harboring mutations at the dimer interface maintain their sensitivity to Selective Estrogen Receptor Degraders (SERDs), including Fulvestrant, recently FDA-approved Elacestrant, and Camizestrant, as well as Selective Estrogen Receptor Modulators (SERMs) including Tamoxifen and Raloxifene. By utilizing machine learning and computational structural analyses, we uncovered that these mutants, unlike Y537 repositions H12, act distinctly through conformational change across the ER α dimer interface. Further cell assays proved that the dimerization leads to increased stability of the receptor and facilitates its nuclear localization, which is required for ER α activation.

Collectively, our finding unveiled a new class of ER mutations that enforce receptor dimerization and activation of the ER signaling pathway. The discovery opens up a new therapeutic interventional possibility, suggesting that targeting dimerization could emerge as a new strategy to combat these malignancies.

PO3-29-04

Patient selection for high RSK2 expression is key for achieving improved PFS in metastatic breast cancer in the PMD-026 Phase 1/1b study

Presenting Author(s) and Co-Author(s):

S. Dunn. Phoenix Molecular Designs, United States

J. Wang. Florida Cancer Specialists/Sarah Cannon Research Institute, United States

H. Han. H. Lee Moffitt Cancer Center, Tampa, Florida, United States

R. Wesolowski. James Cancer Hospital and the Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

A. Patnaik. START San Antonio, United States

S. Bahadur. Banner MD Anderson Cancer Center, United States

N. Palaskas. David Geffen School of Medicine, University of California, Los Angeles, United States

M. Huynh. Phoenix Molecular Designs, United States

A. Jayanthan. Phoenix Molecular Designs, United States

G. Los. Phoenix Molecular Designs, United States

A. Dorr. Phoenix Molecular Designs, United States

Background: PMD-026 is a first in class, reversible, oral small molecule inhibitor of p90 ribosomal S6 kinase (RSK), a kinase family activated by the MAPK and PDK-1 pathways, which regulate substrates involved in cancer cell proliferation and drug resistance. Both pathways are implicated in HR+ and triple negative breast cancer (TNBC). RSK2 can modulate the growth of breast cancer (BC) by promoting cell cycle progression through G2/M, specifically through pYB-1^{S102} which nucleates spindle pole formation in M-phase of cancer cells. This mechanism of action (MOA) for PMD-026 can be monitored by measuring the loss of pYB-1^{S102} and pCDK2^{Y15}, a marker for G2/M arrest. Therefore, PMD-026 presents a novel mechanism to inhibit resistance at G1/S which is common for CDK4/6 inhibitors as well as ADCs such as those that contain Topoisomerase 1 conjugates. Here in, we show for the first time that PMD-026 inhibits P-YB-1^{S102} and pCDK2^{Y15} in a dose-dependent manner in TNBC cells and address whether this could be translated as a pharmacodynamic marker of PMD-026 activity in patients. To guide patient selection, we are co-developing a unique and simple IHC based companion diagnostic (CDx) with Roche based on the principle that activated RSK2 translocates from the cytoplasm into the nucleus. In mBC, RSK2 was found to be highly expressed in ~70% of patients using a staining algorithm. An H-score was developed and ultimately H-score >180 (75% nuclear staining with staining intensity of 2+ or 3+ by IHC) was used as the cut-off in our Phase 1/1b trial retrospective study. This IHC assay will be used to select patients in the upcoming Phase II, as PFS in the PMD-026 Phase 1/1b study showed remarkable differences when comparing patients with high and low RSK2. Results: In this Phase 1/1b study, PMD-026 was evaluated in an ethnically diverse population of women across all breast cancer subtypes. Patients had a median of 5 prior lines of therapy and PMD-026 achieved stable disease in 44% (11/25) of the subjects. Consistent with the MOA, PMD-026 inhibited pCDK2^{Y15} in PBMCs from patients at C1D15. Corresponding plasma concentrations were ~ 1µM, which correlates with the IC₉₀ of PMD-026 in preclinical models. To guide patient selection in the future, the RSK2 IHC with an H:Score >180 was used to evaluate patient outcomes. Using this criterion, PFS was significantly longer in RSK2 high vs low patients (3.6

months vs 1.3 month, HR = 0.27, p = 0.031, N=20 patients representing de novo TNBC and HR+/CDK4/6 refractory subtypes). Upon further analysis, patients who had 5 lines of therapy or less benefited the most. PFS in these less heavily pretreated RSK2 high patients was 4.8 months vs 1.3 months for RSK2 low patients (HR = 0.07, p = 0.001 N=14 representing the same subtypes above). It was clear that the time on study was longer for patients with high RSK2 vs low, and this was specifically noted in de novo TNBC and HR+ patients that previously failed CDK4/6 inhibitors as well as endocrine therapies. A key observation in this study was that the PFS benefit was based on the RSK2 levels and not on any pharmacokinetic differences between patients, as the AUC (p=0.53), Cmax (p=0.73) and plasma levels (p=0.76) did not differ between RSK2 high and RSK2 low groups. These data strongly support the activity of this first in class RSK inhibitor, PMD-026, in RSK2 high breast cancers. Our integrated IHC based CDx strategy plans to prospectively enroll RSK2 high patients for our Phase 2 trials will be described. Conclusions/Translational Significance: CDx guided breast cancer therapeutics are often lacking for the treatment of TNBC, as well as HR+ breast cancers that have failed CDK4/6 inhibitors. The ability to identify patients who could potentially benefit most from RSK-targeted agents such as PMD-026 is an important step forward in delivering practice changing therapies for patients.

PO3-29-05

Clinical risk score to predict overall survival and breast cancer recurrence in phase 3 TAILORx trial and the Surveillance, Epidemiology, and End Results (SEER) Database populations

Presenting Author(s) and Co-Author(s):

S. YANG. Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, Maryland, United States

J. Yu. Eliassen Group, Reston, Virginia, United States

N. Sinaii. NIH Clinical Center, Bethesda, Maryland, United States

Background: Overall survival (OS) is the gold standard and most relevant endpoint in oncology research and patient care. It underscores a need to develop methods to estimate the likelihood of mortality in breast cancer. Methods: We evaluated molecular and clinical measures that predicted mortality risk using multiple logistic regression and developed a clinical risk score (CS) in 8,905 patients from the phase 3 TAILORx trial. Association of CS with mortality in patients at low, intermediate, and high risks was analyzed by Kaplan-Meier and multivariable Cox proportional-hazards regression analyses. The score was validated in an independent population of 148,301 patients with node-negative, hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer in the SEER database. Likelihood ratio (LR) test and c-index were used to compare prognostic information provided by CS and a 21-gene recurrence score (RS) to OS, invasive disease-free survival (DFS), recurrence-free interval (RFI), and distant recurrence-free interval (dRFI). Results: The 10-year mortality rates in low-risk, intermediate risk, and high-risk groups were 3.9% (95% CI 3.1 to 4.8), 37.2% (95% CI 23.4 to 51.1), and 75.8% (95% CI 54.1 to 97.4), respectively ($P < 0.0001$). Compared with low-risk score, intermediate (adjusted HR 45.5, 95% CI 32.2 to 64.9) and high-risk scores (HR 2026, 95% CI 1194 to 3483) were associated with risk of mortality, independent of demographics, tumor grade, RS, tumor size, PR, and treatment factors. The algorithm also predicted DFS, dRFI, and RFI outcomes ($P < 0.0001$ each), outperforming RS by both LR test and c-index estimate. Its validity was corroborated in the SEER population (intermediate risk: HR 9.3, 95% CI 6.7 to 13.3 and high-risk: HR 125.9, 95% CI 85.2 to 189.6). Conclusions: Clinical risk score robustly predicts risk of mortality in early-stage breast cancer populations. It provides more prognostic information than RS to survival and breast cancer recurrences.

PO4-01-01

Prognostic Impact of Adjuvant Trastuzumab for the Treatment of Localized Stage I Breast Cancer - Single Tertiary Center Experience

Presenting Author(s) and Co-Author(s):

S. Sapon-Cousineau. University of Montreal, United States

M. Florescu. Centre hospitalier de l'Université de Montréal, United States

D. Charpentier. Centre hospitalier de l'Université de Montréal, Montreal, Quebec, Canada

R. Younan. Centre hospitalier de l'Université de Montreal, Montreal, Quebec, Canada

E. Patocskai. Centre hospitalier de l'Université de Montréal, Université de Montréal, Montréal, Quebec, Canada

S. Hassan. Centre hospitalier de l'Université de Montreal, Montreal, Quebec, Canada

K. Boulva. Centre hospitalier de l'Université de Montreal, Montreal, Quebec, Canada

J. Ayoub. Centre hospitalier de l'Université de Montréal, United States

Prognostic Impact of Adjuvant Trastuzumab for the Treatment of Localized Stage I Breast Cancer – Single Tertiary Center Experience

Sasha Sapon-Cousineau, Marie Florescu, Danielle Charpentier, Rami Younan, Erica Patocskai, Saima Hassan, Kerianne Boulva, Jean-Pierre Ayoub

Centre hospitalier de l'Université de Montréal, Montréal, Québec, Canada

The HER2 oncoprotein is an established therapeutic target, and the combination of adjuvant chemotherapy and targeted anti-HER2 therapy substantially reduces the risk of recurrence and death over chemotherapy alone in high-risk operable breast cancers that overexpress HER2. However, most studies demonstrating the benefits of anti-HER2 treatments have focused on cohorts at high risk of recurrence. Limited data exists for low-risk cancers to justify this treatment.

We performed a retrospective study from 263 patients treated at our oncology center at the Centre hospitalier de l'Université de Montréal between 2006 and 2019 for HER2-positive, N0 or N0(i+) and T1mic to T1c breast cancers. A total of 227 patients were included, 149 (57%) with anti-HER2 treatment and 78 (30%) without. Patients had a single site of HER2-overexpressing invasive breast neoplasia with a follow-up of at least 6 months. Primary outcome was overall survival. Secondary outcomes were disease-free survival and the impact of tumoral and demographic factors.

Median follow-up period was 6.7 years. Overall survival at 5 years was 97% (CI 94, 100) for the group with anti-HER2 treatment versus 92% (CI 85, 98) for the group without anti-HER2 treatment. The difference in overall survival between the two treatment groups increased with tumor size. Disease-free survival at 5 years was 93% (CI 88, 87) for the group with anti-HER2 treatment versus 82% (CI 74, 92) for the group without anti-HER2 treatment. In subgroup analysis, age and tumor size had a significant impact on the difference in disease-free survival between groups.

Our study demonstrates the significant impact of anti-HER2 targeted therapies on overall survival and disease-free survival for patients with small, HER2 positive localized breast

cancers. Further benefit is seen in certain subgroups, such as older patients and those with tumors larger than 1.0 cm, and this should be considered when determining appropriate treatment.

PO4-01-02

High throughput analysis in HER2 positive locally advanced breast cancer: pCR and mutational status.

Presenting Author(s) and Co-Author(s):

- I. Paris. Fondazione Policlinico Universitario A. Gemelli IRCCS Rome - Italy, United States
- A. Minucci. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- D. Generali. UO Patologia Mammaria , ASST of Cremona, Cremona, Italy
- s. nanni. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- t. d'angelo. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- F. Pavese. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, Italy
- A. Fabi. Precision Medicine in Breast Cancer, Fondazione Policlinico Universitario A. Gemelli,IRCCS Rome - Italy, Rome, Italy
- m. de bonis. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- K. Cannita. Ospedale di Teramo, Italy
- a. piermattei. Department of Woman and Child Health and Public Health, Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- g. tiberi. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- p. fuso. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- l. carbognin. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- s. rotondaro. Università degli studi di L'Aquila, Italy
- c. nero. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- f. giacomini. IRCCS Directorate - Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- t. pasciuto. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- m. marrazzo. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- l. giaco'. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- A. mulè. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- r. masetti. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- g. franceschini. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- g. Garganese. Fondazione Policlinico Agostino Gemelli IRCCS Roma, Italy
- D. Giannarelli. Biostatistic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy., Italy
- g. Scambia. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, Italy

Background

Pathologic complete response (pCR) after neoadjuvant treatment (NAD) is a strong prognostic biomarker associated with improved survival in breast cancer patients, especially with HER2-positive and Triple negative subtypes. PIK3CA is mutated in up to 20% of HER2 positive breast cancers, contributes to anti-HER-2 resistance and may be predictive of the lack of response to anti HER2 NAD. PIK3CA mutations in breast cancer occur primarily at hotspots E545K at exon 9 and H1047R at exon 20. Next generation sequencing has improved our knowledge regarding the biology of the mechanisms behind treatment resistance. The aim of this study is to evaluate the genomic landscape of tissue samples obtained from locally advanced breast cancer

patients treated in an neoadjuvant setting, in order to correlate the genomic analysis to response and clinical outcome.

Methods

DNA extracted from the archival 84 formalin-fixed paraffin-embedded (FFPE) samples from core needle biopsies was subjected to deep sequencing using the TruSight Oncology (TSO) 500 panel (Illumina, San Diego, USA; 523 genes, size: 1.94 Mb), following the manufacturer's protocol, which assesses microsatellite instability (MSI) status, tumor mutation burden (TMB), recurrent somatic copy number variations (sCNV), somatic single nucleotide variants (SNVs). Libraries were sequenced on a NovaSeq 6000 instrument (Illumina) to reach a minimum of 500× read depth. All samples were evaluated for RNA single cell transcriptional profile. 73 of 84 patients were treated with traditional neoadjuvant chemotherapy plus trastuzumab meanwhile 13 of 84 received neoadjuvant chemotherapy plus trastuzumab and pertuzumab. Statistical analysis was performed to detect the genes whose mutation involved in the progression and / or non-response of the disease using the Statistical Package for Social Science (SPSS), release 23.0. Continuous variables were expressed as mean ± SD or median [range], categorical variables were displayed as frequencies and the appropriate parametric (Student's t-test) non-parametric test (X2-test or Mann-Whitney test) was used to assess significance of the differences between subgroups (patients with or without pCR).

Results

In total we analyzed samples of 84 patients. The median age was 48 years. 64 of 84 (76.2%) were triple positive, 66 (78.6%) with G3 and 29 (34.5%) with stage III. The most common frequently mutated genes were PIK3CA (16/84, 19%) and BRCA1 (7/84, 8.3%). The pathogenic variant of BRCA1 (sBRCA1) had a significant association with resistance to treatment: we found a pCR in only 14.3% of sBRCA1 versus 62.3% in sBRCA1 wild type (wt) patients ($p=0.014$). We also identified 11 somatic mutations in hereditary genes (ATM, BRCA1, BRCA2, PALB2, CHEK2, RAD51C, RAD51D). From a germline standpoint we detected 7 pathogenic variants (two affecting BRCA1, two affecting CHEK2, one affecting PALB2, 7/84, 8.3%), which will be clinically confirmed. Among patients with a mutated PI3KCA, 43.8% obtained a pCR versus 61.8% of patients with PI3KCA wt ($p=0.19$). This data probably presents an imbalance due to the sample size A PTEN mutation was identified in 2% of pts (2/84) which obtained no benefit in terms of pCR after NAD versus 59.8% in wt patients ($p=0.09$).

Conclusions

In this preliminary report, genetic drivers such as BRCA1 status may have a clinical implication for prognosis and treatment response after NAD in locally advanced HER2 positive breast cancer. More samples are needed to evaluate the significance of PI3K and PTEN mutations in this patient setting. We are waiting for the results of the RNA single cell transcriptional profile of these samples. Event free survival data is not yet mature at this moment. We would like to acknowledge the contribution of Multi-specialistic Biobank Research Core Facility G-STeP, Fondazione Policlinico Universitario "A. Gemelli" IRCCS (Biobank-FPG) who provided the bio-resources.

PO4-01-03

Dual anti-HER2 Therapy with Pertuzumab and Trastuzumab versus Trastuzumab Alone in Addition to Anthracycline and Taxane-Based Neoadjuvant Therapy in Patients with HER2-Positive Early-Stage Breast Cancer; Real-World Data

Presenting Author(s) and Co-Author(s):

B. Sharaf. King Hussein Cancer Center, United States

F. Tamimi. King Hussien Cancer Center, Jordan

O. Salama. King Hussien Cancer Center, United States

A. Zayed. Khcc, Jordan

O. El Khatib. King Hussein Cancer Center, United States

S. Khater. King hussien cancer center, Jordan

M. Horani. King Hussien Cancer Center, United States

S. Al-Sawajneh. King Hussein cancer Center, United States

Y. AL-Masri. King Hussein Cancer Center, United States

H. Abdel-Razeq. King Hussein Cancer Center, Amman, Jordan

Background: When use in the neoadjuvant setting, anti-HER2 targeted therapy had improved pathologic complete response rate (pCR) in patients with HER2-positive early-stage breast cancer (EBC). Here we present real-world data on the use trastuzumab with or without pertuzumab on the backbone of anthracycline and taxanes-based NSAPB-B27 chemotherapy regimen.

Methods: We retrospectively reviewed records of patients with HER2-positive EBC who received neoadjuvant therapy using the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B27 protocol (4 cycles of adriamycin and cyclophosphamide, followed by 4 more cycles of docetaxel; all given every 3 weeks) with anti-HER2 therapy from Jan 2014 to September 2021, treated at a tertiary care cancer center. The clinicopathological features, treatment received, and outcome were collected from patients' electronic medical records. We estimated 3-year disease-free survival (DFS), a validated endpoint in HER2-positive EBC, using Kaplan-Meier with recurrence and/or death as events. Outcomes were reported in subgroups based on known prognostic factors.

Results: The study comprised 528 patients with a median follow-up of 36 months. Median age was 48 (21-80) years. Hormone receptors (HR) were positive in 379 (71.8%), lymph node-involvement prior to neoadjuvant therapy was reported in 402 (76.1%) patients and 319 (60.4%) had grade-3 disease. Majority (n= 482, 91.3%) were labeled HER2-positive based on immunohistochemistry staining (IHC+3) and the rest were based on IHC+2 with positive FISH/ISH. Dual anti-HER2 therapy (trastuzumab and pertuzumab) was used in 316 (59.8%) patients, single agent trastuzumab in 173 (32.8 %) patients, while 39 (7.4%) others did not receive any anti-HER2 therapy. Except for 9 (1.7%) patients who progressed while on treatment, all patients underwent surgery. Among the whole group, 225 (43.4%) achieved pCR; significantly higher (n=80, 53.7%) in HR-negative compared to 38.3% among those with HR-positive disease, p=0.002. Additionally, pCR was higher in patients who received dual anti-HER2 (46.2%) compared to 39.3% for those treated with trastuzumab and 28.2% for those who did not receive anti-HER2 therapy. Following surgery, 463 (89.4%) of the patients received adjuvant trastuzumab, however, none of them received pertuzumab or TDM1 in adjuvant

sitting.

Estimated 3-year DFS was 86.1% with dual anti-HER2 and 83.0% with trastuzumab alone, $p=0.19$. However, DFS was better among those with node-negative disease; 96.5% compared to 80.9% in node-positive disease, $p < 0.001$. Patients who achieved pCR had significantly better 3-year DFS; 89.3% compared to 80.2% in patients with residual disease, $p= 0.006$.

Conclusions: Even with the wide use of pertuzumab in the neoadjuvant setting, the DFS was not improved compared to trastuzumab alone, and this highlights the importance of switching trastuzumab to TDM1, or to continue with pertuzumab in the adjuvant setting in patient with residual disease.

PO4-01-04

Clinical significance of Circulating tumor DNA (ctDNA) analysis in predicting pathologic complete remission in HER2-positive Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy

Presenting Author(s) and Co-Author(s):

B. Kang. Kyungpook National University Chilgok Hospital, Taegu-jikhalsi, Republic of Korea

S. LEE. Kyungpook National University Chilgok Hospital, Republic of Korea

J. Lee. Kyungpook National University Chilgok Hospital, United States

I. Lee. Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital, United States

J. Park. Kyungpook National University Chilgok Hospital, United States

H. PARK. Department of Breast & Thyroid Surgery, Kyungpook National University Chilgok Hospital, United States

T. Zheng. Huidu Shanghai Medical Sciences Ltd., United States

L. Tan. Predicine, 3555 Arden Rd, Hayward, CA, 94545, United States

L. Chung. Department of Internal Medicine (Hematology and Oncology), Feinberg School of Medicine, Northwestern University, Chicago, IL, USA, United States

S. Jia. Huidu Shanghai Medical Sciences Ltd., United States

P. Du. Huidu Shanghai Medical Sciences Ltd., United States

Y. Chae. Department of Internal Medicine (Hematology and Oncology), Feinberg School of Medicine, Northwestern University, Chicago, IL, USA, United States

Y. Chae. Department of Oncology/Hematology, Kyungbook National University, Chilgok Hospital, Daegu, Republic of Korea, Republic of Korea

Background: Neoadjuvant chemotherapy (NACT) combined with dual anti-HER2 agents followed by surgical resection is the standard treatment for stage II-III HER2-positive breast cancer. Despite the availability of effective therapies as an adjuvant treatment such as adotrastuzumab emtansine (T-DM1) and neratinib, pathologic complete remission (pCR) strongly predicts survival. This study aimed to investigate the role of ctDNA analysis in predicting pCR and clinical outcome using comprehensive ctDNA analysis.

Methods: A total of 34 HER2-positive breast cancer patients who underwent NACT combined with dual anti-HER2 agents and surgical resection were enrolled, including 22 clinical stage II and 12 III patients. Plasma samples were collected at four-time points: before neoadjuvant chemotherapy, after 3 cycles, at the completion of neoadjuvant chemotherapy, and after surgery. low-pass whole-genome sequencing (lpWGS) and whole exome sequencing (WES) in evaluating blood copy-number burden (bcNB), genomic alterations, mutational signatures, blood tumor mutational burden (bTMB). Mutations selected from the baseline sample were monitored for Molecular residual disease (MRD) monitoring. lpWGS yielded negative results, targeted NGS sequencing was conducted.

Results: Among the enrolled patients (N=34), 21 patients (61.8%) had nodal metastasis and 22 patients (64.7%) were hormone receptor-positive. A total 26 patients (76.5%) achieved pCR. Positive ctDNA was detected in 20 patients (58.8%) at baseline. Higher nodal stage was significantly associated with ctDNA positivity at baseline. After surgery, MRD positivity was

observed in 3 patients (8.8%). Among the 26 patients who achieved pCR, only 1 patient (3.8%) showed MRD positivity, while 2 non-pCR patients (25%) demonstrated MRD positivity.

Conclusion: The presence of MRD was significantly associated with non-pCR status. The presence of ctDNA at baseline was associated with a higher nodal stage, suggesting its potential as a prognostic marker. Further studies with larger cohorts are warranted to validate these findings and explore the utility of ctDNA analysis for personalized treatment decisions in HER2-positive breast cancer.

PO4-01-05

The prognostic importance of biological pathway enrichment patterns in trastuzumab-treated early HER2-positive breast cancer

Presenting Author(s) and Co-Author(s):

C. Rönnlund. Department of Oncology and Pathology, Karolinska Institutet, and Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden, Solna, Stockholms Lan, Sweden

Q. Yang. Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden, United States

C. Schagerholm. Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden, United States

T. Foukakis. Karolinska Institutet, Solna, Stockholms Lan, Sweden

I. Fredriksson. Department of Molecular Medicine and Surgery, Karolinska Institutet, and Department of Breast-, Endocrine Tumors and Sarcoma, Karolinska University Hospital, Stockholm, Sweden, Stockholms Lan, Sweden

X. Chen. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden, United States

S. Robertson. Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, United States

E. Sifakis. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden, United States

J. Hartman. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden, United States

Background: Biological tumor signatures of HER2-positive breast cancer may impact patients' response to HER2 targeted treatment and are important to investigate since there is a need for both escalation and de-escalation of HER2-directed treatments. We aimed to examine subgroups of HER2-positive tumors based on different biological pathway enrichment patterns and their prognostic value.

Materials and methods: In a retrospective cohort of 388 early HER2-positive breast cancer patients treated with adjuvant trastuzumab, 356 HER2-positive FFPE samples were successfully analyzed for gene expression patterns using the Human nCounter Breast Cancer 360 panel (Nanostring Technologies). The raw data underwent extensive quality control and normalization in the nSolver software v.4.0 and its Advanced Analysis Module v.2.0 (NanoString Technologies). Unsupervised hierarchical agglomerative clustering was performed on pathway enrichment of nSolver customized biological process. Survival analysis for recurrence-free survival of pathway-driven clustered patients was examined using Kaplan-Meier and multivariable Cox regression models.

Results: Four subgroups of patients with different biological pathway enrichment patterns were observed. The subgroup with the combination of low stromal and low immune biological pathways (Low_stromal/Low_immune) had a significantly worse prognosis than the High_stromal/Low_immune subgroup (RFS HR: 0.4; CI:0.2-0.9, p=0.02) and Low_stromal/High_immune subgroup (RFS HR: 0.4; CI:0.2-0.9, p=0.03). In addition, the

subgroup with upregulation of both stromal and immune pathways (High_stromal/High_immune) showed a better response to trastuzumab than the Low_stromal/Low_immune subgroup even if not statistically significant (HR: 0.4; CI:0.2-1.0, $p=0.06$). Moreover, the clusters of upregulated immune pathways showed the highest levels of tumor infiltrating lymphocytes.

Conclusions: In this trastuzumab-treated early HER2-positive breast cancer cohort, we observed four subgroups with different biological pathway enrichment patterns. The subgroup with the combination of low stromal and low immune biological pathway enrichment was associated with a poorer prognosis than those mainly enriched with either stromal or immune pathways. This study shows the diversity of biological signatures within HER2-positive breast cancer, and results could potentially be used in future studies of HER2 target treatments. External validation is motivated.

PO4-01-06

HER2-positive early breast cancer (EBC): treatment, toxicities and outcomes in a retrospective cohort of elderly patients (pts)

Presenting Author(s) and Co-Author(s):

A. Rezqallah. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, Barcelona, Spain

D. Gómez-Puerto. Vall d'Hebron University Hospital, Barcelona, Spain, Barcelona, Catalonia, Spain

R. Ranchor. Centro Hospitalar Universitário do Porto, 4099-001 Porto, Portugal, Porto, Porto, Portugal

L. Joval-Ramentol. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

L. Sanz. Vall d'Hebron Institute of Oncology, Barcelona, Spain, Spain

M. Borrell. , Vall d'Hebron University Hospital, and Breast Cancer Group, Vall d'Hebron Institute of Oncology, United States

M. Alvarado-Cárdenas. Vall d'Hebron University Hospital, Barcelona, Spain, Barcelona, Catalonia, Spain

A. San-José. Vall d'Hebron University Hospital, Barcelona, Spain, United States

C. Morales Comas. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Spain

M. Espinosa-Bravo. Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus., Barcelona, Spain

M. Altabas. Vall d'Hebron University Hospital, Barcelona, Spain; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, Barcelona, Catalonia, Spain

E. Zamora. Vall d'Hebron University Hospital, Barcelona, Spain, United States

C. Ortiz. Breast Cancer Program. Vall d'Hebron Institute of Oncology/Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

P. Gómez Pardo. Hospital Universitari Vall D'Hebron, Barcelona, Spain, United States

I. Pimentel. Hospital Universitari Vall D'Hebron, Barcelona, Spain, Catalonia, Spain

M. Bellet- Ezquerria. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

M. Arumí. Vall d'Hebron University Hospital, Barcelona, Spain, United States

S. Escrivá-de-Romaní. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

Background:

Approximately one-third of breast cancer cases are diagnosed in women aged ≥ 70 years, presenting a considerable challenge to offer optimal treatment options. Ensuring appropriate care involves taking into account factors such as geriatric evaluation, comorbidities, and life expectancy. However, the lack of literature focusing on the elderly population makes it difficult to choose the correct treatment approach.

Methods:

We conducted a retrospective analysis including all elderly pts (≥ 70 years) with HER2-positive EBC treated at Vall d'Hebron hospital between 2016-2022. We evaluated treatment schemes, toxicities, and outcomes. Disease-free survival and overall survival from the time of diagnosis were assessed using Kaplan-Meier estimates.

Results:

Among 118 pts identified, the median age of diagnosis was 79.5 years (74-85). The main comorbidities were cardiovascular (82.2%), diabetes (19.5%), pulmonary (10.2%), and kidney diseases (9.3%). Stages (s) at diagnosis were: 16.8% sI, 56% sII and 24.8% sIII. 64.8% were hormone receptor-positive, 78.4% were HER2 3+ and 15.2% 2+ (ISH amplified). Median follow up was 29.1 months (m).

Neoadjuvant (NA) treatment was administered to 60.2% of pts (n=71) of which 74.6% (n=53) received chemotherapy (CT) with taxanes (Tax) only (72.5%), anthracyclines (Ac)+Tax (17.6%) and Tax+carboplatin (7.8%). AntiHER2-agents were administered in 80.3% pts (n=57) of which 89.1% received trastuzumab and pertuzumab. 23.9% of pts (n=17) received exclusively aromatase inhibitor and 2.8% (n=2) associated double blockade. Overall, 87.3% (n=103) and 80% of NA treated pts (n=57) underwent surgery, specifically mastectomy in 37.9% and 46.6% pts in the NA group achieved a pathological complete response (pCR). 38.9% pts (n=46) were treated with surgery upfront. Adjuvant treatment (A) was administered to 82.9% (n=97) of pts, with 23.7% (n=23) receiving CT; primarily Tax (82.6%), Ac+Tax (13%) and Tax+carboplatin (4.3%). AntiHER2-agents were administered in 87.6% of pts (n=85).

In the overall population, median disease-free survival (mDFS) and median overall survival (mOS) were 81.1m (95% CI 68.7-not reached [NR]) and 81.1m (95% CI 77.4-NR) respectively. In the pts who underwent surgery, mDFS was 81.1m (95% CI 68.7-NR), whereas mDFS in those who did not, was 17.6m (95% CI 13.1-NA). Pts who received antiHER2-agents in the A setting showed a mDFS of 81.1m (95% CI 81.1-NR) and mOS was NR (95% CI 81.1-NR) compared to those who did not, with a mDFS of 39.7m (95% CI 25.4-NR) and mOS of 77.4m (95% CI 25.4-NR).

Toxicities were reported in 78.3% of pts (n=54) receiving NA treatment and in 54.7% of pts (n=52) in the A setting of which 25.9% (n=14) and 13.4% (n=7) corresponded to grade (G) 3 respectively. Hospitalization, treatment discontinuation and dose reduction were required in 13%, 25.9% and 29.6% of pts with NA treatment and in 23.1% and 19.6% of A pts respectively with no pts requiring hospitalization. NA/A main side effects included asthenia 70.4% (nG3=2)/ 67.3% (nG3=2), diarrhea 64.8% (nG3=4)/ 19.2% (no \geq G3), neuropathy 27.8% (no \geq G3)/ 28.8% (nG3=1), nausea/vomiting 22.2%/3.9% (no \geq G3), infusion reaction 20.4% (nG3=2)/5.9% (no \geq G3) and cardiotoxicity in 3.8% (nG3=1)/ 7.8% (nG3=2).

Conclusions:

Our study provides real world data about the use of tailored treatments to reach a balance between treatment response and tolerance in an elderly population, with low discontinuation rates, satisfactory pCR rates and long-term results in patients treated with antiHER2-agents. It is crucial to evaluate risks and benefits of treatments in frail patients. Therefore, an oncogeriatric assessment program was started in 2021 to prospectively perform dedicated research in this population.

PO4-01-08

Co-expression of estrogen receptor (ER), progesterone receptor (PR), and Ki67 in a single breast cancer cell indicates a favorable prognosis in ER-positive breast cancer

Presenting Author(s) and Co-Author(s):

T. Ueno. Breast Surgical Oncology, Breast Oncology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan, Tokyo, Tokyo, Japan

R. Horii. Saitama Cancer Center, United States

H. Matsumoto. Saitama Cancer Center, United States

M. Ono. Cancer Institute Hospital, Japanese Foundation for Cancer Research, United States

Y. Maeshima. Department of Breast Surgery, Kyoto University Hospital, Graduate School of Medicine, United States

H. Nitta. Roche Tissue Diagnostics, United States

Background:

ER-positive breast cancer is biologically and clinically divided into two subtypes: luminal-A and luminal-B. This classification is mainly based on the status of cellular proliferation. At least two different pathways drive cellular proliferation in ER-positive breast cancer. One is a classical pathway where ER binds to estrogen responsive element (ERE), which leads to the expression of downstream molecules, including PR. The other is a non-classical pathway where a complex of ER and relevant factors bind to different sites than ERE. Growth factor signaling has been suggested to potentiate a non-classical pathway. We hypothesized that examining PR status in ER-positive proliferating cells could tell which pathway is more dominant in ER-positive breast cancer.

Methods:

To test the hypothesis, we used a newly developed triplex immunohistochemistry (IHC) that detects three molecules simultaneously under bright-field microscopy. Postmenopausal patients who were treated with neoadjuvant endocrine therapy with aromatase inhibitors from January 2007 to September 2016 at Saitama Cancer Center were included in this study. ER, PR, and Ki67 expressions were assessed in a single slide using the triplex IHC assay with anti-ER antibody (clone SP1), anti-PR antibody (clone 1E2), and anti-Ki67 antibody (clone 30-9). ER, PR and Ki67 expression was assessed in a single cell nucleus of cancer cells (567 to 4871 cells) from multiple areas in each case. An ER-positive proliferating cell was defined as an ER-positive and Ki67-positive cell. PR status in ER-positive proliferating cells was assessed. When PR was expressed in more than 50% of ER-positive proliferating cells in a clinical case, the tumor was categorized as the PR-positive group. Luminal A and luminal B breast cancers were defined based on the pre-treatment Ki67 labeling index with a cut-off of 14 %. Statistical analyses included the Mann-Whitney test, the log-rank test, and the Cox proportional hazard model.

Results:

Pre-treatment tissues from 55 patients were evaluated. The median age was 62 (range: 54 to 80) years. The patients were grouped into PR-positive and PR-negative groups. The two groups had no differences in age and pre-treatment T and N stages. The median pre-treatment Ki67 labeling index was 5.9 % in the PR-positive group and 9.9 % in the PR-negative group, which showed a statistically significant difference ($P = 0.01$). Clinical response to neoadjuvant endocrine therapy was compared, and no difference was observed. The median post-treatment

Ki67 labeling index was 3.6 % in the PR-positive group and 13.1 % in the PR-negative group with a significant difference ($P = 0.035$). The survival was compared between the two groups. The PR-positive group showed a significantly more favorable disease-free survival (DFS) than the PR-negative group ($P = 0.0079$). To adjust for the background differences including Ki67 and PR status, a multivariate analysis was performed and showed that the PR-positive group had a significantly better DFS than the PR-negative group independent of clinical stage, Ki67 labeling index, and PR status ($P = 0.042$). Breast cancer-specific survival (BCSS) was also better in the PR-positive group than in the PR-negative group after adjusting for clinical stage, Ki67 labeling index, and PR status ($P = 0.043$). Interestingly, among patients with luminal A tumors, those in the PR-positive group showed a better DFS than those in the PR-negative group ($P = 0.022$).

Conclusion:

PR status in ER-positive proliferating cells was an independent prognostic factor in DFS and BCSS and divided patients with luminal A tumors further into two prognostic groups.

PO4-01-09

The Prognostic Impact of Adjuvant Endocrine Therapy by Age for Patients with Small Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor 2 Negative (HER2-) Breast Cancer

Presenting Author(s) and Co-Author(s):

Y. Takahashi. Okayama University Hospital, Department of Breast and Endocrine Surgery, United States

S. Sasada. Hiroshima University, United States

N. Kondo. Nagoya City University Graduate School of Medical Sciences, United States

H. Hashimoto. Core Laboratory, Nagoya City University Graduate School of Medical Sciences, United States

K. Terata. Akita University Hospital, Department of Breast and Endocrine Surgery, United States

K. Kida. Department of Breast Surgical Oncology and Department of Clinical Genetics, St. Luke's international hospital, United States

Y. Sagara. Hakuai Sagara Hospital, Kagoshima, Kagoshima, Japan

Y. Naito. National Cancer Center Hospital East, Kashiwa, Chiba, Japan, United States

K. Anan. Kitakyushu Municipal Medical Center, Kitakyushu, Japan

T. Ueno. Breast Surgical Oncology, Breast Oncology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan, Tokyo, Tokyo, Japan

A. Suto. Department of Breast Surgery, National Cancer Center Hospital, Japan

C. Kanbayashi. Department of Breast Oncology, Niigata Cancer Center Hospital, United States

M. Takahashi. Department of Breast Oncology, National Hospital Organization Shikoku Cancer Center, United States

R. Nakamura. Division of Breast Surgery, Chiba Cancer Center, Chiba, Chiba, Japan

T. Ishiba. Tokyo Medical and Dental University, Tokyo, Tokyo, Japan

M. Tsuneizumi. Department of Breast Surgery, Shizuoka General Hospital, Japan

S. Nishimura. Department of Breast Surgery, Shizuoka Cancer Center Hospital, United States

Y. Ozaki. The Cancer Institute Hospital Of JFCR, Koto-ku, Japan

A. Shimomura. Department of Breast and Medical Oncology, National Center For Global Health And Medicine, Tokyo, Japan

T. Sakai. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States

T. Iwatani. Department of Breast and Endocrine Surgery, Okayama University, United States

H. Shigematsu. Department of Breast Surgery and Oncology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Hiroshima, Japan, Kure, Hiroshima, Japan

K. Tamura. Department of Medical Oncology, Shimane University Hospital, Japan

T. Fujisawa. Gunma prefectural cancer center, United States

T. Hojo. Dept. of Breast Oncology, Saitama Medical University International Medical Center., United States

F. Hara. Breast Medical Oncology, Cancer Institute Hospital of JFCR, United States

T. Shien. Okayama University Hospital, Okayama-city, Okayama, United States

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Backgrounds: We previously reported an analysis of the impact of adjuvant endocrine therapy (ET) for patients with ER+ and HER2- T1a/bN0M0 breast cancer (BC) at ASCO 2023 (Abstract #538). For the whole cohort, adjuvant ET significantly reduced distant metastases, but the absolute overall survival (OS) difference was small. The presence of medical comorbidities related to treatment toxicity and the estimated life-expectancy differ based on age, affecting the clinical impact of ET. There may be settings where comorbidities result in a sufficiently short, expected OS such that the benefit of ET will not outweigh risk. In multivariate analysis, age (<55 vs >55) was not an independent risk factor for distant metastasis. Here we evaluate the impact of adjuvant ET for ER+/HER2- T1a/bN0M0 breast cancer by age-specific subgroups, focusing on younger (< 40) and older (>65) population.

Methods: This is a multicenter retrospective cohort study that evaluated the impact of adjuvant ET for patients with ER+/HER2- T1a/bN0M0 BC who underwent primary breast cancer surgery between 2008 and 2012 in 47 institutes of the Japan Clinical Oncology Group (JCOG). We analyzed distant metastatic-free survival (DMFS) and OS using Kaplan-Meier estimates with log-rank test in patients treated with and without ET in each of three age-specific subgroups (<40, 41-64 and 65+ years of age).

Results: Median follow-up was 9.2 years; the median age of the entire cohort was 55 years. Of 4756 eligible patients, 417 patients were age 65 (1025 (82%) with ET and 227 (18%) without ET).

Of all 3989 (84%) patients with ET (2053 (51%) with Tamoxifen, 2142 (54%) with Aromatase inhibitor, 595 (15%) with LH-RH analog and 76 (2%) with others, includes duplicates). In the < 40 subgroup, 9-year DMFS was 97.2% with ET and 91.0% without ET ($p=0.023$) and 9-year OS was 97.8% with ET and 97.0% without ET ($p=0.954$). In the > 65 subgroup, 9-year DMFS was 92.6% with ET and 84.0% without ET ($p< 0.01$) and 9-year OS was 93.8% with ET and 84.9% without ET ($p< 0.01$). In those aged 41-64, no significant difference was observed in both 9-year DMFS and OS between patients with and without ET ($p=0.328$ and $p=0.731$, respectively) See Table for details.

Conclusions: Adjuvant endocrine therapy was associated with improved distant metastatic-free survival in the younger (<40) and older (>65) population in this large Japanese dataset and was associated with improved overall survival in those >65. Our findings suggest clinically relevant benefit from ET in both younger and older unselected patients with very small ER+ BC. The lack of benefit in patients aged 41-64 is likely due to individual tumor and treatment factors, which will be evaluated and described in detail at the meeting.

Table. The 9-year DMFS and OS of each age-specific three subgroups.

Age (total n=4756)	9-year DMFS (%) (95% CI)*	P-value*	9-year OS (%) (95% CI)*	P-value*
≥40 (n=417)		p=0.023		p=0.954
ET (n=331)	97.2 (94.5-98.6)		97.8 (95.2-99.0)	
No ET (n=86)	91.0 (82.0-95.6)		97.0 (88.5-99.2)	
41-64 (n=3087)		p=0.328		p=0.731
ET (n=2336)	98.0 (97.2-98.5)		98.0 (85.8-99.0)	
No ET (n=454)	97.4 (96.6-98.0)		96.9 (93.2-97.7)	
≤65 (n=1252)		p < 0.01		p < 0.01
ET (n=1025)	92.6 (90.4-94.3)		93.8 (91.8-95.4)	
No ET (n=227)	84.0 (77.3-88.9)		84.9 (78.1-89.7)	

*They are analyzed by using Kaplan-Meier estimates with log-rank test between patients treated with and without ET.

PO4-01-10

Multi-modal artificial intelligence models from baseline histopathology predict prognosis in HR+ HER2- early breast cancer

Presenting Author(s) and Co-Author(s):

D. Kates-Harbeck. West German Study Group, United States

H. Kreipe. Institute of Pathology, MHH Hannover, Germany

O. Gluz. West German Study Group and Breast Center Niederrhein, United States

M. Christgen. Medizinische Hochschule Hannover, Hannover, Niedersachsen, Germany

S. Kuemmel. West German Study Group, Moenchengladbach, Germany; Breast Unit, Kliniken Essen-Mitte, Essen, Germany; Charité - Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany

M. Graeser. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; Department of Gynecology, University Medical Center Hamburg, Moenchengladbach, Nordrhein-Westfalen, Germany

U. Nitz. West German Study Group and Breast Center Niederrhein, United States

S. Mahner. Dept. OB&GYN. LMU University Hospital, Munich, Germany

D. Mayr. Dept. of Pathology. LMU University Hospital, Munich, Germany

R. Wuerstlein. Breast Center, Dept. OB&GYN and CCC Munich, LMU University Hospital, Munich, Germany

A. Mitani. Artera, United States

J. Zhang. Artera, United States

H. Pinckaers. Artera, United States

Y. Ren. Artera, United States

P. Wood. Artera, United States

J. Griffin. Artera, United States

F. Feng. Artera, United States

A. Esteva. Artera, United States

J. Keim-Malpass. Artera, United States

R. Kates. West German Study Group, Moenchengladbach, Germany

N. Harbeck. University of Munich, Munich, Bayern, Germany

Background: Prognostic assessment in HR+ HER2- early breast cancer (EBC) remains challenging given relatively low rates of disease progression. Nuanced risk stratification is needed for decisions regarding systemic therapy. Modern artificial intelligence (AI)-based techniques have already provided substantial medical progress, particularly in prostate cancer. Here, we leverage multi-modal artificial intelligence (MMAI) trained using digital histopathology and clinical data to evaluate whether the MMAI technology can be expanded to other disease indications by applying the technology to the WSG PlanB and ADAPT trials in HR+ HER2- EBC.

Methods: Pre-treatment breast biopsy and surgical hematoxylin and eosin (H&E) slides were digitized from the WSG PlanB and ADAPT trials for HR+ HER2- EBC patients receiving endocrine therapy +/- chemotherapy. Median follow-up in both trials exceeded 5 years. A multi-

modal artificial intelligence architecture was developed and validated on predicting risk of distant recurrence (DR). Time-to-event endpoints were summarized using cumulative incidence curves. Univariable and multivariable Fine-Gray models were used to assess performance; hazard ratios were reported per standard deviation increase of the model score.

Results: A total of 5539 patients from the two trials with H&E images and available follow-up data were used for development and validation of a multi-modal artificial intelligence architecture. The MMAI score derived using the training set was significantly associated with risk of DR in a validation cohort. To put the results into the clinical context in HR+ HER2- EBC, comprehensive validation analyses are currently ongoing and will be presented at the meeting.

Conclusions: We have successfully developed a multiple-instances, learning-based deep neural network for outcome prediction using H&E-stained images. This study provides important evidence that MMAI technology can further personalize breast cancer management by adding standardizable information.

PO4-01-11

Ovarian function suppression (OFS) use beyond five years?: Young breast cancer patient preferences

Presenting Author(s) and Co-Author(s):

K. Dibble. Dana-Farber Cancer Institute, United States

T. Sella. Sheba Medical Center, Tel Aviv, Israel

K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States

C. Snow. Dana-Farber Cancer Institute, United States

A. Nixon. Young Survival Coalition (YSC), United States

P. Spears. University of North Carolina, Chapel Hill, United States

K. Ballman. Mayo Clinic, United States

L. Carey. UNC-Lindberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background. Breast cancer (BC) is the leading cause of cancer-related death in young women worldwide, and late recurrence of hormone receptor-positive disease plays a substantial role. Adjuvant endocrine therapy with 5 years of ovarian function suppression (OFS) and an aromatase inhibitor or tamoxifen is recommended for many young patients with high risk hormone receptor-positive BC. Data are limited regarding extended endocrine therapy among premenopausal BC survivors, and non-existent to inform treatment decisions regarding extending OFS beyond 5 years. We sought to evaluate young BC survivors' perceptions and preferences regarding extending OFS beyond 5 years, and consideration of a potential future study to assess the role of extended OFS.

Methods. From January-April 2023, email invites were sent to the Young Survival Coalition (YSC) listserv (N=14,291) specifically asking members with a history of invasive BC (≤ 45 years at diagnosis; stage I-III without metastatic recurrence) receiving OFS injections for adjuvant endocrine treatment to complete a one-time anonymous online survey. The survey was designed to capture information regarding current endocrine therapy use, patient-provider communication regarding extended endocrine therapy including OFS, OFS-related concerns (rating 0-5 [low: 0-1, moderate: 2-3, severe: 4-5]), and interest in a potential future clinical trial utilizing OFS beyond 5 years. Descriptive statistics were utilized to summarize responses, and two-sided Fishers exact tests and chi-square analyses were used for comparisons.

Results. A total of 1,030 YSC members completed the survey, and 615 were analyzed due to eligibility and completeness of data. The majority were from the United States (n=579, 94.1%) or Canada (n=8, 1.3%), were non-Hispanic white (n=452, 73.5%), non-Hispanic Black (n=46, 7.5%), or Hispanic (n=43, 7.0%), and had been diagnosed with stage II BC (n=316, 51.4%). The average age at survey was 38.1 years (SD=5.15, range=22-54) and at initial BC diagnosis was 34.6 years (SD=4.96, range=20-49). Most (n=510, 83.0%) were within their first 5 years of OFS treatment while 14.5% (n=89) had already been receiving OFS for more than 5 years. Many respondents (n=344, 55.9%) reported discussing OFS use beyond 5 years with their provider, of whom 39.8% (n=245) reported their provider recommending they continue OFS for more than 5 years. Despite reporting moderate and severe concerns regarding OFS side effects (n=476, 77.4%), inconvenience of injection visits (n=272, 44.2%), and high cost of

medication (n=223, 36.3%), most respondents (n=396, 64.4%) would consider continuing OFS beyond 5 years if it would reduce risk of BC recurrence. For nearly half of respondents (n=289, 47.0%) a risk reduction of at least 5% would be required for extended OFS to be worthwhile compared to the remaining 46.3% (n=285) who indicated interest for < 5% risk reduction. When asked hypothetically if they would take part in a clinical trial to determine efficacy of OFS use beyond 5 years, the majority were interested (n=357, 58.0%). Respondents who were interested were less likely to be concerned about the high cost of medication (p=0.003) however they were also less likely to take OFS beyond 5 years if it only led to 1-2% BC risk reduction (p=0.006) compared to those who were not interested. There were no other proportional differences on any other outcome.

Conclusion. Many BC survivors and providers are already considering incorporation of OFS beyond 5 years into adjuvant endocrine therapy despite harboring concerns and lack of data. Efforts to determine the efficacy and benefits of extended OFS are necessary given the risk of late recurrence in this population as well as the potential for significant short- and long-term toxicities. The results from this survey study suggest that future clinical trials evaluating potential benefits and risks of long-term OFS use among young BC survivors are needed and likely feasible.

PO4-01-12

Efficacy of neoadjuvant dose-dense versus standard chemotherapy regimens in ER+HER2-negative breast cancer: a single-center matched-cohort study. Exploratory analysis of immune markers.

Presenting Author(s) and Co-Author(s):

E. Kovalenko. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

E. Artamonova. National Medical Research Center of Oncology na N.N. Blochin, United States

Y. Zhulikov. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

M. Khoroshilov. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

A. Petrovskiy. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

I. Vorotnikov. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

T. Zabolina. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

Z. Kadagidze. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

Introduction: Dose-dense adjuvant CT improves long-term outcomes, which has been proved in clinical trials and meta-analysis. However, the efficiency of the modern dose dense (dd) anthracycline-taxane (A-T) sequential regimens in the neoadjuvant (NA) setting of ER+HER2-breast cancer (BC) has not been assessed. Tumour-infiltrating lymphocytes (TILs) play a key role in the formation of anti-tumor immunity and can be one of the markers of treatment efficacy and prognosis. Studies evaluating TILs in ER+ BC have mixed results. Materials and methods. The aim of the study was to assess the rate of RCB 0-I of 4xddAC (doxorubicine/cyclophosphamide)-T (4xdocetaxel once every 3 weeks or 12xpaclitaxel weekly) NA chemo compared to standart regimen and to study the subpopulation composition of the lymphoid infiltrate and its effect on achieving RCB 0-I. RCB 0-I as a primary end point was chosen due comparable long-term results in ER+HER2- BC as per meta-analysys. Results: The study included pts with stage II-III ER+(ER \geq 10%) HER2- BC who received NA A-T chemo in a single center from Jan 2017 to Aug 2022. The majority of patients (85,2%) had stage III disease. Statistical hypothesis: NA ddAC-T chemo would increase the rate of RCB 0-1 to 32% from 22% with ACq3w (once every 3 weeks)-T, with a study power of 80%, $\alpha = 0.05$, 138 patients should be included in the study.

A total of 315 patients were included, 147 received ddAC-T and 168 - ACq3w-T. After propensity matching analysis 138 patients in each group were included in the final analysis. TILs were studied in core-biopsy samples before NA chemo in 79 patients by flow cytometry. The following 8 subpopulations of lymphocytes were assessed as percentage in the cell pool: CD3+, CD3+CD4+, CD3+CD8+, CD4+CD127+CD25+, CD3-CD19+, CD3-CD16+CD56+, CD3+CD16+CD5+, CD8+CD279+(PD-1). The results are presented in medians (Me) due to abnormal distribution.

The RCB 0 rate was 18.8% in the ddAC-T group vs 14.5% in the ACq3w-T group (p=0.379),

RCB 0-1 - 33.3% vs 21.7% respectively ($p=0.04$). According to subgroup analysis, significant benefit of ddAC regimen found in patients ≤ 50 y.o., cN0, with PR $\geq 20\%$. For the following populations of TILs significant differences in Me for RCB0-I vs RCB II-III were observed: CD3+CD8+, CD3-CD19+, CD3-CD19+, CD8+CD279+. In multivariate analysis CD8+CD279+(PD-1) \leq Me proved to be an independent predictive factor for RCB 0-I ($p=0,048$). Immunological signature CD8+CD279+ \leq Me, CD3+CD8+ \leq Me, CD4+CD25+ $>$ Me, CD3-CD19+ $>$ Me was associated with the rate of 66,7% of RCB 0-I vs 0% with the signature with the opposite values. Conclusion: ddAC-T NA chemo compared to standart regimen in ER+HER2- BC increases RCB0-1 rate. CD8+CD279+(PD-1) \leq Me is an independent predictive factor for RCB 0-I.

PO4-01-13

Effect of interruption or discontinuation of endocrine therapy on the prognosis of breast cancer patients: a cohort study using the real-world database

Presenting Author(s) and Co-Author(s):

Y. Huang. West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

J. Chen. West China Hospital, Sichuan University, United States

Y. Wu. West China Hospital · Sichuan University, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, 610041, China, United States

Background : Adjuvant endocrine therapy is the most important treatment modality as long as one, which can reduce the mortality risk and the recurrence risk for patients with hormone receptor-positive breast cancer. Currently, few studies has reported the association in poor adherence with overall survival(OS) or disease-free-survival(DFS). However, the use of prescription coverage in previous studies to describe patient adherence to endocrine therapy may not be representative of the patient's actual medication. Additionally, previous studies did not distinguish between interruption and discontinuation of endocrine therapy, which is different to clinician. This research used rigorous follow-up data and aims on the effects of discontinuation and interruption on patients with early-stage hormone receptor-positive breast cancer.

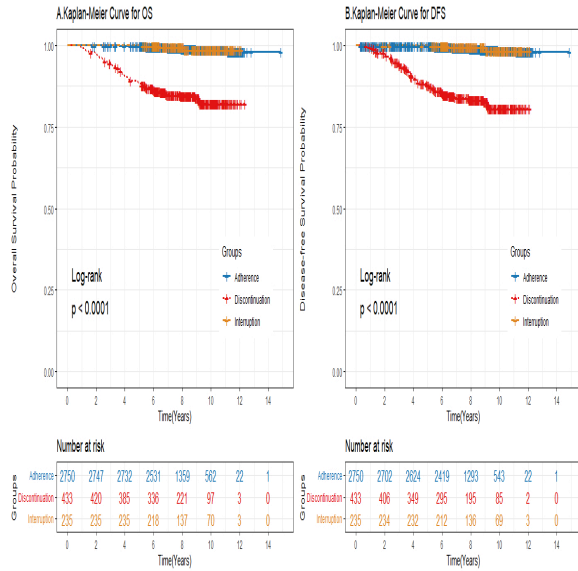
Methods: Based on the Breast Cancer Information Management System (BCIMS), we identified patients diagnosed with stage I-III breast cancer with hormone receptor-positive and received endocrine therapy during January 1, 1990 to January 1, 2018 in West China Hospital (WCH), Sichuan University, China. Briefly, all patients diagnosed with breast cancer were included and prospectively followed from the diagnosis at WCH or the first visit to WCH for breast cancer. Information, including demographic characteristics, medical history, laboratory results, pathological information, treatments and clinical outcomes, were obtained from clinical records and interviews. Kaplan-Meier analysis, Time-Dependent Cox Regression Model, and subgroup analysis were performed to evaluate the effectiveness of interruption or discontinuation of endocrine therapy. And "X-tile" software is used to select cutoff values in survivorship data.

Results:A total of 3,418 eligible patients were included with 8.13(\pm 1.96) years median follow-up. Of these patients, 19.5% did not adhere to standard endocrine regimens, with 6.9% discontinuing and 12.7% discontinuing. The multivariate cox analysis indicates that discontinuation group (DFS:HR=9.71, [95%CI]5.21-18.34,P <0.001; OS:HR=10.41, [95%CI]5.63-19.24,P <0.001) increased the risk of death and breast cancer events compared to the adherence group, but not shown statistical significance difference in the interruption (DFS:HR=1.03,[95%CI]0.23-4.66, P =0.975; OS:HR=1.17, [95%CI]0.26-5.28,P =0.840). We further analyzed the interruption and discontinuation group respectively. In the interruption group, we found cutoff value with 30 months in survival risks but didn't find statistical significance difference in DFS and OS compared to the adherence groups. For the discontinuation group, we divided the patients into low-risk and high-risk groups according to cutoff value (23 months), the final results showed that the high-risk group who took the endocrine therapy less than 23 months had increased the rate of OS(HR=23.98,[95%CI]11.71-49.14, P< 0.001) and DFS(HR=24.03,[95%CI]11.51-50.18, P< 0.001).

Conclusion:This study found that interruption of endocrine therapy may not affect prognosis of

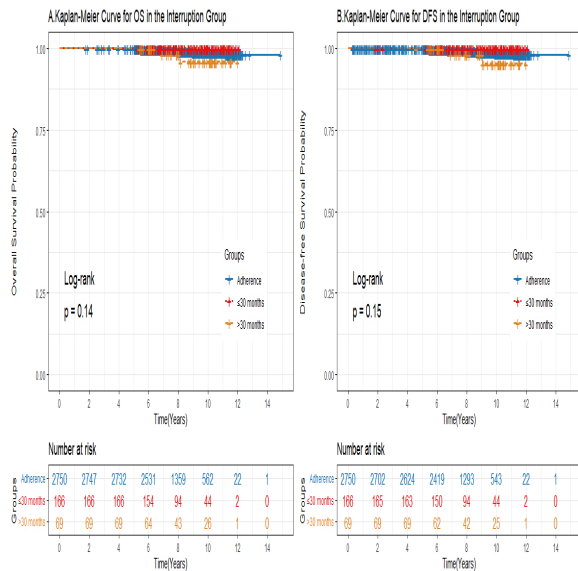
HR+ breast cancer patients, but prolonged discontinuation increases the risk of relapse and death. Therefore, clinicians should educate patients taking endocrine therapy and encourage those who discontinue the drug to take the drug again as soon as possible.

A. Kaplan-Meier Curve for OS

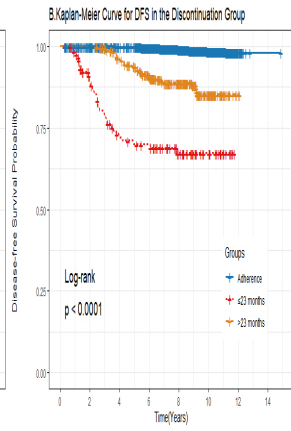
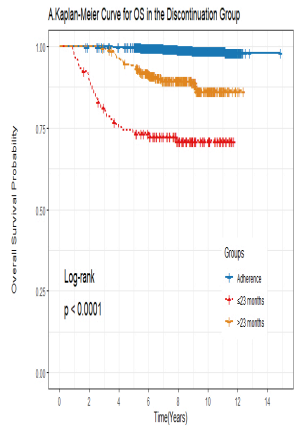


B.A. Kaplan-Meier Curve for DFS

Kaplan-Meier Curve for OS and DFS in the Interruption Group according to the events location



Kaplan-Meier Curve for OS and DFS in the Discontinuation Group according to the total duration of medication



Number at risk

Groups	0	2	4	6	8	10	12	14
Adherence	2750	2747	2732	2531	1359	562	22	1
≤ 2 months	118	105	85	78	50	23	0	0
> 2 months	315	315	300	258	171	74	3	0

Number at risk

Groups	0	2	4	6	8	10	12	14
Adherence	2750	2702	2624	2419	1293	543	22	1
≤ 2 months	118	91	68	63	39	19	0	0
> 2 months	315	315	281	232	160	66	2	0

PO4-01-14

Effects of neoadjuvant endocrine therapy on early-stage breast cancer: a retrospective cohort study of patients during the COVID19 pandemic.

Presenting Author(s) and Co-Author(s):

M. Chamberlin. Dartmouth Hitchcock Medical Center / Dartmouth Cancer Center, United States

T. Miller. Dartmouth College, Lebanon, New Hampshire, United States

M. Buteau. Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire, United States

S. Tau. Dartmouth college, Lebanon, New Hampshire, United States

Background: At the height of the COVID19 pandemic, many surgical procedures across the country including at Dartmouth-Hitchcock Medical Center (DHMC) were postponed to redirect resources. The American Society of Breast Surgeons shared guidelines to manage patients experiencing surgical delays. For estrogen receptor positive (ER+), HER2- early-stage tumors, recommendations were to use neoadjuvant endocrine therapy (NET). NET is usually under-utilized for locally advanced hormone receptor-positive breast cancer (BC) despite literature concluding that chemotherapy and NET have comparable clinical response rates but with lower toxicity for the latter. The COVID19 pandemic thus presented a unique occasion to extend the use of NET for localized BC. Herein, we examined the rate of adoption of NET and associated patient/tumor characteristics at DHMC during the lockdown.

Methods: A retrospective analysis of patients diagnosed with early-stage ER+, HER2- BC between December 2019 and June 2020. Data extracted from chart review included age, menopausal status, tumor stage/grade, body mass index (BMI), and adherence to adjuvant endocrine therapy (ET). A “delay in surgery” was defined as days between surgical consult and surgery over 14 days. Descriptive statistics were applied to data collected on patient/tumor characteristics, and the number of patients accepting or declining NET.

Results: 109 cases were identified within the study period, with 42 found with surgical delay. The median age of the delayed group was 62 and the majority of patients were post-menopausal. 36 patients received NET with most started on an aromatase inhibitor. Median BMI was 28.5. Median duration of treatment was 39.5 days. Three cases were noted to have some decrease in cellularity for pathologic partial response and four had no definite response. The majority of patients on NET had no change in pathological grade. Out of the 36 patients who had NET, 30 (83.3%) remain on adjuvant ET. In contrast, only 59% (43 out of 73 patients) of those who did not receive NET were on adjuvant ET at the median follow up time of 2.75 years post-therapy initiation. Of note, 16 (out of 73) patients who were not on NET were either lost to follow up, had their care transferred to another health network or were not offered ET. Results are reported in Tables 1 and 2.

Conclusions: Delays in surgery during the COVID19 crisis resulted in increased use of NET in early-stage BC. Impact of NET use includes possible increase in long-term adherence to adjuvant ET with a trend towards statistical significance (odds ratio of 3.25, $p=0.08$). A larger sample size is needed to evaluate this finding and a prospective trial is in progress (NCT04568616). NET is a viable treatment option during surgical delays and may help increase long-term adherence to adjuvant ET.

Patient and tumor characteristics

Characteristic	Total (n=42)	%
Age (years)		
Median	62.5	
Range	31-87	
Sex		
Female	42	100
Menopause status		
Pre-menopausal	3	7.1
Peri-menopausal	5	11.9
Post-menopausal	30	71.4
Unknown	4	9.5
Median BMI (kg/m²)	28.52	
Median distance to hospital (miles)	33.1	
Histology		
DCIS	8	19.0
Minimally invasive DC	1	2.4
Invasive carcinoma	33	78.6
Endocrine therapy	n=36	
Tamoxifen	11	30.5
Aromatase inhibitor	25	69.4
Median duration of NET	39.5 (3-250)	

Number of patients on adjuvant ET

	On adjuvant ET	Not on adjuvant ET
NET	30	3
No NET	43	14

PO4-02-01

Characterization of immune and malignant cell evolution upon treatment pressure with aromatase inhibitors in locally advanced estrogen positive breast cancer

Presenting Author(s) and Co-Author(s):

L. Schmiester. University of Oslo, Oslo Centre for Biostatistics and Epidemiology (OCBE), University of Oslo, Norway, Norway

S. Ghannoum. Oslo University Hospital, United States

M. Fongård. Oslo University Hospital, United States

M. Bjørnstad. Oslo University Hospital, United States

K. Selsås. Department of Breast and Endocrine Surgery, Akershus University Hospital, Oslo, Norway, Norway

S. Geisler. Dept. of oncology, Akershus University Hospital, Lørenskog, Akershus, Norway

M. Seyedzadeh. Akershus University Hospital, United States

U. Buvarp. Akershus University Hospital, United States

T. Lüders. Akershus University Hospital, United States

D. Lambrechts. Laboratory of Translational Genetics, VIB Center for Cancer Biology, KU Leuven, Leuven, United States

M. Lyngra. Akershus University Hospital, United States

A. Frigessi. University of Oslo, Oslo Centre for Biostatistics and Epidemiology (OCBE), University of Oslo, Norway, Norway

V. Kristensen. Oslo University Hospital, United States

J. Geisler. University of Oslo, Norway, Lorenskog, Norway

X. Tekpli. Oslo University Hospital, United States

Characterization of immune and malignant cell evolution upon treatment pressure with aromatase inhibitors in locally advanced estrogen positive breast cancer

Leonard Schmiester¹, Salim Ghannoum², Marie Fongaard², Pål Marius Bjørnstad², Knut Selsås³, Stephanie Beate Geisler⁴, Manouchehr Seyedzadeh⁵, Unn-Cathrin Buvarp⁴, Torben Lüders⁶, Diether Lambrechts⁷, Marianne Lyngra⁸, Arnaldo Frigessi¹, Vessela Kristensen^{2,9,*}, Jürgen Geisler^{4,9,*}, Xavier Tekpli^{2,*}

1) University of Oslo, Oslo Centre for Biostatistics and Epidemiology (OCBE), University of Oslo, Norway

2) Department of Medical Genetics, Oslo University Hospital, Oslo, Norway

3) Department of Breast and Endocrine Surgery, Akershus University Hospital, Oslo, Norway

4) Department of Oncology, Akershus University Hospital, Oslo, Norway

5) Department of Radiology, Akershus University Hospital, Oslo, Norway

6) Department of Clinical Molecular Biology (EPIGEN), Akershus University Hospital, Oslo, Norway

7) Laboratory for Translational Genetics, Department of Human Genetics, KU Leuven, Leuven, Belgium

8) Department of Pathology, Akershus University Hospital, Oslo, Norway

9) University of Oslo, Institute of Clinical Medicine, Faculty of Medicine, Oslo, Norway

* Jointly supervised the work, shared corresponding authors

Background

Aromatase inhibitors (AIs) are commonly used in the management of estrogen receptor-positive (ER+) breast cancer, as they effectively reduce estrogen levels which inhibits tumor growth and recurrence. In postmenopausal women with ER+ breast cancer, aromatase inhibitors are increasingly used in selected patients as neoadjuvant therapy to reduce the tumor burden before surgery and to improve overall treatment outcomes.

Clinical trial

The NEOLETEXE trial aimed to treat postmenopausal patients with locally advanced breast cancer. It was a neoadjuvant, randomized, open-label, intra-patient, cross-over, single-center phase II clinical trial. Most patients presented large T3/T4 tumors and/or N2/N3 involvement. Patients were randomly assigned to receive neoadjuvant therapy with either letrozole (2.5 mg daily) or exemestane (25 mg daily) for 3 months followed by a cross-over to the alternative AI for another 3 months followed by surgery. A total of 102 patients were enrolled in the NEOLETEXE trial.

Aim of the study

We aim at using single-cell analyses at different time points of treatment, to characterize evolutionary trajectories of cancer and immune cells in 23 patients from the NEOLETEXE trial.

Methods

Tumor biopsies taken before treatment (baseline) at crossover (after 3 months) and end of neoadjuvant therapy (after 6 months), were analyzed by single-cell RNA (scRNA), T cell receptor (TCR), and B cell receptor (BCR) sequencing. The data were first processed using cell Ranger and the Seurat package.

Results

The main cell types found in tumors were identified through clustering of the scRNA data. We then focused on the epithelial cells to first distinguish between the normal and malignant epithelial cells using the InferCNV algorithm. For each patient, the analysis of inferred copy number events allowed to elucidate the genetic background of clones resistant or sensitive to aromatase inhibitors. This analysis unveiled the evolutionary dynamics of tumor heterogeneity during treatment.

We next examined CD4, CD8, NK cells, and macrophages, using RNA velocity and diffusion pseudotime using CellRank and scVelo to delineate the differentiation trajectories of immune cell types.

Conclusions

We created a detailed map that provides a high-resolution view of the diverse cell types present in tumor biopsies from the NEOLETEXE trial. We characterize the impact of therapies on the evolutionary dynamics of both cancer and immune cells. Our analyzes sought insights into the underlying factors that contribute to the sensitivity and resistance to aromatase inhibitors.

PO4-02-02

Genomic Landscape of ER positive HER2-low early breast cancers in the FLEX Study: MammaPrint, Blueprint and whole transcriptome analysis

Presenting Author(s) and Co-Author(s):

A. Sivapiragasam. Upstate Medical University, United States

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

H. Linden. University of Washington, Fred Hutchison Cancer Center, Seattle, Washington, United States

N. Hunter. Fred Hutchinson Cancer Center, Seattle, Washington, United States

C. Osborne. Baylor Charles A. Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, Texas, United States

S. Diab. Rocky Mountain Cancer Center, Littleton, Colorado, United States

R. Maganini. Ascension Illinois, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

M. Bupathi. Rocky Mountain Cancer Center, US Oncology, Aurora, Colorado, United States

S. Lee. Montefiore Nyack Hospital, United States

T. Kim. Katmai Oncology Group, AK, United States

W. Audeh. Agendia Inc., United States

J. Haan. Agendia NV, United States

A. Menicucci. Agendia Inc, United States

L. Samraj. Agendia Inc., United States

F. Investigators' Group. Agendia, United States

Background: Antibody-drug conjugates (ADCs) continue to emerge for the treatment of a new subset of patients with HER2-low breast cancer. There is limited evidence to demonstrate HER2-low tumors as a distinct biological subtype and why/if these tumors benefit from ADCs. To improve our understanding of this newly defined HER2 category of breast cancers, we evaluated clinical characteristics, MammaPrint (MP), Blueprint (BP), and the whole transcriptomic profile of HER2-low breast cancers in FLEX study.

Methods: FLEX (NCT03053193) is a prospective, observational trial that includes stage I-III breast cancer patients who undergo MammaPrint testing (with or without Blueprint) as standard of care, and consent to full transcriptome and clinical data collection. In this study, clinically ER+/HER2- tumors were analyzed. The HER2-low cohort group (n=1698) was defined as HER2 IHC 1+ (ISH positive excluded) and IHC 2+, ISH Negative, and the HER2-0 group (n=1181) was defined as HER2 IHC 0. MP classified tumors as Low Risk or High Risk (further stratified as High 1 and High 2). MP together with BP categorized tumors as Luminal A (MP Low Risk), Luminal B (MP High Risk), HER2 or Basal. Two-tailed proportional z-test was used to compare clinical features and genomic subtypes of HER2-low vs. HER2-0 and the limma R package for differential gene expression analysis (DGEA). P-values were adjusted for multiple testing by Benjamini-Hochberg; significant differentially expressed genes (DEGs) had a p-value < 0.05 and a fold change >2.

Results: In this FLEX study, clinically ER+/HER2- tumors showed that the clinical characteristics between HER2-low and HER2-0 did not differ significantly except higher percentage of premenopausal within HER2-low (23% vs 17%, $p < 0.01$). Of all HER2-low patients, 46% were MP High Risk as within HER2-0 patients (44%, $p = 0.27$). In both groups with MP High Risk tumors, there was a higher frequency of MP High 1 (83% in HER2-low, 80% in HER2-0) compared to MP High 2 (17% in HER2-low, 20% in HER2-0). BP subtyping showed similar distribution for Luminal subtype between HER2-low and HER2-0, but the frequency of ER+, Basal subtype was lower in HER2-low (2.5%), compared to HER2-0 (4.5%) ($p=0.005$). Principal component analysis (PCA) of the 500 most variable genes did not reveal a separation of HER2-low and -0 tumors, but clustering was apparent when tumors were classified by BP. DGEA within Basal tumors revealed no DEGs. Within Luminal A tumors, more than 1800 DEGs were identified, and within Luminal B tumors, nearly 300 DEGs were identified. However, all DEGs were < 1.5 -fold change: mean, max (1.09, 1.38) for Luminal A and (1.12, 1.44) for Luminal B. In addition, a significant difference ($p < 0.01$) towards increased ERBB2 (HER2) expression was detected from HER2-0 to HER2-low, but there was a large overlap of expression between the 2 groups.

Conclusion: Our study showed that HER2-low and HER2-0 tumors are clinically and biologically similar. The differences in ERBB2 and low-level genome wide expression detected between HER2-low and HER2-0 should be further investigated to determine how these changes affect tumor biology and treatment benefit. The biological heterogeneity among IHC-defined HER2-negative tumors was better captured by MammaPrint and Blueprint than IHC. MammaPrint identified 53% of HER2-low tumors as Low Risk, a subgroup of patients known to have good outcomes without chemotherapy. Our data suggest a subset of patients with HER2-low, MP Low Risk tumors could be spared from the potential toxicities of ADCs. Future studies will investigate the utility of MammaPrint and Blueprint in predicting chemosensitivity and benefit from ADCs, such as T-DXd, in patients with HER2-low tumors.

PO4-02-03

Distribution of MammaPrint, Blueprint, and Response Predictive Subtypes based on ImPrint and Reprint in ER+/HER2- Invasive Lobular Carcinoma – A FLEX sub study.

Presenting Author(s) and Co-Author(s):

R. Mukhtar. University of California, San Francisco, United States

C. Yau. UCSF, United States

D. Wolf. University of California, San Francisco, United States

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

H. Linden. University of Washington, Fred Hutchison Cancer Center, Seattle, Washington, United States

N. Hunter. Fred Hutchinson Cancer Center, Seattle, Washington, United States

R. Mahtani. Miami Cancer Institute, Plantation, Florida, United States

A. Sivapiragasam. Upstate Medical University, United States

T. Feinstein. Piedmont Cancer Institute, United States

F. Yan. Swedish Medical Center, Washington, United States

I. Grady. North Valley Breast Clinic, United States

P. McAuliffe. UPMC Hillman Cancer Center, United States

M. Tsai. Swedish Medical Center, WA, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

B. Mavromatis. UPMC Western Maryland, United States

S. Davis. Texas Oncology, TX, United States

J. Haan. Agendia NV, United States

W. Audeh. Agendia Inc., United States

L. Samraj. Agendia Inc., United States

F. Investigators' Group. Agendia, United States

Background: Invasive lobular carcinoma (ILC), the second most common histologic subtype of breast cancer, is increasingly recognized as a distinct tumor type compared to the more common invasive ductal carcinoma (IDC). While ILC is known to have lower rates of pathologic complete response to neoadjuvant chemotherapy, ILC tumors are biologically heterogeneous. As such, genomic signatures might identify patients with ILC who might benefit from tailored treatment options. The gene expression signature MammaPrint (MP) classifies tumors as having a Low Risk or High Risk of distant recurrence. MP combined with Blueprint (BP), a molecular subtyping signature, categorizes tumors as Luminal A (MP Low Risk), Luminal B (MP High Risk), Basal or HER-2 type. ImPrint is a 53-gene signature that identifies HR+HER2- patients predicted to benefit from immune checkpoint inhibitors. RePrint is a 60-gene DNA repair deficiency (DRD) signature that identifies HR+HER2- patients who may benefit from PARP inhibitors with platinum agents. Response Predictive Subtypes (RPS), used in the I-SPY2 trial, combine clinical subtype and these genomic signatures to personalize treatment planning and improve outcomes. In this study, we determined the distribution of 3 RPS in HR+HER2-: (1) ImPrint-/RePrint-, (2) ImPrint-/RePrint+ (3) ImPrint+, in patients ILC compared

to IDC enrolled in the FLEX trial.

Methods: This study includes 1078 HR+HER2-women with ILC and 6078 with IDC enrolled in FLEX registry. FLEX (NCT03053193) is a prospective, observational trial that includes stage I-III breast cancer patients who undergo MammaPrint testing (with or without BluePrint) as standard of care, and consent to full transcriptome and clinical data collection. MP High Risk tumors were further stratified into High 1 and High 2. ImPrint and Reprint results were used to determine RPS. A two-tailed proportional z-test was used to assess differences between ILC and IDC as well as between RPS.

Results: ILC patients had a significantly lower percentage of MP High Risk tumors in comparison to IDC. Among MP High Risk tumors, those with ILC had significantly more MP High 1 than patients with IDC. BP subtyping in ILC tumors showed significantly lower percentage of Basal, and Luminal B, and higher percentage of Luminal A compared to IDC tumors. For RPS, a higher percentage of ILC tumors were ImPrint-/RePrint- compared to IDC, whereas lower frequencies of ImPrint-/RePrint+ and ImPrint+ were found. Within the ILC ImPrint+ subgroup (n=14), 1 (7.1%) was classified as High 2 and 10 (71.4%) as High 1 and 3 (21.4%) as Low Risk. All 14 (100%) ImPrint+ patients were BP Luminal. In contrast, within the IDC MP High Risk ImPrint+ subgroup (n=328), 233 (71.0%) were High 2, 88 (26.8%) High 1 and 7 Low Risk (2.1%). Furthermore 193 (60.7%) were classified as BP Basal, 2 HER2 (0.6%) and 123 (38.7%) Luminal within this IDC RPS.

Conclusions: This is the first study to investigate the distribution of Response Predictive Subtypes in ILC, which will be beneficial to optimize the treatment selection for patients with early-stage HR+/HER2- ILC. Though the percentage of ImPrint+ is lower in ILC, this study revealed a small subset of patients in ILC with potential response to Immunotherapy. Furthermore, these results underscore the heterogeneity of ILC tumors and generate further hypotheses to investigate the immune cell abundance in ILC compared to IDC and correlate immune cell abundance to ImPrint status.

Table: Genomic and Tumor Characteristics of HR+HER2- ILC and IDC tumors

	ILC	IDC	p-values
MP			
High Risk	338 (31.7%)	2,879 (47.6%)	<0.001
Low Risk	728 (68.3%)	3,163 (52.4%)	<0.001
MP High Risk			
High2	18 (4.5%)	1,355 (31.6%)	<0.001
High1	380 (95.5%)	2,929 (68.4%)	<0.001
BP type			
Basal	1 (0.1%)	267 (4.6%)	<0.001
HER2	1 (0.1%)	5 (0.1%)	1
Luminal B	322 (31.8%)	2,486 (42.8%)	<0.001
Luminal A	689 (68.0%)	3,044 (52.5%)	<0.001
Imprint			
ImPrint-	994 (98.6%)	5,439 (94.3%)	<0.001
ImPrint+	14 (1.4%)	328 (5.7%)	<0.001
Reprint			
RePrint-	1,008 (100.0%)	5,594 (97.0%)	<0.001
RePrint+	0 (0.0%)	173 (3.0%)	<0.001
RPS			
ImPrint-/RePrint-	994 (98.6%)	5,404 (93.7%)	<0.001
ImPrint-/RePrint+	0 (0.0%)	35 (0.6%)	0.025
ImPrint+	14 (1.4%)	328 (5.7%)	<0.001

PO4-02-04

Overall survival and disease recurrence rates in patients with invasive lobular breast cancer of the Penelope^B cohort

Presenting Author(s) and Co-Author(s):

H. Bonnefoi. Institut Bergonié Comprehensive Cancer Centre, Université de Bordeaux, INSERM U1312, and European Organisation for Research and Treatment of Cancer (EORTC), Bordeaux, France

F. Marmé. Med. Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

M. Untch. AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany, Berlin, United States

S. Kim. Asan Medical Center, Seoul, Republic of Korea, United States

H. Bear. Virginia Commonwealth University, Massey Cancer Center, Richmond, Virginia, United States

N. McCarthy. Breast Cancer Trials Australia and New Zealand and University of Queensland Australia, United States

K. Gelmon. BC Cancer Agency, Vancouver, British Columbia, Canada, United States

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

C. Kelly. Cancer Trials Ireland, Dublin, Ireland

T. Reimer. Breast Center, University of Rostock, Rostock, Germany

Z. Zhang. Pfizer, San Diego, California, United States

M. Toi. Graduate School of Medicine, Kyoto University, Kyoto, Japan

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

M. Gnant. Medical University of Vienna, Vienna, Austria

A. Makris. Mount Vernon Cancer Centre, Northwood, England, United Kingdom

N. Hirmas. German Breast Group, Neu-Isenburg, Germany, United States

V. Nekljudova. German Breast Group, Neu-Isenburg, Germany, United States

J. Holtschmidt. German Breast Group, Neu-Isenburg, Germany

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

Overall survival and disease recurrence rates in patients with invasive lobular breast cancer of the Penelope^B cohort

Background: In the PENELOPE^B trial, the addition of 1-year of cyclin-dependent kinase 4/6 (CDK4/6) inhibitor palbociclib to standard endocrine therapy (ET) for women with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) early breast cancer at high risk of recurrence after neoadjuvant chemotherapy (NACT) did not improve invasive disease-free survival (iDFS) or overall survival (OS) in the main study analysis. Invasive lobular breast cancer (ILC) accounts for ~15% of all breast cancers (BC) and represents an underinvestigated subtype of BC with typically less sensitivity to (neo)adjuvant chemotherapy, and poor distant disease-free survival (DDFS) irrespective of response to

NACT. Here, we report the post-hoc analysis results of iDFS, DDFS and OS in pre- and postmenopausal women enrolled on PENELOPE^B and with ILC.

Methods: Patients with HR+/HER2-negative BC without pathological complete response (pCR) after taxane-containing NACT and at high risk of relapse (CPS-EG score ≥ 3 , or 2 and ypN+) were randomized (1:1) to receive 13 cycles of palbociclib 125mg daily or placebo on days 1-21 of a 28-day cycle in addition to standard ET with tamoxifen (TAM) +/- gonadotropin-releasing hormone analogue (GnRHa) or aromatase inhibitor (AI) +/- GnRH. Randomization was stratified by nodal status at surgery, age at first diagnosis (< 50 vs. ≥ 50 years), Ki-67, region, and CPS-EG score. ILC diagnosis was locally assessed and reported by the investigators on the pathology case report form. The primary objective of this post-hoc analysis was to evaluate iDFS, DDFS and OS by treatment arm in patients with high risk ILC.

Results: A total of 1,250 patients were randomized, of whom 110 had ILC and were nearly uniformly distributed between both treatment arms (palbociclib n=58 vs. placebo n=52), with a higher proportion of postmenopausal women (58.6% in the palbociclib arm vs. 53.8% in the placebo arm) compared to premenopausal women (41.4% in the palbociclib arm vs. 46.2% in placebo arm). There was no difference in the distribution of AI/TAM use between the treatment arms.

An estimated absolute 3-year-iDFS difference of 18.3% with palbociclib compared to placebo (iDFS 88.4% [95% CI 76.0-94.6] vs. 70.1% [95% CI 55.3-80.7]) with a HR of 0.66 [95% CI 0.27 – 1.61, log-rank p=0.354] was observed. A comparable 3-year-DDFS difference of 16.3% was observed. An estimated 3-year-OS difference of 16.4% (98.0% [95% CI 86.6 – 99.7] vs. 81.6% [95% CI 67.5 – 90.0]) with a hazard ratio (HR) of 0.27 (95% CI 0.05 – 1.43, log-rank p=0.108) was observed. Out of 12 observed deaths (n=2 palbociclib vs. n=10 placebo), 11 (in placebo arm) were related to metastatic BC.

Conclusions: In this post-hoc analysis, a trend towards improvement in OS and a trend in favor of iDFS and DDFS for the addition of palbociclib to ET was observed among women with HR+/HER2- ILC at high risk of recurrence after NACT, but these differences were not statistically significant. This could represent a valuable treatment option for patients with high risk ILC. Due to the small sample size of the ILC subgroup, further follow-up evaluation is necessary. Moreover, analyses in the ILC subgroup from other adjuvant CDK4/6 inhibitor trials could substantiate these findings.

Key words: early breast cancer, palbociclib, (postneo)adjuvant treatment, premenopausal, invasive lobular carcinoma

Funding: financial support and drug were provided by Pfizer

Overall survival and disease recurrence rates in patients with invasive lobular breast cancer of the PenelopeB cohort

		Palbociclib arm (n=58)	Placebo arm (n=52)	Absolute 3-year différence
iDFS	No. of events	10	17	
	3y iDFS	88.4% [95% CI 76.0-94.6]	70.1% [95% CI 55.3-80.7]	18.3%
	HR [95%]	0.66 [0.27 – 1.61, log-rank p=0.354]		
DDFS	No. of events	10	15	
	3y DDFS	88.4% [95% CI 76.0-94.6]	72.1% [95% CI 57.4-82.4]	16.3%
	HR [95%]	0.84 [0.33 – 2.17, log-rank p=0.726]		
OS	No. of events	2	10	
	3y OS	OS 98.0% [95% CI 86.6 – 99.7]	81.6% [95% CI 67.5 – 90.0]	16.4%
	HR [95%]	0.27 [0.05 – 1.43, log-rank p=0.108]		

Results of iDFS, DDFS and OS.

PO4-02-05

Elevated tumor to aorta ratio of Hounsfield units and late recurrence in patients with estrogen receptor positive breast cancer

Presenting Author(s) and Co-Author(s):

A. Han. Yonsei University Wonju college of Medicine, United States

H. Choi. Yonsei University Wonju college of Medicine, United States

S. Hahn. Inje Pack medical school, United States

I. Cho. Yonsei University Wonju College of Medicine, United States

S. Lim. Yonsei University Wonju college of Medicine, United States

J. Lee. Yonsei University Wonju College of Medicine, United States

Background) More than half of the recurrent disease in breast cancer will happen more than 5 years after initial diagnosis in breast cancer, especially in patients with ER positive disease. Higher proportions of late recurrence lead to escalated treatment and/or or extended treatment for high risk patients. However, it is unclear what characteristics make whom as high risk patients. This study aimed to assess initial tumor vascularity as a prognostic marker for late recurrence.

Methods) Female patients with estrogen receptor positive breast cancer who were diagnosed breast cancer between 2003 and 2018 and disease-free at 5 years after primary breast cancer at Wonju Severance Hospital, Korea, were included. Clinicopathological characteristics were collected. Hounsfield units(HU) on contrast-enhanced computed tomography(CT) was used as a marker indicating tumor vascularity. Tumor to aortic arch ratio(TAR) of HU on contrast enhanced CT was applied to enhance objectivity of measurement. Patients were categorized according to the cut-off values retrieved from the receiver operating characteristic curve. Kaplan-Meier curves were generated to compare recurrence-free survival (RFS) and overall survival (OS). Hazard ratio(HR) with confidence interval(CI) was derived with Cox's proportional hazard model to analyze univariate and multivariate risk factors.

Results) The final cohort included 451 patients with a mean age of 56.21 ± 11.2 (22-83) years.

Two third of patients had estrogen receptor positive disease and a quarter of patients had HER2 overexpressed disease. Initial TAR was 0.345 ± 0.108 (range, 0.062 - 1.114). Patients with recurrence free survival(RFS)-related events had significantly higher TAR than patients who did not(0.39 ± 0.097 vs. 0.34 ± 0.108 , $p=0.012$). Patients with overall survival(OS)-related events also had higher TAR than patients who did not(0.408 ± 0.096 vs. 0.342 ± 0.107 , $p=0.002$). Cutoff value of 0.408 was driven from area under the receiver operating characteristic curve. Patients with TAR higher than 0.408 showed significantly worse RFS($p=0.001$) and OS($p< 0.001$) than patients who had TAR equal or lower than 0.408. Hazard ratio(HR) of TAR in late recurrence was 6.17 (CI, 4.89 – 9.23, $p=0.003$), suggesting it is an independent factor. Other independent factors were age (HR, 1.502; CI, 10.14 – 10.91; $p=0.006$), tumor size (HR, 1.268; CI, 1.071 – 1.502; $p=0.006$), and metastatic nodal disease (HR, 2.770; CI, 1.176 – 6.526; $p=0.020$).

Conclusion) TAR of primary tumor was significantly related with patients RFS and OS. Patients with high TAR larger than 0.408 showed worse RFS and OS than patients who did not. According to the Cox proportional hazard model, TAR was an independent factor along with

age, tumor size, and metastatic nodal disease, suggesting late recurrence may rather be influenced by clinical factor

PO4-02-07

Prevalence of distant metastases in High-Risk Operable Breast Cancer (HROBC) pT1-2 N2a or higher at diagnosis

Presenting Author(s) and Co-Author(s):

V. Parmar. Tata Memorial Centre, United States
N. Kumar AN. Tata Memorial Hospital, United States
B. Ameer Ali. Tata Memorial Hospital, Mumbai, Mumbai, Maharashtra, India
N. Nair. Tata Memorial Hospital, United States
S. Joshi. Tata Memorial Hospital, United States
P. Thakkar. Tata Memorial Hospital, Mumbai, United States
G. Chitkara. Tata Memorial Hospital, Mumbai, Maharashtra, India
V. Gaikwad. Tata Memorial Hospital, United States
V. Vanmali. Tata Memorial Hospital, United States
S. Siddique. Tata Memorial Hospital, United States
P. Popat. Tata Memorial Hospital, Mumbai, United States
S. Shah. Tata Memorial Hospital, Mumbai, United States
S. Desai. Tata Memorial Centre, United States
T. Shet. Tata Memorial Centre, United States
M. Thakur. Tata Memorial Hospital, United States
V. Rangarajan. Tata Memorial Hospital, United States
R. Badwe. Tata Memorial Centre, Mumbai, India

Introduction:

Current standard guidelines do not recommend a routine staging workup in early breast cancer as incidence of de novo metastasis is only 1-2%. Some of these patients are found to have a higher axillary nodal burden after surgery. This prospective study evaluated the incidence of distant metastases in clinically high-risk operable breast cancer (HROBC) who have a higher nodal burden on histopathological report after surgery. The intent was to detect presence of subclinical distant disease that may have an impact on treatment offered and outcome. Currently, there is no compelling data to support a routine metastatic workup in these patients.

Methodology:

A single-centre study approved by Institutional Ethics Committee was carried out enrolling early breast cancer patients with high nodal burden (four or more axillary nodes positive) after definitive surgery. The HROBC group was defined as early breast cancer patients with pT1/2, N2a/N3 stage on surgical histopathology. They underwent a comprehensive metastatic workup, including ultrasound abdomen, bone scan, and CT scan (thorax-abdomen-pelvis) or PET scan before starting their adjuvant treatment. Burden of distant disease was classified into oligometastatic (M1_o) or polymetastatic disease (M1_p). The adjuvant treatment intent was redefined as curative or palliative based on the distant disease burden and treatment was modified accordingly.

Result:

The study accrued 100 HROBC women with pT1-2, pN2a-3 stage disease during 2015-2018

operated upfront for early breast cancer cT1-2 N0-1, of which 97 were included in final analysis. The 3 excluded patients had their surgery elsewhere with clinical diagnosis of early breast cancer with histopathology indicating heavy nodal burden; 2 of them had T3 tumor and 1 had cN3 disease and were deemed a higher stage and would anyway warrant a metastatic work-up and hence were ineligible for the study. Forty percent women were premenopausal, 54 (55.6%) had pN2a disease and 43 (44.4%) had pN3. Staging investigations identified distant metastatic disease (M1) in 8 of 97 women (8.24%). Interestingly, 5 of them had oligometastatic (M1_o) disease (5.15%) and 3 had polymetastatic (M1_p) disease (3.09%). Between the 2 nodal groups, no specific distribution of M1_o or M1_p disease was observed, but the pickup rate of overall distant disease was higher in pN3 (11.4%) as against N2a (5.6%) patients p=NS. The most common sites of metastases observed was bone (5/8) followed by liver (3/8). There was no correlation with ER, PgR or HER2neu status and extent of distant disease. The patients with M1_o disease, completed their adjuvant treatment as planned along with treatment of oligometastatic sites. Only 3.09% patients who were detected with M1_p disease, were treated with a palliative systemic therapy.

Conclusion:

Early detection of metastatic disease, M1_o and M1_p, in clinical HROBC could lead to improved treatment strategies. The findings have the possibility to optimize management of high-risk early breast cancer as a separate clinical entity, requiring staging post hoc after primary surgery, for adequate resource stratification and better outcomes, especially in those with 10 or more axillary nodes positive for metastases. This subset may get identified in the TNM classification for better understanding and management.

PO4-02-08

Outcomes of patients treated with chemotherapy for breast cancer during pregnancy compared with non-pregnant breast cancer patients treated with systemic therapy

Presenting Author(s) and Co-Author(s):

H. Johnson. The University of Texas MD Anderson Cancer Center, United States

C. Warneke. The University of Texas MD Anderson Cancer Center, United States

A. Martinez. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

J. Litton. UT MD Anderson Cancer Center, Houston, Texas, United States

O. Oke. MD Anderson Cancer Center, United States

Introduction: Prior studies comparing outcomes of patients diagnosed with and treated for breast cancer during pregnancy (PrBC) with those of non-pregnant patients with breast cancer report mixed results. Data are sparse for PrBC patients treated with systemic therapy, who may be at risk for poorer outcomes owing to the need to modify regimens or delay initiation of teratogenic agents until the postpartum period. This study aims to compare survival outcomes of PrBC patients treated with chemotherapy during gestation versus matched non-pregnant breast cancer patients treated with systemic therapy.

Methods: Pregnant women with non-metastatic, non-inflammatory breast cancer treated with chemotherapy during gestation on prospective institutional protocols from 1989-2022 were identified. Two non-pregnant patients selected from a departmental database were matched to each PrBC patient using coarsened exact matching based on age at diagnosis (< 30 years old, 30-35, >35), year of diagnosis (< 1997, 1997-2004, >2004), stage at diagnosis (I, II or III), hormone receptor (HR) status, and Human epidermal growth factor receptor 2 (HER2) status. Retrospective chart review was performed to update vital status and other clinical data. Overall survival (OS) was calculated from diagnosis until last known vital status and compared using the Kaplan-Meier method and log-rank test.

Results: 167 PrBC patients were matched to 334 non-pregnant patients (Table 1). Median age at diagnosis was 33 years for both cohorts (IQR: PrBC, 6; non-pregnant 7). Other characteristics are shown in Table 1. Median time from diagnosis to initiation of chemotherapy or oncologic surgery was 25 days (IQR 27) for PrBC patients and 27 days (IQR 37) for non-pregnant patients ($p=0.61$). Anti-HER2 therapy was deferred to the postpartum period for PrBC patients, with median time from diagnosis to therapy initiation of 73 days (IQR 190) compared with 63 days (IQR 143) for non-pregnant patients ($p=0.36$). Median follow-up was 4.5 years (IQR 9.0) for PrBC patients and 5.8 years (IQR 7.5) for non-pregnant patients ($p=0.27$). At last follow-up, 128 PrBC patients (77%) and 222 non-pregnant patients (66%) were alive. Median OS was 24.1 years (95% CI 15.8-undefined) for PrBC patients and 14.0 years (95% CI 10.8-33.8) for non-pregnant patients. OS did not differ significantly between cohorts ($p=0.12$).

Conclusion: This retrospective, matched cohort study suggests that PrBC patients treated with chemotherapy during gestation have comparable OS compared with non-pregnant breast cancer patients treated with systemic therapy, despite treatment modifications and delayed initiation of teratogenic agents. This is the largest reported cohort of PrBC patients treated with a standardized chemotherapy protocol during gestation and therefore adds valuable insight into outcomes of this uncommon presentation of breast cancer. Continued study is needed to

determine whether longer-term outcomes are similar, particularly for patients with triple-negative breast cancer who did not receive immunotherapy during pregnancy.

Table 1

Table 1. Baseline characteristics.

Matching Criterion	Pregnant cohort (N=167)	Non-pregnant control cohort (N=334)
Year of diagnosis		
<1997	15 (9.0%)	30 (9.0%)
1997-2004	33 (19.8%)	66 (19.8%)
>2004	119 (71.3%)	238 (71.3%)
Stage		
I	15 (9.0%)	30 (9.0%)
II	93 (55.7%)	197 (59.0%)
III	59 (35.5%)	107 (32.0%)
Hormone receptor status		
Positive	96 (57.5%)	192 (57.5%)
Negative	67 (40.1%)	134 (40.1%)
Missing	4 (2.4%)	8 (2.4%)
HER2 receptor status		
Positive	32 (19.2%)	64 (19.2%)
Negative	113 (67.7%)	226 (67.7%)
Equivocal	2 (1.2%)	4 (1.2%)
Missing	20 (12.0%)	40 (12.0%)

Baseline characteristics

PO4-02-09

Clinical outcomes of neoadjuvant chemotherapy in HER2-low early breast cancer

Presenting Author(s) and Co-Author(s):

D. Gudelj. Department of Oncology, University Hospital Centre Zagreb, United States

K. Čular. Department of Oncology, University Hospital Center Zagreb, United States

L. Toula. Department of Oncology, University Hospital Centre Zagreb, United States

M. Križić. Department of Oncology, University Hospital Center Zagreb, United States

M. Popović. Department of Oncology, University Hospital Center Zagreb, United States

N. Dedić Plavetić. University Hospital Centre Zagreb, United States

A. Kelečić. Department of Oncology, University Hospital Centre Zagreb, United States

G. Ivanac. Clinical Hospital Dubrava, School of Medicine Zagreb, United States

M. Soče. Department of Oncology, University Hospital Centre Zagreb, United States

I. Kukulj. Department of Oncology, University Hospital Centre Zagreb, United States

T. Silovski. Department of Oncology, University Hospital Center Zagreb, United States

BACKGROUND:

According to immunohistochemistry (IHC) expression of HER2 receptor, breast cancer (BC) can be classified as either IHC score 0, 1+, 2+ or 3+. Until recently, two distinct BC subtypes were recognized depending on the HER2 IHC expression and in situ hybridization (ISH) score: HER2 positive (IHC 3+ or IHC 2+ ISH-amplified) and HER2 negative (IHC 0, 1+ or 2+ ISH negative). More recently a new BC entity termed HER2-low was acknowledged, defined as either HER2 IHC 1+ or 2+ ISH-negative. Given that no treatment benefit was observed in HER2-low group of patients in the pivotal trastuzumab studies, many years had to pass before the discovery of antibody-drug conjugates such as trastuzumab deruxtecan, that led to a significant improvement in the clinical outcome of HER2-low BC, compared to standard therapy options. It is still debated whether HER2-low BC represents a distinct biological subtype. The aim of this study was to determine whether there is an impact of HER2-low status on the effect of neoadjuvant chemotherapy (NACT) and its primary indicator - the rate of the pathologic complete response (pCR).

METHODS:

A retrospective study of 363 BC cases who received NACT between January 2020 and December 2022 at University Hospital Centre Zagreb, Croatia, was conducted with prior Ethics Committee approval. Histopathological characteristics of tumours available from the hospital information system (BIS), including hormone receptor status (ER, PR), HER2 status and Ki-67 at the time of diagnosis and after neoadjuvant treatment, as well as pCR rates, were analysed. pCR rates were calculated for HER2-low and HER2 0 cases. Chi square test was used to analyse association between pCR rate and HER2 status.

RESULTS:

After exclusion of HER2 positive BC cases, as well as cases with missing data, a total of 215 patients were included in the analysis. Of those, 101 (47%) were HER2-low, and 114 (53%) were HER2 negative. The majority of patients (N=151, 70.2%) had luminal BC, while 64 (29.8%) patients had triple negative BC (TNBC). In the luminal group, 86 cases (57%) were HER2-low, and 65 (43%) were HER2 0. In the TNBC group, 15 cases (23.4%) were HER2-low and 49 (76.6%) were HER2 0. The rate of pCR among luminal subtypes was 6.2% for HER2-

low tumours, and 15.4% for HER2 0 tumours ($p=.051559$), approaching statistical significance. In the TNBC group, the pCR rate for HER2-low group was 60%, compared to 40% in the HER2 0 group, trending towards, but not reaching statistical significance ($p=.191564$).

CONCLUSION:

A trend toward higher pCR rates after neoadjuvant chemotherapy was observed in the luminal HER2 0 group compared to HER2-low luminal BC, almost reaching statistical significance. Interestingly, in TNBC there was a trend towards higher pCR rates among the HER2-low group, although a small number of patients precludes any definitive conclusions. Further trials that include novel targeted therapies are needed, as that might lead to significant changes in therapeutic approach, as well as clinical outcome of HER2-low BC patients.

PO4-02-10

Predictive Factors of Nodal Upstaging at Time of Surgery in Clinically Node Negative Patients Undergoing Neoadjuvant Chemotherapy

Presenting Author(s) and Co-Author(s):

R. Melissa. Rush University Medical Center, United States

J. Alexieva. Rush University Medical Center, United States

A. Coogan. Rush University Medical Center, United States

E. Marcus. John H. Stroger, Jr. Hospital of Cook County, United States

J. Wechsler. John H. Stroger, Jr. Hospital of Cook County, United States

Introduction: Neoadjuvant chemotherapy (NAC) can be given with the intent of downstaging breast cancer or to provide prognostic information prior to any surgical intervention in both node negative (N0) and node positive patients (pts). Residual nodal disease following neoadjuvant chemotherapy generally indicates poorer overall prognosis relative to those who are node negative. Several risk factors have been postulated to predict the presence of occult lymph node metastasis: age at diagnosis, tumor size, status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor (HER-2), and BMI. NAC has been shown to eradicate axillary lymph node metastasis in up to 40% of pts. This study aims to evaluate characteristics of clinically N0 pts who underwent NAC and were upstaged to node positive status at the time of surgery. We hope to identify patient related factors that may help predict the presence of occult nodal disease as well compare pathological complete response rate (PCR) in the breast between N0 and patients who were upstaged.

Methods: Data was collected through retrospective chart review of the Stroger Cook County electronic medical records system (CERNER). Pts treated at John H. Stroger Hospital from 2017-2021 with a new diagnosis of cT2-T3 invasive breast cancer who were clinically and radiologically node negative and received NAC were included. We compared demographic data, staging information, cancer characteristics and pathologic complete response rates (PCR) in the breast between those who remained node negative and those who had positive sentinel lymph nodes at the time of surgery. Pts with prior breast cancer diagnosis and those who underwent treatments at an outside institution were excluded. Statistical analysis included 2-tailed t-test and 2-tailed fisher's ($p < 0.05$).

Results: A total of 98 pts were identified, 62 with complete data for analysis, 11 were upstaged at the time of surgery. When comparing pts who had nodal upstaging to those that remained node negative at time of surgery there was no significant difference between average BMI (28.5), age of diagnosis (58 years). Most pts (73%) were T2 at presentation, of those with nodal upstaging at time of surgery, 20% were T3 or higher, while only 5% of those who were not upstaged at surgery were greater than T3 (NS). Upstaged pts had an average tumor size of 4.16 cm while non-upstaged on average were 2.85 cm ($P < 0.01$). ER positive pts (ER+) and PR positive (PR+) were more likely to have nodal upstaging post op ($P < 0.0012$, $P < 0.0013$) when compared to ER negative (ER-) and PR negative (PR-) respectively. The distribution of receptor status was significantly different between groups, the most common receptor status in upstaged patients was triple positive (63%) while triple negative was most common in non-upstaged (41%). Triple positive pts were more likely to be upstaged than those with other receptor statuses (64% vs 40%, $p = 0.0004$). There was a 100% PCR rate in the breast among non-upstaged pts compared to 10% of upstaged patients ($P < 0.0001$). Among all triple negative pts, 42% had PCR, of ER-/PR-/HER2+, 60% had a PCR, ER+/HER 2 negative had a 40% PCR.

Conclusion: Pts with larger presenting tumor size who are node negative at presentation and have undergone chemotherapy are more likely to have occult positive nodes at the time of surgery. ER positive pts and triple positive pts are also more likely to have occult positive nodes at time of surgery. While our sample is small, our breast PCR rate is consistent with other published literature. Further investigation confirming this with larger samples and multi-institutional investigation may help to establish these relationships and elucidate a predictive model. The optimal management of these patients is worthy of further study.

PO4-02-11

Optimizing Taxane-based Chemotherapy in Breast Cancer: Retrospective study comparing 4 cycles of TC to 6 cycles of TC

Presenting Author(s) and Co-Author(s):

A. Ahluwalia. The Brooklyn Hospital Center, United States

M. koifman. The Brooklyn Hospital Center, United States

J. Nannar. Saint Georges University, United States

b. vachhani. The Brooklyn Hospital Center, United States

k. ashraf. Saint Georges University, United States

M. Shulimovich. New York Cancer and Blood, United States

Breast cancer remains one of the most prevalent cancers among women worldwide. First-line chemotherapy options include anthracycline (AC-T) and Taxane (TC) based regimens. While anthracycline-based chemotherapy is most commonly used, the use of anthracycline-sparing regimens is also approved. The US Oncology 9735 trial conducted in the mid 2000s showed that four cycles of docetaxel and cyclophosphamide (TC4) were superior to four cycles of Doxorubicin and cyclophosphamide (AC). The follow-up ABC trials compared six cycles of TC(TC6) to AC-T. This trial showed that while AC-T was superior to TC, the difference was modest. AC-T has remained the standard of care, but TC is an acceptable option. One retrospective analysis involving 143 patients showed TC4 was non-inferior to TC6, and suggested that TC4 had fewer adverse events; however, statistical significance was not reached. The question remains whether six cycles of TC is required, or if four cycles is adequate.

Methods:

Patient information was retrieved from the EMR of a large private oncology group. The EMR was screened for all breast cancer patients who began treatment with TC between 1/1/2011 and 12/31/2021. Patients were required to have continuous follow-up, documented up to at least 6/30/2022. Only patients receiving TC as the first-line setting were included, while patients with metastatic disease were excluded.

Adjusted Kaplan Meier curves for overall survival (OS) and disease-free survival (DFS) were generated. A log-rank test was used to determine the statistical difference between the two curves. OS was defined from the date of the last chemotherapy given to death. DFS is defined from the date of the last chemotherapy given to disease recurrence. The Chi-square analysis test of homogeneity was conducted to evaluate the differences in reported symptoms. Statistical analysis was completed with IBM SPSS version 29. Ethical approval was obtained from The Brooklyn Hospital Center Institutional Review Board.

Results:

A total of 376 charts were reviewed, out of which 224 met the criteria for inclusion. Of these 191 patients received TC4 and 33 received TC6. TC4 patients were noted to be older than TC6 patients. There were a higher percentage of hormone-positive cancers in the TC4 group while the TC6 group had a larger proportion of triple-negative breast cancers. There was a larger proportion of stage III patients that received TC6 than in TC4. TC6 patients were also noted to receive neo-adjuvant chemotherapy at a substantially higher rate. A greater proportion of patients in the TC4 group received breast-conserving surgery, with radiation than the TC6

group. TC6 had a completion rate of 76 % (Table 1). There was a significant difference in DFS noted between TC4 and TC6 ($p = 0.016$) with TC6 patients having a higher rate of relapse. No difference was noted in the overall survival. No differences were seen in side effects between TC4 and TC6, however, there was a trend toward high rates of neutropenia, anemia, and neuropathy seen in the TC6 group (Table 2).

Conclusions:

This real-world retrospective study reviewed patients who received TC in a large community oncology practice. The study reaffirms conclusions seen in previous retrospective studies conducted in the academic setting that there is no difference in overall survival when using six cycles of TC compared to four cycles of TC. Slight detriment was seen in the DFS setting when using TC6 however the small sample size along with the larger proportion of patients with stage III disease make it challenging to interpret this finding. There was a trend towards higher toxicities with TC6 that did not reach significance. Until a prospective randomized study comparing four vs six cycles of TC is conducted no definitive conclusions can be drawn, however, this study contributes to the current body of evidence that four cycles of TC is adequate and could potentially improve the quality of life of patients with early breast cancer.

Patient characteristics

		TCx4		TCx6	
N		191		33	
Age		58		56	
ER/PR +		149	78%	24	73%
Triple neg		42	22%	9	27%
Stage	I	108	57%	15	45%
	IIa	52	27%	5	15%
	IIb	22	12%	3	9%
	IIIa	8	4%	7	21%
	IIIb or IIIc	1	1%	3	9%
Surgery	Lumpectomy	89	47%	11	33%
	Mastectomy	101	53%	22	67%
Radiation		138	72%	19	58%
Treatment completion		Null		25	76%
Neoadjuvant		16	8%	27	82%
Adjuvant		175	92%	6	18%

Patient characteristics including age, hormone status, stage, type of surgery, radiation, and treatment setting.

Adverse effects

	TCx4		TCx6		p = 0.05
	191		33		
Nausea	34	18%	5	15%	0.809
Diarrhea	40	21%	8	24%	0.651
Mucositis	10	5%	3	9%	0.414
Neutropenia	68	36%	17	52%	0.119
Anemia	133	70%	27	82%	0.21
Thrombocytopenia	66	35%	12	36%	0.845
Neuropathy	10	5%	5	15%	0.051

Adverse effect information obtained from physician documentation, and CBC reports documented at time of treatment with TC.

PO4-02-12

MDA iLobular Prognostic Tool: A Novel Approach for Risk Stratification in Invasive Lobular Carcinoma

Presenting Author(s) and Co-Author(s):

J. Mouabbi. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Pasyar. The University of Texas MD Anderson Cancer Center, United States

R. Bassett. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Singareeka Raghavendra. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Hassan. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

R. Layman. The University of Texas MD Anderson Cancer Center, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background: Invasive lobular carcinoma (ILC) is a distinct subtype of breast cancer that differs from the more common invasive ductal carcinoma (IDC) by its unique characteristics that influence prognosis. Recent studies have shown that ILC is associated with worse long-term outcomes compared to IDC. Risk stratification is essential in breast cancer for tailoring treatment plans to the individual patient's needs, maximizing the chances of successful outcomes and minimizing unnecessary interventions. Although there are multiple tools available for breast cancer, there is currently not a risk stratification tool that is specific for ILC. The MDA iLobular prognostic tool is the first risk stratification tool that has been developed specifically for ILC patients.

Methods: We retrospectively searched for patients treated at MD Anderson Cancer Center with a diagnosis of stage I-III ILC in our prospectively collected electronic database. The study focused on two primary endpoints: Overall Survival (OS) and Distant Recurrence Free Survival (DRFS). We utilized univariate and multivariate Cox Proportional Hazard (PH) regression models to assess the statistical significance of all variables. The univariate Cox analysis identified prognostic factors, which were further analyzed using backward and stepwise multivariate Cox proportional hazards regression analysis. This process helped identify statistically significant prognostic factors that were included in the final multivariate models. We estimated hazard ratios and 95% confidence intervals for each factor, considering a P-value of < 0.05 as statistically significant. To evaluate the performance of the fitted multivariate Cox PH regression models for OS and DRFS, we randomly divided two-thirds of the data points into a training dataset, while the remaining one-third constituted the test dataset. We assessed the discrimination capacity of each model using Harrell's C-index.

Results: The study included a total of 4,216 female patients, with a median age of 56 years. The median pathological tumor size was 2 mm, and the median number of lymph nodes was one. Among these patients, 1,376 were pre-menopausal, while 2,837 were post-menopausal. The training cohort was a subset of 2,950 patients and the test cohort was a subset of 1,266 patients. After evaluating various prognostic models, we identified the model with the highest prognostic accuracy for OS and DRFS. This selected model demonstrated a Harrell's C-index

of 0.704 for OS and 0.718 for DRFS on the training dataset and a Harrell's C-index of 0.702 for OS and 0.671 for DRFS on the test dataset. The model incorporated several covariates, including age at the time of diagnosis, number of lymph nodes, pathological tumor size (mm), ER status, tumor grade, ILC histology, and the presence or absence of concomitant LCIS (Table 1).

Conclusion: In conclusion, the MDA iLobular prognostic tool represents a significant advancement as the first dedicated tool for risk stratifying ILC, providing valuable guidance for tailoring therapy to individual ILC patients based on their specific risk profiles.

Table 1. Multivariate Cox proportional hazard model parameter estimates for OS and DRFS

Parameter	Overall Survival			Distant Recurrence-free Survival		
	Hazard Ratio	HR 95% Confidence Limits	p-value	Hazard Ratio	HR 95% Confidence Limits	p-value
Age (year)	1.022	(1.013, 1.031)	<0.001	1.007	(0.999, 1.016)	0.075
Number of lymph nodes	1.068	(1.056, 1.080)	<0.001	1.078	(1.068, 1.089)	<0.001
Pathological tumor size (mm)	1.048	(1.013, 1.085)	0.008	1.061	(1.031, 1.092)	<0.001
ER status						
<10%	-----			-----		
≥10%	0.548	(0.354, 0.849)	0.007	0.620	(0.412, 0.933)	0.022
Grade						
GI	-----			-----		
GII	1.130	(0.862, 1.482)	0.38	1.067	(0.837, 1.361)	0.60
GIII	1.386	(1.017, 1.890)	0.039	1.476	(1.115, 1.953)	0.007
ILC histology						
Non-classical	-----			-----		
Classical	0.632	(0.474, 0.842)	0.002	0.622	(0.480, 0.806)	<0.001
Concomitant LCIS						
Absent	-----			-----		
Present	0.737	(0.608, 0.894)	0.002	0.674	(0.567, 0.801)	<0.001

PO4-02-13

Parity and age first full term pregnancy affects the age of breast cancer diagnosis in breast cancer subtypes defined by estrogen receptor and human epidermal growth factor receptor 2

Presenting Author(s) and Co-Author(s):

J. Zhang. KU Leuven, United States

Z. Liu. KU Leuven, United States

K. Van Baelen. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, Leuven, Vlaams-Brabant, Belgium

M. Vangoitsenhoven. University Hospitals Leuven / RZ Tienen, United States

H. Wildiers. University Hospitals Leuven, United States

A. Soubry. KU Leuven, Leuven, Vlaams-Brabant, Belgium

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

Parity and age first full term pregnancy affects the age of breast cancer diagnosis in breast cancer subtypes defined by ER and HER2

Jiumeng Zhang*, Zhao Liu*, Karen Van Baelen, Maja Vangoitsenhoven, Hans Wildiers, Adelheid Soubry, Patrick Neven

(*) equal contribution

Background: Reproductive factors like parity and age at first full term pregnancy (FTP1) are found to have an impact on the occurrence of breast cancer (BC) in many epidemiological studies. Importantly, since the 70s, an ongoing trend to postpone FTP1 and have less children is observed. Additionally, there is an increasing trend for breast cancer incidence in young women in the past several decades, which may match the changing exposures to reproductive factors over time. To our knowledge, few studies focus on the association between parity, FTP1 and the age of breast cancer diagnosis. In this study, we aimed at studying the association between age at breast cancer diagnosis and reproductive factors (parity and FTP1) in each of the four breast cancer subtypes defined by estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2).

Patients and method: We considered patients who were >34 years old and were diagnosed and/or treated for early BC in University Hospitals Leuven between January 2000 and November 2020. Patient and tumor characteristics were extracted from the patient files. Missing values were filled in by multiple imputation. A linear mixed model with birth cohorts as random effects was built for premenopausal and postmenopausal patients separately to investigate the association between two reproductive factors (parity and age at first full term pregnancy) and age at diagnosis in each of four breast cancer subtypes defined by ER and HER2. ER positivity was defined as >1% of cells staining positive and reflex fluorescence in situ hybridization (FISH) testing was performed for samples that immunohistochemically (IHC) stained for HER2 with IHC score of 2+ or 3+. Parous women are classified into low parity (1 or 2 children) and high parity (≥ 3 children) and FTP1 was divided into $<$ or ≥ 27 years of age. BMI was considered a possible confounder and was corrected for. We first excluded nulliparous people and compared the mean ages at diagnosis in different parity groups and FTP1 groups separately. We created new variable reproductive patterns by taking intersection of parity

categories and FTP1 categories. Then the mean ages at diagnosis in parous groups could be compared with the mean age at diagnosis in nulliparous patients. Step down Bonferroni procedure is applied to correct for multiple comparisons.

Result: 3039 premenopausal patients and 6569 postmenopausal patients at breast cancer diagnosis were included in the study. Patients with early age at FTP1 have older age at diagnosis in case of ER+HER2+ BC in both premenopausal and postmenopausal group as compared to patients with late FTP1 (Table 1). For premenopausal patients with ER-HER2+, early age at FTP1 was associated with older age at diagnosis in comparison to late age at FTP1. Premenopausal patients with ER+HER2- BC that had low parity and late FTP1 were diagnosed 0.66 years later than nulliparous patients ($p= 0,01$).

Conclusion: In both premenopausal and postmenopausal parous patients with early FTP1, an older age at diagnosis was observed in HER2+ cases only. When compared to nulliparous patients, the combination of low parity and late FTP1 was associated with older age at diagnosis for premenopausal patients with ER+ HER2- BC.

Table 1 Differences in mean age at diagnosis between FTP1 groups in parous patients

Menopause	Subtype	Comparison	Estimate (difference in mean age at diagnosis)	p-value
pre	ER+HER2+	<27 vs >=27	1,2030	0,0045
	ER+HER2-	<27 vs >=27	-0,0548	0,7468
	ER-HER2+	<27 vs >=27	1,3519	0,0334
	ER-HER2-	<27 vs >=27	0,4023	0,3326
post	ER+HER2+	<27 vs >=27	1,1764	0,0175
	ER+HER2-	<27 vs >=27	0,0743	0,7069
	ER-HER2+	<27 vs >=27	-0,3750	0,6023
	ER-HER2-	<27 vs >=27	0,3862	0,3815

PO4-02-14

Parity and age first full term pregnancy affects the odds of different breast cancer subtypes defined by estrogen receptor and human epidermal growth factor receptor-2

Presenting Author(s) and Co-Author(s):

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

Z. Liu. KU Leuven, United States

J. Zhang. KU Leuven, United States

K. Van Baelen. Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium, Leuven, Vlaams-Brabant, Belgium

M. Vangoitsenhoven. University Hospitals Leuven / RZ Tienen, United States

H. Wildiers. University Hospitals Leuven, United States

A. Soubry. KU Leuven, Leuven, Vlaams-Brabant, Belgium

Parity and age first full term pregnancy affects the odds of different breast cancer subtypes defined by estrogen receptor and human epidermal growth factor receptor-2

Zhao Liu*, Jiumeng Zhang*, Karen Van Baelen, Maja Vangoitsenhoven, Hans Wildiers, Adelheid Soubry, Patrick Neven.

(*) equal contribution

Background:

A rising trend in the incidence of estrogen receptor (ER)-positive subtype over time is observed in several high-income countries, while the incidence of ER-negative subtype is decreasing in some areas. It has been found that decreased parity and late age at 1st full-term pregnancy (FTP1) can increase the risk of breast cancer (BC). This study aims at investigating the association between two reproductive factors, parity and FTP1, and the odds of BC subtypes in premenopausal and postmenopausal patients.

Patients and method:

This study included patients diagnosed with early-stage BC after the age of 34, who were treated in UZ Leuven between January 2000 and November 2020. The patients were classified into four subtypes defined by ER and human epidermal growth factor receptor-2 (HER2). ER positivity was defined as >1% of cells staining positive while HER2 positivity was based on fluorescence in situ hybridization (FISH) testing of samples with immunohistochemistry score of 2+ or 3+. Baseline-category logit models with subtype as the response (ER+/HER2- as the baseline) and adjusted for age at diagnosis and BMI, were performed for premenopausal and postmenopausal patients separately. First, we exclude nulliparous patients. Parity (1-2 or ≥3) and FTP1 (continuous) were included in the models as the covariates of interest in the first model. To evaluate the effects of reproductive patterns compared to nulliparity, a new variable reproductive pattern was created by taking intersection of parity groups and FTP1 groups (< 27, ≥27). Reproductive pattern was set as the covariate of interest in the second model.

Result:

After imputing the missing values, we included 9606 patients in the study. 8125 of them were parous. In parous patients, high FTP1 was associated with low odds of ER-/HER2- BC relative to ER+/HER2- BC for both premenopausal and postmenopausal patients (table 1). In

postmenopausal patients, low parity was associated with low odds of ER-/HER2- BC and high odds of ER+/HER2+ BC relative to ER+/HER2- BC. There was no evidence that parity affects the odds of subtypes in premenopausal patients.

When investigating the effect of different reproductive patterns compared to nulliparity on the odds of subtypes, there was no evidence that reproductive patterns will affect the odds of subtypes in premenopausal patients. Postmenopausal patients who had FTP1 before 27 years old and had at least three children tended to have higher odds of ER-/HER2- BC relative to ER+/HER2- BC compared to nulliparous patients.

Conclusion:

In parous patients, increased FTP1 was associated with reduced odds of ER-/HER2- relative to ER+/HER2- BC. In postmenopausal patients, patients with at least three children tended to have low odds of ER-/HER2- BC and high odds of ER+/HER2+ BC relative to ER+/HER2- BC. When compared to nulliparity, the combination of having at least three children and having the first child before 27 years old increased the odds of ER-/HER2- BC relative to ER+/HER2- BC in postmenopausal patients.

Table 1 Effect of FTP1, parity on subtype odds

Menopause	Subtype	Effect	Odds ratio (95%CI)	p-value	
pre	ER-/HER2-	FTP1 (continuous)	0.960 (0.935, 0.985)	0.0021	
post			0.969 (0.948, 0.990)	0.0047	
pre	ER-/HER2+		0.992 (0.952, 1.034)	0.7166	
post			1.005 (0.977, 1.034)	0.7081	
pre	ER+/HER2+		0.976 (0.949, 1.004)	0.0962	
post			1.015 (0.992, 1.039)	0.1969	
pre	ER-/HER2-		Parity 1-2 vs ≥3	1.194 (0.899, 1.585)	0.2200
post				0.784 (0.648, 0.949)	0.0124
pre	ER-/HER2+			1.152 (0.723, 1.834)	0.5521
post				0.896 (0.684, 1.173)	0.4228
pre	ER+/HER2+	1.080 (0.795, 1.469)		0.6220	
post		1.300 (1.022, 1.654)		0.0329	
The baseline category is ER+/HER2- subtype					

Table 1

Menopause	Subtype	Effect	Odds ratio (95%CI)	p-value
pre	ER-/HER2-	FTP1	0.96 (0.935, 0.985)	0.0021
post			0.969 (0.948, 0.99)	0.0047
pre	ER-/HER2+		0.992 (0.952, 1.034)	0.7166
post			1.005 (0.977, 1.034)	0.7081
pre	ER+/HER2+		0.976 (0.949, 1.004)	0.0962
post			1.015 (0.992, 1.039)	0.1969
pre	ER-/HER2-	Parity 1-2 vs >2	1.194 (0.899, 1.585)	0.22
post			0.784 (0.648, 0.949)	0.0124
pre	ER-/HER2+		1.152 (0.723, 1.834)	0.5521
post			0.896 (0.684, 1.173)	0.4228
pre	ER+/HER2+		1.08 (0.795, 1.469)	0.622
post			1.3 (1.022, 1.654)	0.0329

The baseline category is ER+/HER2- subtype

Effect of age at first full-term pregnancy and parity on subtype odds

PO4-03-01

Enhancing Breast Cancer Subtyping: APIS Breast Cancer Subtyping Kit Proliferative Signature's Potential for Improved Proliferation Assessment and Recurrence Prediction

Presenting Author(s) and Co-Author(s):

M. Vetter. Cancer Center Baselland, Liestal, Basel-Landschaft, Switzerland

A. Gasior. APIS Assay Technologies, Manchester, England, United Kingdom

E. Chiru. Kantonsspital Baselland, United States

J. Gorniak. APIS Assay Technologies, United States

L. Gough. APIS Assay Technologies, United States

M. Harrison. APIS Assay Technologies, United States

S. Rollinson. APIS Assay Technologies, United States

S. Muenst. Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland, United States

C. Kurzeder. Breast Center, University Hospital of Basel, Basel, Switzerland, Basel-Stadt, Switzerland

Background:

Ki67, a widely recognized biomarker for measuring tumor cell proliferation in breast cancer (BC), plays a crucial role in classifying BC into luminal A and luminal B subtypes, subsequently aiding treatment decisions. However, the inconsistency in Ki67 assessment and the lack of standardization in methods and interpretation of immunohistochemistry (IHC) staining has hindered its recommendation for routine diagnostic use. The standardization of measurement techniques, especially for Ki67, holds immense potential for improving patient treatment outcomes.

The APIS Breast Cancer Subtyping Kit (APIS BCS Kit) addresses these challenges by utilizing RT-qPCR to accurately determine the mRNA expression of BC markers, including Ki67, along with a novel four-gene proliferative signature, comprising four markers (MKI67, CCNA2, KIF23, and PCNA) associated with proliferation and expressed throughout all cell cycle stages, thereby providing a more accurate measure of tumor proliferation.

In this study, we present the preliminary findings of our ongoing evaluation of the APIS BCS Kit proliferative signature's ability to distinguish between Luminal A and Luminal B subtypes and to determine the risk of recurrence in hormone receptor-positive (HR+) patients.

Method:

A total of N=153 retrospectively collected HR+/HER2 negative samples were provided by University of Basel. For each sample the following clinical annotations were included: relapse free survival, treatment regimen (Chemotherapy (ChT) or Hormone Therapy (HT)) as well as OncotypeDx (ODx) risk score (RS). N=40 samples underwent additional testing using PAM50 (Prosigna®) test. Only samples collected since 2018 were included, resulting in 10 observed relapse events (N=7 in HT cohort and N=3 in ChT cohort).

RNA isolation from tissue sections and gene expression analysis were performed as per APIS BCS Kit instructions for use. The agreement of subtype calls between IHC, APIS BCS Kit, and PAM50 was assessed. The correlation between RS obtained from ODx, PAM50 and the APIS

BCS Kit proliferation signature was also explored.

Results:

The agreement between IHC and the APIS BCS Kit subtype call, utilizing Ki67 alone as a measure of proliferation, was 67.3% (103/153). Replacing Ki67 with the APIS BCS Kit proliferation signature increased the concordance to 69.9% (107/153). The concordance between IHC and PAM50 subtype calls was comparable at 62.5% (25/40). The agreement between the APIS BCS Kit and PAM50 subtype call was notably higher (80%; 32/40).

Significant association was observed between the APIS BCS Kit proliferation signature and ODX RS ($P=.0001$), and PAM50 RS ($P=.002$).

In the HT cohort, both ODX and the APIS BCS Kit proliferation signature accurately predicted recurrence (by assigning high RS) in $n=2$ cases. In some cases both the APIS BCS Kit and ODX erroneously assigned low risk and subsequently missed $n=4$ recurrence events. Notably, APIS BCS Kit proliferation signature correctly identified one recurrence event (high RS), which was missed by ODX (low RS).

Conclusion:

The APIS Breast Cancer Subtyping Kit exhibits improved agreement with the PAM50 molecular subtype in contrast to the IHC-derived subtype, indicating that molecular testing may be a more suitable method for determining proliferation and distinguishing between luminal A and B subtypes. Furthermore, there is a significant correlation between the RS generated by APIS Breast Cancer Subtyping Kit proliferation signature and both PAM50 and Oncotype RS. These initial findings indicate that the APIS Breast Cancer Subtyping Kit proliferation signature has the potential to accurately identify patients at risk of recurrence, although additional studies including a larger proportion of events are needed to validate these results.

PO4-03-03

Conditional Use of Serial Serum Tumor Markers CA 15.3 and CEA as Predictors of Disease Relapse in Patients with High-Risk Early-Stage Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Edaily. King Hussien Cancer Center, Jordan
B. Sharaf. King Hussein Cancer Center, United States
M. Sughayer. King Hussein Cancer Center, United States
L. Yousef. King Hussein Cancer Center, United States
H. Abu-Fares. King Hussein Cancer Center, Jordan
S. Abdel-Razeq. King Hussein Cancer Center, United States
H. Abu-Jaish. King Hussein Cancer Center, United States
M. Abunasser. King Hussein Cancer Center, United States
S. Khater. King hussien cancer center, Jordan
A. Zayed. Khcc, Jordan
O. El Khatib. King Hussein Cancer Center, United States
R. Rahal. King Hussein Cancer Center, United States
H. Abdulelah. King Hussein Cancer Center, United States
M. Shraim. King Hussein Cancer Center, United States
H. Abdel-Razeq. King Hussein Cancer Center, Amman, Jordan

Background: Because of the diagnosis at an earlier stage, and the wider availability of more effective therapies, treatment outcomes of patients with breast cancer are getting much better resulting in an increasing proportion of patients surviving their disease, however, a significant percentage of patients with early-stage disease at initial diagnosis may eventually relapse. Residual tumor cells can remain dormant for many years before causing tumor recurrence. Physical examination and mammography are strongly recommended in surveillance guidelines, but data on routine blood tests or imaging is lacking. The revolution made in recent years, following the approval of novel targeted and immunotherapy agents, may have better outcome if started earlier in the disease course with the lowest tumor burden and in patients with good performance status and adequate organs' function. Additionally, early detection of oligometastatic disease can give a chance for cure for a subset of these patients. Levels of CA15.3 and CEA are used in decision making in the metastatic setting but their role in surveillance is still controversial. We aim to investigate whether serial measurement of tumor markers, when it correlates with tumor bulk (conditional), can detect early asymptomatic recurrence among subset of patients with high-risk early-stage breast cancer.

Methods: Patients with high-risk early-stage breast cancer were invited to participate. High-risk features include any of the following: large tumor size (T3/4), grade-3, node-positive, triple-negative, HER2-positive or hormone receptor (HR)-negative disease. Patients were considered eligible if they have elevated CA15.3 and/or CEA at baseline, that subsequently normalize 6 weeks after surgical resection; upfront or following neoadjuvant chemotherapy. Serial testing of the elevated CA15.3 and/or CEA is done every 2 months thereafter, samples are cryopreserved and will not be processed until disease relapse. As such results will not be used for clinical decisions. The study is still ongoing, we here present an interim analysis evaluating the correlation between certain tumor characteristics and elevated serum marker(s) levels.

Results: Since the launch of the study, 367 patients deemed high-risk by the above criteria, accepted to participate. Abnormal baseline CA15.3 and/or CEA was found in 110 (30%); 65 (18%) patients had elevated CA 15.3 while elevated CEA was found in 45 (12%) patients. Abnormal CA 15.3 was found in 27% of cases with T3/4 disease compared with 13% in T1/2 disease ($p=0.001$), and in 21% of node positive disease versus 7% in node negative disease ($p=0.002$), in 9% of HR negative disease versus 20% in HR-positive ($P=0.038$). Tumor grade and HER2 status were not associated with significant difference. Regarding CEA, abnormal levels were detected in 24% of HER2-positive disease compared to 5% of HER2-negative disease ($P < 0.0001$). Other tumor features were not associated with significant difference.

Conclusions: Only a third of patients with high-risk early-stage breast cancer had high level of serum tumor markers at initial diagnosis and thus such markers may correlate with tumor presence. Large tumors (T3/4) and node positive disease were associated with high CA15.3 but not CEA. HER2-status and tumor grade had no effect on CA15.3 level, while HER2 positive disease correlated well with high CEA.

PO4-03-04

Characterization of Gut Microbiome of patients with early-stage breast cancer treated with neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

L. Thommen. University Hospital of Brasilia, United States

V. Heidrich. Centro de Oncologia Molecular, Hospital Sírio-libanês – São Paulo (SP), Brazil., United States

R. Vieira de Andrade. Graduate Program in Genomic Sciences and Biotechnology – UCB - Brasília (DF), Brazil., United States

L. Nardin Weis. Hospital de Base do Distrito Federal, Brasilia, Distrito Federal, Brazil

M. Soares Felipe. Graduate Program in Genomic Sciences and Biotechnology – UCB - Brasília (DF), Brazil., United States

M. Lole Da Cas Vita. Sírio-Libanês Hospital, Brasília, Brazil, United States

T. Alves Pinto. Health Science Graduate Program, University of Brasilia, Brasília, Brazil., United States

A. Camargo. Centro de Oncologia Molecular, Hospital Sírio-libanês – São Paulo (SP), Brazil., United States

R. Barroso-Sousa. Dasa Oncology, United States

Objective: The gut microbiome (GM) has been identified as one of the major environmental factors that can regulate the development and maintenance of the immune system. In oncology, while the importance of GM has been evaluated in more immunogenic tumors such as melanoma, lung carcinoma and clear cell carcinoma, its importance in early-stage breast cancer (eBC) is underexplored. The aim of this study was to characterize the GM of patients with eBC who underwent neoadjuvant chemotherapy (NACT) and to evaluate its association with clinicopathologic prognostic factors and outcomes.

Methods: This was a prospective study conducted at two Brazilian institutions. Fecal samples were collected at baseline (time 1) and prior to surgery (time 2) from 55 patients who received NACT with anthracycline/taxane. Gut microbiome was analyzed by 16S rRNA amplicon sequencing to characterize the α (InvSimpson index) and β (weighted UniFrac distance metric) diversity, as well as taxonomic composition. Clinicopathologic prognostic factors were retrieved from medical records. Pathological complete response (pCR) was defined as the absence of invasive carcinoma in breast and axillary nodes (ypT0/Tis ypN0). Stromal tumor-infiltrating lymphocytes (sTIL) were reported according to the TIL working group criteria. Information about prior use (< 60 days before starting on NACT) of antibiotic (ATB) was obtained directly from patients. Statistical significance was set at $P \leq 0.05$ and analysis of composition of microbiomes (ANCOM-BC2) was used to identify enriched genera with p-values adjusted using FDR correction ≤ 0.25 .

Results: Median age was 49 years (range 31-73). Eleven patients (20%) reported prior antibiotic use at baseline. About 34.5% of patients had HR+/HER2- tumors, 45.4% had triple negative breast cancer (TNBC), and 20% had HER2-positive breast cancer. Fourteen (25%) patients achieved a pCR. Out of 55, 47 (85.4%) had sTIL information. There was no significant difference in alpha diversity ($p = 0.6$) or beta-diversity ($p = 0.8$) between the pCR and residual disease group nor within clinical pathologic factors (age, staging, histological tumor grade,

subtype of breast cancer based on IHC, sTIL). The most abundant taxon in both time 1 and time 2 were the same (*Blautia* at genus level, *Lachnospiraceae* at family level, and *Lachnospirales* at order level), and longitudinal samples collected during NACT showed no significant changes in GM composition. At baseline, we found an enrichment for *Clostridia* sp. among patients who did not use ATB ($p < 0.05$, $pFDR \leq 0.25$). Additionally, we found enrichment for *Bifidobacterium* ($p < 0.05$, $pFDR \leq 0.25$) among patients with HER2 subtype who presented residual disease.

Conclusions: Gut microbiome analysis in early breast cancer is feasible and to our knowledge, this is the first study to evaluate the intestinal microbiota of Brazilian patients with breast cancer. We did not observe any significant association between GM diversity and taxonomic composition with clinical pathologic factors and pCR in this study, nor did we observe changes in the ecological balance of the GM following NACT in breast cancer. Further studies are needed to explore the potential influence of the gut microbial ecosystem on tumor biology and response to neoadjuvant chemo-immunotherapy.

Keywords: Breast Cancer; Neoadjuvant Chemotherapy; Gut microbiota

PO4-03-05

Prognostic value of Ki67 expression in post-treatment tumors of patients with residual triple-negative breast cancer after neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

Y. Kook. Gangnam Severance Hospital, South Korea

S. Lee. Asan Medical Center, United States

S. Baek. Gangnam Severance Hospital, South Korea

M. Kim. Gangnam Severance Hospital, Seoul, Seoul-t'ukpyolsi, Republic of Korea

J. Kim. Gangnam Severance Hospital, South Korea

S. Moon. Gangnam Severance Hospital, South Korea

S. Lee. Gangnam Severance Hospital, South Korea

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

S. Lee. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Introduction

Patients with triple-negative breast cancer (TNBC) who do not achieve pathological complete response (pCR) against neoadjuvant chemotherapy (NAC) have a poor prognosis. The prognosis of these patients can be differentiated using various parameters, including the Residual Cancer Burden (RCB) index and tumor-infiltrating lymphocytes. In this study, we took a different angle and aimed to evaluate the prognostic value of post-treatment Ki67 expression, which was examined in tumors following NAC in patients with non-pCR TNBC.

Methods

A retrospective review of clinical records from February 2008 to December 2021 was conducted of patients from Gangnam Severance Hospital and Asan Medical Center, both in Seoul, South Korea. We included patients with non-metastatic TNBC who underwent NAC including anthracycline and taxane regimens, followed by curative surgery, regardless of adjuvant capecitabine receipt. Ki67 expression and the RCB index were evaluated using residual tumors obtained from surgery. High Ki67 expression was defined as $\geq 20\%$. The 5-year recurrence-free survival (RFS) was estimated using Kaplan-Meier analysis, and hazard ratios (HR) were calculated using Cox regression analysis.

Results

This study included 338 patients with available Ki67 expression data in residual tumors. Among them, 110 patients (30.9%) had low Ki67 expression, while 228 patients (64%) had high Ki67 expression. At a median follow-up of 34 months, those with low Ki67 expression had a 5-year RFS rate of 82.6%, while those with high Ki67 expression had a rate of 58.3%, with a HR of 0.345 (95% CI 0.210-0.565, $p < 0.001$). When stratified by the RCB index, the 5-year RFS of RCB-I patients was 93%, RCB-II patients 70.2%, and RCB-III patients 40.5%. When assessing survival outcomes based on both Ki67 expression and the RCB index, patients with RCB-I and

low Ki67 (n=26) had a 100% 5-year RFS rate. Patients with RCB-I and high Ki67 (n=24) had a rate of 83.3%. Notably, in patients with RCB-III and high Ki67 (n=62), the 5-year RFS rate was 35.5% and there was no significant difference in RFS based on the receipt of adjuvant capecitabine (median RFS: capecitabine - 18 months, observation - 15 months, p-value=0.994).

Conclusions

Our findings demonstrate the prognostic value of Ki67 expression in residual TNBC after NAC, indicating that cases with low Ki67 expression have a favorable outcome. Combining Ki67 expression with the RCB index allows identification of patients with good residual disease (i.e. low Ki67 expression and RCB-I) who could be potential candidates for de-escalating adjuvant treatments such as capecitabine or pembrolizumab. However, for patients with high Ki67 expression and RCB-III, novel strategies are required to improve survival outcomes beyond the use of capecitabine.

PO4-03-06

Body mass index and response to neoadjuvant chemo-immunotherapy among women with primary triple negative breast cancer

Presenting Author(s) and Co-Author(s):

S. Shen. Memorial Sloan Kettering Cancer Center, United States

S. Myers. Memorial Sloan Kettering Cancer Center, United States

Y. Chen. Memorial Sloan Kettering Cancer Center, United States

S. Downs-Canner. Memorial Sloan Kettering Cancer Center, United States

N. Abuhadra. Memorial Sloan Kettering Cancer Center, United States

T. Traina. Memorial Sloan Kettering Cancer Center, United States

M. Robson. Memorial Sloan Kettering Cancer Center, New York, United States

N. Iyengar. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Elevated body mass index (BMI) is associated with lower rates of pathologic complete response (pCR) after neoadjuvant chemotherapy in patients with breast cancer. The addition of PD-1 receptor inhibition with pembrolizumab to neoadjuvant chemotherapy is now considered the standard of care for patients with stage II or III triple negative breast cancer (TNBC) based on results from the KEYNOTE-522 (KN-522) trial. In other cancer types such as melanoma and lung cancer, patients with overweight/obesity have better survival outcomes following treatment with immunotherapy compared to patients with normal weight, despite a higher incidence of any-grade immune-related adverse events (irAEs). Whether BMI is associated with differential response and toxicity in patients with TNBC treated with neoadjuvant chemo-immunotherapy is unknown.

Methods: Patients with stage II-III TNBC treated with neoadjuvant chemotherapy plus pembrolizumab per the KN-522 regimen from 8/2021 – 9/2022 at Memorial Sloan Kettering Cancer Center were included in this retrospective study. Patient characteristics, tumor characteristics, treatments, surgical pathology information, and irAEs were abstracted from medical records. pCR was defined as absence of invasive or in situ carcinoma in breast and axillary node tissue surgical specimens. BMI was categorized per standard definitions: underweight/normal weight < 25 kg/m², overweight 25-29.9 kg/m², and obese ≥30 kg/m². Wilcoxon rank sum tests, Pearson's chi-squared tests, and Kendall rank correlation tests were used to test associations between variables.

Results: 143 patients were included in this study. 57 patients (39.8%) were underweight/normal weight, 46 (32.2%) were overweight, and 40 (28.0%) were obese. Overall, 79/143 patients (55.2%) experienced a pCR. Among patients with a pCR, median BMI was 26.3 kg/m² (interquartile range [IQR] 23.1-30.5 kg/m²); among patients without a pCR, median BMI was 26.1 kg/m² (IQR 23.6-30.0 kg/m²; p >0.9). There was no significant association between BMI category and pCR (p=0.9). Overall, 63/143 (44%) of patients experienced an irAE; 42 (29.4%) required treatment for an irAE. There were no associations between BMI and the incidence (p=0.5) or frequency (p=0.7) of irAEs.

Conclusions: In this TNBC cohort treated with neoadjuvant chemo-immunotherapy, BMI was not associated with rates of pCR or irAEs. These findings highlight the divergent impact of BMI

on immunotherapy response across cancer types. Confirmatory studies in independent cohorts are needed.

PO4-03-07

The impact of chemotherapy relative dose intensity on pathological complete response in patients with triple negative breast cancer treated with neoadjuvant chemotherapy.

Presenting Author(s) and Co-Author(s):

R. Buonaiuto. University of Naples, Federico II, Naples, Campania, Italy
G. Neola. University of Naples, Federico II, United States
A. Caltavuturo. University of Naples, Federico II, United States
P. Trasacco. University of Naples, Federico II, United States
F. Mangiacotti. University of Naples, Federico II, United States
G. Pecoraro. University of Naples, Federico II, United States
M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy
E. Pietrolungo. University of Naples, Federico II, United States
P. De Placido. University of Naples, Federico II, United States
S. De Placido. Department of Clinical Medicine and Surgery, University of Naples "Federico II, Napoli, Italy, United States
V. Forestieri. Department of Clinical Medicine and Surgery, University of Naples "Federico II, Napoli, Italy, United States
M. Giuliano. Department of Clinical Medicine and Surgery, University of Naples "Federico II, Napoli, Italy, United States
G. Arpino. University of Naples, Federico II, Campania, Italy
C. De Angelis. University of Naples Federico II, Napoli, Italy

Background: Neoadjuvant chemotherapy (NACT) is the preferred treatment approach for early-stage triple negative breast cancer (TNBC). Achieving pathologic complete response (pCR) after NACT is associated with improved event-free survival and overall survival in patients with TNBC. Major research efforts have been deployed to identify predictive biomarkers for pCR in TNBC. However, the values of chemotherapy (CT) relative dose intensity (RDI) in predicting pCR remain unclear.

Methods: A retrospective analysis was conducted among 96 consecutive patients with early stage TNBC who received NACT between February 2018 and January 2023 at the University of Naples Federico II (Naples, Italy). Patients' demographics, clinical-pathological features, and type of CT schedules were retrieved from electronic medical records. pCR was defined as the absence of residual invasive or in situ carcinoma in primary tumor and/or lymph nodes, upon chemotherapy administration. RDI was calculated as the ratio of delivered to planned CT dose intensity. RDI was defined as low if $< 85\%$ or high if $\geq 85\%$, respectively. Univariate and multivariate logistic regression were used to evaluate the association between age, tumor stage, RDI, CT regimen dose type, and pCR.

Results: All patients were included in the analysis. Median age at diagnosis was 51 years (range 28-75). Sixty-five (68%) and 31 (32%) patients were diagnosed with stage II and stage III TNBC, respectively. Nineteen (19%) patients received a sequential schedule of anthracycline plus cyclophosphamide (AC) and a taxane (T). Sixty-one (64%) patients received AC followed by concurrent carboplatin-paclitaxel (CaP). Sixteen (17%) patients received the anti-PD1 pembrolizumab in addition to ACCaP chemotherapy backbone (ACCaP-Pem). Fifty-four (56%)

patients received a dose-dense AC-based CT. A pCR was achieved in 59 (61%) patients. Interestingly, patients who received a dose-dense AC based neoadjuvant CT had higher chance to achieve a pCR compared with those treated with a non dose-dense AC based CT (70% vs 46%, $p = 0.03$). Overall, 79 (82%) and 17 (18%) patients received a RDI high and RDI low CT, respectively. No difference in terms of age, body mass index, performance status, tumor stage, type of chemotherapy was observed between the two groups (Table 1). At univariate analysis RDI high (OR 5.18, 95%CI: 1.65-16.31, $p=0.005$) and dose dense AC-based CT (OR 2.42, 95%CI: 0.18-0.97, $p=0.04$) were significantly associated with pCR. In a multivariate model including RDI, age, tumor stage, and AC regimen dose type, RDI was the only variable independently associated with pCR (OR 4.60, 95% CI: 1.40-15.06, $p = 0.01$).

Conclusion: A chemotherapy RDI $\geq 85\%$ independently predicts pCR in early stage TNBC patients treated with standard NACT. In our cohort, one in five patients received a suboptimal chemotherapy dose intensity affecting at least in part tumor response. Studies with larger TNBC patient populations are warranted to confirm the impact of RDI on pCR and long-term outcomes.

Table 1

Table 1	# of pts	RDI High	RDI Low
Age			
≥ 50	53 (55%)	42 (44%)	11 (11%)
< 50	43 (45%)	37 (39%)	6 (6%)
Body Mass Index (BMI)			
<25	41 (43%)	33 (34%)	8 (8%)
≥25	55 (57%)	47 (49%)	8 (8%)
Tumor Clinical Stage (TNM)			
II	65 (68%)	55 (57%)	10 (10%)
III	31 (32%)	24 (25%)	7 (7%)
AC Based Dose Dense Regimen			
Yes	54 (56%)	45 (47%)	9 (9%)
No	42 (44%)	34 (35%)	8 (8%)
Chemotherapy Regimens			
AC + Taxane	11 (11%)	8 (8%)	3 (3%)
AC dd + Taxane	8 (8%)	6 (6%)	2 (2%)
AC + Carboplatin-Paclitaxel	15 (16%)	13 (14%)	2 (2%)
AC dd + Carboplatin-Paclitaxel	46 (48%)	39 (41%)	7 (7%)
AC + Carboplatin-Paclitaxel-Pembrolizumab	16 (17%)	13 (14%)	3 (3%)

PO4-03-08

Enhanced Assessment of Clinical Behavior of TNBC and TPBC using Quantified Levels of HER2, Estrogen and Progesterone Receptor Proteins and Expression of Their Cognate Genes

Presenting Author(s) and Co-Author(s):

J. Wittliff. University of Louisville, LOUISVILLE, Kentucky, United States

M. Daniels. University of Louisville, United States

Background: Renewed interest in clinical relevance of low-HER2 protein in breast cancer management prompted a retrospective investigation of a unique de-identified Database of quantified biomarkers associated with patient outcomes. Currently, IHC of ER, PR and HER2 proteins provides semi-quantitative results, at times complicated by variation in methods and interpretation (cf. ASCO/CAP Guidelines). Our goal was to ascertain relationships of these clinical analytes to predict cancer relapse when quantified for protein products and cognate gene expression. Methods: Database contained 2756 quantified HER2 results by ELISA (Oncogene Sciences) or by EIA (Triton Diagnostics) of which 198 patients had associated clinical outcomes. No definition of HER2-low has been accepted for IHC, although > 50% of biopsies may be categorized as HER2-low (cf. ASCP CE Programs). Microarray results obtained for ~ 22,000 genes using RNA purified from LCM-procured carcinoma cells of 247 primary breast biopsies were analyzed. ESR1, PGR and ERBB2 gene expression levels in 276 biopsies had been validated by RTqPCR. To assess distribution and dispersion of HER2 protein, cumulative relative frequency distribution analyses were employed, focusing on cut-offs within interquartile range. Permutations and combinations of the 3 biomarkers based on IHC definitions (cf. ASCO/CAP Guidelines) were examined. Tertiles and quartiles of data sets were used to explore association between biomarker levels and clinical outcomes. Box plots depicted protein and gene expression levels, Progression-Free Survival (PFS), or Overall Survival (OS) across ER/PR/HER2 categories and compared differences using a Kruskal-Wallis ANOVA Rank Test. Cox regressions were used to contrast hazard ratios among the ER/PR/HER2 groups. Kaplan-Meier plots visualized survival rates among groups and a log-rank test detected statistical discrepancies. We investigated differences between groups for categorical variables using chi-squared tests (Fisher's exact test for non-normally distributed data), while for ordinal variables, ANOVA tests were used (Kruskal-Wallis for non-normally distributed data). Categorical variables were summarized as count (%), and ordinal variables were summarized as median [IQR]. Analyses were performed using R version 4.2.2 (Innocent and Trusting). Results: Neither quantified ER or PR alone nor ER/PR collectively were related to HER2 oncoprotein levels. Influence of menopausal status on biopsy biomarker profiles was investigated. With a median cutoff for HER2 protein, patients with ER+/PR+/HER2+ (TPBC) exhibited increased OS, whereas those with TNBC had decreased OS, of 8 combinations possible. Using tertiles and quartiles, TPBC was exhibited by 34-37% of specimens compared to TNBC, which represented 9.1-12.7% of biopsies when biomarker proteins were quantified. After qPCR data were stratified by ER/PR/HER2 status with a 50% quantile cut for HER2, 39% were TPBC and 10% were TNBC. Using microarray data with the same cutoffs, only 14% were TPBC and 17% were TNBC. Once TPBC were identified by either microarray or by qPCR, increased ESR1, PGR and ERBB2 expression collectively was associated with increased PFS and OS of patients. In general, biopsies that were TNBC or other combinations of biomarker's gene expression correlated with poorer prognosis and overall survival. Conclusions: Quantifying levels of ER, PR and HER2 proteins as well as of ESR1, PGR and ERBB2 expression were correlated with prediction of clinical outcomes of TNBC, TPBC and patients with other biomarker subsets. Results support quantitative assessment of these biomarkers in

biopsies to assess utility of the HER2-low type in personalizing breast cancer management and prediction of risk of relapse.

PO4-03-09

Profile of circulating natural killer cells in stage III triple negative breast cancer before and after neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

L. de Barros Batista. Instituto de Medicina Integral Professor Fernando Figueira IMIP, United States

J. Telles. Instituto de Medicina Integral Prof. Fernando Figueira ,Iacog, Brazil

C. Santos. Instituto D'Or de Pesquisa e Ensino (IDOR), Recife, Brazil, Brazil

A. Souza. Instituto de Medicina Integral Prof. FERNANDO Figueira, Brazil

M. Salgado. Hospital de Câncer de Pernambuco - HCP, Recife, Brazil, Pernambuco, Brazil

L. Torres. Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, Brazil; Hospital de Cancer de Pernambuco (HCP), Recife, Brazil; Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil, Recife, Pernambuco, Brazil

Background: Triple negative breast cancer (TNBC) is the most aggressive subtype of breast cancer. The treatment for locally advanced disease is based on neoadjuvant chemotherapy and immunotherapy, with complete pathological response (pCR) serving as a predictor of disease-free survival. Although the presence of immune cell infiltration in the tumor has a favorable prognostic impact, there is a lack of predictive biomarkers for complete pathological response to neoadjuvant chemotherapy (NAC). Objective: to analyze the profile of circulating Natural Killer (NK) cells and NK subpopulations (NK FAS+ and NK PD1+) in association with the occurrence of complete pathological response after neoadjuvant chemotherapy in women with clinical stage III TNBC. Methods: This was a longitudinal prospective and translational cohort study, including women aged 18 to 60 years with stage III TNBC diagnosed between March 2015 and July 2017, with a follow-up of 24 months. A comparison control group consisted of 30 healthy women aged 18 to 60 years without prior or current cancer diagnosis and no family history of breast cancer. Peripheral blood samples were collected before NAC and before surgery. Flow cytometry was used to analyze the percentage levels of NK cells and NK subpopulations (NK FAS+ and NK PD1+). The Shapiro-Wilk test was initially applied to assess the normality of quantitative variables. The non-parametric Mann-Whitney test was used for comparison between two groups. The statistical significance level was set at $p < 0.05$. Overall survival (OS) was estimated using the Kaplan-Meier method. Statistical analysis was performed using GraphPad Prism v9.5.1. Results: The median age was 45 years. Stage IIIA was identified in 28% of the patients, while IIIB was observed in 72%. Regarding pathological response, 14 patients (48%) achieved pCR, while 15 patients (52%) had a non-complete pathological response (non-pCR). The 2-year OS was 86%, with no median reached. Higher percentage levels of NK cells, NK FAS+, and NK PD1+ were observed in the patient group compared to the control group, with significant differences. There was a significant increase in the percentage levels of NK cells after NAC compared to pre-NAC levels, and a reduction in NK PD1+ levels. NK cell levels were significantly higher in patients with stage IIIA compared to stage IIIB, while NK FAS+ levels were lower. NK cell and NK FAS+ subpopulation levels were significantly higher in patients who achieved pCR compared to non-pCR patients, with no difference in NK PD1+ cell levels. Conclusions: Elevated levels of circulating NK cells and NK FAS+ subpopulation collected from peripheral blood before NAC may serve as potential biomarkers for pCR in patients with TNBC.

PO4-03-10

HER2 Expression in Triple-Negative Breast Cancer: Clinicopathologic Features and Response to Neoadjuvant Chemotherapy

Presenting Author(s) and Co-Author(s):

Z. Morante. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

I. Otoya. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Surquillo, Lima, Peru

N. VALDIVIESO. e cancer, Lima, Peru

C. Calle. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

H. Fuentes. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

S. Neciosup. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

C. Castañeda. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

T. Vidaurre. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

M. Falla. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Peru

V. Colomo. Oncosalud - AUNA, Lima, Peru

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

BACKGROUND:

Half of the primary breast cancers reported as HER-2 negative have low HER-2 expression, defined as an immunohistochemical (IHC) score of 1+ or 2+, with negative in situ hybridization. Among these cases, 37% correspond to the triple-negative immunophenotype. The primary objective of this study was to evaluate HER-2 expression in patients with triple-negative breast cancer and compare the clinicopathologic features and response to neoadjuvant chemotherapy between HER-2 negative (0) and HER-2 low (1+/2+) subtypes.

METHODS:

We retrospectively analyzed 157 patients with early-stage triple-negative breast cancer who underwent neoadjuvant chemotherapy followed by surgery with curative intent and met the study's inclusion criteria. These patients were treated at the National Institute of Neoplastic Diseases between 2010 and 2021. HER-2 analysis was performed using immunohistochemistry (IHC), and in cases of HER-2 (2+) amplification, in situ hybridization was performed.

RESULTS:

Of all the included patients, 107 were classified in the HER-2 negative group (68%), and 50 were classified in the HER-2 low group (32%). Seventy-four percent of patients with HER-2 negative were in the age range of 40-64 years, compared to 68% in the HER-2 low group. A significant difference was found between the HER2-negative and HER2-low groups regarding age and Ki67. The median age of HER-2 low patients is significantly higher than the median age of HER-2 negative patients (52 years vs. 45 years, respectively). No significant association was found between HER-2 status and clinical stages or histological grade. However, the median Ki67 percentage of HER-2 negative patients is significantly higher than the median Ki67 of HER-2 low patients (70% vs. 50%, respectively ($p=0.035$)). Thirty-two percent of patients with HER-2 negative achieved a pathological complete response (pCR) compared to 18% of patients with HER-2 low. There were no differences in the pCR rate in the HER-2 1+ and 2+ subgroups. Among the patients included in both groups, who achieved pCR, no disease

progression was observed at the time of analysis.

CONCLUSIONS:

Patients in the HER-2 negative group had a higher rate of complete pathological response to neoadjuvant chemotherapy compared to those in the HER-2 low group. No differences were observed in the pCR rate between HER-2 1+ and 2+ subgroups, suggesting that HER2 expression levels within the low range may not significantly impact treatment response.

General characteristics	0, N = 107 ¹	1+, N = 31 ¹	2+, N = 19 ¹	p-value ²
Age (years)	45 (41, 54)	52 (40, 64)	49 (44, 57)	0.088
Age group (years)				0.033
< 40	22 (21%)	5 (16%)	1 (5.3%)	
40 -64	79 (74%)	19 (61%)	15 (79%)	
> 65	6 (5.6%)	7 (23%)	3 (16%)	
Histological type				0.6
Ductal	73 (89%)	23 (79%)	12 (86%)	
Lobular	1 (1.2%)	0 (0%)	0 (0%)	
Mixed ductal/lobular	1 (1.2%)	0 (0%)	0 (0%)	
Others	7 (8.5%)	6 (21%)	2 (14%)	
Not reported	25	2	5	
Tumor size (cm)	6.00 (4.00, 8.00)	6.00 (3.50, 8.00)	6.50 (4.00, 8.75)	0.7
Unknown	1	0	1	
T				>0.9
T1	1 (0.9%)	0 (0%)	0 (0%)	
T2	28 (26%)	10 (32%)	5 (26%)	
T3	41 (39%)	11 (35%)	6 (32%)	
T4	36 (34%)	10 (32%)	8 (42%)	
Not reported	1	0	0	
Lymph nodes				>0.9
0	36 (34%)	10 (32%)	7 (37%)	
1-3	71 (66%)	21 (68%)	12 (63%)	
Clinical stage				0.5
IIA	18 (17%)	2 (6.5%)	1 (5.3%)	
IIB	26 (25%)	12 (39%)	6 (32%)	
IIIA	21 (20%)	6 (19%)	3 (16%)	
IIIB	37 (35%)	9 (29%)	7 (37%)	
IIIC	4 (3.8%)	2 (6.5%)	2 (11%)	
Not reported	1	0	0	
Histological grade				0.3
II	11 (12%)	6 (21%)	4 (24%)	
III	79 (88%)	22 (79%)	13 (76%)	
Not reported	17	3	2	
Ki67 (%)	70 (50, 80)	50 (30, 70)	50 (40, 73)	0.035
Not reported	23	6	0	

¹Median (IQR); n (%)

²Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-squared test

Clinical and pathological characteristics after surgery	0, N = 107 ¹	1+, N = 31 ¹	2+, N = 19 ¹	p-value ²
Surgery type				0.2
Lumpectomy	16 (15%)	5 (16%)	0 (0%)	
Quadrantectomy	13 (12%)	1 (3.2%)	3 (16%)	
Radical Mastectomy	78 (73%)	25 (81%)	16 (84%)	
Axillary management				>0.9
Sentinel Lymph Node Biopsy	27 (25%)	8 (26%)	5 (26%)	
Axillary lymph node dissection	77 (72%)	22 (71%)	14 (74%)	
Both	3 (2.8%)	1 (3.2%)	0 (0%)	
c-erbB2				0.3
0	29 (27%)	3 (9.7%)	5 (26%)	
1+	11 (10%)	3 (9.7%)	2 (11%)	
2+	8 (8.6%)	5 (16%)	1 (5.3%)	
Not reported	61 (57%)	20 (65%)	11 (58%)	
Ki67	60 (50, 80)	55 (23, 70)	60 (50, 80)	0.4
Not reported	63	21	12	
Residual tumor size (cm)	5 (4, 15)	8 (4, 30)	8 (4, 33)	0.4
Not reported	21	9	4	
Lymph nodes				0.5
0	47 (44%)	15 (48%)	11 (58%)	
1-3	60 (56%)	16 (52%)	8 (42%)	
RCB				0.7
0	24 (32%)	4 (17%)	5 (29%)	
I	7 (9.2%)	3 (13%)	2 (12%)	
II	20 (20%)	9 (38%)	3 (16%)	
III	25 (33%)	8 (33%)	7 (41%)	
Not reported	31	7	2	
Adjuvant chemotherapy				0.2
Yes	49 (46%)	20 (65%)	11 (58%)	
No	58 (54%)	11 (35%)	8 (42%)	
Radiotherapy				0.3
Yes	92 (88%)	28 (93%)	15 (79%)	
No	13 (12%)	2 (6.7%)	4 (21%)	
Not reported	2	1	0	
Status progression				0.5
Yes	48 (46%)	12 (40%)	10 (59%)	
No	56 (54%)	18 (60%)	7 (41%)	
Not reported	3	1	2	

¹Median (IQR); n (%)

²Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-squared test

PO4-03-11

Discerning the impact of ctDNA detection on patient decisions in early-stage breast cancer

Presenting Author(s) and Co-Author(s):

T. Ballinger. Indiana University School of Medicine, Indianapolis, Indiana, United States

G. Zimet. Indiana University School of Medicine, United States

E. Railey. Research Advocacy Network, United States

M. Smith. Research Advocacy Network, United States

B. Schneider. Indiana University School of Medicine, United States

Background: Detection of circulating tumor DNA (ctDNA) after neoadjuvant therapy for triple negative breast cancer (TNBC) is associated with increased risk of recurrence. Ongoing trials aim to determine whether knowledge of specific genomic mutations in ctDNA can inform targeted adjuvant therapy to improve prognosis. The impact of knowledge of ctDNA status on patient treatment decisions weighing benefit and toxicity is unknown.

Methods: 401 women were recruited via the Research Advocacy Network from Young Survivors' Coalition, Living Beyond Breast Cancer, and Pink-4-Ever Ending Disparities. Participants had to self-report a history of non-metastatic breast cancer and have received chemotherapy in the prior 6 months to 10 years to be eligible. Participants completed a 27 question Qualtrics survey detailing demographics and experience with prior chemotherapy. Based on estimations from prior data, participants were presented with scenarios mimicking residual TNBC and unknown, negative, or positive ctDNA status with corresponding risk of recurrence of 40%, 20%, or 55% respectively. Participants were then presented with 12 scenarios (in random order) combining various degrees of absolute risk reduction (5%, 15%, 35%) with established toxicity profiles of four possible post-neoadjuvant therapies (capecitabine, immunotherapy, PARP inhibitor, and PI3K inhibitor). Participants rated scenarios in terms of acceptability from 0-100. A general linear model with repeated measures (3 X 4) was used to determine the contributions of risk reduction and toxicity to acceptability. Models were also run with the addition of between subject factors: age group (< 40; >40), stage of cancer (Stage 1; Stage 2/3), and previous experience with toxicity (Yes; No), to examine whether any of these factors moderated the effects of risk reduction and toxicity. Effect sizes were determined by partial h^2 .

Results: 286 eligible respondents completed the survey with evaluable responses. Average age was 41.2 (range 27-75). When the hypothetical risk of recurrence decreased from 40% (ctDNA-unknown) to 20% (ctDNA-negative), significantly less participants preferred adjuvant capecitabine vs. no therapy (95.1% versus 63.3%, $p < 0.001$). Across the 12 scenarios, both benefit ($F=448.5$, $p < 0.001$; preference for greater benefit) and toxicity ($F=33.64$, $p < 0.001$; preference for lower toxicity) significantly influenced acceptability, but benefit had a much larger effect size than toxicity ($h^2=0.76$ and 0.26 , respectively). There was no significant interaction effect, and the pattern of results was not moderated by age, stage of cancer, or prior experience with chemotherapy toxicity. The most preferred scenario (greatest benefit, lowest toxicity) had a mean rating of 87.8/100; however, even when presented with the scenario with the lowest benefit and highest toxicity, the mean rating was still 31.5/100, suggesting that this combination would be acceptable to some individuals.

Conclusions: Knowledge of ctDNA-negative status significantly reduced the number of participants preferring adjuvant capecitabine over no further therapy. When faced with ctDNA-positive status, participants preferred maximum risk reduction regardless of toxicity profile. As genomic technology advances, it is imperative that researchers and treating physicians understand its impact on patient decision making.

PO4-03-12

De-escalating treatment with neoadjuvant chemotherapy in early triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

A. Gasol Cudós. Hospital Universitari Arnau de Vilanova de Lleida, United States

N. Tuset Der-Abraín. Hospital Universitari Arnau de Vilanova de Lleida, United States

Neoadjuvant chemotherapy (NAT) is a standard treatment in early triple-negative breast cancer, but the regimen and duration of this treatment are controversial. We analyze a cohort of early triple negative breast cancer treated with NAT with different schemas to determine its efficacy.

272 patients treated with NAT since 2001 to 2020 were selected. The median age of the group was 57 years (27-85), initial size 30 mm (9-122) and Ki67 expression was 60 (7-100). 107 patients (39.3%) had histologically confirmed initial axillary involvement and the regimens of chemotherapy used were carboplatin AUC 5 + weekly paclitaxel (80 mg/m²) x 4 cycles in 56 cases (21%) (SCHEME A), same scheme followed by 4 cycles of adriamycin 50 mg/m² + cyclophosphamide 500 mg/m² in 85 cases (31%) (SCHEME B), Adriamycin 50 mg/m² + cyclophosphamide 500 mg/m² x 4 cycles in 44 (16%) (SCHEME C) and Adriamycin 50 mg/m² + cyclophosphamide 500 mg/m² x 4 cycles followed by docetaxel 100 mg/m² x 4 cycles in 87 (32%) (SCHEME D). We achieved a 51% of pathologic complete response (pCR), and a total of 24% of recurrences. The proportion of pCR and recurrence according to the different schemes is represented in the following table.

SCHEMA	A (20%)	B (31%)	C (16%)	D (32%)
pCR	62%	63%	41%	37%
Recurrence in pCR	3%	7%	16%	9%
Recurrence in nonpCR	9%	16%	50%	63%

The clinical factors associated with recurrence were the initial size (OR 8.6), the initial axillary involvement (OR 4.21) and the absence of pCR (OR 8.14), and for patients with pCR it was only the initial axillary involvement (OR 3.4). Patients that received schema A in NAT only presented a total of 5% of recurrence (3/56), only in patients with initial axillary involvement.

The NAT schema with carboplatin AUC 5 + weekly paclitaxel (80 mg/m²) x 4 cycles is safe in patients without initial nodal involvement with high pathologic complete response (62%) and lower recurrence rate (9% in nonPCR and 3% in pCR). Therefore, it could be considered as a standard scheme of neoadjuvant chemotherapy for patients without axillary involvement.

PO4-03-13

High B7-H3 expression with low PD-L1 expression identifies armored-cold tumors suggesting potential anti-B7-H3 therapy in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

J. Mei. The First Affiliated Hospital of Nanjing Medical University, United States

Y. Cai. Nanjing Medical University, United States

Z. Fu. The First Affiliated Hospital of Nanjing Medical University, United States

Y. Yin. The First Affiliated Hospital of Nanjing Medical University, United States

Background: Triple-negative breast cancer (TNBC) is generally regarded as the most aggressive subtype among breast cancer. B7 homolog 3 protein (B7-H3), also known as CD276, is an emerging immune checkpoint molecule, which plays a dual role in the immune system. Multiple anti-B7-H3 therapies has been raised, such as DS-7300, MGA271, MGD009, and B7-H3 chimeric antigen receptor T-cell immunotherapy (CAR-T). However, the expression of B7-H3 in TNBC and its value as a biomarker identifying therapeutic options has not been elucidated

Methods: A total of 165 samples (83 non-TNBC and 82 TNBC) were included in this study, and 6 samples included paired para-tumor samples. In addition, 30 TNBC patients receiving standardized neoadjuvant chemotherapy (NAT) were recruited. After 8 cycles of NAT, the response to NAT was assessed by RECIST1.1 criterion before surgical operation. Moreover, multiple public cohorts of breast cancer and TNBC were obtained, including the TCGA dataset, the METABRIC dataset, the GSE176307 (durvalumab-based therapy) dataset, the PRJNA558949 (durvalumab-based therapy) dataset, the GSE194040 (paclitaxel-based therapy) dataset, and the GSE34138 (anthracycline-based therapy) dataset. Based on multiple in-house and public cohorts, we investigated the expression features of B7-H3 in breast cancer and checked the anti-tumor effect of the B7-H3 monoclonal antibody in mouse model. We also developed a novel classifier combined B7-H3 and PD-L1 expression in TNBC.

Results: B7-H3 was highly expressed in tumor tissues in the in-house and the TCGA cohorts. B7-H3 expression did not differ significantly between non-TNBC and TNBC samples in the in-house and the TCGA cohorts, excepting for the METABIRC cohort. There was no notable difference in CD8⁺ cells infiltration between B7-H3 low and high expressed non-TNBC samples, but CD8⁺ cells was notably higher in the B7-H3 low expressed TNBC samples. The similar findings were also observed in the TCGA and the METABIRC cohorts. In addition, enrichment analysis of transcriptome data and analysis of in-house samples showed that B7-H3 was positively related to most collagens. Moreover, anti-B7-H3 therapy significantly inhibited tumor growth in mouse TNBC model, notably increased immune cells infiltration, and also reduced collagen deposition within the tumor. Given the notable value of PD-L1 in predicting immunotherapy responses, we also combined B7-H3 and PD-L1 expression to establish a novel subtyping strategy. TNBC patients with B7-H3^{high}PD-L1^{low} feature exhibited the lowest anti-tumor immune infiltration and higher collagen deposition level. In the durvalumab-dependent cohort, paclitaxel-dependent cohort, anthracycline-dependent cohort, and our recruited NAT cohort, the B7-H3^{high}PD-L1^{low} subgroup exhibited the lowest therapeutic response.

Conclusions: Overall, this research provides a novel subtyping strategy based on the

combination of B7-H3/PD-L1 expression that could potentially be applied to predict the therapeutic responses in TNBC, and suggests a potential biomarker-guided anti-B7-H3 therapy. Based on the classifier, we can select potential beneficiaries to deliver personalized medical services.

PO4-04-01

Antitumor activity and safety of sacibertinib (Hemay022) in combination with endocrine therapy in patients with ER and HER2 both positive metastatic breast cancer: A phase Ib study

Presenting Author(s) and Co-Author(s):

H. Li. Department of Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, Beijing, China (People's Republic)

Q. Zhang. Department of Breast Oncology, Harbin Medical University Cancer Hospital, Harbin, China, United States

R. Zhang. Department of Breast Oncology, Peking University Cancer Hospital & Institute, United States

Y. Liu. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital and Institute, 100142, China, United States

X. Hu. Tianjin Hemay Pharmaceutical CO. China, United States

Antitumor activity and safety of sacibertinib (Hemay022) in combination with endocrine therapy in patients with ER and HER2 both positive metastatic breast cancer: A phase Ib study

Huiping Li^{1,*}, Qingyuan Zhang², Ruyan Zhang¹, Yaxin Liu¹, Chang Liu³, Xianjun Hu³

¹ Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital and Institute, 100142, China;

² Department of Breast Oncology, Harbin Medical University Cancer Hospital, Harbin, China;

³ Tianjin Hemay Pharmaceutical CO. China

* Corresponding author: Huiping Li, email: huipingli2012@hotmail.com

Abstract

PURPOSE Sacibertinib (Hemay022) is a novel irreversible tyrosine kinase inhibitor (TKI) blocking epidermal growth factor receptor and human epidermal growth factor receptor 2 (HER2). This study aimed to explore the safety and efficacy of sacibertinib plus endocrine therapy in patients with estrogen receptor-positive (ER+) and HER2+ metastatic breast cancer (MBC). **PATIENTS AND METHODS** Using a phase 1b 3+3 dose escalation and expansion study design, patients with ER+/HER2+ MBC were treated with sacibertinib (200mg-500mg daily) plus endocrine therapy including exemestane, letrozole, fulvestrant. The safety, pharmacokinetic and clinical efficacy, including objective response rate (ORR), clinical benefit rate (CBR), disease control rate (DCR) and progression-free survival (PFS) were assessed.

RESULTS A total of 55 ER+/HER2+ MBC patients pretreated with chemotherapy and anti-HER2 therapy were enrolled in the study between March, 2018 and July, 2021. The incidence of ORR ranged from 17.6% to 42.9%, DCR ranged from 63.0% to 86.8%, CBR ranged from 42.3% to 69.7%, and the overall median PFS was 9.0 (95% CI, 5.5 ~ 11.00) months. In the 400 mg Sacibertinib plus exemestane cohort (N = 18), ORR was 38.9% (7/18), DCR was 72.2% (13/18), CBR was 66.7% (12/18), and median PFS was 8.9 months; In the 500 mg Sacibertinib plus exemestane cohort (N = 12), ORR was 25.0% (3/12), DCR was

100.0%(12/12), CBR was 50.0%(6/12), and median PFS was 9.0 months. The ORR, CBR, and DCR were better in the 400 mg and above dose cohorts than in the 200 mg and 300 mg cohorts. The DCR of the 500 mg combined with exemestane cohort was better than that of the other dose cohorts. Sacibertinib plus endocrine therapy was well-tolerated without dose-limiting toxicities. The most frequent grade 3 adverse events included diarrhoea (9.1%), leucopenia(5.5%), neutropenia (3.6%). One (1.8%) had grade 4 hydropericardium.

CONCLUSION Sacibertinib plus endocrine therapy had a favorable safety profile and antitumor activity in patients with ER+/ HER2+ MBC, 400-500mg daily showed more efficacy, supporting further assessment in randomized studies.

This figure showed response of Sacibertinib plus endocrine therapy in ER+/ HER2+ metastatic breast cancer.

PO4-04-02

Real-world first line use of trastuzumab biosimilar (HLX02), pertuzumab and chemotherapy for Chinese patients with HER2-positive metastatic breast cancer

Presenting Author(s) and Co-Author(s):

R. Zhang. Department of Breast Oncology, Peking University Cancer Hospital & Institute, United States

G. Song. Department of Breast Oncology, Peking University Cancer Hospital & Institute, United States

X. Liu. Peking University Cancer Hospital & Institute, United States

H. Li. Department of Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, Beijing, China (People's Republic)

Background: HLX02 (Zercepac[®]) is the first manufactured trastuzumab biosimilar in China. Its similar efficacy, safety, and immunogenicity compared with Herceptin was confirmed in phase III clinical trials in patients with HER2-positive advanced breast cancer. Nevertheless, the real-world evidence of HLX02 combined with pertuzumab and chemotherapy in HER2-positive advanced breast cancer in China is still warranted.

Methods: In this real world observational study, patients with HER2-positive advanced breast cancer who received HLX02, pertuzumab and chemotherapy as first line treatment at Beijing Cancer Hospital from April 2020 to April 2023 were retrospectively and prospectively included. The primary outcome was progression-free survival (PFS), and secondary outcomes included overall survival (OS), objective response rate (ORR), disease control rate (DCR) and adverse events (AEs).

Results: A total of 55 patients (including one male) were included in this study and analyzed. The median age was 57 (range: 49, 62) years. Nearly one-third of tumors were estrogen receptor-positive (n=20, 36.4%). Thirty patients (54.5%) had newly-diagnosed stage IV disease. Visceral metastasis was reported in 40 patients (72.7%), most commonly observed in liver (n=22, 40%) and lung (n=19, 34.5%). Seven patients received prior anti-HER2 therapy during (neo-) adjuvant therapy (n=7, 12.7%). Taxane was the most commonly administered chemotherapy regimen (n=51, 92.7%), including 56.4% albumin-bound paclitaxel, 20% liposomal paclitaxel and 18.2% docetaxel. Objective response was observed in 44 patients, leading to an ORR of 80%, and the DCR achieved 100%. HLX02 and pertuzumab was continued as maintenance therapy in 50 patients (90.9%), among which 17 combined with endocrine therapy (30.9%) and 6 combined with oral chemotherapy (10.9%). With a median follow-up of 9.8 months (range: 0.6-38.2). Progressive disease (PD) occurred in 12 of 55 patients (21.8%) and no deaths occurred. The median PFS was 24.8 months (95% confidence interval [CI]: 16.9- not estimated). The 12-month and 18-month PFS rate was 84.0% (95%CI: 72.9-96.9) and 58.8% (95%CI: 41.5 ~ 83.2), respectively. OS cannot be estimated yet due to immature data. HLX02-related diarrhea and infusion-related reaction was reported in 2 (3.6%) and 1 (1.8%) patients, respectively. LVEF values were monitored before and after drug administration, no clinical significant decline in LVEF and cardiac toxicity was observed.

Conclusions: The trastuzumab biosimilar HLX02 demonstrated comparable efficacy and safety to Herceptin when combined with pertuzumab and chemotherapy for Chinese patients with HER2-positive advanced breast cancer in real world first-line treatment, which suggested that

HLX02 may provide another option of Her2-targeted therapy combined with pertuzumab for Chinese patients. The benefit regarding long-term survival need to be further verified.

Table 1. Effectiveness

Table 1. Effectiveness

Effectiveness	N=55
Best clinical response	n (%)
Complete response (CR),	1 (1.8)
Partial response (PR)	43 (78.2)
Stable disease (SD)	11 (20.0)
Progressive disease (PD)	0
ORR (CR+PR)	44 (80.0)
DCR (CR+PR+SD)	55 (100.0)
Median PFS, month (95% CI)	24.8 (16.9 ~ NA)
PFS rate (% , 95% CI)	
12-month	84.0 (72.9 ~ 96.9)
18-month	58.8 (41.5 ~ 83.2)

PO4-04-03

Empowering Oncologists to Develop Individualized Management Strategies for HER2+ Metastatic Breast Cancer: Findings from a Quality Improvement Initiative

Presenting Author(s) and Co-Author(s):

R. Mahtani. Miami Cancer Institute, Plantation , Florida, United States

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

I. Dewald. PRIME Education, United States

C. Anderson. PRIME Education, United States

J. Carter. PRIME Education, United States

C. Heggen. PRIME Education, United States

K. McKinnon. PRIME Education, Georgia, United States

Background: Rapidly evolving evidence in the treatment of metastatic HER2+ metastatic breast cancer (MBC) can present challenges in aligning practice with the latest clinical data and guideline recommendations. In this ongoing quality improvement initiative, we identify and address real-world challenges healthcare professionals (HCPs) face in individualizing treatment plans, adverse event management, and patient-centered care for HER2+ MBC.

Methods: From 9/2022 to 12/2022, 22 HCPs who treat patients with breast cancer (BC) along with 52 patients with HER2+ MBC from 2 large US community oncology clinics completed tethered surveys assessing practice patterns, challenges, and attitudes related to individualized and patient-centered care for HER2+MBC. Patient charts (n=100) were audited to assess current practice patterns and to track changes over time. Inclusion criteria included a confirmed HER2+ MBC diagnosis, prescription for two or more lines of HER2+ breast cancer treatment, and ≥ 1 visit in the one-year chart abstraction period. HCPs participated in audit-feedback sessions to assess site-specific challenges and gaps and developed action plans for improvement. Follow-up chart audits and HCP surveys will evaluate changes in practice patterns 6 months after the educational intervention.

Results: The most frequently reported HCP challenges included coordination of care (41%) and individualizing treatment plans (32%). The most frequently reported patient challenges included feeling confident in treatment plan (30%) and being unable to meet work or home responsibilities (22%). In tethered surveys, there were discordant findings between patient and HCP perceptions related to goals for treatment, patient education, and patient-centered care. For example, 82% of HCPs reported often or always asking patients about treatment preferences, but only 8% of patients reported their doctor asked. While HCPs overwhelmingly thought surviving as long as possible was their patients' top goal (82%), patients reported their top goals for treatment were improving quality of life (57%) and controlling symptoms (41%). Additionally, while HCPs thought patients had the most difficulty managing nausea/vomiting (68%) and diarrhea (59%), patients reported they have the most difficulty managing fatigue (46%) and hair loss (44%). Baseline chart audits highlighted several areas for improvement in guideline-aligned care, including treatment selection, sequencing, and supportive care. Based on identified gaps, providers developed and implemented action plans, such as increasing use of patient navigators, referring patients for palliative care at time of diagnosis, improving multidisciplinary team-based approaches, and implementing tools and resources to stay up-to-date on clinical evidence and guidelines.

Full findings from baseline surveys and chart audits will be presented, along with follow-up surveys and chart audits to measure impact.

Conclusions: Through this QI initiative, we identified gaps in individualized, guideline-aligned, patient-centered care for patients with HER2+ MBC, and HCPs developed and are implementing action plans for improvement. The methods and findings from this initiative demonstrate key opportunities to improve outcomes for patients with HER2+ MBC in community oncology clinics.

PO4-04-04

A Multicenter, Retrospective, Real World Study of Inetetamab Combined with Pyrotinib and Vinorelbine as Treatment for HER2-positive Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

Y. Yin. The First Affiliated Hospital of Nanjing Medical University, United States

W. Li. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

X. huang. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

N. Jin. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

X. Wu. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

C. Sun. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

Y. Hua. The First Affiliated Hospital of Nanjing Medical University, United States

Background Inetetamab, a new human epidermal growth factor receptor 2 (HER2) targeted antibody to optimize the ADCC effect, has shown great effectiveness in treating HER2-positive metastatic breast cancer. Pyrotinib, another HER2 targeted drug, is a typical representative of TKI drugs, which not only has a strong HER2 antagonistic effect but also can synergize with monoclonal antibodies to amplify the ADCC effect. Here, we investigated the efficacy and safety of inetetamb combined with pyrotinib and vinorelbine as treatment or HER2-positive metastatic breast cancer. Methods From Jan 2020 to July 2023, 77 HER2-positive metastatic breast cancer patients received inetetamb combined with pyrotinib and vinorelbine were enrolled in this study. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR), and safety profiles were reported. Results The patients' median age at enrollment was 53 years, 35 patients (45.5%) had hormone receptor-positive disease and 54 patients (70.1%) had visceral metastasis. The median PFS was 10.03 months (95% confidence interval [CI] 6.66 to 13.41 months). ORR was 62.3% (48/77) and CBR reached 77.9% (60/77). The most common adverse event (AE) was diarrhea, occurring in 36 patients (46.8%). While the most common grade III/IV AEs included neutropenia (9[11.7%]), leukopenia (8[10.4%]) and diarrhea (5[6.5%]). No treatment-related serious adverse events or treatment-related deaths occurred. Conclusion The combination regimen of inetetamab combined with pyrotinib and vinorelbine showed an encouraging efficacy and favorable safety in patients with HER2 positive metastatic breast cancer.

PO4-04-05

HER2 immunohistochemistry (IHC) expression in HER2-positive (HER2-pos) metastatic breast cancer (mBC): clinical and prognostic differences between IHC 2+ and IHC 3+ populations.

Presenting Author(s) and Co-Author(s):

A. Dri. Department of Medicine, University of Udine, Italy; Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy., United States

E. Blondeaux. IRCCS Ospedale Policlinico San Martino, United States

C. Bighin. University of Genova, Genova, United States

S. Gasparro. IRCCS Regina Elena National Cancer Institute, Rome, United States

S. Russo. Department of Medical Oncology, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC) Udine, Italy, Italy

L. Foffano. Department of Medicine (DAME), University of Udine, Udine, Italy., United States

P. Pugliese. ASST Lariana, Como, United States

A. Fontana. Pisa University Hospital, Pisa, United States

E. Cortesi. Department of Pathology, Oncology and Radiology, Sapienza University of Rome, Rome, Italy., United States

A. Ferzi. ASST Ovest Milanese, Ospedale di Legnano, Legnano, Italy, United States

F. Riccardi. Antonio Cardarelli Hospital, Naples, United States

V. Sini. Centro Oncologico S. Spirito-Nuovo Regina Margherita, ASL Roma 1, Rome, United States

L. Boni. IRCCS Ospedale Policlinico San Martino, Genoa, Genova, Italy

A. Fabi. Precision Medicine in Breast Cancer, Fondazione Policlinico Universitario A. Gemelli, IRCCS Rome - Italy, Rome, Italy

F. Montemurro. Candiolo Cancer Institute, FPO-IRCCS, United States

M. De Laurentiis. Breast Unit, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy., United States

G. Arpino. Federico II University Naples - Italy, United States

L. Del Mastro. University of Genova - IRCCS Ospedale Policlinico San Martino, United States

L. Gerratana. Medical Oncology and Cancer Prevention, Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy., United States

F. Puglisi. Department of Medicine (DAME), University of Udine, Udine, Italy and Department of Medical Oncology - CRO Aviano, National Cancer Institute, IRCCS, Aviano, Friuli-Venezia Giulia, Italy

Background: The exploration of heterogeneity in mBC has gained significant interest in optimizing therapeutic strategies. While the impact of differential HER2 IHC staining has been extensively studied in HER2-low neoplasms, limited data is available regarding IHC 2+ and IHC 3+ categories in HER2-pos mBC. The aim of our study is to compare, the clinical variables, metastatic patterns, and prognosis between patients classified as IHC 2+ and IHC 3+ in HER2-pos mBC.

Methods: Pts with HER2 pos mBC, determined by HER2 IHC staining of 3+ or 2+ with

amplification at the in situ hybridization assay, were selected from the GIM14 study database for analysis. Associations among variables were assessed by conducting logistic regression analyses. Additionally, prognostic factors for overall survival (OS) and time to treatment failure (TTF) were evaluated using both uni- and multi-variable Cox regression models.

Results: A total of 766 HER2-pos mBC pts were included in the analysis. Among them, 302 (39%) had IHC score of 2+ and 464 (61%) had a IHC score of 3+. Central nervous system (CNS) metastases (mts) were observed in 68 (9%) pts (32% IHC 2+; 68% IHC 3+), lymph node (LN) mts in 330 (43%) pts (46% IHC 2+; 54% IHC 3+), lung (LU) mts in 182 (24%) pts (46% IHC 2+; 54% IHC 3+), liver (LI) mts in 227 (30%) pts (45% IHC 2+, 55% IHC 3+), skin (SK) mts in 68 (9%) pts (28% IHC 2+; 72% IHC 3+) and pleural (PL) mts in 40 (5%) pts (47% IHC 2+, 53% IHC 3+).

In univariable (uni) analysis, IHC 3+ compared to IHC 2+ was significantly associated with SK mts (OR 1.76, P=0.043) and less likely to be associated with LI (OR 0.71, P=0.031), LU (OR 0.70, P=0.036), and LN (OR 0.63, P=0.002) mts. In multivariable (multi) analysis, LN mts maintained statistical significance (OR 0.62, P=0.004). In subgroup analysis, among IHC 3+ patients, factors associated with worse OS pts were neo Tx (HR 1.55, P=0.032), adjuvant radiotherapy (HR 1.34, P=0.042), neo ChT (HR 1.63, P=0.002), CNS mts (HR 1.98, P=0.002), and LI mts (HR 1.68, P< 0.0001). In multi analysis, CNS mts (HR 1.73, P=0.028) and LI mts (HR 1.47, P=0.017) remained prognostic for IHC 3+ subgroup. The only factor associated with worse OS in IHC 2+ pts was LI mts (HR 1.67, P=0.005).

Multi analysis in the overall HER2-pos population identified neo chemotherapy (ChT) (HR 1.49, P=0.009), CNS mts (HR 1.53, P=0.003) and PL mts (HR 1.50, P=0.036) as negative prognostic factors for OS, while PL mts (HR 1.74, P=0.048) were associated with a shorter time to treatment failure (TTF).

Conclusions: Our exploratory data revealed that HER2-pos mBC with a IHC score of 3+ is less likely to be associated with LN mts and with visceral mts. The site of mts has prognostic significance, as CNS mts are associated with worse OS in pts with an IHC score of 3+ pts, while LI mts are associated with worse OS in both IHC 2+ and 3+ subgroups. However, the IHC score itself (2+ or 3+) does not have independent prognostic value. The relationship between HER2 IHC staining and treatment outcomes requires further investigation to better understand its potential impact on clinical practice.

PO4-04-06

Exploring the use of tyrosine kinase inhibitors (TKIs) in the management of HER2-positive metastatic breast cancer post trastuzumab emtansine (T-DM1) therapy failure: Insights from a real-world study

Presenting Author(s) and Co-Author(s):

Y. Yin. The First Affiliated Hospital of Nanjing Medical University, United States

C. Sun. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

Y. Hua. The First Affiliated Hospital of Nanjing Medical University, United States

N. Jin. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

W. Li. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

X. huang. Jiangsu hospital the first affiliated hospital with Nanjing medical university, United States

Background

Trastuzumab emtansine (T-DM1) is the established standard second-line treatment for HER2-positive metastatic breast cancer (MBC) patients who have previously received trastuzumab. However, there is ongoing debate regarding the subsequent therapeutic options following T-DM1 failure. This study aimed to evaluate the efficacy and safety of tyrosine kinase inhibitors (TKIs)-based therapy in HER2-positive MBC patients with resistance to T-DM1.

Methods

During the period from September 2018 to October 2021, a multicenter real-world study was conducted, enrolling a total of 53 patients diagnosed with HER2-positive metastatic breast cancer (MBC). These patients underwent TKIs-based therapy following the failure of T-DM1 treatment. The primary focus of the study was on evaluating progression-free survival (PFS) as the main endpoint. Secondary endpoints encompassed objective response rate (ORR), overall survival (OS), clinical benefit rate (CBR), and safety assessments.

Results

A total of 53 patients received TKIs-based therapy as a second-line or later treatment. The median progression-free survival (PFS) for TKIs-based therapy was 11.9 months (95% CI 7.9-15.9). The objective response rate (ORR) and clinical benefit rate (CBR) were found to be 19.6% and 72.5%, respectively. Among patients with brain metastasis (n=12), a median PFS of 10.5 months (95% CI 7.5-13.5) and an intracranial ORR of 33.3% were observed. Patients treated with pyrotinib (n=21) showed improved PFS compared to those treated with lapatinib (n=30), as well as patients who had derived favorable benefit from T-DM1 (PFS \geq 6 months). Hormone receptor status (HR) and response to T-DM1 were identified as independent factors affecting the effectiveness of TKIs-based therapy. The most frequently reported adverse events included thrombocytopenia (23.6%), diarrhea (15.7%), leucopenia (15.7%), and hand-foot syndrome (15.7%).

Conclusion

TKIs-based therapy demonstrated favorable effectiveness and safety in HER2-positive metastatic breast cancer (MBC) patients who had previously received T-DM1 but experienced treatment failure. This includes patients with brain metastases. Notably, individuals who derived

favorable benefits from prior T-DM1 treatment displayed significantly prolonged progression-free survival (PFS) when undergoing subsequent TKIs-based therapy.

PO4-04-07

Efficacy, safety and translational study of pyrotinib combined with albumin-bound paclitaxel as firstline treatment of HER-2 positive metastatic breast cancer

Presenting Author(s) and Co-Author(s):

h. Li. Department of Breast Medical Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, China (People's Republic)

X. Man. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

S. Yin. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

D. Zhou. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

B. Zhang. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

S. Fang. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

f. zheng. Department of Breast Medical Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, United States

C. Li. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

X. Wang. Shandong Cancer Hospital and Institute, United States

W. Huang. Shandong Cancer Hospital & Institute, Radiation Oncology, China, United States

L. Wang. Shandong Cancer Hospital & Institute, Radiation Oncology, China, United States

Q. He. The 960th Hospital of the PLA Joint Logistics Support Force, Surgery, China, United States

H. Fu. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, China (People's Republic)

Y. Zhang. Qingdao Municipal Hospital (Group), Medical Oncology, China, United States

C. Liu. The 960th Hospital of the PLA Joint Logistics Support Force, Surgery, China, United States

L. Dong. Liaocheng Tumor Hospital, Surgery, China, United States

X. Zhao. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

L. Xu. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

X. Sun. Shandong Cancer Hospital & Institute, Jinan, Shandong, China, United States

B. Fan. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

L. Song. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, United States

z. zhou. Breast Cancer Center, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, United States

Q. Tan. Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, China (People's Republic)

J. Yu. Shandong Cancer Hospital & Institute, Radiation Oncology, China, United States

Objective: Breast Cancer is one of the most common malignant tumors in women. HER-2 is a driver gene for poor prognosis in breast cancer. Anti-HER-2 drugs have significantly improved the prognosis of patients with HER-2 positive metastatic breast cancer. There is still a lack of exploration of first-line anti-HER2 treatment options and translational studies only for patients with metastases after adjuvant and/or neoadjuvant trastuzumab therapy. This study is based on our previous clinical trial of pyrotinib in combination with albumin-bound paclitaxel in first line for patients with HER-2-positive metastatic breast cancer after adjuvant and/or neoadjuvant trastuzumab therapy, with the aim of exploring the efficacy and adverse events in the enrolled patients. And to explore the markers associated with Progression Free Survival (PFS) by using Olink technique to detect blood samples from patients. To provide a better screening of the benefit population and provide guidance for the treatment of HER-2 positive metastatic breast cancer.

Methods: From December 2019 to July 2023, our previous clinical trial prospectively enrolls 27 patients with HER-2-positive metastatic breast cancer after adjuvant and/or neoadjuvant trastuzumab therapy. Pyrotinib (400 mg, po, qd) combined with albumin-bound paclitaxel (200 mg, ivdrip, d1, d8, q21d) was used as the first-line treatment regimen. Patients were evaluated for efficacy. Survival analysis was performed by using the Kaplan-Meier method. Blood samples were collected during treatment. We selected 21 blood samples from patients, and dynamically detected plasma protein changes by Olink technique. Differential protein analysis between groups according to hormone receptor status, trastuzumab primary/secondary resistance, and the presence of visceral metastases. And the proteins associated with PFS were analyzed.

Results: Among the 27 patients whose efficacy had been evaluated, 7 patients were evaluated as CR, 18 patients as PR, and 2 patients as SD. The objective response rate was 92.6%, and the disease control rate was 100%. The median follow-up was 17.8 months and the median PFS has not yet been reached. Diarrhea is the most common adverse event. Grade 3 or higher adverse events include diarrhea, leukocytopenia, neutropenia, and hand-foot syndrome. The progression free survival was significantly worse in patients with visceral metastases ($P=0.01$). Results of Olink protein dynamic assay showed a significant downregulation of CEACAM5, TXLNA, PVRL4 and ERBB2. Differential proteins between groups showed that there were no significant differential proteins between the hormone receptor-positive and negative groups at the baseline node, but 7 proteins were upregulated in the hormone receptor-positive group compared with the negative group at the progression node, with EMS-1, WIF-1, and hK14 being the most significant. Compared to primary resistance, trastuzumab secondary resistance appeared 4 proteins upregulated at the baseline node, with hK14 and CYR61 being the most significantly; and 33 proteins were upregulated at the progression node, with CYR61, CXL17, FURIN, and ABL1 being the most significantly. Patients with high expression of TLR3 and low expression of RET at the baseline node had longer PFS.

Conclusions: This study demonstrates that pyrotinib in combination with albumin-bound paclitaxel as a first-line treatment regimen shows good efficacy and a manageable safety for patients with HER-2-positive metastatic breast cancer after adjuvant and/or neoadjuvant

trastuzumab therapy. PFS was shorter in patients with visceral metastases. TLR3 and RET were the proteins that significantly associated with PFS in patients.

PO4-04-08

Design and Development of the APIS ESR1 Mutations Kit to Detect Eleven Mutations Relevant to Acquired Endocrine Therapy Resistance

Presenting Author(s) and Co-Author(s):

A. Gasior. APIS Assay Technologies, Manchester, England, United Kingdom

C. Whitfield. APIS Assay Technologies, United States

A. Campbell. APIS Assay Technologies, United States

C. Hoy. APIS Assay Technologies, United States

S. Holdsworth. APIS Assay Technologies, United States

J. Mukose. APIS Assay Technologies, United States

R. Nana. APIS Assay Technologies, United States

S. Shammakhi. APIS Assay Technologies, United States

B. Scales. APIS Assay Technologies, United States

J. Gorniak. APIS Assay Technologies, United States

Introduction:

Estrogen receptor 1 (ER/ESR1) mutations have arisen as key biomarkers for endocrine therapy resistance in ER positive (ER+) breast cancer (BC) patients: detecting these mutations is key to guiding researchers to better understand acquired resistance during treatment. Ongoing clinical trials, which explore the prevalence of ESR1 mutations under various treatments, commonly use next-generation sequencing (NGS)-based assays. However, the NGS panels available are costly, can have long turnaround times and require specialist equipment and software. Research use only digital PCR assays are also available but have similar drawbacks to NGS. A targeted qPCR-based assay is more time and cost effective, and does not require specialist equipment.

Here, we demonstrate the APIS ESR1 Mutations Kit, a targeted, sensitive, and robust qualitative qPCR assay able to detect eleven ESR1 mutations across ESR1 exons 5 (E380Q), 7 (S463P) and 8 (P535H, L536R, L536Q, L536H, L536P, Y537C, Y537S, Y537N and D538G). The assay is designed to assess circulating-free DNA (cfDNA) samples, reducing the need for invasive procedures in clinical settings and can make use of standard cfDNA extraction kits. Therefore, the APIS ESR1 Mutations Kit provides the flexibility for researchers in any conventional molecular biology laboratory to explore ESR1 mutations with high sensitivity and specificity.

Methods:

The APIS ESR1 Mutations Kit provides all components and controls required to assess samples. For kit development, mutation-specific DNA fragments were spiked into wildtype background DNA (either cfDNA extracted from pooled healthy donor plasma, human genomic DNA, or DNA fragments); the Limit of Blank (LoB) and Limit of Detection (LoD) were determined using these samples. To determine linearity, a dilution series of DNA fragments ranging from 5 to 10,000 copies per reaction was assessed. All PCR runs were performed using a QuantStudio™5 Dx (ThermoFisher) instrument.

Results:

The performance studies showed the APIS ESR1 Mutations Kit can detect D538G at 0.4 %

mutant allele frequency (MAF) and Y537S at 0.06 % MAF. All other mutations can be detected at ≤ 1.0 % MAF. By using clamp and blocking technologies, each design is mutation specific, enabling identification of specific amino acid mutations. In addition, the assays can perform in high wild-type backgrounds, enabling lower limit of blanks with $\geq 95\%$ confidence and threshold cut-offs to enhance the sensitivity of the assay. The linearity of each target is within 90-110% from 50 to 10,000 copies per reaction.

Conclusions:

The ESR1 Mutations Kit demonstrated high sensitivity and performance as a qualitative qPCR assay to detect eleven ESR1 mutations.

Mutations detected with the APIS ESR1 Mutations Kit

Exon	Mutations to be detected	Nucleic acid change	COSMIC ID	LoD (MAF)
5	E380Q	c.1138G>C	COSM3829320	1%
7	S463P	c.1387T>C	COSM4771561	0.08%
8	P535H	c.1604C>A	COSM4944018	0.4%
	L536R	c.1607T>G	COSM4774826	0.4%
	L536Q	c.1607_1608delinsA G (TC>AG)	COSM4766050	0.8%
	L536H	c.1607T>A	COSM6843697	0.8%
	L536P	c.1607T>C	COSM6906109	0.9%
	Y537S	c.1610A>C	COSM1074639	0.06%
	Y537N	c.1609T>A	COSM1074635	0.2%
	Y537C	c.1610A>G	COSM1074637	0.4%
	D538G	c.1613A>G	COSM94250	0.4%

PO4-04-09

Incidence, prevalence, risk factors, and impact of fatty liver disease in metastatic HR+/HER2- breast cancer patients treated with Endocrine Therapy and CDK 4/6 Inhibitor

Presenting Author(s) and Co-Author(s):

D. Malon Gimenez. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., United States

C. Molto Valiente. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., United States

S. Prasla. Joint Department of Medical Imaging(JDMI), University Health Network, Toronto, ON, Canada., United States

D. Cuthbert. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., United States

A. Mittal. Health Sciences North, Northern Ontario School of Medicine, Sudbury, ON, Canada, United States

F. Tamimi. Princess Margaret Cancer Centre, Division of Medical Oncology, University of Toronto, Department of Medicine, Toronto, ON, Canada, United States

M. Di Iorio. Princess Margaret Cancer Centre, University of Toronto, United States

M. Li. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., United States

N. Pathak. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., Toronto, Ontario, Canada

E. Amir. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

K. Jhaveri. Joint Department of Medical Imaging(JDMI), University Health Network, Toronto, ON, Canada, United States

M. Nadler. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

Background: In patients with early-stage breast cancer (BC), non-alcoholic fatty liver disease (NAFLD) is associated with increased recurrence, cardiovascular events, and non-cancer death. Endocrine therapy increases the risk of NAFLD. The impact of cyclin-dependent kinases 4/6 inhibitors (CDKi) combined with endocrine therapy on NAFLD and prognostic association in metastatic breast cancer is unknown. Here, we characterize the incidence, prevalence, risk factors, and treatment outcomes of NAFLD in women with metastatic HR+/HER2- BC.

Methods: We conducted a retrospective cohort study of patients with advanced HR+/HER2- BC receiving first line endocrine and CDKi at Princess Margaret Cancer Centre, Toronto, Canada between January 2018 – June 2022. Patients were excluded if they had liver disease, prior chemotherapy, or no access to CT scans. Demographic, treatment, toxicity, and survival data were extracted. Liver Attenuation Index (LAI) on contrast-enhanced portal venous phase CT scan was utilized. NAFLD was defined as LAI >25 HU. Univariable binary-logistic regression analysis was used to assess independent predictive factors of NAFLD. Statistical significance was defined as $p < 0.05$. Quantitative significance was defined by the Burnand criteria. Time to treatment failure (TTF) was assessed using Cox proportional hazards modeling.

Results: Of approximately 90 eligible patients, 40 are included in this analysis. Baseline demographics included median age 61 years, 72% post-menopausal, 58% de-novo metastatic disease, and 27% visceral disease. Of 40 patients, 28 (70%) had NAFLD at anytime (12 at baseline and 16 incident). Associations with NAFLD are shown in Table 1. Presence of NAFLD was associated quantitatively but not statistically with age > 65 (OR 2.6), post-menopausal status (OR 2.6), and inversely associated with prior chemotherapy (OR 0.27) and visceral disease (OR 0.38). Lack of NAFLD at any time was significantly associated with worse TTF (mean TTF 497 versus 1228 days, HR=4.28, 95% CI: 1.89-9.68, p< 0.001). Patients without NAFLD at baseline also had a worse TTF (mean 903 vs 1186 days) compared to those with it at baseline, but this difference was not statistically significance (HR=1.93, 95%CI: 0.77-4.83, p= 0.163). No significant differences were found in grade 3/4 adverse events. Patients who have presented NAFLD at any time received an average of 1.36 subsequent lines of therapy compared to 2.08 in those without.

Discussion & Conclusion: This analysis demonstrated an association between presence of NAFLD and longer TTF. This may reflect reverse causation whereby longer exposure to ET and CDKi increases the observation of NAFLD or that these are distinct populations with different molecular pathways leading to differences in response to treatment and prognosis. It is noteworthy that the median time to develop NAFLD in the incident group was 339 days, and the group that never developed NAFLD was on treatment longer than this. Overexpression of CDK 4/6 pathway, could increase sensitivity and duration to treatment with CDKi but produce adverse metabolic changes of increased lipid synthesis, as described in pre-clinical models. If this hypothesis is confirmed, synergistically addressing these metabolic changes with physical exercise, dietary, or pharmacological interventions may improve these patients' fitness for subsequent lines of therapy.

Table 1

Table 1.

	NO NAFLD at any time	NAFLD at anytime	NO NAFLD baseline	NAFLD baseline
N	12	28	28	12
AGE	57.4 (33,92)	61 (39,87)	57.4 (33.92)	62.8 (47,75)
BMI BASELINE	29.75	27.41	27.91	28.57
MENOPAUSE	7 (58.33%)	22 (78.57%)	18 (64.28%)	11 (91.67)
DIABETES M.	3 (25%)	5 (17.86%)	4 (14.28%)	4 (33.33%)
DYSLIPIDEMIA	2 (16.67%)	6 (21.42%)	4 (14.28%)	4 (33.33%)
PRIOR BREAST CANCER	7 (58.33%)	10 (35.71%)	13 (46.42%)	4 (33.33%)
PRIOR CHEMOTHERAPY	6 (50%)	6 (21.42%)	9 (32.14%)	3 (25%)
PRIOR ENDOCRINE THERAPY	6 (50%)	9(32.14%)	11 (39.28%)	4 (33.33%)
VISCERAL DISEASE (LIVER, CNS)	5 (41.67%)	6 (21.42%)	8 (28.57%)	3 (25%)
Grade 3/4 adverse events	9 (75%)	23 (82.14%)	23 (82.14%)	9 (75%)
SUBSEQUENT LINES	2.08	1.36	1.85	1.17
TTF (mean days)	496.6	1228.35	903.11	1185.90

PO4-04-10

Selection criteria for second-line treatments after Cyclin-dependent kinase 4/6 inhibitors failure in Hormone Receptor positive metastatic breast cancer patients: the preliminary experience of the HERMIONE-13 trial

Presenting Author(s) and Co-Author(s):

M. Cazzaniga. Phase 1 Research Centre, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy / Department of Medicine and Surgery, University of Milano-Bicocca, Italy, United States

E. Rossi. Bicocca Bioinformatics, Biostatistic and Bioimaging Centre (B4), University of Milano Bicocca, Monza , Italy, United States

A. Turla. Oncology Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza,Italy / University of Brescia, United States

M. Ambroggi. Oncology, AUSL di Piacenza- Ospedale Guglielmo da Saliceto, Piacenza, Italy, United States

A. Baggi. Oncology Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy / University of Brescia, United States

R. Berardi. Ospedali Riuniti di Ancona, Italy

F. Borella. Gynecology and Obstetrics 1U, Departments of Surgical Sciences, City of Health and Science, University of Turin,Turin, Italy., United States

S. Capici. Phase 1 Research Centre, Fondazione IRCCS San Gerardo dei Tintori, Monza Italy, United States

F. Cicchiello. Oncology Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy, United States

L. Coltelli. UOC Oncologia Medica Livorno, AUSL Toscana Nord Ovest, Italy, United States

U. De Giorgi. Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori Dino Amadori, Meldola, Italy, United States

A. Ferro. Oncologia medica S. Chiara, Trento, United States

O. Garrone. Medical Oncology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, United States

M. Giordano. Oncology Department, ASST-Lariana, Como, Italy, United States

E. Landucci. Department of Medical Oncology, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy, United States

M. Mazzotta. Medical Oncology Unit, Sandro Pertini Hospital & Sant'Eugenio Hospital, Rome, Italy, United States

G. Moretti. IRCCS AUSL Reggio Emilia, United States

R. Palumbo. Medical Oncology, IRCCS-ICS Maugeri, Pavia, Italy, United States

F. Pepe. Phase 1 Research Centre, Fondazione IRCCS San Gerardo dei Tintori, Monza , Italy, United States

P. Vici. Phase IV Clinical Study Unit , IRCCS Regina Elena National Cancer Institute, Rome, Italy, United States

F. Zustovich. UOC Oncologia, Belluno, AULSS 1 Dolomiti , Italy, United States

V. Cogliati. Phase 1 Research Centre, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy / Fondazione Umberto Veronesi, United States

BACKGROUND:

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) represent the standard of care for hormone receptor-positive (HR⁺)/ Human Epidermal Growth Factor 2 negative (HER2-) metastatic breast cancer (MBC); no consensus actually exists for second-line (2L) treatments. The HERMIONE-13 trial evaluates the adopted therapeutic options after CDK4/6i failure and the potential factors that influence these choices.

METHODS:

HERMIONE-13 is a retrospective and prospective multicentric observational trial involving 15 Italian Centers. Information about therapies after disease progression to CDK4/6i from January 2016 until December 2020 was collected for the present analysis, aiming at evaluating which are the clinical criteria guiding the choice of 2L therapy after CDK4/6i failure.

RESULTS:

114 pts have been enrolled: 14 pts (12.3%) received neoadjuvant treatment, 80 (70.2%) adjuvant therapy, of whom 46 (57.5%) chemotherapy (CT)+ endocrine therapy (ET) and 33 (41.3%) ET alone. Among the 79 pts treated with adjuvant ET, 44 pts (55.7%) showed primary or secondary endocrine resistance. 39 pts (34.2%) received first-line (1L) CDK 4/6i in combination with Fulvestrant (F), the remaining with aromatase inhibitors (AIs). Median duration of 1L CDK4-6i was 10.4 months (interquartile range (IQR) 4.7-17.4). Median age at 2L start was 59.5 years (IQR 51-68). As 2L therapy, 79 pts (69.3%) received CT±targeted therapy (TT) and 35 (30.7%) ET±TT. Visceral metastases at the beginning of 2L were documented in 46 pts (40.4%). Comorbidities were present in 48 (42.9%) of the pts, mainly cardiac diseases (25, 22.3%); 71 pts (63.4%) showed a 1L-related adverse events (AEs) (NA: 2 pts), mainly hematological toxicity (60, 53.6%).

Among 79 pts treated with adjuvant ET, 60 (76%) were addressed to 2L CT±TT, while 19 (24%) to an ET-based therapy. A longer duration of 1L was observed in pts treated with 2L ET±TT (12.5 months, 7.2-22.2) in comparison with those treated with CT±TT (8.7 months, 4.2-14.9). The majority of pts treated with 1L F+CDK 4/6i underwent 2L CT-based treatment, as summarized in Table 1. Analyzing the population treated with 2L CT±TT, we observed that median age was 58 years (49-67), slightly lower than that of pts treated with ET±TT (63, 54-69). Among pts with visceral metastases, 30 pts (65.2%) were addressed to 2L CT±TT and 16 pts (34.8%) to ET±TT; CT±TT was also the favorite choice for the majority of pts with concomitant disease (33, 68.8%) and with previous CDK4/6i-related toxicity (47, 66.2%).

Among age, visceral metastases, comorbidities, adjuvant treatment, duration of 1L therapy, use of 1L F and 1L related AEs, univariate analysis revealed that previous use of adjuvant ET (p=0.021), 1L F (p< 0.001), duration of 1L treatment (p=0.043) and age at 2L start (p=0.053) are all factors influencing the choice of 2L therapy. At the multivariate logistic regression model, only the use of F in association with CDK4/6i as 1L treatment and age at 2L therapy were associated with the choice between ET±TT vs CT± TT, with a backward selection, as summarized in table 2.

CONCLUSION:

The preliminary results of our study suggest that previous F in combination with CDK4/6i is a statistically confirmed predictor of choice for subsequent CT, whereas the increase in age is significantly associated with the choice for ET. Further research is needed to investigate the optimal sequencing of treatments following CDK4/6i and to determine predictive factors of response to 2L therapies.

Table 1

FULVESTRANT	2L TREATMENT		
	ET+/- TT	CT+/- TT	Total
YES	3 (7.7)	36 (92.3)	39 (34.2)
NO	32 (42.7)	43 (57.3)	75 (65.8)
TOTAL	35 (30.7)	79 (69.3)	114

2L choices in 1L F+CDK 4/6i pts.

Table 2

Independent factors	Multivariate logistic regression model		
	P-value	OR	95% CI
Administration of 1L Fulvestrant: YES vs NO	<0.001	0.10	0.03-0.37
Age at the end of 1L treatment (years)	0.036	1.05	1.00-1.09

Statistical model with the significant variables.

PO4-04-11

Exposure–response analyses of GO39932: a Phase Ia/b study of giredestrant in estrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer

Presenting Author(s) and Co-Author(s):

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Y. Lien. Genentech, Inc., South San Francisco, CA, USA, United States

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

E. Lim. Garvan Institute of Medical Research, St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia

M. Cannon. Genentech, Inc., South San Francisco, CA, USA, United States

R. Anziano. Pharmetheus, Uppsala, Sweden, United States

J. Langenhorst. Pharmetheus, Uppsala, Sweden, United States

K. Yoshida. Genentech, Inc., South San Francisco, CA, USA, United States

V. Malhi. Genentech, Inc., South San Francisco, CA, USA, United States

M. Gates. Genentech, Inc., South San Francisco, California, United States

J. Eng-Wong. Genentech, Inc., South San Francisco, CA, USA, United States

C. Li. Genentech, Inc., South San Francisco, CA, USA, United States

M. Shah. Genentech, Inc., South San Francisco, CA, USA, United States

P. Perez-Moreno. Genentech, Inc., South San Francisco, California, United States

J. Yu. Genentech, Inc., South San Francisco, CA, USA, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

BACKGROUND

Giredestrant (GIR) is a highly potent, nonsteroidal, oral, selective estrogen receptor antagonist and degrader (SERD). The Phase Ia/b GO39932 study (NCT03332797) investigated GIR ± palbociclib (palbo) and ± a luteinizing hormone-releasing hormone agonist for patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer who had disease progression on prior endocrine therapies. In the single-agent dose-escalation stage, patients received 10, 30, 90, or 250 mg of once-daily (QD) GIR. In the dose-expansion stage, patients received 30, 100, or 250 mg of QD GIR. Safety and tolerability of 100 mg GIR + 125 mg palbo was also explored in the dose-escalation and -expansion stages. Results showed that GIR was well tolerated and potentially clinically active as a single agent and in combination with palbo, including in patients with ESR1-mutated tumors. To inform the selection of the clinical dose for GIR late-stage development based on risk–benefit considerations, exposure–response (E–R) analyses for efficacy and safety endpoints were conducted using single-agent GIR data.

METHODS

Exposure metrics included maximum concentration at steady state and area under the concentration–time curve at steady state. The association between the exposure metrics and efficacy endpoints (objective response rate [ORR] and clinical benefit rate [CBR]) or safety endpoints (all adverse events [AEs], Grade ≥ 3 AEs, selected AEs of interest [sAEIs], including all-grade hepatotoxicity, and bradycardia) were evaluated.

RESULTS

Data cutoff was September 17, 2021. A total of 111 patients were enrolled in the single-agent GIR cohort. Of these 111 patients, 107 were pharmacokinetic-evaluable and included in the analysis.

ORR in patients with measurable disease at baseline was 20% (16/81 patients) and CBR was 49% (54/111). No significant associations were observed between exposure and ORR or CBR, including in patients with ESR1-mutated tumors and those with no mutation detected ($p > 0.05$). There were 92/107 patients (86%) with AEs of any grade, overall. Seventy-two (67%) had sAEs, 19 (18%) experienced hepatotoxicity (all events were reported as liver function test abnormalities), 11 (10%) had bradycardia, and 20 (19%) had Grade ≥ 3 AEs. Increasing exposure did not significantly increase the incidence of all AEs, Grade ≥ 3 AEs, sAEs, or bradycardia at the dose range of 10 to 250 mg ($p > 0.05$). For hepatotoxicity, the analysis suggested that higher exposure may lead to a higher probability of events ($p = 0.0065$); however, at the clinically relevant exposure range for the 30 mg dose, the incidence of hepatotoxicity was low and the predicted exposures were at the shallower slope of the relationship.

CONCLUSIONS

Single-agent GIR did not exhibit a significant association between exposure and efficacy endpoints at a dose range of 10 to 250 mg, regardless of ESR1 mutation status, indicating that the efficacy of GIR might have reached a plateau at low dose levels.

At the clinically relevant exposure range of the 30 mg dose, GIR exposure was not associated with an appreciable increase in the incidence of AEs.

The Phase Ia/b study design and subsequent E–R results enabled dose selection to be based on risk–benefit considerations, rather than the traditional maximum tolerated dose paradigm, in line with the United States Food and Drug Administration’s oncology dose optimization recommendations.

The E–R results also indicate that GIR may have a relevant wide therapeutic window. Overall, these data support the 30 mg clinical dose of GIR that was selected, with a favorable risk–benefit profile, for further clinical studies.

PO4-04-12

A Phase 1b/2 study of palazestrant (OP-1250) in combination with ribociclib or alpelisib in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative, advanced and/or metastatic breast cancer

Presenting Author(s) and Co-Author(s):

V. Borges. University of Colorado Anschutz Medical Center, United States

C. Alemany. AdventHealth, Orlando, Florida, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

S. Nunnery. Vanderbilt University Medical Center, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

M. Tonda. Olema, San Francisco, California, United States

M. Shaw. Olema Oncology, San Francisco CA, USA, United States

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

Background: Endocrine therapy (ET) when administered with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors has improved outcomes in patients (pts) with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (BC) or metastatic breast cancer (MBC) and is the current standard of care for first-line treatment. Addition of the PIK3 inhibitor alpelisib to ET significantly improved progression-free survival in pts with PIK3CA-mutated, ER-positive, HER2-negative MBC, and alpelisib + fulvestrant is the standard of care for second or later-line treatment. Most pts will acquire resistance to ET, with mutations in ESR1 constituting the most common mechanism of resistance.

Palazestrant (OP-1250) is a small molecule oral complete ER antagonist (CERAN) and selective ER degrader (SERD) that binds the ligand binding domain of ER and completely blocks ER-driven transcriptional activity in both wild-type (ESR1-wt) and mutant (ESR1-mut) forms of ER. In preclinical studies, palazestrant in combination with ribociclib demonstrated activity in both ESR1-wt and ESR1-mut xenograft models and showed efficacy in brain metastasis xenograft models. In a Phase 1/2 monotherapy study in pts with ER-positive, HER2-negative MBC, palazestrant was well tolerated with demonstrated antitumor efficacy and favorable pharmacokinetics (PK) supporting once a day (qd) dosing at the recommended Phase 2 dose (RP2D) of 120 mg. The aim of this study is to evaluate the safety, PK, and antitumor activity of palazestrant + ribociclib or alpelisib in pts with ER-positive, HER2-negative advanced BC or MBC.

Methods: Eligible pts have evaluable ER-positive, HER2-negative advanced BC or MBC; ≤ 2 prior ETs (prior CDK4/6 inhibitors allowed); and ≤ 1 prior line of chemotherapy. In the alpelisib arm, pts must have a PIK3CA mutation in the tumor or ctDNA. Patients are administered oral palazestrant at escalating doses of 30, 60, and 120 mg qd in combination with the approved dose of oral ribociclib (600 mg qd; days 1–21 of 28-day cycle) or approved dose of oral alpelisib (300 mg qd) in a 3+3 design to identify the RP2D. The dose-expansion part will assess additional safety and PK parameters and the antitumor activity of palazestrant in combination with ribociclib or alpelisib (NCT05508906).

Results: As of June 15, 2023, 10 pts have received 30 mg and 60 mg doses of palazestrant in combination with ribociclib (n=6) or alpelisib (n=4). No dose-limiting toxicities have been observed. After administration in the first two combination dose levels of 30 and 60 mg, palazestrant exposure was consistent with monotherapy administration; exposure data show no drug–drug interactions (DDI) when compared to published exposure parameters. Most reported treatment-emergent adverse events (TEAEs) were grade 1 or 2 and consistent with the known safety profiles of all 3 drugs. In the ribociclib arm, the TEAEs occurring in ≥ 2 pts included grade 1 nausea (n=4), grade 1 constipation (n=2), and neutropenia (grade 2, n=1; grade 3, n=3). For the 3 pts in the 30 mg palazestrant + alpelisib cohort, the only TEAE occurring in ≥ 2 pts was grade 1 diarrhea. One pt had grade 1 hyperglycemia.

Conclusions: In this ongoing study, palazestrant in combination with ribociclib or alpelisib was well tolerated, and enrollment to the palazestrant 120 mg dose with ribociclib or alpelisib is ongoing. No new safety signals were observed for the 3 drugs, and no clinically significant DDIs were observed between palazestrant and ribociclib or alpelisib at the doses evaluated. Exposure of each drug was consistent with observed monotherapy exposure levels. Updated data will be presented.

PO4-04-13

Impact of dose reduction of CDK4/6 inhibitors on progression-free survival in Mexican patients with hormone receptor-positive, HER2-negative metastatic breast cancer: a retrospective single-center study

Presenting Author(s) and Co-Author(s):

A. Meraz-Brenez. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, United States

A. Aranda-Gutierrez. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, United States

H. Gonzalez-Sanchez. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, United States

B. Martinez-Cannon. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

L. Verduzco-Rodriguez. Hospital Regional de Rio Blanco, United States

H. Verduzco-Aguirre. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

Background

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) have been demonstrated to prolong survival in women with hormone receptor-positive, HER-2 negative, metastatic breast cancer. However, these treatments often require dose adjustments due to adverse effects, resulting in a reduction in 30-50% of cases. There is evidence suggesting a relationship between dose intensity and progression-free survival (PFS), but data in the Hispanic population are limited. Therefore, the objective of the study was to explore the association between dose reduction of CDK4/6i inhibitors and PFS in patients with metastatic breast cancer.

Methods

We conducted a retrospective single-center study involving patients diagnosed with hormone receptor-positive, HER-2 negative metastatic breast cancer (MBC) between 2020 and 2023. Eligible patients were those who received at least one cycle of palbociclib, abemaciclib, or ribociclib and had a follow-up period of more than three months since the initiation of CDK4/6 inhibitor (CDK4/6i) treatment. Patient data were collected from electronic medical records. We analyzed demographic and clinicopathological characteristics and estimated the PFS in patients who had any dose reduction within the first 12 weeks compared to those who did not, using Kaplan-Meier plots and compared the differences in survival using the log-rank test. A Cox regression analysis was performed to estimate survival hazard ratios (HR).

Results

Among 41 patients, the mean age at CDK4/6i initiation was 61.0 years (SD 12.9), 22 (53.7%) were postmenopausal at diagnosis, 25 (61%) had recurrent disease, and 22 (53.7%) were receiving CDK4/6i in the first-line setting. Bone metastases were present in 30 (73.2%), and visceral metastases in 22 (53.7%). Regarding type of CDK4/6i, 33 (80.5%) received palbociclib, 7 (17.1%) ribociclib, and 1 (2.4%) abemaciclib. At 12 weeks, 12 patients (29.3%) had a dose reduction (Table 1).

With a median follow-up since CDK4/6i initiation of 407 days (95% confidence interval (CI) 272-542), 19 events were recorded, with a median PFS of 12.6 months (95% CI 8.0-17.3) for the

overall population. Median PFS was 9.7 months (95% CI 0.6-18.8) in patients who had a dose reduction at 12 weeks and 35.2 months (95% CI 0-72.2) in those who did not (p=0.014). The univariate Cox proportional hazard model showed that dose reduction was associated with a worse PFS (hazard ratio 3.1; 95% CI: 1.20–7.80, p = 0.0019)

Conclusion

In this cohort of Mexican patients with hormone receptor-positive, HER2-negative metastatic breast cancer we found that dose reduction of CDK4/6 inhibitors within the first 12 weeks of treatment was associated with worse PFS. Given the retrospective nature of this analysis, we believe that these findings should be replicated in prospective studies.

Patient characteristics

Characteristic (N=41)	Frequency (%)
Age in years (mean, SD)	61 (12.9)
Hormonal status	
Pre/Perimenopausal	19 (46.3)
Postmenopausal	22 (53.7)
Metastatic disease presentation:	
Recurrent	25 (61%)
De novo	16 (39%)
Line of therapy	
First line	22 (53.7%)
Second or later	19 (46.3%)
Bone Metastases	
No	11 (26.85)
Yes	30 (73.2%)
Visceral Metastases	
No	19 (46.3%)
Yes	22 (53.7%)
CDK4/6 inhibitor received	
Palbociclib	33 (80.5%)
Ribociclib	7 (17.1%)
Abemaciclib	1 (2.4%)
CDK4/6 inhibitor dose reduction	
No	29 (70.7%)
Yes	12 (29.3%)

PO4-04-14

Change of first-line treatment pattern in metastatic luminal breast cancer: Results from the Austrian AGMT_MBC-Registry

Presenting Author(s) and Co-Author(s):

G. Rinnerthaler. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological an Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

S. Gampenrieder. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological an Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

A. Pichler. Internal Medicine - Department for Haemato-Oncology, LKH Hochsteiermark, Leoben, Austria, United States

W. Herz. Department of Surgery, Breast Health Center, LKH Hochsteiermark, Leoben, Austria, United States

A. Petzer. Internal Medicine I for Hematology with Stem Cell Transplantation, Hemostaseology and Medical Oncology, Ordensklinikum Linz Barmherzige Schwestern – Elisabethinen, Linz, Austria, United States

R. Pusch. Internal Medicine I for Hematology with Stem Cell Transplantation, Hemostaseology and Medical Oncology, Ordensklinikum Linz Barmherzige Schwestern – Elisabethinen, Linz, Austria, United States

M. Balic. Divison of Oncology, Department of Internal Medicine, Medical University Graz, Austria

C. Suppan. Division of Oncology, Department for Internal Medicine, Medical University Graz, Graz, Austria, United States

S. Heibl. Department of Internal Medicine IV, Klinikum Wels-Grieskirchen GmbH, Wels, Austria, United States

L. Scagnetti. Department of Internal Medicine IV, Klinikum Wels-Grieskirchen GmbH, Wels, Austria, United States

M. Sandholzer. Department of Internal Medicine II, Academic Teaching Hospital Feldkirch, Feldkirch, Austria, United States

C. Schmitt. Department for haematology and internal oncology, Med Campus III, Kepler University Hospital Linz, United States

A. Zabernigg. Department of Internal Medicine, County Hospital Kufstein, Kufstein, Austria, United States

D. Egle. Department of Gynaecology, Medical University Innsbruck, Innsbruck, Austria, United States

P. Pichler. University Hospital St.Pölten, Department for Internal Medicine 1, St. Pölten, Austria, United States

C. Hager. Department of Gynecology and Obstetrics, City Hospital, Dornbirn, Austria, United States

F. Roitner. Department of Internal Medicine II, Hospital Braunau, Braunau, Austria, United States

J. Andel. Department of Internal Medicine II, Pyhrn-Eisenwurzen Klinikum Steyr, Steyr, Austria, United States

K. Strasser-Weippl. Department of Medicine I, Clinic Ottakring, Vienna, Austria, United States

R. Bartsch. Medical University of Vienna, Department of Medicine I, Division of Oncology, Vienna, Austria, Austria

M. Hubalek. Department of Gynecology, Breast Health Center Schwaz, Schwaz, Austria, United States

M. Knauer. Tumor and Breast Center Eastern Switzerland, St. Gallen, Switzerland, United States

C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria

R. Greil. Department of internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute – Laboratory for Immunological and Molecular Cancer Research (SCI-LIMCR), Paracelsus Medical University, Salzburg Austria, Cancer Cluster Salzburg, Austria, United States

Background: For patients with HR+/HER2- (luminal) metastatic breast cancer (MBC), international guidelines recommend endocrine-based first-line therapy [ET] in combination with a CDK4/6 inhibitor for most patients. Only for patients with imminent organ failure, first-line chemotherapy should be considered. To clarify changing patterns of first-line treatments over time in an Austrian population of luminal MBC patients, we analyzed the data from the MBC registry of the Austrian Study Group for Medical Tumor Therapy (AGMT-MBC-Registry).

Methods: The AGMT-MBC-Registry is an ongoing multicenter registry for MBC patients in Austria. Only patients with luminal MBC and sufficient outcome data were included in this analysis. Patients were assigned to one of the following groups according to the year of start of first-line treatment for MBC: 2001-2010, 2011-2013 (no CDK4/6i available for first-line in both periods), 2014-2016 (CDK4/6i available in early access programs and clinical trials for first-line only), 2017-2019, and 2020-2022 (CDK4/6i available in both periods). Time to first chemotherapy (TTC) defined as start of first-line treatment until first application of a cytotoxic agent, and overall survival (OS) defined as start of first-line treatment until death were calculated by the Kaplan-Meier method and compared using the log-rank test. OS analysis was adjusted for disease free survival (DFS) category (de novo, DFS < 24 month, DFS ≥ 24 month), menopausal status (pre-, postmenopausal, unknown), age at diagnosis of metastatic disease (continuous), number of metastatic sites at diagnosis (1, 2-3, > 3), visceral disease (no, yes), and Charlson comorbidity index at diagnosis (continuous).

Results: As of May 16th 2023, 1,330 patients with HR+/HER2- disease receiving at least one treatment-line for MBC were evaluable. First-line treatments significantly changed over time ($P < 0.001$). In patients diagnosed between 2001 and 2010, 61.4% were treated with first-line chemotherapy compared to 10.0% in patients diagnosed between 2020 and 2022 (Table 1). Additionally, TTC also significantly increased over time ($P < 0.001$; Table 2). In contrast, the proportion of patients treated with a first-line CDK4/6i plus endocrine therapy combination increased over time from 4.4% in 2014-2016 up to 75.5% in the period of 2020-2022. Additionally, adjusted median overall survival estimates significantly increased over time ($P < 0.001$; Table 2).

Table 1: First-line treatment pattern over time

Period	N	ET	ET plus CDK4/6i	Chemotherapy	Others*
2001-2010	220	84 (38.2%)	0 (0.0%)	135 (61.4%)	1 (0.5%)
2011-2013	238	116 (48.7%)	0 (0.0%)	110 (46.2%)	12 (5.0%)
2014-2016	318	174 (54.7%)	14 (4.4%)	99 (31.1%)	31 (9.7%)
2017-2019	293	60 (20.5%)	190 (64.8%)	36 (12.3%)	7 (2.4%)
2020-2022	249	22 (8.8%)	188 (75.5%)	25 (10.0%)	14 (5.6%)
Overall	1,318	456 (34.6%)	392 (29.7%)	405 (30.7%)	65 (4.9%)

Legend: N - number of patients, ET - endocrine therapy (tamoxifen, aromatase inhibitor and/or fulvestrant), CDK4/6i - CDK4/6 inhibitor; * e.g. endocrine treatment plus everolimus or investigational study treatment

Table 2: Time to first chemotherapy (TCC) and overall survival (OS) over time

Period	Median TTC [months]	Adjusted median OS [months]
2001-2010	0.0 (0.0 - 0.0)	49.4 (41.2 - 56.6)
2011-2013	4.3 (0.0 - 13.8)	48.2 (38.3 - 69.7)
2014-2016	20.0 (14.0 - 26.4)	60.3 (50.2 - 77.5)
2017-2019	40.1 (33.3 - 59.8)	60.8 (52.8 - NR)
2020-now	30.4 (27.6 - NR)	NR (NR - NR)

Legend: N - number of patients, NR - not reached

Conclusion: In our registry, the proportion of patients with luminal MBC treated with first-line chemotherapy significantly decreased over time, whereas the proportion of patients treated with first-line CDK4-6 inhibitors significantly increased. This is in line with the change of guideline recommendation as well as the availability of CDK4-6 inhibitors over the last 2 decades. The availability of new treatment options has significantly increased median overall survival over time.

PO4-05-01

Clinical outcomes of breast cancer and its relationship with access to health care in Brazil: prospective study in HER2 negative/hormone receptor positive metastatic disease - BREAST (BRazilian outcomE for metAStatic breast cancer)

Presenting Author(s) and Co-Author(s):

V. Sanvido. Universidade Federal de São Paulo/ Hospital do Coração (Hcor), United States

L. Pontes. Hcor Research Institute, United States

R. Machado. Hcor Research Institute, United States

M. Nicola. Hcor Research Institute, United States

J. Gomes. Hcor Research Institute, United States

L. Barbante. Hcor Research Institute, United States

N. Valeis. Hcor Research Institute, United States

A. Cavalcanti. Hcor Research Institute, United States

A. Nazário. Universidade Federal de São Paulo, United States

Background: Cancer survival is one of the key measures of the effectiveness of cancer services and captures whether people have access to effective treatment. The survival rate of breast cancer in low and middle-income countries is notably different from high-income countries; this disparity in survival reflects limited access to first-line systemic therapy for advanced and metastatic tumors. Recent studies have shown benefit of combining cyclin-dependent kinase 4 and 6 inhibitors (CDK 4/6) with endocrine therapies in hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer. However, in Brazil, the population has limited access to these drugs, mainly in the public health service. The commercialization of CDK 4/6 inhibitors was only released in the national territory in 2018, but until nowadays it is not accessible for most patients.

Objective: The aim of this project is to assess whether patients without private health insurance may experience worse outcomes compared to women with private insurance, primarily due to limited access to a specific class of medication during their treatments. The study seeks to gain insights into the clinical outcomes of patients with HR+ HER2- metastatic breast cancer based on their access to health insurance coverage within a real-world setting.

Methods: Multicenter, prospective observational study, with patients divided into two groups: one with patients from the public health system and the second with patients treated at the private service. Whereas that the hazard ratio for the primary outcome in the private system compared to the public health system is like that observed in the PALOMA study (0.58), and that event rates after 18 months of follow-up are also similar (approximately 45% and 35%), then a total of 298 patients will provide the study power of 80%, significance level of 5%. This calculation considers a sample size ratio of 1 patient in the private health system for every 2 patients in the public health system. The inclusion criteria specify women with HR+ HER2- metastatic breast cancer who initiated first-line treatment from 2019. Patients will be followed for 24 months and stratified based on the use or non-use of CDK 4/6 inhibitors. The study was approved by the local ethics committee and registered with Clinical Trials (NCT05559528).

Results: A total of 300 patients were evaluated, with 199 (66.3%) in the public health system and 101 (33.7%) in the private service. The mean age was 58 years, and 76.2% were

postmenopausal. In terms of metastasis site, 84.7% had non-visceral disease, predominantly with bone metastasis (75.7%), which is an expected characteristic of this type of tumor. The use of CDK 4/6 inhibitors at any point in the treatment of metastatic disease was 7.0% in the public health system versus 90.1% in the private service. As a preliminary outcome, with a median time since the diagnosis of metastatic breast cancer of 22.8 months, a mortality rate of 10% was identified in the public health system group compared to 5% in the private service group.

Conclusions: The results of our study highlight the disparity in the treatment of metastatic breast cancer among patients in relation to access to healthcare. Patients dependent on the public health system experience higher mortality rates. These findings are crucial for supporting discussions on improving local policies regarding access to medications that have been proven to enhance the prognosis of these patients.

PO4-05-02

The clinical impact of NOLUS in unresectable/metastatic hormone receptor-positive (HR+) /HER2-negative breast cancer

Presenting Author(s) and Co-Author(s):

W. Tajiri. Japan/National Organization Kyushu Cancer Center, United States

Y. Nakamura. Japan/National Organization Kyushu Cancer Center, United States

J. Kawasaki. Japan/National Organization Kyushu Cancer Center, United States

Y. Koi. National Organization Kyushu Cancer Center, United States

S. Akiyoshi. National Organization Kyushu Cancer Center, United States

C. Koga. Japan/National Organization Kyushu Cancer Center, United States

E. Tokunaga. Department of Breast Oncology, NHO Kyushu Cancer Center, Japan

Background

A non-luminal disease score (NOLUS) is pathology-based predictive model to identify PAM50 non-luminal disease within HR+/HER2-negative breast cancer. NOLUS is a new model, therefore, its clinical utility is not sufficiently elucidated. In this study, the clinical impact of NOLUS was investigated in unresectable/metastatic estrogen receptor (ER) positive (ER+) /HER2-negative breast cancer.

Patients and Methods

The total of 61 patients, who were diagnosed unresectable/metastatic ER+/HER2-negative breast cancer between 2010 and Apr 2023, were included in this study. A NOLUS status was calculated with formula: $-0.45 \times \text{ER} - 0.28 \times \text{PR} + 0.27 \times \text{Ki67} + 73.02$ and diagnosed as NOLUS-positive (≥ 51.38) and NOLUS-negative (< 51.38) according to the previous reports (Pascual T et al, Front Oncol 2019; 9:303). The relationships between NOLUS status and clinicopathological factors and the prognosis were analyzed.

Results

Among 61 patients, 10 patients (16.4%) were NOLUS-positive and 51 (83.6%) were NOLUS-negative. NOLUS-positivity was significantly associated with progesterone receptor (PgR)-negativity ($p=0.0051$) and higher histological grade (0.0234), and had tendency to have shorter recurrence free interval and liver metastasis. NOLUS-positivity was not associated with age, menopausal status and the Ki67. The proportion of the patients whose first line treatment for unresectable/metastatic was endocrine therapy with or without targeted therapy was higher in the NOLUS-negative group. NOLUS-positivity was significantly associated with shorter overall survival (OS; log-rank $p=0.0012$). Uni- and multivariate analysis, NOLUS-positivity was the poor prognostic factor for OS.

Conclusion

The prognosis in of the patients with NOLUS-positive unresectable/metastatic HR+/HER2-negative breast cancer was significantly poor. NOLUS is useful to predict the prognosis of these patients.

NOLUS and clinicopathological characteristics.

Factors		NOLUS-negative (n=51)	NOLUS-positive (n=10)	p-value
Age	median (range)	56 (36-87)	59 (49-78)	
menopausal status	pre/peri	13 (25.5)	1 (10)	0.2512
	post	38 (74.5)	9 (90)	
PgR	negative	5 (9.8)	5 (50)	0.0051
	positive	46 (90.2)	5 (50)	
Ki67 (%)	mean±SE	32.5±2.6	42±5.8	0.1456
Histological grade	1	8 (15.7)	0 (0)	0.0234
	2	24 (47.1)	2 (20)	
	3	19 (37.2)	8 (80)	
Recurrence free interval	≤ 2years	8 (15.7)	4 (40)	0.0992
	2years <	43 (84.3)	6 (60)	
liver metastasis	no	41 (80.4)	5 (50)	0.0542
	yes	10 (19.6)	5 (50)	
1st line treatment	endocrine = target therapy	40 (78.4)	5 (50)	0.0755
	chemotherapy, etc	11 (21.6)	5 (50)	

NOLUS-positivity was significantly associated with progesterone receptor (PgR)-negativity (p=0.0051) and higher histological grade (0.0234), and had tendency to have shorter recurrence free interval and liver metastasis. NOLUS-positivity was not associated with age, menopausal status and the Ki67.

Univariate and multivariate analysis for OS after recurrence

Table 2 Univariate and multivariate analysis for OS after recurrence

Factors		univariate anal	
		HR	95%CI
PgR	positive vs. negative	0.54	0.22-1.28
HG	3 vs. 1, 2	1.12	0.54 - 2.56
Liver meta	yes vs. no	1.76	0.77-4.00
RFI	≤ 2years vs. 2years <	1.63	0.69-3.85
first line therapy	endocrine therapy vs. chemotherapy etc	0.28	0.11-0.65
NOLUS	positive vs. negative	3.7	1.58-8.62

RFI; recurrence free interval

NOLUS-positivity was significantly associated with shorter overall survival (OS; log-rank p=0.0012). Uni- and multivariate analysis, NOLUS-positivity was the poor prognostic factor for OS.

PO4-05-03

Cell-free tumor DNA analysis in advanced or metastatic breast cancer patients enrolled in the German registry study PRAEGNANT

Presenting Author(s) and Co-Author(s):

H. Hübner. Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Bayern, Germany

P. Wimberger. Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Sachsen, Germany

E. Laakmann. Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany, United States

E. Ruckhäberle. Department of Gynecology and Obstetrics, University Hospital Düsseldorf, Düsseldorf, Germany, United States

M. Ruebner. Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich-Alexander-University Erlangen-Nürnberg, Germany

T. Link. Department of Gynecology and Obstetrics, Carl Gustav Carus Faculty of Medicine and University Hospital, TU Dresden, Dresden, Germany, United States

E. Belleville. ClinSol GmbH & Co. KG, Würzburg, Germany, United States

I. Faull. Guardant Health, Inc., Redwood City, California, United States

M. Hausch. Guardant Health, Inc., Redwood City, USA, United States

D. Wallwiener. Department of Obstetrics and Gynecology, University of Tübingen, Tübingen, Germany, United States

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

H. Tesch. Oncology Practice at Bethanien Hospital Frankfurt, Frankfurt, Germany, Germany

S. Brucker. Research Institute for Women's Health, University of Tuebingen, Tuebingen, Germany, United States

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

V. Müller. Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

T. Fehm. University Hospital Düsseldorf, Düsseldorf, Germany

Background

Accurate molecular profiling is crucial for optimal treatment decisions in advanced or metastatic breast cancer. Liquid biopsies, such as circulating cell-free tumor DNA (cfDNA, cftDNA or ctDNA), provide a non-invasive approach to monitor molecular alterations in the tumor. The German PRAEGNANT registry study aims to investigate such molecular biomarkers for precision medicine and their practical integration into clinical practice. In this context, cftDNA testing was performed as part of a PRAEGNANT research subproject, with the objectives of understanding the physician's rationale for initiating cftDNA testing, identifying detected alterations, and assessing the clinical impact of the associated findings

Methods

Patients with advanced or metastatic breast cancer were prospectively enrolled in the PRAEGNANT registry study (NCT02338167). The decision to undergo cfDNA testing was based on the physician's discretion. Blood samples were collected using Streck cfDNA BCT tubes and sent to the GUARDANT Health central laboratory for cfDNA extraction and subsequent next-generation sequencing analysis, employing the FDA-approved GUARDANT360 CDx test, a 74 gene panel including all guideline-recommended biomarkers, including single nucleotide variants (SNVs), indels, fusions and amplifications. Recruitment of patients occurred at four PRAEGNANT study centers between April 2022 and July 2023. The GUARDANT360 CDx report, along with a questionnaire regarding the testing intent and clinical impact of the results, was provided to the treating physician.

Results

46 patients were eligible for analysis as per clinical characteristics. CfDNA analysis was successfully performed for all 46 cases. 38 (83%) harbored at least one somatic alteration in the analyzed genes. Fifteen patients (33%) harbored alterations in TP53, thirteen (28%) in PIK3CA. Five patients (11%) harbored mutations in ESR1. Somatic mutations in BRCA1 or BRCA2 were detected for five (11%) and six (13%) patients, respectively. One BRCA2 mutation was categorized as synonymous and one BRCA2 and three BRCA1 alterations as variants of uncertain significance. Eight patients (17%) harbored mutations in ATM. Most patients included were HR+HER2- (N=27, 58%). In this subgroup, eight (30%) patients had a PIK3CA alteration, five (19%) with an indication for treatment with alpelisib, eight (30%) a mutation in ATM, BRCA1 or BRCA2 and four (15%) in ESR1.

Questionnaires regarding intention of testing and clinical impact were completed by 43 treating physicians (93%). Among them, 33% of patients had current indications for PARP inhibitor treatment, and 61% would consider it at the next change of therapy if a BRCA1 or BRCA2 mutation was detected. Additionally, 21% of patients had a current indication for alpelisib treatment if a relevant PIK3CA mutation was found, and 58% would consider it in the next line of treatment. Overall, cfDNA testing influenced the current or future treatment decisions in 35% of patients.

Discussion

The high prevalence of somatic alterations in TP53, PIK3CA, ESR1, and BRCA1/2 genes, identified through cfDNA testing with GUARDANT360 CDx, highlights their potential as biomarkers for targeted therapies in advanced/metastatic breast cancer. Detection of specific mutations influenced treatment decisions, such as eligibility for alpelisib or PARP inhibitors and might further facilitate treatment with elacestrant in future treatment lines after its approval in Germany. These findings demonstrate the clinical impact of cfDNA testing in guiding personalized treatment selection. Additionally, the identification of such somatic alterations within a registry study like PRAEGNANT presents a unique opportunity to consider enrolling these patients into biomarker-guided clinical trials.

PO4-05-04

Comparative effectiveness of Palbociclib plus Aromatase inhibitor versus fulvestrant alone as initial endocrine therapy for HR+/HER2- advanced breast cancer in Chinese clinical practice: a real-world study

Presenting Author(s) and Co-Author(s):

J. Yue. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

x. Wang. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College., United States

J. Ju. National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

Z. Yang. National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

T. Wei. National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

P. Yuan. National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

M. Gao. Breast Disease Center, Peking University First Hospital, Beijing 100034, China, United States

L. Xu. Breast Disease Center, Peking University First Hospital, Beijing 100034, China, United States

Y. Guan. Department of Medical Oncology, Beijing Chao-Yang Hospital, Capital Medical University, United States

Background:

In the real world, there are still a large number of HR+/HER2- advanced breast cancer patients receiving initial endocrine therapy with fulvestrant monotherapy in China, especially patients with bone metastases only. It is due to lack of data comparing the effective between Palbociclib combined with AI and fulvestrant monotherapy as initial endocrine therapy. On the other hand, there are economic factors and access issues. According to the National Cancer Center's previous clinical experience, Palbociclib combined with AI is superior to fulvestrant monotherapy in HR+/HER2- advanced breast cancer patients receiving initial endocrine therapy. Therefore, we collected and summarized the previous clinical data in our center to compare the effective of Palbociclib combined with AI and fulvestrant monotherapy for HR+/HER2-advanced breast cancer patients receiving initial endocrine therapy in China.

Patients and methods:

This is a retrospective real-world study of multicenter studies. It aimed at verifying the effective of Palbociclib combined with AI and fulvestrant monotherapy for HR+/HER2-advanced breast cancer patients receiving initial endocrine therapy in China. A total of 392 patients with ≥ 3 months of follow-up received Palbociclib plus AI or fulvestrant alone in the first-line setting between April 1, 2015 and February 1, 2023. Stabilized inverse probability treatment weighting (sIPTW) was used to balance baseline demographic and clinical characteristics. Real-world

progression-free survival (rwPFS) and overall survival (OS) were analyzed.

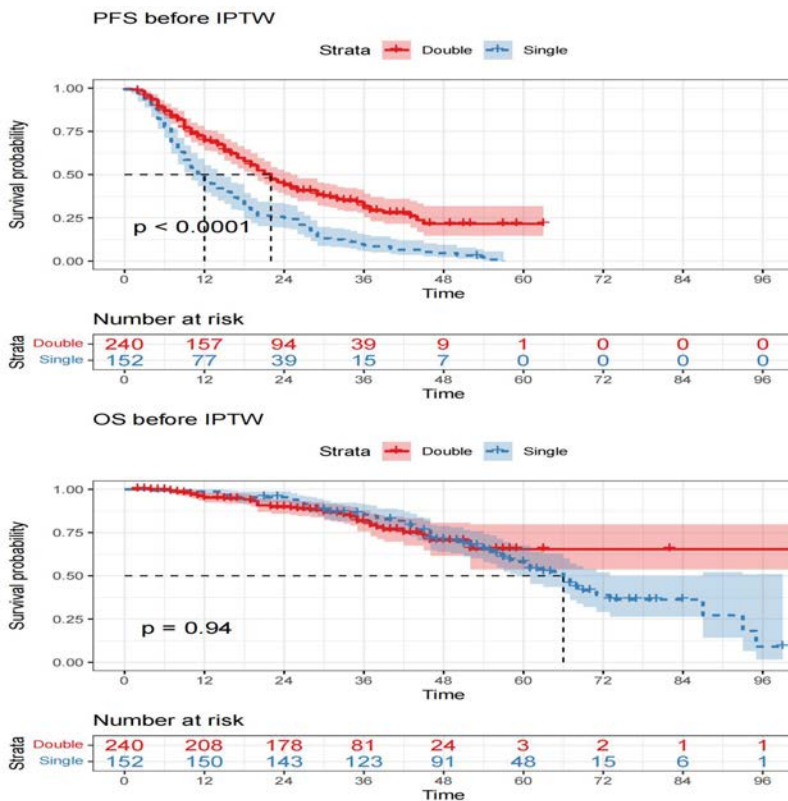
Results:

After sIPTW adjustment, a median follow-up of 37 months (range 34-40) in the Palbociclib group and 59 months (range 56-61) in those taking fulvestrant alone. Palbociclib combination regimen was associated with significantly longer median rwPFS compared to fulvestrant alone (22.0 vs 14.0 months; HR,0.469;95% CI 0.370–0.594, $p < 0.0001$). Median OS was not reached in the Palbociclib group and was 57 months (95% CI 54.0–66.0) in the fulvestrant group(HR,0.666; 95% CI 0.437–1.017, $p < 0.94$).

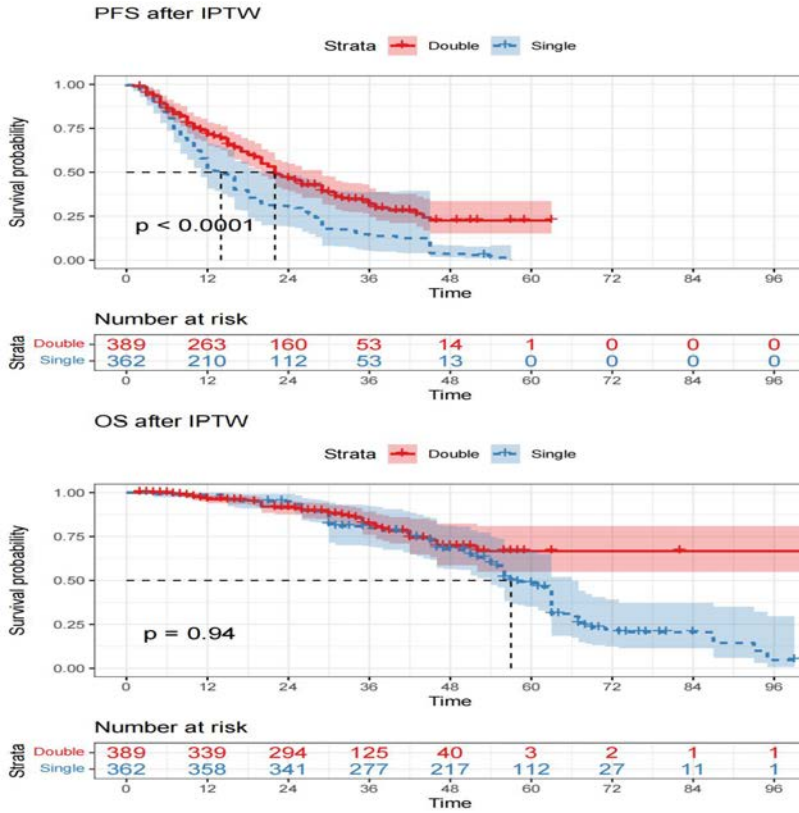
Conclusion:

In the real-world population of patients, palbociclib combined with AI endocrine therapy is superior to fulvestrant monotherapy in HR+/HER2- advanced breast cancer patients receiving initial endocrine therapy.

PFS and OS before IPTW



PFS and OS after IPTW



patient characteristics

Characteristic	Unadjusted total cohort		P	Cohort after IPTW		P	
	Placebo (N=240)	Placebo (N=152)		Placebo (N=240)	Placebo (N=152)		
Age	Mean(SD)	59.3 (12.73)	59.8 (13.27)	0.006	59.40 (12.33)	59.07 (12.33)	0.772
Disease stage at initial diagnosis	I	26 (10.4)	20 (13.2)	0.084	42.9 (11.0)	37.8 (10.4)	0.837
	II	189 (78.4)	166 (109.7)		181.6 (46.7)	184.4 (100.0)	
	III	73 (29.6)	53 (34.3)		121.0 (31.1)	95.0 (26.2)	
	IV	30 (12.0)	10 (6.6)		43.4 (11.3)	44.0 (12.7)	
Tumor histological subtype	Not documented	0 (0.0)	1 (0.7)		0.0 (0.0)	1.0 (0.3)	
	pcp	63 (26.2)	47 (30.9)	0.009	106.3 (26.1)	93.6 (25.6)	0.913
	pcp + Strk1/Strk2/Strk3	135 (56.2)	89 (58.5)		226.7 (56.0)	217.0 (141.0)	
	pcp + Strk1/Strk3	37 (15.3)	13 (8.6)		26.5 (6.8)	22.0 (6.3)	
Lymph node metastases	Yes	25 (10.4)	17 (11.2)		47.4 (12.0)	39.4 (11.2)	
	No	84 (35.0)	40 (26.3)	$= 0.003$	171.9 (31.3)	122.5 (33.4)	0.912
	NA	13 (5.4)	10 (6.6)		21.8 (5.5)	18.5 (5.4)	
Pathological grading	G	6 (2.5)	5 (3.3)	0.243	13.8 (3.5)	10.2 (2.8)	0.96
	G2	183 (76.2)	120 (78.9)		201.9 (75.1)	203.3 (72.7)	

Menstrual status	Yes	31 (12.9)	22 (14.5)		52.9 (13.6)	57.3 (15.6)	
	NA	202 (84.0)	128 (84.0)		302.7 (76.0)	311.8 (81.7)	
Hormonotherapy	Yes	107 (44.6)	36 (23.0)	$= 0.003$	139.6 (36.0)	145.2 (40.1)	0.414
	NA	139 (57.8)	117 (77.0)		245.0 (60.0)	217.0 (60.9)	
Visceral disease (VD)	Yes	4 (1.7)	0 (0.0)		0.0 (0.0)	0.0 (0.0)	
	NA	94 (39.2)	78 (51.3)	0.024	171.5 (44.1)	138.7 (38.3)	0.393
Number of metastatic sites (MS)	Yes	846 (350.8)	74 (48.7)		217.2 (55.9)	228.5 (61.2)	
	0	100 (41.7)	78 (51.3)	0.006	173.4 (44.8)	170.0 (46.0)	0.71
	1	460 (191.0)	45 (29.6)		104.5 (27.9)	82.0 (22.6)	
	2	68 (27.5)	28 (18.4)		30.2 (7.5)	36.9 (10.8)	
Multifocal tumors	Yes	174 (72.5)	138 (90.8)	$= 0.003$	312.0 (80.5)	321.0 (88.6)	0.910
	NA	32 (13.3)	14 (9.2)		46.9 (12.1)	41.2 (11.4)	
Visceral invasion	Yes	29 (12.1)	21 (13.8)		29.0 (7.5)	0.0 (0.0)	
	NA	143 (59.5)	134 (88.4)	$= 0.003$	266.0 (76.0)	273.0 (76.4)	0.971
Adjusted median therapy time $= 2$ years	Yes	56 (23.3)	13 (8.6)		68.9 (17.2)	69.2 (19.4)	
	NA	211 (88.0)	141 (91.4)		215.1 (53.8)	210.1 (59.6)	
		36 (15.0)	17 (11.2)	0.183	60.4 (15.0)	32.5 (9.0)	0.572

Family history of cancer	> 5 years and $= 5$ years	79 (32.9)	66 (43.4)		137.9 (35.5)	114.2 (31.5)	
	Yes	69 (28.7)	50 (32.9)		116.7 (30.0)	139.1 (38.1)	
Family history of cancer	Yes	96 (40.0)	26 (16.4)		83.8 (21.9)	77.5 (21.4)	
	NA	138 (57.5)	123 (80.0)	0.794	312.5 (80.4)	297.7 (82.2)	0.718
		42 (17.5)	29 (19.1)		76.4 (19.6)	64.5 (17.8)	

PO4-05-05

Immune Activation Signatures for predicting CDKi primary response in advanced breast cancer patients

Presenting Author(s) and Co-Author(s):

L. Costa. Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal

C. Tang. Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Avenida Prof. Egas Moniz, 1649-028 Lisboa, Portugal., United States

E. Yates. Proteotype Diagnostics Ltd, United States

Q. Shi. Data Science Knowledge Center, Nova School of Business and Economics, Carcavelos, Portugal, United States

W. Sukdao. Proteotype Diagnostics Ltd, United States

P. Corredeira. Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Avenida Prof. Egas Moniz, 1649-028 Lisbon, Portugal., United States

G. Costa. Oncology Division, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, 1649-028 Lisbon, Portugal., United States

H. Pais. Oncology Division, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, 1649-028 Lisbon, Portugal., United States

C. Abreu. Oncology Division, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, 1649-028 Lisbon, Portugal., United States

L. Ribeiro. Oncology Division, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, 1649-028 Lisbon, Portugal., United States

R. Teixeira de Sousa. Hospital of Santa Maria, Lisbon, Portugal, United States

S. Torres. Centro Hospitalar Lisboa Norte, Portugal, United States

A. Mansinho. Oncology Division, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, 1649-028 Lisbon, Portugal., United States

S. Casimiro. Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Avenida Prof. Egas Moniz, 1649-028 Lisbon, Portugal., United States

A. Cavaco. Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Avenida Prof. Egas Moniz, 1649-028 Lisbon, Portugal., United States

P. Alves. Oncology Division, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, 1649-028 Lisbon, Portugal., United States

A. Rodrigues. Oncology Division, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, 1649-028 Lisbon, Portugal., United States

L. Szeneszi. Oncology Division, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, 1649-028 Lisbon, Portugal., United States

G. Bernardes. Yusuf Hamied Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom. Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Avenida Prof. Egas Moniz, 1649-028 Lisbon, Portugal., United States

Background

Cyclin Dependent Kinase inhibitors (CDKi's) in combination with Endocrine Therapy (ET) have

changed the first line management of patients with the most common subtype (HR+, HER2-) of metastatic breast cancer (MBC), improving progression-free survival (PFS) and overall survival.

However, in approved indications for advanced breast cancer, approximately 20% of patients have been observed to have no response to CDKis and ET, and to progress after starting these therapies. Unlike other targeted therapeutics, there is no companion diagnostic or other clinically reliable biomarker for clinical decision support to indicate which patients will and will not benefit from CDKi therapy.

Methods

We have developed a novel platform that measures the Immune Activation Signature of patient plasma samples. Via simple measurements of the total concentration of protein-incorporated amino acid residues within patient plasma samples, the platform is designed to reveal changes in the proportion of immunoglobulins and albumin, and class-switching among immunoglobulins. For that purpose, we use Bioorthogonal chemical labelling reactions to label the protein-incorporated amino acids residues within the plasma.

We measured the plasma samples of N=30 HR+, HER2- MBC patients, median age 54 years old, who were baseline naïve for CDKi's treatment (16 on palbociclib, 11 on ribociclib, and 3 on abemaciclib) and ET.

Eighteen patients had metastatic visceral disease and 12 patients had bone-only MBC. All patients were prospectively followed, and response assessed according to RECIST criteria on a CT scan every 3-months.

Results

Non-responding patients developed objective progressive disease during the first 6 months after starting CDKis and ET. In this cohort, 4 patients (13%) were classified as non-responders.

The median PFS in non-responding patients was 4.5 months (4.03-5.02) and the median PFS in the cohort of responding patients was 16.6 months (6.8 – 40.9). The Immune Activation Signatures of the Responding and Non-Responding patients are shown in table 1.

We analyzed the results with classical statistics and machine learning. A multivariate analysis of variance (MANOVA) test of the null hypothesis that the Immune Activation Signatures of Non-Responders and Responders are the same gave $p = 0.00388$.

We analyzed the measured Immune Activation Signatures using a supervised machine learning classifier and observed in a held-back validation set correct prediction of 100% of non-responding patients and 95% accurate predictions overall.

Conclusions

According to these results, this platform may provide a clinically helpful biomarker for clinical decision support in the advanced or aggressive breast cancer context (patients with visceral metastasis bordering on visceral crisis), or for patient stratification in new indications.

Immune Activation Signature measurements (mean values in Clinical Outcome)

Table 1: Immune Activation Signature measurements (mean values in Clinical Outcome)

Lysine (K), Tyrosine (Y), Tryptophan (W), Cysteine (C) and Free (reduced) Cysteine (CF).					
Clinical Outcome	[K (μM)]	[Y (μM)]	[W (μM)]	[C (μM)]	[CF (μM)]
Non-Responders	892.03	796.16	144.11	558.64	13.10
Responders	1007.89	667.40	131.60	570.82	12.95
MANOVA test	p = 0.00388				

PO4-05-06

Hormone receptor-positive HER2-low metastatic breast cancer (mBC): evolution of HER2 status after CDK4/6 inhibitor treatment

Presenting Author(s) and Co-Author(s):

A. de Nonneville. Institut Paoli-Calmettes 3C, France

P. FINETTI. Predictive Oncology Laboratory, Inserm Umr1068, Aix Marseille University, France

L. Boudin. Predictive Oncology Team, Inserm, CNRS, Institut Paoli-Calmettes, Cancer Research Center of Marseille, Aix-Marseille University, Marseille, France, United States

L. Usclade. Predictive Oncology Team, Inserm, CNRS, Institut Paoli-Calmettes, Cancer Research Center of Marseille, Aix-Marseille University, Marseille, France, United States

L. Mescam. Pathology Department, Institut Paoli-Calmettes, Marseille, France, United States

E. Durieux. Pathology Department, Institut Paoli-Calmettes, Marseille, France, United States

A. Boucraut. Pathology Department, Institut Paoli-Calmettes, Marseille, France, United States

F. VIRET. Institut Paoli-Calmettes 3C, France

E. Mamessier. Predictive Oncology Team, Inserm, CNRS, Institut Paoli-Calmettes, Cancer Research Center of Marseille, Aix-Marseille University, Marseille, France, United States

A. Gonçalves. Institut Paoli-Calmettes, France

F. BERTUCCI. Predictive Oncology Laboratory, Inserm Umr1068, Aix Marseille University, France

Background

Trastuzumab deruxtecan (T-DXd) is approved for HER2-low but not HER2-0 mBC. Therefore, identifying HER2-low status is of great clinical importance. Prior studies have shown HER2-low status is dynamic between primary tumor and metastatic relapse and between primary tumor and post-neoadjuvant chemotherapy residual tumor, and expert recommendations are to reiterate biopsies throughout the course of the disease. However, there is no data on when to repeat these biopsies. We provide here the first data on the evolution of HER2-low status in hormone receptor-positive (HR+) mBC before and after endocrine therapy (ET) in association with CDK4/6 inhibitor (CDK4/6i).

Methods:

Patients with pre-CDK4/6i+ET tumor biopsy were identified from a single large academic center database. Patients with unknown HER2 status were excluded. Pathological, clinical, and demographic data were extracted from clinical files. HER2-low was defined as HER2 IHC 1+, or 2+ with non-amplified HER2 by ISH, and HER2-0 by IHC score of 0+. Pathology central review for all paired pre- and post-treatment biopsies was performed by three expert breast cancer pathologists.

Results:

304 consecutive patients with HR+/HER2- mBC treated with CDK4/6i+ET and who had immediate pre-treatment biopsy were included. Of these, 117 (38%) were HER2-0, and 187 (62%) were HER2-low. Clinical and demographic data did not differ between both groups. Patients received CDK4/6i+ET as first-line treatment in 48% of cases. Among this cohort, 49 patients had paired biopsies immediately after CDK4/6i+ET treatment. The discordance rate between pre- and post-CDK4/6i+ET HER2-status was 51% with 64% of HER2-0 patients becoming HER2-low and 38% of HER2-low switching to HER2-0. Among the 49 patients with

paired biopsies, 43 had available material to perform a central pathology review. Of these, 22 (51%) were HER2-0, and 21 (49%) were HER2-low. Central pathology review showed a concordance level of 82% with pathology records, resulting in a modification of HER2 status in 7 HER2-0 patients as HER2-low, leading to a total of 65% of patient's eligibility to T-DXd. Post-CDK4/6i+ET biopsy identified a switch to HER2-low in 10 additional HER2-0 patients resulting in a total of 38/43 (88%) candidates to T-DXd. No case became HER2 3+ after treatment. Neither baseline HER2 status, nor change in HER2 status after treatment affected the clinical outcome on CDK4/6i+ET (objective response, progression-free survival, overall survival).

Conclusion:

HER2-low status is dynamic, and 64% of mBC HER2-0 patients switched to HER2-low after a line of CDK4/6i+ET treatment. Since such a switch would guide post-progression treatment with T-DXd in patients initially not candidate, these results suggest that biopsy should be repeated early in the course of mBC to assess eligibility for T-DXd therapy. Our central pathology review of pre-treatment biopsies reclassified 24% of HER-0 patients as HER2-low, suggesting that pathology review is a legitimate first step before repeating biopsy or in the case of difficulty to re-biopsy. In our series, 88% of patients had a biopsy sample classified as HER2-low after pathological review of pre-treatment slides, followed by post-CDK4/6i+ET rebiopsy of HER2-0 cases.

PO4-05-07

Differential dynamics of fragmentomic and epigenetic circulating tumor DNA (ctDNA) features in first-line Palbociclib and Ribociclib treatment for Hormone Receptor (HR) positive, HER2 negative metastatic breast cancer (MBC)

Presenting Author(s) and Co-Author(s):

C. Noto. Department of Medicine, University of Udine, Italy; Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy., United States

L. Cucciniello. Unit of Medical Oncology and Cancer Prevention, Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, United States

E. Molteni. Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

s. bolzonello. IRCCS CRO, United States

A. Franzoni. Institute of Human Genetics, University of Udine, United States

I. da Ros. IRCCS CRO, United States

S. Buriolla. Department of Medicine, University of Udine, Italy; Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

A. Dri. Department of Medicine, University of Udine, Italy; Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy., United States

L. Foffano. Department of Medicine (DAME), University of Udine, Udine, Italy., United States

S. Spazzapan. Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

S. Russo. Department of Medical Oncology, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC) Udine, Italy, Italy

B. Pastò. IRCCS CRO, United States

G. Cudia. Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy., United States

G. Targato. Department of Medicine, University of Udine, Italy; Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

S. Della Rossa. Department of Medicine, University of Udine, Italy; Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy., United States

M. Bonotto. Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

A. Minisini. Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

G. Damante. Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

B. Belletti. Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, United States

L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

F. Puglisi. Department of Medicine (DAME), University of Udine, Udine, Italy and Department of Medical Oncology - CRO Aviano, National Cancer Institute, IRCCS, Aviano, Friuli-Venezia Giulia, Italy

Background: Cyclin-dependent kinase inhibitors (CDK4/6i) in combination with endocrine therapy (ET) represent the cornerstone for the management of HR positive, HER2 negative MBC. However, the lack of prospective cohorts comparing the distinctions among palbociclib (PAL), ribociclib (RIB) and abemaciclib (ABE) poses a significant clinical knowledge gap. The aim of this ancillary analysis was to explore the differential clinical impact of CDK4/6i by leveraging new ctDNA biomarkers in a prospective clinical study.

Methods: A total of 114 patients (pts) with HR positive, HER2 negative MBC were prospectively enrolled in the multicenter MAGNETIC.1 study (CRO-2018-56) from January 2018 to January 2023. At baseline (BL) and every 3 months (mos.), ctDNA samples were collected concurrently with radiological restaging. The samples were then analyzed through methylation-specific (MS) droplet digital PCR (ddPCR), ddPCR fragmentomics, and next generation sequencing. Matched pairs of variations were tested through Wilcoxon signed rank test, and survival was analyzed by log-rank test.

Results: Out of the 114 pts enrolled, 59 received PAL, 48 RIB, and 16 ABE. In the de novo subgroup, 51.4 % of pts were treated with PAL, 42.9% with RIB, and 5.7% with ABE. Among the pts who received PAL, 7 harbored an ESR1 mutation at BL (D538G: 2, H377R: 1, Y537N: 1, Y537S: 3). Additionally, 12 pts had PIK3CA mutations, and 2 pts had AKT1 mutations. In the RIB group, 5 and 2 pts, respectively, had a PIK3CA- and AKT-mutated MBC, while no ESR1 mutations were detected.

When comparing matched pairs of variations, it was found that at BL, at first radiological restaging (T1), and at 6 mos. after initiation of CDK4/6i (T2), only PAL showed significantly higher levels of promoter A and B methylation (promA and promB) at T1 ($P = 0.0005$ and $P = 0.0056$, respectively for promA and promB),

A significant decrease in promA and promB levels was detected at T2 for PAL ($P = 0.0005$ and $P < 0.0001$ respectively for promA and promB) but not for RIB. Both PAL and RIB demonstrated a significant decrease in ctDNA short fragments at T1 ($P = 0.0263$ for PAL and $P = 0.0001$ for RIB), However, PAL showed a significant rebound at T2, with an increase in 80% of samples ($P = 0.0014$). The same was not seen with RIB. After a median follow-up of 34.8 mos., there were no significant differences between PAL and RIB in terms of PFS ($P = 0.2573$) and OS ($P = 0.3783$). The PFS rates at 12 and 24 mos. were 69% and 48% for PAL, and 76% and 64% for RIB. The OS rates at 12 and 24 mos. were 94% and 84% for PAL, compared to 97% and 82% of RIB, respectively.

Conclusions

This analysis of MAGNETIC.1 highlighted significant differences in ctDNA biomarkers between palbociclib and ribociclib, suggesting their potential impact on the development of endocrine resistance. Further biomarker-driven clinical trials leveraging this concept are needed to refine the sequencing algorithms for CDK4/6i.

PO4-05-08

Primary endocrine therapy resistance in patients with de novo HR+/HER2- metastatic breast Cancer: a National Cancer Information Database Analysis in China

Presenting Author(s) and Co-Author(s):

Z. Chen. Department of Medical Oncology (Breast), Zhejiang Cancer Hospital, Hangzhou, United States

X. Shao. Department of Medical Oncology (Breast), Zhejiang Cancer Hospital, Hangzhou, United States

Y. Zheng. Department of Medical Oncology (Breast), Zhejiang Cancer Hospital, Hangzhou, United States

W. Cao. Department of Medical Oncology (Breast), Zhejiang Cancer Hospital, Hangzhou, United States

j. chen. Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China (People's Republic)

W. Wu. Ningbo Medical Center Lihuili Hospital, United States

T. Wang. Department of Medical Oncology, Yiwu Hospital, Affiliated to Hangzhou Medical College, Yiwu, United States

X. Wang. Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, United States

Background: Endocrine therapy resistance was classified as primary and secondary, guiding the first-line (1L) treatment choices for hormone receptor positive, HER2-negative (HR+/Her2-) metastatic breast cancer (mBC). However, it is unknown whether it is primary ET resistance or not to the stage IV de novo patients. Therefore, We performed a retrospective study to predict primary resistance in advance in de novo patients and have a more appropriate treatment strategy.

Methods: We identified newly diagnosed with stage IV de novo HR+/HER2- mBC patients received single-agent endocrine therapy (ET) or ET plus CDK4/6 inhibitors (CDK4/6i) in 1L setting from January 1, 2020 to Jun 30, 2022, using the National Cancer Information Database (NCID) in China. Primary ET resistance (PER) was defined as switching to second-line treatment within 6 months after receiving the 1L ET±CDK4/6i, whereas secondary ET resistance (SER) patients were those who received 1L ET±CDK4/6i treatment more than six months. The Chi-Square test was used to compare the baseline characteristics of PER and SER patients.

Result: A total of 217 patients who met the inclusion criteria were included in the analysis, among which 161 patients received single-agent ET and 56 patients received ET plus CDK4/6i. 18.4% of the patients were classified as PER patients, whereas 81.6% showed SER patients. PER patients were younger (median age of 52 years vs. 58 years in SER patients, $p=0.01$). In terms of clinicopathological characteristics, patients with PER have a higher percentage of liver metastases (14/40 (35%) vs. 20/177 (11.3%) in SER, $p < 0.01$), distant lymph node metastases (19/40 (34%) vs. 45/177 (25.4%) in SER, $p = 0.01$), and bone metastases (30/40(75%) vs. 97/177(54.8%) in SER, $p = 0.02$). Furthermore, the PER rate was 21.7% (35/161) in patients received single-agent ET, compare with 8.9% (5/56) in ET plus CDK4/6i patients, $p=0.04$. Regarding the following treatment pattern in the PER patients, a high percentage of patients received chemotherapy, accounting for 50%, 30% still received another endocrine therapy, and

the remaining 20% patients received CDK4/6i combined with endocrine therapy.

Conclusions: There is still a significant proportion of de novo HR+/HER2- mBC patients with primary endocrine resistance, a relatively low proportion of PER in patients receiving endocrine in combination with CDK4/6i.

The proportion of primary endocrine resistance across treatment regimens in de novo HR+/HER2- metastatic breast Cancer

	Primary ET resistance (N, %)	Secondary ET resistance (N, %)	P value
Single-agent ET n=161	35, 21.7%	126, 78.3%	P= 0.0440
ET +CDK4/6i n=56	5, 8.9%	51, 91.1%	

PO4-05-09

Phase I study of the FGFR inhibitor rogaratinib, fulvestrant and palbociclib in advanced hormone receptor-positive (HR+) breast cancer (BC) with FGFR1/2 amplification and/or overexpression (FGFR1/2+)

Presenting Author(s) and Co-Author(s):

N. Martínez-Jáñez. Medical Oncology Hospital Universitario Ramón y Cajal. Madrid. Spain.
GEICAM Spanish Breast Cancer Group., TRES CANTOS, Madrid, Spain

S. Pernas. SOLTI Cancer Research Group, Barcelona, Spain Institut Catala d'Oncologia;
IDIBELL, L'Hospitalet, Barcelona, Spain

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

B. Bermejo. Hospital Clínico Universitario de Valencia, Valencia, Spain, United States

J. Guerra. Hospital Universitario de Fuenlabrada, Madrid, Spain

S. Mouron. CNIO - Spanish National Cancer Research Center, United States

M. Quintela-Fandino. CNIO - Spanish National Cancer Research Center, Madrid, Spain

Background: Novel therapies are needed upon progression to first-line CDK4/6 inhibitor (CDK4/6i) plus aromatase inhibitor (AI) in advanced HR+ BC. One frequent alteration driving resistance to CDKi plus AI is FGFR1/2 amplification or overexpression. In preclinical FGFR1/2+ HR+ BC models, combined CDK4/6, ER and FGFR blockade was more effective than single- or double combinations (Breast Cancer Res; 23:21-37; 2021). Rogaratinib (ROGA) is a selective FGFR1-4 kinase inhibitor with significant activity in FGFR-aberrant tumors. We aimed to study the tolerability and preliminary efficacy of ROGA added to fulvestrant (FUL) and palbociclib (PAL) in patients (pts) with FGFR1/2+ HR+ BC progressing on first-line CDK4/6i plus AI.

Methods: ROGABREAST (NCT04483505) was a single-arm, prospective, multicentric, open-label, phase I dose-escalation trial following a classic 3+3 schedule. Pts were pre-screened for FGFR1/2 amplification and/or overexpression by FISH and RNAScope. Women >18 year-old with advanced HR+ BC progressing on first-line CDK4/6i plus AI, and adequate organ function were included. Pts received ROGA monotherapy q12 hours in day 1. In day 2, pts continued ROGA and started FUL (500 ug IM) plus PAL (100 mg/day on days 1-21). FUL was repeated in day +15. Cycle 1 was 29 days-long and followed by 28-day cycles (continuous ROGA q12 hours days 1-28, FUL 500 ug day 1, and PAL 100mg/d days 1-21). Level 1 was ROGA 400 mg/bid and escalated 200 mg/bid increments. FUL dose was not modified. PAL was allowed to escalate inpatient to 125 mg/d after cycle 2 in pts experiencing ≤ grade 1 tolerable side effects as the greatest toxicity in cycle 1. PK and PD (FGF23 and phosphate levels) profiles were obtained in days +1 and +15. DLT-assessment period was cycle 1-2.

Results: from 12/2020 to 5/2022, 67 pts were screened; 29 were FGFR1/2+ (22 and 5 RNAScope-positive for FGFR1 and FGFR2; 17 and 3 FISH-positive for FGFR1 and FGFR2). Nine pts entered the study. Six were enrolled in level 1, where 1 DLT (grade 3 diarrhea) occurred, and 3 in level 2 (600 mg ROGA bid; no DLTs). Grade 3 hyperphosphatemia, adequately controlled with diet and chelants (33% of the patients) and grade 2 non-tolerable dactylitis/onycholysis (11%) were the most frequent severe toxicities after the DLT period. Other toxicities were mild and well-tolerated (grade 1-2 diarrhea and hyperphosphatemia occurred in 66 and 44% of the pts, respectively). Median PFS was 113 days and 44% of the pts had a PFS > 180 days, with no apparent relationship with FGFR1 or 2 status, or mutations

found via WES. The trial was terminated after completion of level 2 due to rogaratinib development discontinuation.

Conclusions: Triple FGFR1/2, CDK4/6 and ER blockade appears safe at standard drug dosages and shows promising clinical activity in second-line HR+ FGFR1/2+ BC patients progressing on CDK4/6i plus AI.

PO4-05-10

A Carryover Effect: Antibody Drug Conjugates Constantly Provide a Substantial Improvement in Overall Survival more than in Progression-free Survival.

Presenting Author(s) and Co-Author(s):

I. Chen. Department of Medical Oncology, National Taiwan University Cancer Center; Graduate Institute of Oncology, National Taiwan University, United States

C. Lin. Department of Medical Oncology, National Taiwan University Cancer Center, Taiwan (Republic of China)

Y. Lu. National Taiwan University Hospital, Taipei, Taiwan.

Background: In metastatic breast cancer (MBC), progression-free survival (PFS) improvement does not always translate into overall survival (OS) benefit. Multiple treatment options after progression resulted in a long post-progression survival in MBC patients, and these would make the dissociation of PFS benefit and OS benefit. We have reported the constant correlation of PFS improvement and OS improvement in anti-HER2 containing treatment (Breast 2021; 59:211-220). The relationship between PFS and OS improvement in antibody drug conjugate has not been thoroughly examined.

Methods: “Metastatic breast cancer” and “antibody drug conjugate” (ADC) were used as keywords to search for randomized clinical trials that report both PFS and OS. Hazard ratios (HR) and median survival were analyzed. Increments in PFS (delta PFS) and increments in OS (delta OS) were compared between studies.

Results: A total of 8 trials were identified and summarized in table 1. The target of ADC was HER2 (N=6) or Trop2 (N=2). In DESTINY-Breast 03 trial, the control arm was another ADC (T-DM1). The control arms in all the other 7 trials were chemotherapy. The HR of PFS (range 0.28-0.66) was smaller than HR of OS (range 0.48- 0.83) in all of the trials. The median OS was not reached (NR) in 1 of the trials (DB-03) and was thus removed from the analysis for delta PFS and delta OS. In the comparison of delta PFS, the increments of median PFS fell between 1.5 and 10.9 months(m). The increments of median OS were between 1.6 and 12.7 m. All the delta OS are greater than the delta PFS in the 7 trials with available PFS and OS data.

Conclusion: In MBC, ADCs targeting HER2 and Trop2 both constantly provide improvement of OS greater than PFS. Further investigation on the potential mechanism is warranted.

PO4-05-11

Effects of body mass index on the treatment outcome of patients with metastatic breast cancer in the real world

Presenting Author(s) and Co-Author(s):

K. Lee. Division of Hematology Oncology, Department of Internal Medicine, School of Medicine, Ewha Womans University, Republic of Korea

A. Ham. Ewha Womans University Medical Center, United States

S. Lee. Ewha Womans University Hospital, United States

J. Jo. Ewha womans university medical center, United States

S. Hong. Ewha Womans University Hospital, United States

J. Lee. Ewha Womans University Hospital, United States

H. Lee. Ewha Womans University Hospital, United States

S. Gwark. Ewha Womans University Hospital, United States

J. An. Ewha Womans University Hospital, United States

H. Kim. Ewha Womans University Hospital, United States

J. Lee. Ewha Womans University, School of Medicine,, Seoul, Seoul-t'ukpyolsi, Republic of Korea

J. Woo. Ewha Womans University College of Medicine/Ewha Womans University Mokdong Hospital, United States

W. Lim. Department of Surgery, Ewha Womans University School of Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

B. Moon. Ewha Womans University Hospital, United States

S. Ahn. Ewha Womans University Hospital, United States

H. Lee. Ewha Womans University Hospital, United States

Effects of body mass index on the treatment outcome of patients with metastatic breast cancer in the real world

Ahrong Ham¹, Sewon Lee¹, Jungmin Jo¹, Soo Ji Hong², Ji Eun Lee², Haena Lee², Sungchan Gwark², Jeongshin An², Hyun Goo Kim², Jun Woo Lee², Joohyun Woo², Woosung Lim², Byung-In Moon², Sei Hyun Ahn², Hye Ah Lee³, Kyoung Eun Lee¹

¹Department of Hematology and Oncology, Ewha Womans University Mokdong Hospital, Ewha Womans University, Seoul, Korea

²Department of Surgery, Ewha Womans University Mokdong Hospital, Ewha Womans University, Seoul, Korea

³Clinical Trial Center, Ewha Womans University Mokdong Hospital, Ewha Womans University, Seoul, Korea

Purpose: Metastatic/recurrent breast cancer has a relatively long survival compared to other cancers and depending on the biologic subtype, the treatment outcome is different. In general, obesity or overweight is associated with poor prognosis of breast cancer, but the relationship between body mass index (BMI) and prognosis in metastatic cases is not clear. The aim of this

study is investigating the effect of BMI on survival outcome through long-term follow-up in single institution, retrospectively.

Method: This study included the patients with metastatic/recurrent breast cancer who has been diagnosed from January 2000 to December 2022 in an institution. BMI was calculated based on weight at diagnosis of metastatic disease, divided into 4 groups according to Asian-Pacific classification, and clinical characteristics including biologic subtype and overall survival (OS) were retrospectively reviewed. The statistical analysis was performed using Kaplan-Meier survival analysis and Cox proportional hazard model.

Result: A total of 679 patients were enrolled. Median age was 51 years-old (25~89), 672 patients (99.0%) were female and 425 patients (62.6%) showed pre-menopausal status. The frequencies of HR+, HER2, and TNBC subtype were 335 (50.7%), 191 (28.9%), and 135 (20.4%), respectively and the BMI classification was 33 (5.5%), 251 (41.6%), 124 (20.5%), 196 (32.4%) for underweight, normal, overweight, and obesity, respectively. During a median follow-up of 33.8 months, the median OS in each of the HR+, HER2+, and TNBC subgroups was 54.9 (95% CI 38.7-71.1), 62.8 (95% CI 47.8-77.8), and 20.8 months (95% CI 12.0-29.7). In univariate analysis, there was no statistically significant difference in OS according to BMI in whole patients, however, in the HER2-positive group, the underweight BMI group showed poor OS ($p=0.045$). In multivariate analysis, the factors affecting OS were age (HR 0.59, 95% CI 0.41-0.87, $p=0.008$), poor ECOG PS (HR 8.35, 95% CI 2.54-27.49, $p<0.001$), TNBC subtype (HR 2.14, 95% CI 1.56-2.94, $p<0.001$), visceral metastasis (HR 2.13, 95% CI 1.63-2.79, $p<0.001$), 5% or more weight loss during treatment (HR 1.46, 95% CI 1.09-1.97, $p=0.012$) and obesity BMI group (HR 0.69, 95% CI 0.51-0.94, $p=0.019$).

Conclusion: In the case of patients with metastatic/recurrent breast cancer, there is concern about an increase in body weight, a known risk factor for breast cancer, while receiving palliative aim treatment. For the past 20 years, the mainstay of treatment for metastatic/recurrent breast cancer has been cytotoxic chemotherapy or anti-HER2 agents, and in this case, the higher BMI group patients showed better treatment outcomes compared with normal BMI patients.

PO4-05-12

High expression of SLC9A2 is correlation with lymphatic metastasis and poor survival in breast cancer

Presenting Author(s) and Co-Author(s):

B. CONG. 1. Cardiff University School of Medicine; 2. Shandong Cancer Hospital and Institute, United States

X. CAO. 1. Cardiff University School of Medicine; 2. Tianjin Medical University; 3. Shandong Cancer Hospital and Institute., United States

W. Jiang. Cardiff University, United States

L. Ye. Cardiff University, United States

Background: SLC9A2 encodes Na⁺/H⁺ exchanger 2 which is an essential solute carrier protein on the surface of multiple cells. The prediction potentials of SLC9A2 in lymphatic metastasis and survival were unknown but explored in this study of breast cancer.

Methods: Expression of SLC9A2 was determined in breast cancers (n=127) using real time quantitative polymerase chain reaction. Transcript levels of this gene was analysed in the breast cancers for the implication in lymph node involvement and survival using Mann-Whitney test with SPSS (Version 27). The relation of prognosis was also analysed by Kaplan Meier plotter in breast cancer.

Results: In lymph node positive breast cancer, the expression of SLC9A2 shown an increase trend than no metastasis (n=43, median=25.9, interquartile range [IQR] [0.9-215.4] vs. n=44, median=4.9, IQR [0.2-31.8], p=0.1213). SLC9A2 expression in TNM stage II was significantly higher than stage I (n=31, median=42, IQR [0-195] vs. n=47, median=3.3, IQR [0.2- 31.6], p=0.0267) and also showed in the pathological type of invasive ductal carcinoma (n=27, median=42, IQR [3- 550] vs. n=35, median=3.3, IQR [0.2-31.8], p=0.0223). Kaplan Meier plotter showed over survival of SLC9A2 high expression was significantly worse than SLC9A2 low expression (66 months vs. 123.6 months, Hazard Ratio [HR]=1.57 [1.3-1.9], p=0.000), also found in estrogen receptor (ER) positive (63.8 months vs. 173.7 months, HR=2.19 [1.6-3.01], p=0.000). In patients with tamoxifen therapy, SLC9A2 high expression also had poor survival comparing to low expression (HR=2.86 [1.4-5.86], p=0.0026).

Conclusions: High expression of SLC9A2 is correlation with lymph node metastasis and poor survival in breast cancer. SLC9A2 could be as a predictor for lymphatic involvement and survival and might be an indicator for detection of resistance to endocrine therapy.

PO4-05-13

Expression of DLC1/STARD12 and variants in clinical breast cancer and implication in skeletal metastasis

Presenting Author(s) and Co-Author(s):

B. CONG. 1. Cardiff University School of Medicine; 2. Shandong Cancer Hospital and Institute, United States

J. Lane. Cardiff University, United States

X. CAO. 1. Cardiff University School of Medicine; 2. Tianjin Medical University; 3. Shandong Cancer Hospital and Institute., United States

T. Martin. Cardiff University, Cardiff, United States

R. MANSEL. University Llandough Hospital, United States

E. Davies. 3Wales Breast Centre, University Llandough Hospital, Cardiff CF64 2XX, UK, United States

W. Jiang. Cardiff University, United States

Introduction: Deleted in Liver Cancer 1 Protein, DLC1, also known as StAR Related Lipid Transfer Domain Containing 12 (StarD12), is a known negative regulator of the Rho GTPases and at the cellular level regulates cell migration. DLC1 gene transcription produces multiple isoforms of the DLC1 protein. The present study examined the clinical and prognostic implications of DLC1 isoforms, DLC1/V1/V2/V3, in relationship with Rho GTPases in human breast cancer.

Methods: Expression of three DLC1 isoforms was evaluated in a cohort of breast cancer tissues and against the clinical, pathological and clinical outcome of patients. DLC1 expression was also assessed and compared against Rho GTPases, including Rho and Rho GTP Dissociation Inhibitor (Rho GDI), in the same cohort.

Results: DLC1/V3 had a significant impact on the overall survival of patients and high levels were linked to shorter survival (Hazard Ratio=3.551 (95%CI 1.332-9.471, p=0.011), a prediction that was independent of other factors in multivariate analysis. RUC analysis demonstrated a significant predictive value for bone metastasis with DLC1/V3 (RUC=0.714, p=0.020), showing a Hazard ratio of 9.0 (1.8-44.5, p=0.007). Similarly, high DLC1/V2 expression was also linked to a shorter overall survival (p=0.035). DLC1/V2 did not show a significant correlation with bone metastasis. In contrast to V3 and V2 variants, DLC1 had a marginal overall survival benefit for the patients, in that patients with high DLC1 had a longer survival (p=0.056). DLC1/V3 had a contrasting correlation with Rho-A (r=-0.203, p=0.015) and Rho-GDI-G (r=0.194, p=0.019) and the combined expression of DLC1/V3 and RhoA/Rho-GDI-G further identified patients with poorer clinical outcome.

Conclusions: DLC1 and its variants have differing impacts on breast cancer; whereas DLC1 appears to be a tumour suppressive molecule, its variant isoform-3 was more oncogenic and a significant negative prognostic factor, together with its regulators Rho and Rho GDI.

PO4-05-14

Gene expression in metastatic breast cancer – patterns and prognostic potential

Presenting Author(s) and Co-Author(s):

J. Tutzauer. Lund University, United States

A. Larsson. Lund University, United States

K. Aaltonen. Lund University, United States

P. Bendahl. Lund University, United States

C. Bergenfelz. Lund University, United States

C. Levin Tykjaer Jørgensen. Lund University, United States

L. Rydén. Region Skane / Lund University, United States

Introduction

Metastatic breast cancer (mBC) is the leading cause of breast cancer mortality. However, mBC has a considerable variance in prognosis and course of disease, reflecting a substantial biological heterogeneity. Despite this, there is a lack of prognostic biomarkers validated for mBC. New prognostic markers and improved understanding of the molecular variants of mBC could aid in prognostication and personalizing treatments, and lead to the discovery of novel drug targets.

The primary objective of this study was to explore the prognostic value of gene expression (GEX) in the distant metastasis (DM) of mBC. Secondly, we aimed to identify molecular subtypes of mBC, and describe their biological niches.

Methods

We used a cohort of mBC patients enrolled in a prospective trial (NCT01322893) that includes tissue from primary tumor (PT) and matched lymph node metastasis (LNM) and/or DM (1). The inclusion criteria were diagnosed mBC with a life expectancy of >2 months, ECOG score of 0-2, and an age of >18 years. RNA was extracted from formalin-fixed, paraffin-embedded tumor tissue. GEX data were acquired for n=123 PT, n=71 LNM, and n=74 DM using the NanoString Breast Cancer 360 assay, which comprises 758 genes and >30 GEX signatures.

The relationships between GEX and the endpoints overall survival (OS) and progression-free survival (PFS) were assessed using cox proportional hazards regression with GEX as a continuous score. Multivariable cox regressions were adjusted for PAM50 of the DM, number of metastatic sites, visceral metastasis, ECOG, and age at mBC diagnosis.

Visualization by heatmap and k-means clustering were used to identify GEX patterns. When clustering single genes, we included only the 100 genes with the highest standard deviation.

Results

In relation to PFS, we found prognostically unfavorable roles of DM GEX of the signatures for Treg cells (HR=1.3, p=0.02), cytotoxicity (HR=1.3, p=0.03), and p53 (HR=1.3, p=0.02). Further, our data indicate prognostically favorable value of DM GEX of ESR1 (HR=0.77, p=0.02), PGR (HR=0.65, p=0.002), FOXA1 (HR=0.76, p=0.02), and AR (HR=0.68, p=0.0006). The prognostic value of AR remained in multivariable analysis. In relation to OS the first 2 years after mBC prognosis, we found prognostically favorable value of DM GEX of B7H3 (HR=0.65, p=0.04), TGFB (HR=0.53, p=0.02) and the signatures for stroma (HR=0.7, p=0.05) and claudin-low

(HR=0.61, p=0.02). Finally, our data suggests that the previously published PAM50MET panel performs well as a prognostic indicator, especially when considered on a continuous scale, for PFS (HR=1.3, p=0.0023) and OS (HR=1.3, p=0.003) (2).

Based on the 100 most highly variable genes, we identified five stable tumor clusters with distinct GEX profiles, where some strongly associated with metastatic site. Using the same approach on the GEX signatures, we established four GEX profiles able to outperform PAM50 in identifying tumors with poor OS in this material.

Conclusion

In this study, we demonstrate prognostic value for GEX-based panels in DM samples. First, we find GEX signatures related to hormone responsiveness to be favorable, and genetic instability to be unfavorable for mBC prognosis. We also demonstrate AR to be an independent marker for better PFS. Further, we confirm the prognostic value of PAM50MET, a previously published panel with the advantage of including only PAM50 genes and clinical parameters. Finally, we identify new GEX profiles related to metastatic site and outcome.

These results illuminate the biological differences between mBC in relation to outcome and metastatic site. Better understanding of the mBC GEX subtypes may open new venues for tailored treatment.

References

1. DOI: [10.3390/cancers13071592](https://doi.org/10.3390/cancers13071592)
2. DOI: [10.1158/1078-0432.CCR-20-2793](https://doi.org/10.1158/1078-0432.CCR-20-2793)

PO4-06-02

Frequency of presentation and outcomes of stage IV breast cancer over the past decade: a population-based study

Presenting Author(s) and Co-Author(s):

J. Avila. St Elizabeth's Medical Center, United States

J. Leone. Grupo Oncológico Cooperativo Del Sur (GOCS), Neuquen, Argentina

N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

C. Vallejo. Grupo Oncológico Cooperativo del Sur (GOCS), Neuquen, Argentina

M. Hassett. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Leone. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Over the past decade, there have been major advances for the treatment of patients (pts) with metastatic breast cancer (MBC). For pts with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative MBC, newer treatments include CDK 4/6 inhibitors among other targeted therapies; for HER2+ MBC, we have seen the development of antibody-drug conjugates (ADC) and other anti-HER2 agents; and for triple-negative breast cancer (TNBC) options include immunotherapy, ADCs, and PARP inhibitors. The aims of this study were to evaluate time trends in clinical characteristics, frequency of presentation and outcomes of pts with stage IV breast cancer over the past decade.

Methods: Using data from the Surveillance, Epidemiology, and End Results (SEER) program, we identified pts diagnosed with breast cancer between 2010-2020. Pts required to have known HR and HER2 status and known stage at diagnosis. We described the proportion of stage IV disease overall for each tumor subtype and evaluated trends in the proportion of stage IV over time. Outcomes were evaluated by breast cancer-specific survival (BCSS) using Kaplan-Meier. Among stage IV pts, we conducted multivariable cox models to assess changes in BCSS over time, stratified by tumor subtype and adjusted for age at diagnosis, race and ethnicity, sex, tumor grade, histology, surgery, radiation therapy, chemotherapy, sites of distant metastases, marital status, median household income, rurality and US region. We evaluated overall survival as a secondary endpoint.

Results: We included 443,631 pts of whom 24,788 (5.59%) had stage IV disease at diagnosis. Pts with stage IV breast cancer had a median age of 61 years and a median follow up of 57 months (IQR 28 – 89 months). When compared to stage I-III, stage IV pts were more often of Black race (10.4% for stage I-III vs 15.7% for stage IV), less often married (56.7% vs 43.5%, respectively) and less often HR+/HER2- (74.1% vs 59.9%, respectively); all $p < 0.001$. Among pts with stage IV, the frequency of each metastatic site at initial diagnosis was: bone 66.45%, lung 30.47%, liver 25.79%, and brain 7.9%. Across all years (2010-2020), the proportion of stage IV disease varied significantly by tumor subtype: 4.6% in HR+/HER2-, 8.5% in HR+/HER2+, 11.3% in HR-/HER2+, and 7.1% in TNBC; $p < 0.001$. The proportion of stage IV increased modestly during 2010-2020 in HR+/HER2- tumors (4.6% in 2010 to 5.1% in 2020, p for trend = 0.01), in HR-/HER2+ (10% in 2010 to 13.7% in 2020, p for trend < 0.001), and in TNBC (6.9% in 2010 to 7.8% in 2020, p for trend = 0.001). No significant difference was observed in the proportion of stage IV over time in HR+/HER2+ (p for trend = 0.76). Rate of

BCSS at 5 years was: 32.51% for HR+/HER2-, 43.92% for HR+/HER2+, 37.28% for HR-/HER2+, and 10.97% for TNBC; $p < 0.001$. In adjusted Cox models, BCSS improved significantly over time for each additional year in HR+/HER2- (adjusted Hazard Ratio [HzR] 0.982, $p = 0.01$), in HR+/HER2+ (adjusted HzR 0.945, $p < 0.001$), and in HR-/HER2+ (adjusted HzR 0.959, $p = 0.03$). The improvement in BCSS over time in TNBC was not significant (adjusted HzR 0.982, $p = 0.15$). Overall survival results were similar to those of BCSS both in 5-year rates as well as Cox model results.

Conclusions: In this population-based study, we saw that the proportion of pts presenting with de-novo stage IV varied significantly by tumor subtype, being as low as 4.6% in HR+/HER2- and as high as 11.3% in HR-/HER2+ disease. These proportions have unfortunately increased over time in most subtypes, highlighting a need for additional research to identify the reasons behind these trends. BCSS improved significantly over time in HR+/HER2- and in both HER2+ subtypes, coinciding with a time period of important therapeutic advances. TNBC remains a highly unmet medical need and further follow up is needed to assess the impact of newer treatments.

PO4-06-03

A comparative study between RECIST 1.1 using MRI and PERCIST 1.0 using PET/CT to evaluate the response in patients of carcinoma breast receiving neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

A. Dhar. AIIMS, New Delhi, New Delhi, Delhi, India

K. Sharma. AIIMS, New Delhi, New Delhi, Delhi, India

Introduction: Breast cancer is the most common cancer in women leading to the major public health problem with an estimated new cases of 2,261,419 (11.7%). Depending upon the stage at presentation, the primary modalities vary. Presently, the primary option for HER2-positive, Triple negative cancers of size more than 2cm or nodal involvement and locally advanced breast cancer is neoadjuvant chemotherapy (NACT). Accurate assessment of the tumor response and residual cancer after undergoing NACT is considered crucial for reducing the number of local recurrence cases and to predict the prognosis as patients who achieve pathological complete response (pCR) after NACT have a longer disease free period and better overall survival as compared to non-responders. In our study we have compared the two commonly used criteria i.e. RECIST 1.0 and PERCIST 1.0.

Methodology: 70 patients diagnosed with breast cancer requiring neoadjuvant chemotherapy were recruited in the study conducted in the department of surgical disciplines, AIIMS Delhi from January 2021 to December 2022. Each patient underwent a contrast enhanced MRI breast and whole body FDG PET/CT at the beginning of chemotherapy and after completion of chemotherapy within a stipulated time of two to three weeks. For RECIST 1.1 criteria, response assessment was done using MRI and PERCIST used PET/CT. The response was compared with the gold standard histopathological size.

Results: Concordance between the RECIST 1.1 and PERCIST 1.0 response classifications was seen in 27 (39.1%) cases, while discordance was seen in 42 (60.8%). A significant difference was observed between RECIST 1.1 and PERCIST 1.0 ($k=0.1309$, $p<0.0001$) for response classification. Tumor response was upgraded in 32 and downgraded in 2 patients using PERCIST 1.0 as compared to RECIST 1.1. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy to predict pCR along with comparison among different molecular subtypes is shown in the table below.

Conclusion: RECIST 1.1 showed high specificity, PPV and accuracy in predicting pathological complete response but tends to underestimate it whereas PERCIST 1.0 showed higher sensitivity with a tendency to overestimate. RECIST 1.1 had a high level of specificity and NPV as compared to the PERCIST 1.0, which showed a high level of sensitivity and PPV. Thus, they act as complementary modalities for predicting pathological complete response. The accuracy to predict pCR was higher for the triple-negative phenotype and Her2 neu enriched with PERCIST 1.0 as compared to RECIST 1.1, while that of PERCIST 1.0 was lower for luminal type.

Comparison of RECIST 1.1 and PERCIST 1.0

			Sensitivity	Specificity	PPV	NPV	Accuracy
All Patients	RECIST	Value	20.00%	82.03%	0.56%	99.51%	81.74%
		95% CI	7.71 - 38.57%	66.47 - 92.46%	0.21% to 1.47%	99.39% to 99.61%	70.60% to 90.02%
	PERCIST	Value	100.00%	66.67%	1.49%	100.00%	66.83%
		95% CI	88.43% to 100.00%	49.78% to 80.91%	0.96% to 2.30%		54.46% to 77.71%
		P value	P = 0.0001	P = 0.0393	P = 0.5889	P = 0.5619	P = 0.0459
Luminal	RECIST	Value	22.22%	80.00%	0.56%	99.51%	79.71%
		95% CI	6.41 - 47.64%	59.30% to 93.17%	0.17% to 1.76%	99.33 - 99.64%	64.68 - 90.42%
	PERCIST	Value	100%	52.00%	1.04%	100%	52.24%
		95% CI	81.47 - 100%	31.31 - 72.20%	0.69 - 1.55%		36.38 - 67.68%
Her 2 not enriched	RECIST	Value	28.57%	100%	100%	99.64%	99.64%
		95% CI	3.67 - 70.94%	15.81 - 100.0%		99.43 - 99.78%	
	PERCIST	Value	100%	100%	100%	100%	100%
		95% CI	59.04% to 100.00%	15.81% to 100.00%			66.37% to 100.00%
TNBC	RECIST	Value	0.00%	83.33%	0	99.40%	82.92%
		95% CI	0.00% to 52.18%	51.59% to 97.91%		99.23% to 99.53%	57.21% to 96.46%
	PERCIST	Value	100%	91.67%	5.69%	100.00%	91.71%
		95% CI	47.82% to 100.00%	61.52% to 99.79%	0.91% to 28.26%		68.02% to 99.47%

Comparison of RECIST 1.1 and PERCIST 1.0

PO4-06-04

Understanding metastasis mixed-treatment responses through genomic analyses

Presenting Author(s) and Co-Author(s):

S. Garcia-Recio. University of North Carolina, Chapel Hill, NC, North Carolina, United States

P. Zagami. Division of Medical Oncology, Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC USA, Chapel Hill, North Carolina, United States

A. Wheless. Division of Medical Oncology, Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC USA, North Carolina, United States

K. Thomas. Department of Radiology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA., North Carolina, United States

L. Carey. Division of Medical Oncology, Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill
Division of Medical Oncology, Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC USA, North Carolina, United States

C. Perou. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA, United States

Background

Early-stage and metastatic breast cancer (MBC) exhibit genomic heterogeneity, with inter-patient variability between primary tumors, intra-patient variability of primary tumors versus metastasis, and even between different metastatic sites within the same patient. Response to therapy in MBC can also be heterogeneous, termed "mixed response", with different degrees of responsiveness to the same drug(s) across metastatic sites within the same patient. Whether this treatment response variability is influenced by factors such as intrinsic characteristics of metastatic lesions and/or the microenvironment is unknown. Through genomic analysis, we aim to identify genomic features that may explain mixed clinical responses across metastatic sites, which will also provide valuable insights into treatment sensitivity and resistance.

Methods

Eligible patients with MBC were identified from the UNC Rapid Autopsy Program (RAP) with primary tumors and multiple metastases (≥ 2 different sites) with RNA sequencing data. An independent radiologist retrospectively reviewed imaging studies to identify patients with mixed radiographic responses to a defined line of therapy. The response to treatment was categorized for each metastasis, defined as a complete or partial response, as stabilization ≥ 6 months. Tumor measurements were performed for each patient at different time points. We performed supervised learning with linear regression incorporating "RNA sequencing-based gene expression signatures" as a fixed effect and "patient" as a random effect. We performed two different analyses: (1) Using all tumors and (2) using Basal-like tumors only. We finally selected significant signatures with a p-value >0.05 .

Results

Ten patients with mixed response were identified, and 33 metastases were used for the analysis; 3 had de novo stage IV disease, 5 had triple-negative (TNBC), 4 HER2+, and 4 hormone receptor+ (HR+/HER2-) disease. Of 33 metastases, 6 were brain, 8 liver, 7 lung, and 12 "other". Regarding intrinsic subtype, 15 metastatic tumors were Basal-like, 3 HER2-Enriched (HER2E), 6 Luminal A, and 9 Luminal B. In this dataset, 6 metastatic lesions showed response

and 27 non-response. When analyzing all 33 metastases, KRAS high expression, KRAS amplicon, 16q23 amplicon, and apocrine features correlated with response independently of metastatic site. Higher T reg and CDKN2A gene expression levels were associated with non-response in metastasis. Within Basal-like subtype metastases only (N=15), CD8 T cells, PI3K pathway, KRAS gene and amplicon, 16q23 amplicon, and Basal-like-associated 5q11 loss correlated with response. However, T reg cells, higher levels of CDKN2A gene, and stem-cell-like features were associated with treatment non-response.

Conclusions

By examining matched metastases with discordant responsiveness to treatment within individual patients, this genomic analysis provides valuable insight into treatment sensitivity and resistance. Higher T reg cells and CDKN2A gene expression values correlate with non-response, while the KRAS gene, KRAS amplicon, and the 16q23 amplicon were associated with response. These results suggest that the molecular tumor and microenvironment features of metastases may contribute to sensitivity and resistance to therapy in MBC. Further validation and exploration are needed in larger multi-metastatic cohorts to fully understand the clinical implications of these findings.

PO4-06-05

The prognostic impact of age at diagnosis of metastatic breast cancer according to estrogen receptor status: a single-center, retrospective study

Presenting Author(s) and Co-Author(s):

J. Woo. Ewha Womans University College of Medicine/Ewha Womans University Mokdong Hospital, United States

A. Ham. Ewha Womans University Mokdong Hospital, United States

S. Lee. Ewha Womans University Hospital, United States

J. Lee. Ewha Womans University Hospital, United States

S. Hong. Ewha Womans University Hospital, United States

H. Lee. Ewha Womans University Mokdong Hospital, United States

S. Gwark. Ewha Womans University Hospital, United States

J. Lee. Ewha Womans University, School of Medicine,, Seoul, Seoul-t'ukpyolsi, Republic of Korea

H. Kim. Ewha Womans University Mokdong Hospital, United States

J. Jo. Ewha womans university medical center, United States

W. Lim. Department of Surgery, Ewha Womans University School of Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

B. Moon. Ewha Womans University Hospital, United States

S. Ahn. Ewha Womans University Hospital, United States

H. Lee. Ewha Womans University Hospital, United States

K. Lee. Division of Hematology Oncology, Department of Internal Medicine, School of Medicine, Ewha Womans University, Republic of Korea

Background: Young age is associated with poor prognosis and aggressive biology in early breast cancer, especially in luminal subtypes. But the prognostic impact of age in metastatic breast cancer (MBC) is unclear. Also it is known that chemotherapy is more effective in estrogen receptor (ER)-negative tumors than in ER-positive tumors and young patients respond better to chemotherapy. The authors tried to evaluate the impact of age on disease outcome according to ER status.

Methods: We collected individual patient data from January 2000 to December 2022 from the Ewha Womans University Mokdong Hospital. Total 419 ER-positive and 238 ER-negative patients who had been treated for MBC were included for analysis. We compared clinical characteristics and overall survival (OS) of patients among three age groups (< 35, 35 to 50 and >50 years) at MBC diagnosis in ER-positive and -negative tumors.

Results: The proportion of patients aged < 35, 35-50 and > 50 years was 3.1%, 46.6% and 32.3% in ER-positive tumors, and 2.7%, 14.8% and 18.4% in ER-negative tumors. Although most characteristics of tumors according to age were comparable, bone metastasis was more common in patients aged 35-50 years than the other age groups in ER-positive (51.8% vs. 36.0% in >50 years, P=0.006) and time to first metastasis was shorter in younger patients in ER-negative tumors (72.2% between 6 and 24 months vs. 31.1% in patients >50 years, P=0.003). The median follow-up time was 65 months. Overall survival rate was not different according to age in ER-positive tumors (P=0.909). On the other hands, younger patients had a

higher risk of death in ER-negative tumors ($P=0.015$). In multivariate analysis, young age at MBC diagnosis (< 35 years) with short time to metastasis (6 to 24 months), visceral metastasis, triple negative breast cancer was correlated with poor overall survival in ER-negative tumors ($P=0.014$, HR 1.77).

Conclusions: Young age at MBC diagnosis was associated with a higher risk of death in ER-negative tumors, not in ER-positive tumors. These observations may suggest that physicians should consider the impact of age at diagnosis of metastasis and time course of disease in evaluating survival potential and determining a treatment strategy in metastatic breast cancers.

PO4-06-06

Clinical Implications of Body Mass Index (BMI) in BRCA-associated Advanced Breast Cancer Patients Treated With PARP (Poly ADP-Ribose Polymerase) Inhibitors.

Presenting Author(s) and Co-Author(s):

F. Akkoc Mustafayev. University of Texas MD Anderson Cancer Center, United States

M. Munsell. University of Texas MD Anderson Cancer Center, United States

R. Layman. The University of Texas MD Anderson Cancer Center, United States

C. Yam. Breast Medical Oncology Department, The University of Texas MD Anderson Cancer Center, United States

A. Gutierrez Barrera. University of MD Anderson Cancer Center, United States

B. Arun. UT MD Anderson Cancer Center, Houston, Texas, United States

Background: PARP inhibitors (PARPi) have demonstrated promising results in patients with advanced as well as early breast cancer carrying germline BRCA1/2 pathogenic variants (PV). Although there is increasing attention to the effect of BMI on the outcomes of cancer patients, there is limited data on its effect on BRCA-associated advanced breast cancer patients receiving PARPi therapy. In this report, we evaluate the effect of BMI on the outcomes of advanced breast cancer patients with a BRCA PV and who received PARPi therapy. Methods: Patients with BRCA 1/2 germline PVs who presented to the University of Texas MD Anderson Cancer Center Breast Medical Oncology clinics and were treated with PARPi between 2008-2022 as part of their treatment for metastatic or recurrent disease were included in the analysis. The patients were divided into four groups according to BMI level as follows: underweight ($< 18.5 \text{ kg/m}^2$), normal weight ($18.5\text{-}24.9 \text{ kg/m}^2$), overweight ($25\text{-}29.9 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$). Descriptive statistics, the Kaplan-Meier method, the Cox proportional hazards regression model, and Fisher's exact test were used to report patient characteristics and outcomes. Progression-free survival (PFS) was calculated from the start of the PARPi therapy to the time of progression or death. Overall survival (OS) was calculated from the start of the PARPi therapy to the time of death of any cause. Results: One hundred and seven patients were treated with PARPi. The median BMI was 25.9 kg/m^2 ($14.8\text{-}61.2$). In patients who received ≥ 2 cycles of PARPi, the overall response rate was 100% in the underweight group ($n=4$, 3.8%), 65.8% in the normal weight group ($n=43$, 41%), 64% in the overweight group ($n=30$, 28.6%), and 58.3% in the obese group ($n=28$, 26.7%). The median PFS was 5.4 months, 9.2 months, 9 months, and 8.6 months in underweight, normal weight, overweight, and obese patients, respectively. While the obese patients had a better outcome in terms of PFS ($p = 0.0288$), there was no significant difference observed in OS between BMI groups. Conclusion: In this analysis, we showed that obese patients with BRCA-associated advanced breast cancer had a better PFS. Future studies analyzing body composition parameters in BRCA-associated breast cancer patients treated with PARPi therapy could shed more light on the impact of obesity on outcomes.

PO4-06-07

Efficacy and safety of futibatinib in patients with locally advanced/metastatic triple-negative breast cancer harboring FGFR2 gene amplification: final results from the phase 2, open-label FOENIX-MBC2 study

Presenting Author(s) and Co-Author(s):

A. Giordano. Dana Farber Cancer Institute, Harvard University, Boston, MA, United States

N. Unni. University of Texas Southwestern Medical Center, Dallas, Texas, United States

S. Damodaran. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

T. Crook. Sarah Cannon Research Institute, London, UK, United States

T. Bachelot. Medical Oncology, Centre Léon Bérard, Lyon, France

F. Piacentini. University of Modena and Reggio Emilia, MODENA, Emilia-Romagna, Italy

H. Soto Parra. University Hospital Policlinico Vittorio Emanuele, Catania, Italy, United States

I. Krop. Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, United States

M. Shimura. Taiho Oncology, Inc., Princeton, New Jersey, United States

G. Tomlinson. Taiho Oncology, Inc., Princeton, New Jersey, United States

M. Gil. Taiho Oncology, Inc., Princeton, New Jersey, United States

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France

Background:

Triple-negative breast cancer (TNBC) accounts for ~15% of breast cancers and represents an aggressive subtype with limited targeted therapeutic options. Fibroblast growth factor receptor (FGFR) signaling plays an important role in breast tumorigenesis and metastasis. The phase 2 FOENIX-MBC2 study (NCT04024436) was designed to evaluate responses to futibatinib, a highly selective and potent irreversible covalent inhibitor of FGFR1–4 (FDA-approved for intrahepatic cholangiocarcinoma), in patients with metastatic breast cancer. Here, we report final efficacy and safety data for futibatinib in the cohort of patients with advanced/metastatic TNBC harboring FGFR2 gene amplification.

Methods:

Eligible patients had locally advanced/metastatic TNBC with measurable disease per RECIST v1.1, an ECOG performance status of 0/1, and progressive disease after ≥1 prior chemotherapy-containing regimen for advanced disease. Patients were positive for FGFR2 gene amplification determined by analysis of tumor tissue or circulating tumor DNA. Patients received oral futibatinib 20 mg once daily until disease progression, unacceptable toxicity, or other discontinuation criteria were met. The primary endpoint was objective response rate (ORR) by RECIST v1.1 in patients with centrally confirmed FGFR2 amplification. Responses (complete response and partial response) required confirmation after at least 4 weeks. Secondary endpoints included the 6-month progression-free survival (PFS) rate, PFS, duration of response (DOR), and overall safety.

Results:

Overall, 21 female patients with TNBC were enrolled (median age: 53 years) in this cohort. Patients had received a median 5 lines of prior systemic therapy. Overall, 2 patients had a confirmed partial response (ORR: 9.5%; 95% confidence interval [CI]: 1.2, 30.4), with a median DOR of 6.1 months (range: 3.1–9.2 months). Five (23.8%) patients had stable disease. PFS at 6 months was observed in 4 patients (19.0%; 95% CI: 5.4, 41.9) and the median PFS was 1.9 months (95% CI: 1.6, 4.0). Twenty patients (95.2%) had ≥ 1 treatment-related adverse event (TRAE), including 7 (33.3%) with a Grade 3 TRAE (no Grade 4 or 5). Common TRAEs (any grade) included hyperphosphatemia (85.7% of patients), constipation, diarrhea, fatigue, and dry skin (each in 23.8% of patients). Anemia was the only Grade 3 TRAE observed in more than 1 patient (n=2, 9.5%). Overall, 28.6% of patients had a serious adverse event (SAE; any cause), and 1 patient had an SAE leading to death (ischemic stroke). None of the SAEs or deaths were considered treatment-related.

Conclusions:

In heavily pretreated patients with metastatic TNBC harboring FGFR2 gene amplification, futibatinib monotherapy demonstrated modest anticancer activity. Futibatinib was tolerable and had an acceptable safety profile, consistent with previous data. Further biomarker work to identify patients who might benefit most from futibatinib is ongoing.

PO4-06-08

ZP4 AS A NOVEL TARGET FOR CAR T CELL THERAPY IN TRIPLE NEGATIVE BREAST CANCER

Presenting Author(s) and Co-Author(s):

L. Somes. Baylor College of Medicine, Houston, Texas, United States

J. Lei. Baylor College of Medicine, United States

P. Shafer. Baylor College of Medicine, United States

X. Yi. Baylor College of Medicine, United States

D. Chamorro. Baylor College of Medicine, Houston, Texas, United States

E. Madaras. Rice University, United States

M. Lewis. Baylor College of Medicine, Houston, Texas, United States

B. Zhang. Baylor College of Medicine, United States

V. Hoyos. Baylor College of Medicine, United States

Triple negative breast cancer (TNBC) has the worst prognosis of BC subtypes, largely due to lack of approved targeted therapies. Chimeric antigen receptor (CAR) T cells have demonstrated great success in certain hematological malignancies; however, in the treatment of solid cancers, CAR T cells are faced with a variety of obstacles that limit their efficacy, including on-target/off-tumor toxicity. To minimize these toxicities, the ideal CAR T cell target must be overexpressed by the tumor and absent from vital organs. Cancer/germline (CG) antigens satisfy this need, as their expression is restricted to male or female germ cells. Using a bioinformatic pipeline to identify novel CG antigens expressed in TNBC and other solid cancers, we have identified zona pellucida glycoprotein 4 (ZP4) as a candidate CG antigen target for CAR T cell therapy. This protein is a component of the human zona pellucida matrix, an extracellular structure that surrounds the oocyte and functions in folliculogenesis, species-specific fertilization, and early development. We have identified ZP4 expression in approximately 10% of TNBC cases from available RNAseq and proteomic databases and have confirmed ZP4 expression in several TNBC PDX models. The overall purpose of this study is to redirect T cells against ZP4 by engineering and validating a second generation ZP4-specific CAR.

We have generated a library of monoclonal antibody (mAb) candidates against the extracellular portion of human ZP4. Antibody clones were screened, and their specificity validated via ELISA and flow cytometry, and the three strongest binders (z108, z128, and z164) were selected for further investigation. By IHC, we confirmed that the ZP4 mAb clones stained the area surrounding normal oocytes and did not show binding to any of the 23 normal tissues screened. The variable regions of the antibody heavy and light chains were sequenced using 5'RACE and used to assemble second generation CAR constructs composed of the variable heavy and light chain fragments separated by a linker, a CH2/CH3 hinge domain, a CD28 transmembrane domain, a CD28 co-stimulatory domain, and the CD3z signaling domain. Activated T cells transduced with retroviral supernatant express the ZP4 CAR constructs at high levels. While all ZP4 CAR T cells demonstrate antigen-specific cytotoxic killing of ZP4+ target tumor cells in short-term in vitro assays, z128 ZP4 CAR T cells demonstrate superior persistence and efficacy in long-term repeat tumor challenge in vitro assays and orthotopic in vivo mouse models.

In summary, ZP4 is a promising target for TNBC and we have successfully engineered ZP4

specific CAR T cells. ZP4 CAR T cells effectively target and kill ZP4+ cells in in vitro cytotoxicity assays but perform differently in repeat tumor challenge assays and in vivo. Future studies will elucidate the precise differences between our three candidate CAR constructs and further test the effector function, trafficking, proliferation, and persistence of z128 ZP4 CAR T cells in vivo using ZP4+ PDX models. This work has exciting potential to bring a novel CAR T cell therapy to patients with TNBC, without concerns for on-target off-tumor toxicity.

PO4-06-10

Targeting necroptosis in breast cancer induced by Ophiobolin A

Presenting Author(s) and Co-Author(s):

T. Ojo. Baylor University, Waco, Texas, United States

S. Ranganathan. Baylor University, Waco, Texas, United States

Targeting necroptosis in breast cancer induced by Ophiobolin A

Santhalakshmi Ranganathan¹, Tolulope Ojo¹, Alagu Subramanian¹, Alexander Kornienko², Antonio Evidente³, Daniel Romo⁴ and Joseph Taube¹, ¹Department of Biology, Baylor University, Texas, USA, ² Department of Chemistry and Biochemistry, Texas State University, San Marcos, TX, USA, ³ Department of Chemical Sciences, University of Naples Federico II, Complesso Universitario Monte Sant'Angelo, Naples, Italy, ⁴ Department of Chemistry and Biochemistry, Baylor University, Waco, TX, USA.

Santha_Ranganathan@baylor.edu and Joseph_Taube@baylor.edu.

Abstract

Necroptosis or programmed necrosis is a form of cell death distinct from apoptosis. Necroptotic cells display the character of rounding of the cell, gain in cell volume, rupture of plasma membrane and release of intra-cellular contents. Although few key necroptosis regulators including receptor interacting protein kinase 3 (RIPK3) and mixed lineage kinase domain like pseudokinase (MLKL) has been identified, their role/ mechanism in inducing cell death in triple-negative breast cancer (TNBC) which lack RIPK3 expression remains elusive. Ophiobolin A is a compound naturally made by fungus and potently kills cancer cells especially TNBC. Our current study investigated the cell death mechanism(s) induced by Ophiobolin A (natural product) in breast cancer cell lines.

The mechanism of cell death elicited by OpA was analyzed by applying inhibitors for specific pathways including apoptosis, necroptosis, ferroptosis and paraptosis, by analyzing markers of cell death using flow cytometry and western blotting. The formation of necrosomes was analyzed with exogeneous expression of RIPK3 tagged with green fluorescence protein (GFP) in HeLa, MDA-MB-231, MDA-MB-468 cell lines which lacks endogenous RIPK3 expression and in MCF7 estrogen receptor (ER) positive cell line. OpA induced necrosome formation was identified by formation of puncta in TNBC and HeLa cells which lack RIP3 expression, however, necrosomes were not detectable in ER positive cells. Clinical relevance of RIPK3 and MLKL has been analyzed using bioinformatic tools. Effect of OpA In vivo has been analyzed using Immune compromised SCID mice.

The data obtained in the present study indicates that OpA has an increased anticancer effect in TNBC compared to the estrogen receptor (ER) positive breast cancer cells. Cells having undergone EMT were shown to have more sensitivity towards OpA when compared to uninduced cell lines, which is sensitive to Necrostatin-1, an inhibitor of necroptosis. However, apoptosis, ferroptosis and paraptosis inhibitors failed to rescue cell death which clearly confirms that OpA induces necroptosis cell death pathway in EMT undergone cells. OpA treatment significantly increased puncta in TNBC compared non-TNBC cells, further confirming the

necroptotic cell death in TNBC. Bioinformatic analysis revealed that RIPK3 is negatively correlated with breast cancer and has least over-all survival in patients who lack RIPK3 expression. OpA treatment showed a significant tumor regression in tumor bearing SCID mice. All together our findings identify that OpA induce necroptosis in EMT-enriched TNBC. The study further needs an in-depth analysis of molecular mechanism induced by OpA and involvement of EMT in necroptotic cell death.

Key words: Triple-negative breast cancer, EMT, Ophiobolin A, Necroptosis, cell death mechanism

PO4-06-11

Development of fully human anti-progranulin monoclonal antibodies as inhibitors of triple negative breast cancer cell growth and tumor formation.

Presenting Author(s) and Co-Author(s):

G. Serrero. A&G Pharmaceutical Inc, Columbia, Maryland, United States

J. Dong. A&G Pharmaceutical Inc., Columbia, Maryland, United States

J. Hayashi. Precision Antibody, Columbia, Maryland, United States

C. Dong. Precision Antibody, Columbia, Maryland, United States

Triple negative breast cancer (TNBC) is characterized by invasiveness and poor survival. Identifying novel TNBC targeted therapies to potentiate standard of care (SOC) therapy, is an unmet need. In the past 4 years, several targeted therapies for TNBC have been approved by the Food and Drug Administration (FDA). However, the identification of targeted therapies against other biological drivers of TNBC remains important. Progranulin

(PGRN/GP88) is a biological driver of tumorigenesis, survival, and drug resistance in breast cancer. PGRN/GP88 tissue expression is an independent prognostic factor of recurrence while elevated serum PGRN/GP88 level is associated with poor outcomes such as progression of disease and shortened survival. PGRN/GP88 expression is elevated in 30% TNBC. The importance of inhibiting PGRN/GP88 effect on the proliferation and tumor growth of triple negative breast cancer cells was previously established. In the current study, in association with Precision Antibody, we developed anti-PGRN/GP88 fully human monoclonal antibodies by immunizing TC transgenic humanized mice with recombinant human progranulin. Within 60 days since the start of immunization, several fully human monoclonal antibodies were successfully developed, characterized by several functional assays including neutralization, inhibition of PGRN/GP88 cell surface binding, proliferation, migration in MDA-MB-231 cells in vitro and in vivo.

Results: The inhibition of PGRN/GP88 action by fully human monoclonal antibodies inhibited proliferation and migration in a dose-and time-dependent fashion in TNBC cells. Octet analysis determined Kd in the range of 10^{-11} M to 10^{-10} M. Transwell assay showed that anti-PGRN treatment inhibited migration. In vivo xenograft studies with MDA-MB-231 cells injected in athymic nude mice showed that several fully human anti-PGRN antibodies inhibited tumor growth when compared to antibody control treated mice. In vivo dose response of AG01 in MDAMB-231 tumor bearing mice will be provided.

Conclusion: PGRN/GP88 represents a therapeutic target for TNBC with two companion diagnostics (tissue test and ELISA to measure GP88 circulating levels). The use of the TC transgenic mice allows for the rapid development of fully human high affinity monoclonal antibodies bypassing the need for chimerization or humanization of mouse monoclonal antibodies. The development of fully human anti-progranulin antibodies provides novel targeted therapeutic option for TNBC.

This work is supported by a an SBIR grant 5R44 CA 224718 from the National Cancer Institute to GS.

PO4-06-12

Distinction of basal-like and triple-negative basal-like breast cancers utilizing a novel comprehensive single-cell liquid biopsy-based test

Presenting Author(s) and Co-Author(s):

A. Cunsolo. Epic Sciences, United States

D. Bourdon. Epic Sciences, San Diego, California, United States

E. Lam. Epic Sciences, United States

G. Di Caro. Epic Sciences, United States

N. Dharajiya. Epic Sciences, United States

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

L. Schwartzberg. William N. Pennington Cancer Institute - Renown Health, United States

Introduction:

Breast cancer is a highly heterogeneous disease and is a leading cause of death for women worldwide. Triple-negative breast cancer (TNBC), the most aggressive form of the disease, is clinically defined by the lack of expression of estrogen receptor (ER) and progesterone receptor (PR), as well as lack of over-expression of human epidermal growth factor receptor-2 (HER2). Approximately 70% of all TNBC cases exhibit basal-like cells, characterized by high basal expression of keratins as well as extensive genomic instability with copy number gains and losses across most chromosomes. In this study we show that novel single cell genomic evaluation coupled with immunofluorescence (IF) protein analysis of CTCs can detect TNBC with basal-like genomic features as well as basal-like tumors with expression of ER and HER2.

Materials and Methods:

Epic Sciences' DefineMBC™ liquid biopsy test characterizes CTC proteomics and genomics as well as ctDNA for the treatment of metastatic breast cancer. Blood samples from 813 metastatic breast cancer patients, with either newly diagnosed or progressing disease, with historical tissue subtype [HR(+)HER2(-), HR(+/-)HER2(+), and TNBC] supplied by the referring physician were collected and tested. Up to 5 CTCs were selected and isolated from each sample based on morphology and IF signal. DNA was extracted from individual cells, and whole genome amplified and sequenced at low coverage. Copy number analysis was performed to determine copy number gains and losses across chromosomes, as well as large scale-state transitions (LSTs) and ERBB2 amplification. CTCs characterized with high chromosomal instability (e.g., exhibiting >30 LSTs; 1Q firestorm and 8Q stair step) and high levels of cytokeratin expression (mean fluorescence intensity signal >10K) were categorized as basal-like.

Results:

By previous metastatic tissue biopsy, 77% were HR(+), 8% were HER2(+), and 12% were TNBC. CTCs categorized in DefineMBC as basal-like subtype (9.8 % of all samples tested) showed to be highly present in patients called as TNBC (79% basal-like). Additionally, 54% of HR(+) and 23% of HER2(+) had basal-like CTCs. Patients characterized with TNBC by metastatic tissue biopsy and by DefineMBC exhibited basal-like cells in 88% of the cases.

Conclusion:

The results show a novel clinical assay which utilizes CTC protein detection as well as single-cell genomic analysis to identify tumors driven by basal-like cells. Generally, TNBC is classified

with negative biomarker expression. We show that CTCs in TNBC display genomically basal-like cells. CTCs from HR(+) and HER2(+) tumors may express basal-like features with preserved ER and HER2 expression. The comprehensive nature of DefineMBC™ utilizing genomic analysis of detected CTCs has provided a new tool to diagnose both basal-like TNBC and basal-like hormone receptor positive and HER2 over-expressing tumors.

PO4-06-13

Palliative care utilization in triple negative metastatic breast cancer patients and impact on survival: A nationwide analysis

Presenting Author(s) and Co-Author(s):

S. Kashanian. University of Texas Southwestern Medical Center, Dallas, Texas, United States

S. Kanjwal. University of Texas Southwestern Medical Center, United States

L. Brown. Parkland Health, United States

N. Premnath. University of Texas Southwestern Medical Center, United States

N. Sadeghi. University of Texas Southwestern Medical Center, Dallas, Texas, United States

Introduction:

Patients with metastatic triple negative breast cancer (TNBC) experience inferior outcomes compared to other breast cancer phenotypes. In some advanced malignancies, early referral to palliative care (PC) has been associated with an improvement in disease related quality of life and disease-specific mortality. The frequency at which metastatic TNBC patients receive palliative care is unknown. Here, we evaluate the rate of palliative care utilization in metastatic TNBC patients and its impact on overall survival (OS).

Methods:

We used the National Cancer Database (NCDB) to identify metastatic TNBC patients between 2018 to 2019 and examined the relationship between sociodemographic factors and PC use , comparing OS in patients who did vs those who did not receive PC. Chi-square and Wilcoxon tests were used to compare categorical and continuous variables, respectively. OS was evaluated by Kaplan-Meier method using SPSS software.

Results:

We identified 2,940 patients between 2018-2019 with metastatic TNBC. Overall, PC use among all metastatic TNBC patients was low at 24.9% (732/2940). Age, race/ethnicity, insurance status, low-income quartile, and Charlson-Deyo comorbidity index did not affect PC use. Median OS was shorter in patients who had received PC compared to those who had not (10 vs 12 months, $p = 0.001$). There were more deaths among patients who received PC compared to those who did not (75% vs 65%, $p < 0.0001$).

Among patients with metastatic TNBC who were deceased ($n=1,985$), only 27.5% (545/1985) received palliative care prior to death. Rate of PC use did not differ by age, race/ethnicity, insurance status, low-income quartile, or Charlson-Deyo comorbidity index. In patients who received PC, median OS was not significantly different compared to those who had not received PC (7 vs 8 months, $p = 0.20$) (Table 1).

Conclusion:

We observed a low rates of palliative care utilization in patients with metastatic TNBC. Our analysis also showed an unexpected lower OS among patients who received PC, likely reflecting PC use late in the course of the disease, and among patients with high disease burden and/or those with an aggressive course. Given the importance of palliative care in symptom control, improving quality of life, reducing end-of-life chemotherapy use, and reducing cost of care, further studies are needed to understand barriers to PC use among breast cancer patients.

Table 1

Table 1

Characteristics of Deceased Metastatic TNBC Patients

Characteristic	Deceased Metastatic TNBC Patients (n = 1985)		p-value
	Palliative Care Received (n = 545)	No Palliative Care Received (n = 1440)	
Age (years)			
Median Age	63	63	0.78
≤39 – n(%)	34 (6)	96 (7)	0.85
40-64 – n(%)	264 (48)	687 (48)	
65-74 – n(%)	127 (23)	318 (22)	
≥75 – n(%)	120 (22)	339 (24)	
Race/Ethnicity			
Hispanic – n(%)	39 (7)	116 (8)	0.78
Non-Hispanic Black – n(%)	148 (27)	394 (27)	
Non-Hispanic White – n(%)	358 (66)	930 (65)	
Insurance Status/Income Quartile			
Uninsured – n(%)	30 (6)	67 (5)	0.43
Low-Income (lowest quartile) – n/total n*(%)	112/456 (25)	296/1247 (24)	0.72
Charlson-Deyo Comorbidity Index			
0 – n(%)	404 (74)	1094 (76)	0.58
1 – n(%)	81 (15)	200 (14)	
2 – n(%)	39 (7)	83 (6)	
3 – n(%)	21 (4)	63 (4)	
Median Survival (months)			
	7	8	0.20

*Total n for lowest income quartile, reflective of available data

PO4-07-01

Deep learning guided radiation therapy machine selection via a multi-headed dose prediction model

Presenting Author(s) and Co-Author(s):

A. Maniscalco. Medical Artificial Intelligence and Automation (MAIA) Lab, Department of Radiation Oncology, UT Southwestern Medical Center, United States

E. Mathew. Medical Artificial Intelligence and Automation (MAIA) Lab, Department of Radiation Oncology, UT Southwestern Medical Center, United States

D. Parsons. Medical Artificial Intelligence and Automation (MAIA) Lab, Department of Radiation Oncology, UT Southwestern Medical Center, United States

A. Rahimi. University of Texas Southwestern Medical Center, Dallas, Texas, United States

M. Arbab. UTSW, United States

P. Alluri. UTSW, United States

X. Li. UTSW, United States

M. Lin. Medical Artificial Intelligence and Automation (MAIA) Lab, Department of Radiation Oncology, UT Southwestern Medical Center, United States

S. Jiang. Medical Artificial Intelligence and Automation (MAIA) Lab, Department of Radiation Oncology, UT Southwestern Medical Center, United States

D. Nguyen. Medical Artificial Intelligence and Automation (MAIA) Lab, Department of Radiation Oncology, UT Southwestern Medical Center, United States

Background: Accelerated Partial Breast Irradiation (APBI) is gaining popularity for the treatment of appropriately selected breast cancer patients in lieu of whole breast irradiation regimens due to its comparable clinical outcomes and improved patient convenience and quality-of-life. Currently, several machines for delivery of APBI are available such as CyberKnife, Elekta Unity, Varian Ethos and Varian TrueBeam. Each treatment machine yields a unique distribution of radiation dose, so a given modality may afford particular advantages or liabilities based on a patient's anatomy. Existing methods for identification of an ideal modality that best suits a patient's unique anatomical features are generally lacking, manual, and resource intensive. To overcome this limitation and personalize modality selection, we propose a deep learning (DL) based multi-modality dose prediction model. The model takes a patient's computed tomography (CT) scan, segmented planning target volumes (PTVs) and segmented organs at risk (OARs) as input, and outputs predicted dose distributions for all trained modalities. Differences may then be evaluated between each radiation treatment modality's corresponding dose distribution and dose volumetric histograms (DVH) to select the optimal modality for each patient.

Methods: Our dataset contains 16 partial breast patients, each with 4 unique treatment plans generated for 4 distinct modalities – CyberKnife, Elekta Unity, Varian Ethos and Varian Truebeam. 10, 2, and 4 patients were dedicated to the train, validation and test datasets respectively. Our model's architecture is a U-net with a shared encoder and 4 independent dose decoders, in which each decoder predicts dose for one modality. Each training patient's CT scan, PTVs, OARs, and a PTV distance map are input to the model during training, and the shared encoder shares the input data's latent representations with each of the 4 decoders. The 4 distinct dose distributions from each training patient are used as labels for the 4 corresponding decoders to supervise model training. The mean squared error, mean squared log error, and DVH losses are minimized during model training. The model trained until

validation loss converged. The 4 dose distributions were predicted in ~ 1 minute per test patient, yielding 16 dose distributions in the test dataset. Model performance across the test dataset was evaluated by calculation of the mean absolute percent error (MAPE) of dose differences within the patient's body between the model's predicted doses and label doses, relative to patient prescription dose.

Results: The performance of the multi-modal dose prediction model was evaluated in terms of dose differences throughout each patient's body across the 16 test dose distributions as compared to the actual planned doses. The average MAPE of the multi-modal dose predictions was $1.27 \pm 0.38\%$ of a patient's prescription dose as compared to the actual planned dose across the test dataset. For a prescription dose of 3000 cGy, that corresponds to an average MAPE of 38.1 ± 11.4 cGy.

Conclusion: Our multi-modality dose prediction model's novelty lies in its rapid provision and comparison of accurate and detailed dosimetric data for each treatment modality. This model can empower treating radiation oncologists to make informed decisions in radiation therapy machine selection on a patient-by-patient basis, potentially optimizing radiation treatment plans by reduction of delivered dose to organs at risk.

Multi-modality dose prediction differences in terms of MAPE	MAPE for Modality #1: CyberKnife	MAPE for Modality #2: Elekta Unity	MAPE for Modality #3: Varian Ethos	MAPE for Modality #4: Varian TrueBeam	MAPE average & standard deviation across patient(s)
Patient #1	1.0413%	1.1962%	0.8211%	0.7247%	$0.9458 \pm 0.2131\%$
Patient #2	1.7674%	2.0344%	1.3753%	1.6792%	$1.7141 \pm 0.2717\%$
Patient #3	1.6525%	1.3437%	0.8876%	0.7002%	$1.1460 \pm 0.4325\%$
Patient #4	1.2250%	1.3195%	1.2102%	1.2733%	$1.2570 \pm 0.0496\%$
MAPE average & standard deviation across modality(ies)	$1.4216 \pm 0.3446\%$	$1.4734 \pm 0.3795\%$	$1.0736 \pm 0.2633\%$	$1.0943 \pm 0.4712\%$	-

PO4-07-02

Development of an Artificial Intelligence-based breast cancer detection model using Plasma Lipidomic Signature

Presenting Author(s) and Co-Author(s):

- A. Batarseh. BCAL Diagnostics, Sydney, New South Wales, Australia
- A. Lim. BCAL Diagnostics, Sydney, New South Wales, Australia
- C. Kehelpannala. BCAL Diagnostics, Sydney, New South Wales, Australia
- F. Vafae. OmniOmics.ai, Pagewood, New South Wales, Australia
- F. Koch. OmniOmics.ai, Pagewood, New South Wales, Australia
- D. Pascovici. Insight Stats, Croydon Park, New South Wales, Australia
- D. Li. BCAL Diagnostics, Sydney, New South Wales, Australia
- K. Heffernan. BCAL Diagnostics, Sydney, New South Wales, Australia
- G. Lamoury. Northern Sydney Cancer Centre | University of Sydney, St Leonards, New South Wales, Australia
- B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

Background:

Mammography is the current diagnostic standard for breast cancer screening and monitoring. However, accessibility challenges, accuracy issues and patient discomfort all contribute to reduced patient compliance and utilization, resulting in a need for more effective diagnostic tools. An artificial intelligence (AI)-based lipidomic blood test may add significant value to early breast cancer detection rate and improve outcomes for patients. We have previously reported a series of lipidomic studies (n=793) and derived a lipid signature from plasma-enriched extracellular vesicles (EVs) that effectively distinguished people with localized breast cancer from cancer-free controls. Here we report the development of a breast cancer detection AI model from lipidomic data assessed directly using plasma samples.

Methods:

Lipids in both EVs and plasma collected from fasted breast cancer and control blood samples (n=256) were extracted and analysed by liquid chromatography-high resolution mass spectrometry (LC-HRAM-MS). Over 400 manually curated lipids were quantified. A bootstrapped analysis using Boruta, a robust and statistically rigorous feature selection algorithm based on random forest feature importance, was employed to identify cancer discriminatory lipid signatures in EV and plasma lipidomes consistently selected across 2000 bootstrap samples. The resulting lipid signature was then used to train an ensemble of 18 distinct machine learning models for cancer status prediction using a majority vote to aggregate the individual predictions. Model performance and variability were assessed over 2000 iterations of leave-group-out cross-validation (LGOCV) using an 80/20 train-test split. Average patient-level predictions across LGOCV iterations were recorded for both EV- and plasma-derived models and the two modalities were compared using an exact paired samples test (McNemar's test).

Results:

Both the EV- and plasma-derived lipid signatures performed well in distinguishing breast cancer samples from controls. The development of a bioinformatics AI pipeline enabled the creation of a robust ensemble model achieving an F1 score of 0.89 in plasma with LGOCV. The final

plasma ensemble predictive performance of 86.1% ($\pm 4.5\%$) in accuracy, 91.4% ($\pm 5.4\%$) in sensitivity, and 78.7% ($\pm 8.6\%$) specificity was achieved, which is comparable to that of EV (accuracy: $86.1 \pm 4.4\%$, sensitivity: $90.4 \pm 5.3\%$, specificity: $80.2 \pm 8.7\%$). Paired samples analysis using McNemar's test indicated no significant differences between models trained on EV- and plasma-derived lipid signatures in either the sensitivity ($p=0.65$), specificity ($p=0.49$), or accuracy ($p=0.42$).

Conclusion:

The initial study demonstrated the high performance of a plasma-enriched extracellular vesicle-derived lipid biomarker signature for early breast cancer detection. Direct assessment of the lipidomic signature from plasma showed promise in simplifying the test. Assessing plasma directly offered advantages in terms of scalability, higher throughput, and ease of implementation. Further verification of the lipid signature in an upcoming study involving 500 plasma samples is planned. Ongoing studies will further optimize the plasma lipidomic signature and strengthen our AI pipeline. These findings support the potential clinical application of AI-based lipidomic profiling as a blood-based screening tool for breast cancer detection.

Disclosure of Interest: This project is sponsored by BCAL Diagnostics Limited.

PO4-07-03

Machine learning breast cancer risk prediction using sequential past mammograms - a pilot study

Presenting Author(s) and Co-Author(s):

L. Leong. Department of Diagnostic Radiology, Singapore General Hospital, Singapore

M. Xu. Institute for Infocomm Research, A*STAR / National University of Singapore, United States

W. Huang. Institute for Infocomm Research, A*STAR, United States

E. Zhang. Institute for Infocomm Research, A*STAR / Nanyang Technological University, Singapore

E. Loh. Singapore General Hospital, United States

S. Teo. Department of Diagnostic and Interventional Imaging, KK Women's and Children's Hospital, Singapore

G. Lim. Kk Womens and childrens Hospital, Singapore

V. Tan. National Cancer Centre Singapore, United States

Y. Sim. Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, Singapore

F. Strand. Breast Imaging Unit, Karolinska University Hospital, United States

R. Tan. Department of Breast and Gynaecology, Division of Medical Oncology, National Cancer Centre Singapore, Singapore

Background and Aim

Some studies have reported the use of mammogram AI deep learning algorithms to accurately predict the risk of future breast cancer development in women. In these studies, random and unrelated mammograms were independently used for training of the AI model. We propose a novel deep learning system using sequential past mammograms instead of random studies and aimed to determine if it can further improve risk prediction in a pilot study.

Methods

Pre-training of the backbone of a Swin-transformer machine learning model was performed by applying region-of-interest lesional masks of benign and malignant on a training set of 1644 mammograms derived from the open-access Curated Breast Imaging Subset of Digital Database for Screening Mammography dataset. To further develop the model, deep learning training and validation were performed on the Cohort of Screen-age Women (CSAW) open-access screening mammogram set which was derived from the long term data of 873 women who developed breast cancer for the first time and 7850 non-cancer women. We then compared the diagnostic accuracy of a model using sequential past mammograms for training against the standard, non-sequential model. For the sequential model, imaging segmentation of the potential cancer site on mammography was performed on all past, pre-cancer mammograms obtained within 60 to 2555 days of cancer diagnosis in the pre-processing stage for breast cancer cases. AI training was then carried out by combining the pre-cancer mammograms belonging to the same woman in a temporal sequence using a transformer encoder. The learning rate started from 1e-6 and decayed 10 times every 10 epochs. For the non-sequential model, we removed the temporal encoder and used random, unrelated mammogram studies for training. Validation was performed on a dataset consisting of 75 pre-cancer mammograms from breast cancer cases and 69 mammograms from non-cancer cases.

Results

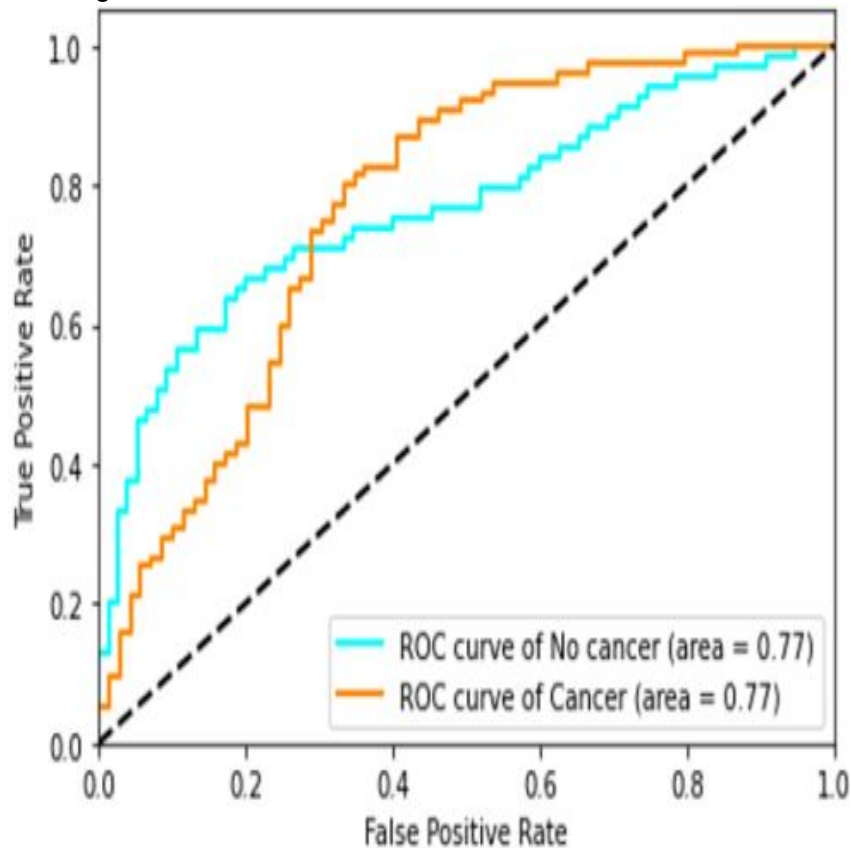
Sensitivity, specificity and overall accuracy on the validation set were 77.3% (58/75), 68.1% (47/69) and (105/144) 72.9% respectively for the sequential model compared to 69.3% (52/75), 69.6% (48/69) and 69.4% (100/144) respectively for the non-sequential model.

Conclusion

The study showed that deep learning breast cancer risk prediction can be further improved by using sequential past mammograms instead of random mammograms for AI model training. This can also potentially enhance other AI risk prediction models that employ combined mammogram and traditional breast cancer clinical risk factors. A larger validation study will be useful.

Contact information: email Lester Leong at lester.leong.c.h@singhealth.com.sg

ROC curve for breast cancer risk prediction using AI deep learning training with sequential past mammograms.



PO4-07-04

Breast Cancer HER2 Status Prediction from Hematoxylin-Eosin Stained Images Using Point Cloud Transformer

Presenting Author(s) and Co-Author(s):

B. Li. CAS Key Laboratory of Molecular Imaging, Institute of Automation, Chinese Academy of Sciences, Beijing, China (People's Republic)

Z. Liu. CAS Key Laboratory of Molecular Imaging, Institute of Automation, Chinese Academy of Sciences, Beijing, China (People's Republic)

Y. Du. CAS Key Laboratory of Molecular Imaging, Institute of Automation, Chinese Academy of Sciences, China (People's Republic)

J. Tian. CAS Key Laboratory of Molecular Imaging, Institute of Automation, Chinese Academy of Sciences, United States

Background: Human epidermal growth factor receptor-2 (HER2) status is a key factor in determining the treatment strategy for breast cancer patients. Patients with HER2-positive status are more likely to benefit from HER2-targeted therapy, leading to improved prognosis. In current routine diagnostic practice, pathologists utilize Hematoxylin-Eosin (HE) stained tumor tissues for histopathological assessment. Subsequently, IHC assessment and/or FISH test are performed to evaluate the HER2 status. However, manual assessment results may be affected by tissue usability and observer-subjectivity. Therefore, there is a necessity to predict the HER2 status directly from HE images to minimize time and cost while ensuring enhanced consistency.

Methods: We identified 608 HE diagnostic slides with HER2 status from The Cancer Genome Atlas in breast cancer (TCGA-BRCA). It contains 474 HER2-positive slides (IHC 3+, IHC 2+ and FISH positive) and 134 HER2-negative slides (IHC 0, IHC 1+, IHC 2+ and FISH negative). To analyze these slides, we first tiled the HE images into patches with a fixed size of 256×256 at 20× magnification. Then the patch-level feature was derived from a self-supervised pretrained transformer. Meanwhile, artificial intelligence (AI) methods are adopted to predict HER2 status from HE images. To capture the long-distance patch relations within a slide, we represented the patches as distinct points and utilized the Point Cloud Transformer model for HER2 status prediction. Specifically, 1024 patches (points) in each slide were randomly selected and input into the Point Cloud Transformer. This process yielded a slide-level prediction result for the HER2 status. Furthermore, Graph Attention Network (GAT), Graph Sample and Aggregate Network (Graph SAGE), and hierarchical Point Cloud Network (PointNet++) were adopted to compare the effectiveness of HER2 status prediction using Point Cloud Transformer. Of note that Point Cloud Transformer incorporated attention mechanisms for point aggregation compared to PointNet++.

Results: The Point Cloud Transformer was trained with 5-fold cross-validation, and the area under the curve (AUC) of the receiver operating characteristic (ROC) curve was reported. The performance of point-based models outperformed the graph-based models. And the Point Cloud Transformer achieved the highest AUC of 0.7496 among all AI models. The detailed AUC for each AI model was shown in Table 1.

Conclusion: Our study revealed that the HER2 status can be predicted directly from HE images without using IHC images. Furthermore, point-based models have demonstrated the ability to capture long-distance relations among patches, surpassing graph-based models in terms of prediction performance. To further enhance performance, we adopted a better point

aggregation method, such as the Point Cloud Transformer, which held promise for further improving the accuracy of predictions in the future.

Table 1: AUC of HER2 status prediction from HE images in the TCGA-BRCA dataset

Method	GAT	Graph SAGE	PointNet++	Point Cloud Transformer
AUC	0.6640	0.6737	0.7201	0.7496

PO4-07-05

Clinical evaluation of image-based risk profiling in breast cancer histopathology and comparison to an established gene expression assay

Presenting Author(s) and Co-Author(s):

S. Robertson. Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, United States

Y. Wang. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, and Stratipath AB, Stockholm, Sweden, United States

W. Sun. Department of Oncology-Pathology, Karolinska Institutet, and Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden, United States

E. Karlsson. Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, United States

S. Kang Lövgren. Stratipath AB, Stockholm, Sweden, United States

M. Rantalainen. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, and MedTechLabs, BioClinicum, Karolinska University Hospital, Stockholm, Sweden, United States

J. Hartman. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden, United States

Background: Among oestrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative early breast cancer, a significant proportion of patients are categorised as intermediate risk, based on classic clinico-pathological variables, thus providing limited information to guide adjuvant chemotherapy decisions. Prognostic risk profiling is an integrated part of modern breast cancer diagnostics to provide additional risk information for this patient group. Among the established prognostic assays based on gene expression, the Prosigna assay is widely used and provides an individual risk of recurrence (ROR) score and identifies intrinsic subtypes with associated survival outcomes. Pioneering artificial intelligence-based precision diagnostics, Stratipath Breast, is a deep learning-based image analysis tool that utilises digitised histopathological whole slide images to stratify intermediate risk patients in terms of risk of recurrence.

Materials and methods: The study included 234 invasive breast tumours from patients with early ER-positive HER2-negative breast cancer, clinically assessed as intermediate risk tumours and eligible for chemotherapy. All tumours had therefore previously been analysed by the Prosigna assay in clinical routine at point of diagnosis between 2020 and 2022 at the Karolinska University Hospital and Södersjukhuset, Stockholm, Sweden. Clinicopathological data including Prosigna results (ROR score, risk group and intrinsic subtype) were extracted from medical records, along with the corresponding archived haematoxylin and eosin (HE)-stained formalin-fixed paraffin-embedded tissue slides. The HE slides were subsequently digitised and analysed by the Stratipath Breast tool. The agreement between the two tests for risk stratification was evaluated in this real-world breast cancer case series.

Results: The Prosigna assay classified 76 (32.5%), 110 (47.0%) and 48 (20.5%) tumours as low, intermediate and high risk, respectively. The Stratipath Breast analysis identified 116 (49.6%) tumours as low risk and 118 (50.4%) as high risk. Among Prosigna intermediate risk

tumours, 52 (47.3%) were stratified as low risk and 58 (52.7%) as high risk by Stratipath Breast. The overall agreement between the two tests for low risk and high risk groups was 71.0%, with a Cohen's linear kappa of 0.42. Twelve of the 48 Prosigna high risk cases were classified as Stratipath low risk. ROR scores were higher in the Stratipath high risk group compared to the low risk group ($p < 0.001$), across all cases as well as in the Prosigna intermediate group. Among the 176 histological grade (NHG) 2 tumours, 97 (55.1%) and 79 (44.9%) were stratified as Stratipath low risk and high risk, respectively, whereas 66 (37.5%), 83 (47.2%) and 27 (15.3%) were stratified as Prosigna low, intermediate and high risk, respectively. The majority of NHG1 (10 of 12) and NHG3 (37 of 46) tumours were stratified as Stratipath low risk and high risk, respectively. For both risk profiling tests, NHG and Ki67 proliferation index differed between risk groups.

Conclusions: In this study of clinically assessed intermediate risk ER-positive HER2-negative breast cancer, we observed a moderate agreement between Prosigna and Stratipath Breast for low risk and high risk groups. In addition, image-based risk profiling stratified more of the NHG2 tumours as high risk.

PO4-07-06

Development of MRI-based Radiomics Nomogram for the Prediction of Recurrence in Patients with Luminal-type Breast Cancer: A Nested Case-Control Study

Presenting Author(s) and Co-Author(s):

M. Song. Asan Medical Center, Seoul, Republic of Korea

H. Shin. Asan Medical Center, University of Ulsan College of Medicine, United States

Purpose: The aim of this study was to develop a radiomics nomogram using breast MRI data and preoperative pathologic information to predict oncotype DX recurrence score (RS) in patients with estrogen receptor-positive early-stage breast cancer (EBC).

Materials and methods: In this retrospective study, a total of 493 patients with EBC, diagnosed through core needle biopsy and who underwent preoperative breast MRI at a single institution between 2011 and 2017, were included. The patients were categorized based on RS, age at surgery, and nodal status, as suggested by the TAILORX trial, and out of the included patients, 249 were identified as likely to benefit from chemotherapy, while 244 were deemed safe to forgo chemotherapy. Radiomic features were extracted from three-dimensional segmentations of each tumor, and computer-extracted image phenotypes (CEIP) were generated from early post-contrast T1-weighted images, percent enhancement (PE) maps, and signal enhancement ratio (SER) maps. The patient cohort was divided into a training set (n=329) and a validation set (n=164). Feature selection and radiomics score construction were performed using elastic net, and a prediction model was developed using multivariate logistic regression analysis. The radiomics score, along with independent pathologic risk factors, was incorporated into a radiomics nomogram. Internal validation was conducted using an independent validation set (n=164).

Results: The radiomics score, composed of 24 selected CEIPs, demonstrated a significant association with recurrence prediction (C-index, 0.769 for training set and 0.745 for validation set). The independent pathologic predictors included in the nomogram were histology, estrogen receptor status, progesterone receptor status, nuclear grade, histologic grade, HER1, CK56, P53, and Ki67 status, with a C-index of 0.858 for the training set and 0.774 for the validation set. Adding the radiomics score to the pathologic nomogram resulted in incremental values of 0.054 and 0.092, respectively. The radiomics nomogram showed favorable prediction of low-risk RS, with a C-index of 0.912 for the training set and 0.866 for the validation set.

Conclusion: This study demonstrated that an MRI-based radiomics nomogram incorporating the radiomics score and preoperatively obtained pathologic data can effectively predict oncotype DX RS and the benefit of adjuvant chemotherapy in EBC patients. The model improves risk assessment availability and timeliness for patients with EBC.

PO4-07-07

The construction and clinical research value of the prediction model of sentinel lymph node metastasis based on indocyanine green fluorescence quantification in breast cancer

Presenting Author(s) and Co-Author(s):

Y. Wu. Biobank, The First Affiliated Hospital with Nanjing Medical University, United States

W. Zhang. Department of General Surgery, The First Affiliated Hospital with Nanjing Medical University, United States

j. tang. The First Affiliated Hospital with Nanjing Medical University, United States

Objective: To establish a prediction model of sentinel lymph node metastasis by quantitative indocyanine green fluorescence analysis in breast cancer.

Methods: From May 2023 to June 2023, 20 patients with breast cancer underwent modified radical mastectomy in the General Surgery Department of Jiangsu Provincial People's Hospital were chosen for research and analysis. Sentinel lymph node were taken from all the patients. The sentinel lymph nodes were located by using the double staining method of subcutaneous injection of Methylene blue and intravenous injection of indocyanine green. The postoperative pathology is used as the standard for evaluating the presence or absence of metastatic cancer in lymph nodes. At the same time, the transcutaneous fluorescence of sentinel lymph node was recorded and the peak time of fluorescence intensity curve was plotted. To establish a logistic diagnostic prediction model and fluorescence threshold, the sentinel lymph node was incised during operation and the fluorescence of sentinel lymph node was recorded again. The criteria for ICG positive determination are determined by the Youden index, which was used to judge the lymph nodes above the threshold in the Logistic diagnostic prediction model. Lymph nodes below the threshold determined in the Logistic diagnostic prediction model are the criteria for ICG negative determination. Cases with less than 3 sentinel lymph node were excluded.

Results: 19 cases were ultimately selected. Methylene blue staining data was taking as the judgment standard of sentinel lymph node. Fluorescence imaging was 100% in 14 patients, 66.7% (2/3) in 1 patient, and 125%-150% (5/4-6/4) in 4 patients. Fluorescence quantification values below 2.91 are negative lymph nodes, and values above 4.69 are positive lymph nodes. Moreover, caution is required between 2.91 and 4.69. Combining with the fluorescence dynamic attenuation curve, the positive group has a plateau curve, while the negative group mostly has a decline curve. Combining fluorescence quantification with fluorescence dynamic attenuation curve, the diagnostic rate of positive lymph nodes has a lower false negative rate compared to simple fluorescence quantification and fluorescence dynamic attenuation curve.

Conclusion: The quantitative difference value of indocyanine green fluorescence angiography can be used to predict the positive metastasis of sentinel lymph node in breast cancer, making it an attempt to exempt sentinel lymph node biopsy.

Keywords: Indocyanine green; Fluorescence quantitative analysis; Fluorescence dynamic attenuation curve; Sentinel lymph node

PO4-07-08

Impact of an MRI/US fusion imaging for preoperative planning using non-wire localization technique in breast conserving surgery in patients with non-mass enhancement on MRI. A prospective multicenter study.

Presenting Author(s) and Co-Author(s):

S. Nakano. Aichi Medical University Hospital, Aichi, Japan, Japan

M. Futamura. Department of Breast Surgery, Gifu University Hospital, Japan

K. Kamei. Department of Surgery, Ogaki Municipal Hospital, United States

T. Uematsu. Department of Breast Imaging and Breast Intervention Radiology, Department of Clinical Physiology, Shizuoka Cancer Center Hospital, United States

M. Yoshida. Department of Breast Surgical Oncology, Showa University School of Medicine, United States

S. Akashi-Tanaka. Department of Surgical Oncology, Tokyo Women's Medical University, United States

J. Sakakibara. Chiba University, United States

I. Isomoto. Department of Radiology, St. Francis Hospital, United States

H. Satake. Department of Radiology, Nagoya University Graduate School of Medicine, United States

m. takahashi. Department of Surgery, Keio University School of Medicine, United States

M. Hatono. Department of Breast and Endocrine Surgery, Okayama University Hospital, United States

J. Araki. Department of Radiology, Tokyo Metropolitan Tama Medical Center, United States

[Background] Preoperative breast MRI is used to evaluate for additional and extent disease for newly diagnosed breast cancer patients with dense breasts. The potential benefit of preoperative MRI is still being controversial. However, when breast conserving surgery (BCS) is considered for non-mass enhancement (NME) on MRI, the precise image-guided localization is required. Although breast ultrasound (US) plays an adjunctive role in evaluation of MRI findings in preoperative planning for BCS, NME is less likely than a mass or focus to have a US correlate. Furthermore, the presence of NME increases the re-operation rate in BCS because of the difficulty in evaluating the tumor margin. An MRI/US fusion imaging has recently been developed that uses either real-time virtual sonography TM (RVS) or volume navigation TM (Vnav), and can overlay an US with the MRI image of the same site in real time by using magnetic position tracking system. The purpose of this prospective multicenter study was to evaluate the effect of MRI/US fusion imaging for preoperative planning using non-wire localization technique in BCS in patients with NME.

[Methods] In 3 Japanese hospital, 13 patients who had lesions with NME that exceeded the US hypoechoic area were enrolled in this study from 2019 to 2022. Written informed consent was acquired, and then an additional supine MRI using a body surface coil was performed. During preoperative planning before BCS, RVS/Vnav was used to determine the NME enhancing area and to mark the area on the skin. Tissue markers were inserted under US at a location assessed by RVS/Vnav as the edge of extent of NME. We analyzed both the surgical margin positivity rate and the reoperation rate.

[Results] The preoperative diagnosis by core needle biopsy were 6 DCIS and 7 invasive ductal

carcinoma. NME distribution types were 7 segmental, 3 focal, 2 linear 4 and 1 regional. The median diameters of the NME and hypo-echoic lesions were 31 mm (range: 18–39 mm) and 16 mm (range: 9–32 mm), respectively ($p = 0.0005$). After confirming the localization of the tissue marker with intraoperative US, 12 lumpectomy and 1 quadrantectomy were conducted. The median specimen weight was 63g (range: 54-105g). In the final pathologic diagnosis of excised specimens were 5 DCIS and 8 IDC. In 8 cases (62%), the pathologic diameter was larger than the US diameter. All surgical margins were negative. None of the patients required additional resection.

[Conclusions] The findings of study suggest that preoperative planning using non-wire localization technique under MRI/US fusion imaging for BCS in patients with NME could improve both a surgical margin positive rate and a reoperation rate.

PO4-07-09

CONTRAST-ENHANCED MAMMOGRAPHY IN LOCAL STAGING OF SCREEN-DETECTED BREAST CANCER: ADDITIONAL LESIONS AND CHANGES TO CLINICAL MANAGEMENT

Presenting Author(s) and Co-Author(s):

C. MacCallum. Royal Melbourne Hospital, Australia

K. Elder. Royal Melbourne Hospital, Melbourne, VIC, Australia

C. Nickson. Daffodil Centre, The University of Sydney, a joint venture with Cancer Council New South Wales. Melbourne School of Population and Global Health, The University of Melbourne, Australia

K. Ruecker. Royal Melbourne Hospital, United States

A. Park. Royal Melbourne Hospital, Melbourne, VIC, Australia

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

Background

BreastScreen Australia, a mammographic population screening program, provides assessment of suspected breast cancer to the point of diagnosis using a combination of conventional imaging and percutaneous biopsy. Comprehensive local staging, not performed at BreastScreen, determines the extent of disease and may identify additional clinically significant breast abnormalities. Local staging options include completion of bilateral mammographic work-up, ultrasound, and/or contrast-based imaging (CBI) (magnetic resonance imaging (MRI) or contrast-enhanced mammography (CEM)), with biopsy as required.

We introduced CBI for local staging after diagnosis of screen-detected cancer at our academic hospital breast service in Melbourne, Australia. We report diagnostic findings for otherwise occult disease and their impact on treatment decisions in women who underwent CEM for local staging.

Material and methods

Women with screen-detected breast cancer who underwent CEM for local staging between November 2018 to April 2022 were identified retrospectively. The reporting breast-specialised radiologist compared BreastScreen and CEM images to identify additional enhancing abnormalities. Additional abnormalities were further investigated with preoperative percutaneous biopsy, surgical biopsy, or problem-solving CBI. Additional CEM-detected abnormalities were documented, with invasive cancer or DCIS recorded as true positive (TP) and any other findings as false positive (FP). Impact on surgical decisions was assessed.

Results

204 patients underwent CEM. 62/204 (30%) patients had 76 additional abnormalities, of which 36 (47%) were TP and 40 (53%) FP. CEM identified otherwise occult malignant lesions in 30/204 (15%) patients. TPs comprised 75% invasive cancers and 25% DCIS. 83% (30/36) of malignant abnormalities were ipsilateral to the index lesion, while 17% (6/36) were contralateral. The majority of additional invasive cancers were Grade 2 (20/27, 74.1%), followed by Grade 1 (4/27, 14.8%) then Grade 3 (3/27, 11.1%). All additional invasive cancers had the same phenotype as the patient's index cancer (ER+/HER2-), except for one abnormality which was ER+/HER2+ where the index cancer was ER+/HER2-. The FP abnormalities consisted of normal breast tissue (20/40, 50%), benign lesions (16/40, 40%) and atypical proliferative lesions (4/40, 10%).

Occult malignancies were more common for patients with higher background parenchymal enhancement (20% for moderate/marked vs 4% for minimal/mild, $p=0.0023$), with no statistically significant differences found by breast density (BIRADS A or B = 12%, vs BIRADS C or D = 20%, $p=0.23$) or by age (40-49=38%, 50-59=13%, 60-69=13%, $\geq 70=19%$, $p=0.88$). Additional abnormalities found on CEM resulted in surgical management change in 45/204 (22%) patients, including wider resection (24/45), conversion to mastectomy (8/45), contralateral breast surgery (6/45), additional ipsilateral excision (5/45), and bracketing (2/45).

Conclusions

The use of CEM for local staging of screen-detected breast cancers identified otherwise occult malignancy in 15% of patients. Age and mammographic density did not identify groups at minimal risk of additional findings. Pathology of additional malignancy suggests it is clinically significant. CEM may improve local staging and direct appropriate management of screen-detected breast cancers.

PO4-07-10

Validation of An Ultrasound-Based Scoring System of Axillary Metastasis in Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Van Decar. Brooke Army Medical Center, United States

E. Carpenter. Brooke Army Medical Center, United States

A. Adams. Brooke Army Medical Center, United States

J. Shore. Brooke Army Medical Center, United States

I. Dragusin. Brooke Army Medical Center, United States

E. Davis. Cancer Vaccine Development Program, United States

C. Tork. Brooke Army Medical Center, United States

R. Krell. Brooke Army Medical Center, United States

T. Graybeal. Brooke Army Medical Center, United States

K. Clifton. Washington University in St Louis School of Medicine, United States

A. Buckley. Washington University School of Medicine in St. Louis, United States

G. Clifton. Brooke Army Medical Center, United States

Introduction:

Ultrasound is the imaging modality of choice in the evaluation of axillary involvement in breast cancer. Our group previously created a scoring method to predict axillary lymph node metastasis (ALNM) based on ultrasound characteristics. In this study we validated the model and tested it among different Memorial Sloan Kettering Breast Cancer Sentinel Lymph Node Metastasis Nomogram¹ (MSK) subgroups.

Methods:

The ultrasound score (table 1) was previously developed using data collected at a single institution from 2019 – 2021 by allocating points based on the regression coefficients of variables found to significantly predict ALNM. Subsequent evaluation of the discrimination of this model found it was robust to different patient demographic and tumor characteristics based on receiver operating characteristic curve analysis². In this study, we validated the test statistics of our score at an outside institution. We also pooled patients from both institutions and evaluated the score performance in different MSK subgroups by the likelihood for sentinel node metastasis based off of clinical and pathologic data without accounting for imaging findings.

Results:

Between 2019-2021, 140 patients with breast cancer were analyzed for validation of the axillary ultrasound scoring system and when combined with the dataset of patients from the index institution, 358 pooled patients were stratified by predicted ALNM positivity according to MSK. In the validation cohort, the NPV for low risk (0-1) scores was 87%, while the PPV for high-risk (5+) scores was 71%. Overall in the combined cohort, 241 (67%) patients had low risk (0-1) axillary ultrasound scores and 33 (9%) had high risk (5+) scores. In this combined cohort, NPV was 84% (203/241 low-risk score patients were node negative), while PPV for high-risk scores was 85% (28/33 high risk score patients were node positive). When analyzed according to level of MSK predicted ALNM rates, for patients with < 50% predicted ALNM positivity, the NPV of low-risk scores was 87-89% and the PPV for high-risk axillary scores was 100%. For patients

with >50% predicted ALNM positivity, the NPV of low-risk scores was 66% and the PPV of high-risk scores was 82%.

Conclusions:

A scoring system to predict ALNM among biopsy proven breast cancer patients undergoing upfront surgery was successfully developed from a multivariate model based on axillary ultrasound characteristics. This model was validated at a separate institution. The scoring system shows advantageous negative and positive predictive values for axillary node metastasis, especially among patients with < 50% predicted nodal involvement based on the MSK nomogram. This data may help foster better communication about ALNM risk between radiologists and treating clinicians to inform treatment decisions.

Scoring System for Likelihood of ALNM based on Ultrasound Characteristics

Predictor	Level	Score Value
Ultrasound Length (mm)	≤ 10 mm	0
	≤ 20 mm	1
	> 20 mm	2
Cortical Thickness (mm)	≤ 3 mm	0
	> 3 mm	1
Presence of Hilum	Yes	0
	No	2
Shape	Oval	0
	Irregular	1
	Round	4
Table 1. Scoring System for Likelihood of ALNM based on Ultrasound Characteristics.		

PO4-07-11

FDG-PET is superior to bone scintigraphy for the detection of bone metastases in breast cancer patients

Presenting Author(s) and Co-Author(s):

L. Kenny. Imperial College London, London, England, United Kingdom

M. Tin-U. Imperial College London, England, United Kingdom

Background: Bone is the commonest site for metastases in breast cancer patients, with up to 44% of patients having bone as their sole site of metastatic disease. Patients are at increased risk of morbidity from skeletal related events (SRE) from bone metastases due to pathological fractures and spinal cord compression. Early diagnosis is crucial so that bone modifying agents can be used to prevent SREs and other agents such as CDK4/6 inhibitors can be considered. Bone scintigraphy is the most widely performed first investigation for patients at high risk or symptomatic from bone metastases.

Methods: We performed a meta-analysis comparing FDG-PET and bone scintigraphy using PubMed, Science Direct, and Embase for the literature search. 1009 patients were included in the study. Data for 2x2 contingency tables was selected and QUADAS-2 was used for quality assessment. Diagnostic accuracy was performed using Graph pad Prism 9.5.1 and R studio 2022. Pooled sensitivity and specificity of FDG-PET/CT was 96.6% (95% CI=91.5%-98.7%) and 96.8% (95% CI=82.1%-99.5%) respectively. Respective results for BS were 88.3% (95% CI=79.8%-93.5%) and 81.3% (95% CI=63.1%-91.7%). Sensitivity and specificity of FDG-PET/CT was significantly higher than BS (P=0.0063, P= 0.0068, respectively). The diagnostic odds ratio and area under ROC curve were significantly higher for FDG-PET/CT than BS (654.36 vs 35.24, and 0.980 vs 0.877, respectively).

Conclusion: FDG-PET is superior to bone scintigraphy for the detection of bone metastases in breast cancer. The benefits of replacing BS with FDG-PET/CT are evident. However other technologies such as DW-MRI should be considered. Large multicentre prospective trials with strict FDG-PET/CT imaging protocols compared to DW-MRI both for disease detection and monitoring of response are required to strengthen the evidence in this field, to help inform imaging guidelines and best practices in the future. Newer technologies such as [¹⁸F]estradiol (FES)-PET and [¹⁸F]GE-226 for HER2 expression also warrant further investigation in ER positive and HER2 positive breast cancer.

PO4-07-12

Concordance of Breast ultrasound (US) and breast Magnetic resonance imaging (MRI) for local (tumor size and node involvement) staging in patients with breast cancer before neoadjuvant chemotherapy treatment (NACT).

Presenting Author(s) and Co-Author(s):

A. Pareja. Fundacion CTIC, United States

S. Cervera. Fundacion CTIC, United States

M. Bravo. Fundacion CTIC, United States

S. Franco. Luis Carlos Sarmiento Angulo Cancer Treatment and Research Center CTIC, Bogotá D.C., Colombia, United States

J. Caicedo. Fundacion CTIC, United States

W. Mantilla. Luis Carlos Sarmiento Angulo Cancer Treatment and Research Center CTIC, United States

Introduction Breast cancer is the main cause of cancer-related deaths in Colombia, with many patients diagnosed with locally advanced (LABC) or metastatic disease. In the locally advanced setting, the use of NACT offers the opportunity of downstage BC and allows to adjust therapy based on the response, but, considering emerging therapies available in LACB as immunotherapy in triple negative BC (TNBC), dual HER2 blockade in HER2 positive BC or adjuvant iCDK 4/6 in luminal BC the importance of accurate pre NACT staging has become critical, we aim to explore the concordance of US and MRI as a method of BC staging in the NACT setting. **Methods:** EVA (Evidence – Verification – Analysis) is a prospective institutional multi-tumor registry that aims to gather demographic, clinical, and genomic variables from patients treated at Fundación CTIC, in Bogota Colombia, based on this registry, we recover the data from the patients that were treated with NACT and were staged with a US and an MRI before the initiation of treatment, dis concordance between the two methods was establish if a different Tumor size (change from T2 to T3 for example), a different node stage (chance from N2 to N2) or the discordant detection of multifocal disease, a descriptive analysis were performed. **Results:** 30 Patients were included in the analysis, The mean age was 51,7 years (28 – 79), 15/30 patients were ER of PgR positive BC, 11/30 HER2 positive BC (7/11 HER2 positive and 4/11 Luminal B HER2 positive) and 4/30 were TBNC. 28/30 patients were ductal carcinoma, with 1/30 lobular carcinoma and 1/30 medullary carcinoma. Mean ADC in luminal A-like BC was 0,9, 0,66 (0,4 – 0,9) in luminal-B HER2 negative BC, 0,77 (0,4 – 0,9) in HER2 positive BC, and 0,83 (0,7 – 0,9) in TNBC Concordance between US and MRI was only seen in 14/30 patients. The causes of discordance were Tumor size on 9/16 (change from T2 to T3 or evidence of pectoral muscle involvement), node staging on 11/16 (8/11 patients were node down staged based on MRI image), and evidence of multifocal disease not seen in the US on 2/16. **Conclusion:** Considering the high discordance rate between US and MRI, and the implications of accurate staging before NACT, we think that MRI should be considered as a routine evaluation before NACT. This is a small sample so a larger cohort would be needed for confirmation of this observation, based on the design of EVA, we expect to further evaluate the significance and uses in the NACT setting.

PO4-08-01

Methylsterol monooxygenase 1 (MSMO1) modulates endoplasmic reticulum stress through cholesterol metabolic reprogramming to alter chemotherapy sensitivity in breast cancer

Presenting Author(s) and Co-Author(s):

H. Ren. Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

L. Wangxu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, 200032 China, United States

Y. Chi. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, China, United States

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China. Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Background

Endoplasmic reticulum stress (ER stress) is a process in which cells activate unfolded protein response and other signaling pathways in response to misfolded and unfolded protein aggregation and calcium ion balance disturbance in the endoplasmic reticulum cavity. Depending on the intensity of endoplasmic reticulum stress, it can not only induce chaperone expression to play a protective effect, but also induce apoptosis independently. Metabolic reprogramming is one of the characteristics of tumor, which refers to the metabolic changes that cells make in response to various stimuli. Here, we demonstrate that methylsterol monooxygenase 1 (MSMO1) regulates cellular cholesterol metabolism and influences breast cancer susceptibility to chemotherapy by regulating the relative intracellular T-MAS content.

Methods

RNA-seq was performed on core needle biopsy samples from 26 patients receiving neoadjuvant chemotherapy for breast cancer to screen for genes that may influence neoadjuvant chemotherapy sensitivity. Cell proliferation, CCK8 assay and apoptosis assay were performed for MSMO1 phenotype study. Transmission electron microscopy (TEM) was conducted to visualize the structure of endoplasmic reticulum. Western Blot was used to detect the activation level of the unfolded protein response pathway. The relative content of sterols in MSMO1 knockdown cells was detected by targeted lipid mass spectrometry. AO/PI staining of breast cancer organoids was performed to verify the effect of MSMO1 metabolic substrate T-MAS on chemotherapy drug sensitivity.

Results

RNA-seq of core needle biopsy samples from breast cancer patients receiving neoadjuvant chemotherapy suggested that MSMO1 was highly expressed in non-pCR patients, and clinical survival data suggested that MSMO1 was associated with poor prognosis in patients with all types of breast cancer, suggesting that MSMO1 might be related to chemotherapy sensitivity of breast cancer. Phenotypic experiments revealed that MSMO1 regulates chemotherapy sensitivity of breast cancer both in vivo and in vitro. Ectopic overexpression of MSMO1 promoted cancer cell resistance to chemotherapy. To uncover the underlying mechanisms, RNA-seq of MSMO1 knock-down cells were carried out and identified that MSMO1 was

associated with ER stress. TEM and western blot assay indicated that downregulation of MSMO1 expression leads to endoplasmic reticulum swelling and activation of the unfolded protein response. Considering that MSMO1 is a cholesterol metabolizing enzyme, targeted lipids mass spectrometry was performed to detect the changes in the contents of various intermediate metabolites in the cholesterol pathway, which indicated that the relative content of T-MAS, a metabolic substrate of MSMO1, was significantly up-regulated in MSMO1 knockdown cells. Then, in order to verify whether this metabolite can independently regulate ER stress, breast cancer cells were given T-MAS externally, and TEM and Western Blot analysis indicated that T-MAS could induce ER stress and activate the unfolded protein response independently. Apoptosis assay and AO/PI staining of breast cancer organoids revealed that T-MAS can improve the sensitivity of breast cancer to chemotherapy drugs.

Conclusion

In summary, these results shed light on the role of MSMO1 in cholesterol metabolism reprogramming, which adjust the endoplasmic reticulum stress state of cells by changing the relative content of intracellular T-MAS, and thereby influencing the sensitivity of breast cancer chemotherapy. As an intermediate metabolite of cholesterol metabolism, T-MAS has potential clinical application value of chemotherapy sensitization.

PO4-08-02

Genetic testing among patients with triple-negative breast cancer at a single health system: a quality improvement project

Presenting Author(s) and Co-Author(s):

M. Godbole. Henry Ford Cancer Institute, Henry Ford Health System, Detroit, Michigan, United States

M. Nyhuis. Henry Ford Health System (HFHS), United States

T. Washburn. Henry Ford Health System (HFHS), United States

J. Hirth. Henry Ford Health System (HFHS), United States

H. Ali. Henry Ford Cancer Institute, Henry Ford Health System, Detroit, Michigan, United States

Background:

Breast cancer is the most common type and the second leading cause of cancer-related deaths in women. Approximately 15-20% of patients have triple-negative breast cancer (TNBC) at diagnosis. TNBC is aggressive, difficult to treat, prone to relapse, and associated with an increased mortality rate. The incidence of BRCA1/2 mutation is about 20% in patients with TNBC (Hartman et al. 2012).

Despite the high prevalence of germline mutations in cancer susceptibility genes among TNBC patients, many do not receive genetic counseling (GC) or genetic testing (GT). National Comprehensive Cancer Network (NCCN) guidelines now recommend GT for all patients with TNBC, regardless of age, especially after the approval of Poly Adenosine diphosphate Ribose Polymerase (PARP) inhibitors for targeted therapy against BRCA1/2 mutations.

The aim of this quality improvement (QI) project was to identify patients with TNBC who did not receive GT and design an intervention to understand potential barriers to receiving GC and GT.

Methods:

We implemented a QI project to identify previously diagnosed adult patients with TNBC (18 years and older) of any stage (early or advanced/metastatic) without prior GT or family history of genetic disorders with active follow-up at the Henry Ford health breast cancer clinic. Eligible patients diagnosed between January 2015 and January 2020 from the Syapse Learning Health Network database were included. Baseline information as well as additional data including demographics, breast cancer treatment details, and whether GT and/or GC was offered or not was obtained through electronic health record review after institutional review board committee approval. Bi-monthly meetings were held amongst breast cancer providers, genetic counselors, and nurse navigators to develop an intervention to contact the patients who did not undergo GT and/or GC. After obtaining the list of patients who did not undergo GT and/or GC despite meeting eligibility criteria, they were contacted by their primary breast cancer providers via telephone regarding their willingness to obtain GT and/or GC at this time and participate in a questionnaire-based interview to understand barriers towards the same.

Results:

In the 5 years, a total of 123 patients were noted to have been diagnosed with triple-negative breast cancer. Of these, 93 patients were actively being followed at the Henry Ford breast clinic at the time of the QI project. 2 of the 9 patients who underwent GT and GC were positive for BRCA1/2 mutation. Of the remaining 83 patients that did not receive GC or GT, 65 (78.3%) had no clear reason explained in the chart, 27 patients (32.5%) chose not to get tested, 23 (27.7%)

were not deemed to be eligible upon initial assessment and 4 (4.8%) had pending orders placed by breast surgeons upon initial diagnosis. Unfortunately, 29 of these 83 patients were noted to have been deceased when the intervention was being designed. Remaining 54 patients were contacted by their primary breast cancer oncologists to determine their willingness in participating in the questionnaire-based interview.

Conclusion:

Based on the results of our QI project, we have now developed a process to contact the identified patients and renew the offer for GT and GC as well as participation in a questionnaire-based interview to understand the potential barriers to testing. We also plan to improve physician education and awareness by conducting mini sessions during our annual symposium meetings as well as grand rounds and develop a protocol for ordering GT and GC in patients with TNBC at our institution.

PO4-08-03

Prognostic Effect of Ductal Carcinoma in Situ in Breast Cancer with BRCA1/2 Mutations

Presenting Author(s) and Co-Author(s):

K. Yoon. Seoul National University Bundang Hospital / Department of Surgery, Seongnam, Kyonggi-do, Republic of Korea

E. Kim. Seoul National University Bundang Hospital, Seoul National University College of Medicine, United States

H. Shin. Seoul National University Bundang Hospital, United States

Abstract

Background: Although Breast Cancer Susceptibility Gene (BRCA)-associated invasive breast cancer has been extensively studied, there are few reports on ductal carcinoma in situ (DCIS) in patients with BRCA1/2 mutations. This study aims to evaluate the prognostic effect of DCIS in breast cancer patients with pathologic variants of BRCA1/2 genes.

Methods: Retrospective analysis was performed on a prospective cohort of 157 patients who were found positive for BRCA1/2 mutations through genetic testing from August 2003 to January 2022 at Seoul National University Bundang Hospital. Survival outcomes were compared between patients who had both invasive ductal carcinoma (IDC) and DCIS components (IDC-DCIS group, n = 121) and patients who had IDC only (IDC group, n = 36). Cox regression analysis was performed for evaluation of predictive factors for recurrence.

Results: Among the 157 patients, 65 (41.4%) patients showed BRCA1 mutations, 90 (57.3%) patients had pathological variants of BRCA2, and 2 (1.3%) patients tested positive for both BRCA1/2 mutations. There was no difference in baseline clinical characteristics between the IDC-DCIS and IDC groups. When pathological features were compared, the IDC-DCIS group was more likely to express positivity in both estrogen receptor (IDC 5 (13.9%) vs. IDC-DCIS 74 (61.2%), $P < 0.001$) and progesterone receptor status (IDC 5 (13.9%) vs. IDC-DCIS 67 (55.4%), $P < 0.001$). Tumors in the IDC group were associated with a higher histologic grade ($P = 0.004$). There was no statistically significant difference in 5-year disease-free survival between the two groups (IDC 83.6% vs. IDC-DCIS 89.3%, $P = 0.989$). In univariate Cox regression analysis, younger age at diagnosis was a significant predictor for recurrence (hazard ratio (HR) 2.236, $P = 0.049$); salpingo-oophorectomy showed a risk-reducing effect (HR 0.106, $P < 0.001$). Further multivariate analysis found only the effect of salpingo-oophorectomy to be prognostic (HR 0.112, $P < 0.001$). Presence of DCIS was not a risk factor for recurrence in patients with BRCA1/2 mutations (HR 1.006, $P = 0.989$).

Conclusion: BRCA1/2-positive breast cancer with DCIS components is more likely to be hormone receptor-positive and of lower grade compared to patients with IDC only. A tailored approach might be necessary in establishing treatment options for breast cancer patients with BRCA1/2 mutations according to the presence of DCIS.

PO4-08-04

Comparison of Outcomes and Prognosis between BRCA Pathogenic Variant Carriers Undergoing Breast-Conserving Surgery versus Mastectomy for Breast Cancer

Presenting Author(s) and Co-Author(s):

K. Kida. Department of Breast Surgical Oncology and Department of Clinical Genetics, St. Luke's international hospital, United States

J. Takei. Department of Breast Surgical Oncology and Department of Clinical Genetics, St. Luke's international hospital, Chu-o-ku, Tokyo, Japan

M. Suzuki. Center for Medical Genetics, St. Luke's international hospital, Chuo, Tokyo, Japan

M. Okawa. St. Luke's International Hospital, United States

S. Kazama. St. Luke's International Hospital, United States

S. Kondo. St. Luke's International Hospital, United States

M. Yamanaka. Department of Clinical Genetics and Division of Integrated Women's Health, St. Luke's international hospital, United States

A. Yoshida. Department of Breast Surgical Oncology and Department of Clinical Genetics, St. Luke's international hospital, United States

Introduction:

While outcomes are similar following breast-conserving surgery (BCS) or mastectomy among patients with sporadic breast cancer, data are still controversial for germline BRCA pathogenic variant carriers. We previously compared outcome following BCS between BRCA pathogenic variant carriers and non-carriers, and reported higher ipsilateral breast recurrence and comparable prognosis in the carriers. The purpose of this current study was to compare outcomes among BRCA pathogenic variant carriers undergoing BCS versus mastectomy in long-term follow-up period.

Methods:

Women with a BRCA pathogenic variant and a stage 0-III breast cancer who underwent definitive surgery from 1987–2021 were retrospectively identified from institutional database. Factors including clinicopathologic information and treatment characteristics were identified. Subsequent local recurrence, regional recurrence, distant recurrence, contralateral breast cancer (CBC), breast cancer-specific survival (BCSS), and overall survival (OS) rates were compared between BCS and mastectomy using Kaplan-Meier method and log-rank test. The chi-square test and t-test were used to compare patient characteristics between the two groups.

Results:

A total of 232 BRCA mutation carriers with 257 cancers including 25 patients with synchronous bilateral breast cancer were identified. Surgical treatment included BCS for 82 cancers and mastectomy for 175 cancers including nipple-sparing mastectomy for 51 cancers. Patient age at surgery and cancer stage did not statistically differ between BCS and mastectomy groups. Comparing to patients choosing mastectomy, patients who underwent BCS were less likely to be aware of their genetic status before surgery and were more likely to receive radiation therapy ($p < 0.001$). Contralateral risk reducing mastectomy was performed in 22.5% (18/80) in the BCS group and 48.7% (74/152) in the mastectomy group ($p < 0.001$) concurrently or at any time after the first definitive surgery. Risk reducing salpingo-oophorectomy was performed in 40% (32/80) in the BCS group and 49% (75/152) in the mastectomy group ($p = 0.17$).

At 7.5 years median follow-up, local recurrence rate was statistically higher in the BCS group than in the mastectomy group (20.0% in BCS vs. 4.6% in mastectomy, $p = 0.043$). In patients who underwent nipple-sparing mastectomy, 4.0% (2/51) had local subcutaneous recurrence and no nipple-areolar recurrence was observed. Median duration from the first definitive surgery to ipsilateral local recurrence was 10.0 years in the BCS group and 2.3 years in the mastectomy group. Regional lymph node recurrence (11.2% in BCS vs. 6.4% in mastectomy, $p = 0.62$), distant recurrence (13.7% vs. 9.2%, $p = 0.84$), CBC (15.0% vs. 8.6%, $p = 0.70$), BCSS (88.8% vs. 94.1%, $p = 0.65$) and OS (87.5% vs. 94.1%, $p = 0.49$) rates did not statistically differ between two groups.

Conclusions:

With 7.5 years median follow-up, higher local recurrence rate was observed in BCS than in mastectomy among BRCA pathogenic variant carriers. Our results found no statistical difference between BCS and mastectomy in regional recurrence, distant recurrence, CBC, and prognosis, indicating relatively higher risk in BCS. While BCS could be an option for BRCA pathogenic variant carriers willing to continue high-risk breast surveillance, shared decision making should be carefully performed based on the long-term local recurrence risk.

PO4-08-05

Disparities in Genetic Testing Patterns and Positivity Among Patients with Breast Cancer in the CancerLINQ Real-World Oncology Database

Presenting Author(s) and Co-Author(s):

O. Kantor. Brigham and Women's Hospital/Dana-Farber Cancer Institute, United States

A. Jones. Brigham and Women's Hospital, United States

B. Bychkovsky. Comprehensive Breast Health Center, Brigham and Women's Hospital; Breast Oncology Program, Dana-Farber Brigham Cancer Center Division of Cancer Genetics and Prevention; Dana-Farber Cancer Institute; Harvard Medical School, United States

A. Laws. Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, United States

A. Weiss. Division of Surgical Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States

H. Rana. Dana Farber Cancer Institute, United States

J. Garber. Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Division of Cancer Genetics and Prevention, Dana-Farber Cancer Institute, United States

R. Scheib. Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Women's Health, Department of Medicine, Brigham and Women's Hospital, United States

M. Chavez. UT MD Anderson Cancer Center, Houston, Texas, United States

E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

E. Mittendorf. Dana Farber Cancer Institute, Boston, Massachusetts, United States

Introduction:

Indications for hereditary genetic testing (GT) continue to expand among breast cancer patients (pts), with some guidelines suggesting offering germline GT to all pts diagnosed with breast cancer. The objective of this study was to explore patterns of germline GT and prevalence of pathogenic and likely pathogenic variant (PV) frequency by age, sex, race and ethnicity, and stage at diagnosis within a large, real world oncology database.

Methods:

The American Clinical Society for Oncology CancerLINQ Discovery breast dataset was used to identify pts with a stage 0-III breast cancer diagnosis who underwent breast surgery at initial diagnosis from 1990-2022. Genetic testing was identified as an available test result from at least one of the following genes: BRCA1/2, ATM, CHEK2, PALB2, TP53, BARD1, BRIP1, CDH1, MHL1, MSH2, MSH6, NF1, RAD51C, or RAD51D. Descriptive statistics were used for comparisons, and adjusted multivariable regression predicting receipt of GT was performed.

Results:

Overall, 76,978 pts with breast cancer were identified. Of these, 16,284 (21.1%) underwent GT.

There were differences in the proportion of pts that underwent GT by age, sex, self-reported race and ethnicity, and stage at diagnosis (Table). Genetic testing decreased with increasing age (59.2% in < 40 vs 7.5% in ≥ 70 , $p < 0.001$) and was more common in men (45.9% vs 21.1% of women, $p < 0.001$). Genetic testing rates ranged from 18.1-27.7% by race and ethnicity ($p < 0.001$), with the lowest rates in Non-Hispanic Black (18.1%) and American Indian/Alaskan Native pts (18.2%) and the highest rate in Hispanic pts (27.7%). Genetic testing also differed by stage at diagnosis, with 19.3% of stage I pts vs 25.7% of stage III pts having genetic testing ($p < 0.001$). On multivariable analysis adjusted for age, sex, race and ethnicity, and stage, male sex was associated with increased likelihood of GT (OR 5.12, 95% CI 4.04-6.49 compared to female sex, $p < 0.001$) while increasing age (OR 0.05, 95% CI 0.04-0.06 in age ≥ 70 compared to age < 40, $p < 0.001$) and Non-Hispanic Black or American Indian/Alaskan Native race and ethnicity were associated with decreased likelihood of GT (OR 0.69, 95% CI 0.65-0.73 for Non-Hispanic Black and OR 0.71, 95% CI 0.50-1.00 for American Indian/Alaskan Native pts, compared to Non-Hispanic White pts, $p < 0.001$); stage was not independently associated with GT.

Among those that had GT, PVs were detected in 2,974 (18.3%) pts. PVs were more common in pts < 40 years (27.3% vs 15.0-17.6% in pts ≥ 40 , $p < 0.001$) and in men (26.4% vs 18.2% in women, $p < 0.001$). Compared by race and ethnicity, PVs were highest among American Indian/Alaskan Native patients (30.2%) and lowest in Non-Hispanic White and Asian/Pacific Islander patients (18.6% and 17.0%, respectively, $p < 0.001$). There was also a higher prevalence PVs with increasing stage (16.5% for stage 0 and 23.8% for stage III, $p < 0.001$). Among those with PVs, the distribution was as follows: BRCA1 n=937 (31.5%), BRCA2 n=1176 (39.5%), TP53 n=315 (10.6%), CHEK2 n=238 (8.0%), ATM n=214 (7.2%), and PALB2 n=200 (6.7%).

Conclusions:

Differences in patterns of GT and PV frequency by age, sex, race and ethnicity, and stage were prevalent. Importantly, despite lower rates of GT, PV frequencies were similar or higher among minority patients and similar among all pts aged 40 and older. Inclusive testing practices and expansion of genetic testing coverage are needed to work towards equitable access to and acceptance of genetic testing.

Genetic Testing And Positivity Rates

	Had Genetic Testing		Positive Result	
	N= # tested/# total (%)		N= # positive/# tested (%)	
Age at Diagnosis				
<40	2,445/ 4,127	(59.2%)	717/2,630	(27.3%)
40-49	5,542/13,388	(41.4%)	1,021/5,799	(17.6%)
50-59	4,125/20,057	(20.6%)	764/4,342	(17.6%)
60-69	2,759/21,046	(13.1%)	440/2,904	(15.2%)
≥70	1,352/17,998	(7.5%)	214/1,426	(15.0%)
Unknown	61/362	(16.9%)	23/67	(34.3%)
Sex				
Female	16,076/76,361	(21.1%)	2,919/16,076	(18.2%)
Male	144/314	(45.9%)	38/144	(26.4%)
Race and Ethnicity				
Non-Hispanic White	10,265/49,013	(20.9%)	1,906/10,265	(18.6%)
Non-Hispanic Black	1,729/9,601	(18.1%)	335/1,729	(19.4%)
Hispanic	870/3,140	(27.7%)	195/870	(22.4%)
Asian/Pacific Islander	558/2,150	(26.0%)	95/558	(17.0%)
American Indian/Alaskan Native	43/236	(18.2%)	13/43	(30.2%)
Other/Unknown	2,819/12,838	(22.0%)	430/2,819	(15.3%)
Stage				
Stage 0	6,316/29,264	(21.6%)	1,040/6,316	(16.5%)
Stage I	5,578/28,903	(19.3%)	945/5,578	(16.9%)
Stage II	3,546/15,522	(22.8%)	788/3,546	(22.2%)
Stage III	844/3,289	(25.7%)	201/884	(23.8%)

PO4-08-06

Causal Relationships and Familial Aggregation of Mammogram Risk Scores: Insights from Breast Cancer in Twins and Families

Presenting Author(s) and Co-Author(s):

Z. Ye. University Of Melbourne, Melbourne, Victoria, Australia

S. Li. University Of Melbourne, United States

G. Dite. Genetic Technologies, Fitzroy, Victoria, Australia

T. Nguyen. University Of Melbourne, United States

R. MacInnis. University Of Melbourne, United States

J. Hopper. University of Melbourne, United States

Background: Mammogram risk scores based on texture and density, determined by brightness thresholds, are associated with breast cancer risk differently and could reveal distinct information about breast cancer risk. This study aimed to investigate the causal relationships between these intercorrelated risk scores and the familial aggregation of a texture-based mammogram measure, shedding light on the relevance to breast cancer aetiology.

Methods: We analysed data from the Australian Mammographic Density Twins and Sisters Study, including 3195 breast-cancer-free women from 1519 families. The dataset comprised 527 pairs of monozygotic (MZ) twins, 271 pairs of dizygotic (DZ) twins, and 1599 sisters. The average age at mammography for sister pairs ranged from 40 to 70 years. Mammogram risk scores based on texture (named Cirrus) and three density-defined areas (light, bright, and brightest) that were spatially independent were generated. The Inference about Causation from Examination of Familial Confounding (ICE FALCON) method was employed for causal inference. Familial aggregation and the variance of Cirrus were assessed as a function of age using a multivariate normal model for pedigree analysis. The classic twin model was employed but allowing for varying shared environmental effects among different sister pairs. The single-nucleotide polymorphism (SNP)-based heritability was estimated using genetic variants from both closely and distantly related individuals. Model fits were compared using likelihood ratio tests and the Akaike Information Criterion.

Results: Causal analysis using ICE FALCON revealed significant positive causal effects, with Cirrus, light areas, and bright areas influencing the brightest areas (accounting for 34%, 55%, and 85% of the associations, respectively). Similarly, light areas and bright areas demonstrated causal effects on Cirrus (accounting for 37% and 28% of the associations, respectively). No age-related differences in familial correlations or Cirrus variance were found for women aged 40 to 70 years. Familial correlations were estimated at 0.51 (0.03) for MZ pairs and 0.16 (0.03) for combined DZ and non-twin sister pairs, with no significant difference between DZ and non-twin sister pairs ($P=0.3$). Additive genetic effects accounted for up to 32% (5%) of the variance, consistent with SNP-based heritability estimates of 36% (12%). MZ-specific environmental effects contributed to at least 20% (3%), while shared environmental effects for DZ and non-twin sibling pairs accounted for less than 40% of that for MZ pairs.

Conclusion: In a mammogram, the lighter (less dense) areas causally influence the brightest (highly dense) areas, including through textural features. These causal relationships provide insights into the relative importance of different mammogram features in breast cancer aetiology. For example, the brightest areas are more aetiologically important for screen-

detected breast cancer, while the light areas are more aetiologically important for interval breast cancer. Additionally, specific textural features capture aetiologically independent breast cancer risk information from dense areas. We also confirm the partial heritability of Cirrus, the texture-based mammogram measure, substantially influenced by environmental factors (familial and non-familial). As well as genetic factors, Cirrus could be determined by factors operating at times of life when MZ pairs share their environments to a greater extent than do DZ and non-twin sisters, starting in utero and prior to adulthood, and remaining constant thereafter. These insights from twin and family data enhance our understanding of mammogram risk scores and their implications for breast cancer risk assessment.

PO4-08-07

Background parenchymal enhancement (BPE) on breast magnetic resonance imaging as a biomarker of breast cancer risk among BRCA1/2 carriers

Presenting Author(s) and Co-Author(s):

A. McCarthy. University of Pennsylvania, Bala Cynwyd, Pennsylvania, United States

A. Nguyen. University of Pennsylvania, Philadelphia, Pennsylvania, United States

W. Mankowski. University of Pennsylvania, Philadelphia, Pennsylvania, United States

E. Cohen. University of Pennsylvania, United States

S. Ehsan. Department of Biostatistics, Epidemiology & Informatics, University of Pennsylvania, United States

R. Gillette. Department of Medicine, University of Pennsylvania Perelman School of Medicine, United States

L. Pantalone. University of Pennsylvania, United States

S. Weinstein. Department of Radiology, University of Pennsylvania, United States

E. Conant. University of Pennsylvania, Philadelphia, Pennsylvania, United States

S. Domchek. University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, United States

D. Kontos. Department of Radiology, University of Pennsylvania, United States

Introduction: BRCA1/2 carriers are recommended to undergo dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) screening of the breasts annually. Fibroglandular tissue (FGT) may enhance with MRI contrast agent termed background parenchymal enhancement (BPE). BPE is believed to be a marker of hormonally responsive breast tissue, as BPE is impacted by aromatase inhibition and by oophorectomy. BPE has been shown to be more strongly associated with breast cancer risk than breast density. We hypothesize that BPE may serve as a useful dynamic marker of breast cancer risk among BRCA1/2 mutation carriers, given their frequent MRI screening.

Methods: We identified female BRCA1/2 carriers from the University of Pennsylvania Cancer Risk Evaluation Program with no personal history of breast or ovarian cancer at the time of breast MRI. Patients diagnosed within 6 months were excluded to remove prevalent cancer cases at MRI. Among 421 eligible patients, 42 were diagnosed with breast cancer. BPE was quantified from all available breast MRIs using a validated, fully automated method to segment fibroglandular tissue (FGT) and quantify BPE. For preprocessing, the N4ITK algorithm was used for bias-field artifact correction and FGT was segmented using a soft-margin support vector machine classifier using the T1-weighted nonfat-saturated breast MRI. FGT was segmented and quantified in 3D. For BPE quantification, the T1-weighted nonfat-saturated image and the derived FGT mask were registered to the pre-contrast DCE-MRI. The first post contrast DCE-MRI and FGT mask were used to compute the relative enhancement map compared to the pre-contrast image. We calculated BPE metrics in two ways. First, the median BPE enhancement was calculated as the median enhancement of all voxels within the FGT mask. Second the BPE enhancement ratio was calculated as the proportion of voxels enhancing at $\geq 20\%$. We performed Cox proportional hazards regression to estimate the hazard ratios for breast cancer per standard deviation unit increase in each BPE metric, with first MRI as the time origin and censoring upon bilateral mastectomy, ovarian cancer diagnosis, death, or loss to follow-up and adjustment for age at MRI, menopause status, volumetric breast density

(VBD), body mass index (BMI), and BRCA1 vs. BRCA2 mutation. BPE, VBD, BMI, and menstrual status were included as time varying covariates, enabling inclusion of multiple BPE measurements per woman.

Results: The mean age at first MRI was 39 for cases and 41 for non-cases, and the mean number of MRIs was 4. There were no significant differences in median BPE (14% vs. 14%, $p=0.965$) or BPE ratio (34% vs. 36%, $p=0.769$) between cases and non-cases. In regression analyses adjusted for age and menstrual status, median BPE was significantly associated with breast cancer risk ($HR=1.12$, $p=0.025$). The HR was similar in the fully adjusted model, though did not reach statistical significance ($HR=1.11$, $p=0.055$). Higher BPE ratio was significantly associated with increased breast cancer risk in both minimally ($HR=1.21$, $p=0.005$) and fully adjusted models ($HR=1.21$, $p=0.012$).

Conclusions: Our results suggest that BPE is significantly associated with breast cancer diagnosis among BRCA1/2 carriers undergoing breast MRI screening. Both median BPE and BPE ratio metrics were associated with breast cancer risk, even after adjusting for breast density and when accounting for multiple measurements of BPE over time, suggesting that BPE may provide additional risk information for BRCA1/2 carriers.

Table 1: Results of Cox proportional hazards regression with time varying covariates

Table 1: Results of Cox proportional hazards model with time varying covariates												
	Minimally adjusted			Fully adjusted			Minimally adjusted			Fully adjusted		
	N=42 cases, 379 controls			N=32 cases, 355 controls			N=42 cases, 379 controls			N=32 cases, 355 controls		
	HR*	95% CI	p-value	HR*	95% CI	p-value	HR*	95% CI	p-value	HR*	95% CI	p-value
Median BPE enhancement	1.121	1.014-1.238	0.025	1.113	0.998-1.241	0.055
BPE enhancement Ratio	.	.	.				1.213	1.061-1.386	0.005	1.207	1.042-1.398	0.012
Age	1.001	0.982-1.020	0.935	0.995	0.975-1.016	0.639	1.001	0.982-1.020	0.916	0.996	0.976-1.017	0.704
Pre vs. postmenopausal	0.914	0.569-1.469	0.711	0.864	0.520-1.420	0.554	0.903	.563-1.446	0.670	0.858	0.521-1.411	0.546
Volumetric Breast Density	.	.	.	0.992	0.981-1.003	0.157	.	.	.	0.992	0.981-1.003	0.131
Body Mass Index	.	.	.	0.992	0.959-1.026	0.656	.	.	.	0.991	0.958-1.025	0.590
BRCA2 vs. BRCA1	.	.	.	0.864	0.626-1.192	0.373	.	.	.	0.833	0.603-1.151	0.268
*Hazard ratio per standard deviation unit increase in BPE metric												

PO4-08-08

Is it time for a European BRCA Mutation Registry? An Italian experience

Presenting Author(s) and Co-Author(s):

E. De Matteis. Prevention Department ASL Lecce, Lecce, Puglia, Italy

M. Ciccicarese. Regional Agency for Social and Health Development, Bari, Puglia, Italy

P. Tarantino. Medical Genetics Unit "Vito Fazzi Hospital" –Lecce, Lecce, Italy

T. Grassi. Science Department Salento University-Lecce, Lecce, Puglia, Italy

F. Bagordo. Pharmaceutical sciences Department, University " Aldo Moro"- Bari, United States

E. Rizzo. Science Department Salento University-Lecce, Puglia, Italy

M. Tumolo. National Research Council (CNR), Puglia, Italy

G. Ronzino. . Oncology Unit "Vito Fazzi" Hospital Lecce, Puglia, Italy

M. De Giorgio. Prevention Department ASL Lecce, United States

S. Mauro. Medical Genetics Unit "Vito Fazzi Hospital" –Lecce, Puglia, Italy

N. Di Renzo. Oncological Department, United States

Background: Knowledge of BRCA 1/2 mutation plays an important role in cancer care. The National Plan to improve BRCA detection in order to increase access to target agents and ameliorate the prevention strategy has several implementations in the Italian regions. Recent guidelines are considering extending genetic testing to a larger population, regardless of family history. We present our experience in Apulia Region on the detection of BRCA 1/2 and its clinical implication at the regional level, to underline the importance of spreading the extension of BRCA detection at the regional level and to propose the creation of a European register for BRCA patients, based on population-based BRCA 1/2 testing.

Methods: This is an observational study conducted at a Familiar Cancer Service of the Lecce Hospital. Participants completed a questionnaire (socio-demographic epidemiology of cancer and lifestyle factors), genetic counseling and BRCA testing. Notably, genetic testing for BRCA mutations was carried out based on family cancer history since 2018, according to the Italian cancer guidelines (AIOM) and related updates in 2019 and 2023. A mutational analysis of exons and adjacent intronic regions of BRCA1/BRCA2 genes was performed by Sanger sequencing and MiSeq Illumina NGS platform.

Results:

Between 2014 and May 2023 a total of 4365 patients were enrolled in the study, of whom 2426 (56%) was evaluable for BRCA detection, 18% men (n=440) and 82% female (n=1986). Median age at diagnosis was 57 yrs. 65% of patients had a cancer diagnosis (n=1575) and 35% were healthy carriers (n=851). In particular, breast cancer (BC) was present in 63% of patients (n=1048), ovarian cancer (OC) in 21% (n=352), pancreatic cancer in 5% (n=85), prostate cancer in 4% (n=65), melanoma in 1% (n=13), and other cancers in 6% (n=92).

The table 1 (uploaded) shows the results of patients with BC (n=1048)

The presence of BRCA mutation is observed in 20.52% of BC patients (1:4.87).

Conclusion

These data confirm that BRCA mutation detection is an emerging need to improve prevention and early diagnosis according to the European Beating Cancer Plan. Therefore, it is crucial to

improve this topic at regional level until the creation of a shared BRCA registry among European countries.

Histological Subtype	Freq.%	BRCA+mut	BRCA1+mu	BRCA2+mu	BRCA-	VUS	Not defined (ND)
Ductal	66.32	19.42	65.93	34.07	72.37	6.47	1.73
Lobular	7.35	9.09	42.86	57.14	83.12	3.90	3.90
Ductal plus lobular	1.24	23.08	66.67	33.33	69.23	0.00	7.69
Other	25.10	26.61	64.08	35.92	61.98	7.60	3.80
Immunohistochemistry subtype	Freq.%	TOT BRCA+mut	BRCA1+mut	BRCA2+mut	BRCA-	VUS	ND
Triple negative (TN)	23.76	31.73	89.87	10.13	61.04	6.43	0.80
Endocrine responsive (ER/PGR+)	76.24	17.02	50.74	49.26	73.47	6.51	3.00

PO4-08-09

Concordance analysis of paired breast cancer core needle biopsies and surgical excision samples using the Oncotype DX Breast Recurrence Score® assay

Presenting Author(s) and Co-Author(s):

A. Nassar. Mayo Clinic, United States

J. Carter. University of Alberta, Edmonton, Alberta, Canada

P. Innis. Exact Science, United States

S. Seerapu. Exact Sciences, United States

C. Russell. Exact Sciences, United States

H. Hanna. University of South Florida, Jacksonville, Florida, United States

A. Lochala. Arkansas Technical University, Jacksonville, Florida, United States

M. Liu. Natera, United States

INTRODUCTION:

The Oncotype DX Breast Recurrence Score® (RS) assay is validated to predict risk of distant recurrence at 10 years and the benefit of adjuvant chemotherapy in patients with estrogen receptor (ER)+, HER2- early breast cancer who receive 5 years of endocrine therapy. The feasibility of Oncotype DX® testing with diagnostic core needle biopsies (CNB) was demonstrated through analysis of a large commercial laboratory experience. The neoadjuvant ADAPT study showed the clinical utility of deriving the Recurrence Score® (RS) result from CNB as well. However, data are limited on concordance of RS results from paired CNB and surgical samples. Our primary objective was to determine the degree of concordance of RS results between paired tissue samples from the same primary breast tumor of patients with early stage, ER+, HER2- invasive breast cancer who had a CNB and subsequent surgical excision (SE; lumpectomy or mastectomy) without intervening systemic therapy.

METHODS:

Patients with a commercial RS result on either CNB or subsequent SE were identified through medical record and clinical database review. A pathologist reviewed archival tissue samples to confirm eligibility and selected the other paired CNB or SE block most representative of the tumor tissue for subsequent study Oncotype DX testing.

Descriptive statistics were used to summarize patient and tumor characteristics. Wilcoxon signed rank, McNemar's and Cochran-Mantel-Haenszel tests were used to compare RS between SE and CNB paired samples. Cohen's Kappa and 95% confidence intervals (CIs) were used to compare the agreement of categorical RS (0-25 and 26-100) result between SE and CNB paired samples. Lin's concordance correlation and 95% CIs were used to compare agreement of continuous RS between paired samples.

RESULTS:

A total of 134 patients were identified with paired CNB and SE samples with a median time of 34 (range 5-103) days between collections. Of the 134 patients, a commercial RS result was available for 25 (18.7%) with CNB and 109 (81.3%) with SE. A study RS result was then generated on the other paired sample. Median age was 62 years (range 33-99; 23 patients [17%] were age ≤50 vs. 111 [83%] age >50). Cases were predominantly node negative (107/134 node negative vs. 26/134 node positive; 1/134 unknown) invasive ductal carcinomas (104/134 ductal vs. 18/134 classic lobular vs. 12/134 other). Mean RS results were 15.6 (range

0-56) and 16.6 (range 0-59) for CNB and SE, respectively ($p = 0.003$), with no statistically significant differences in RS category defined as low vs. high risk (119/134 CNB vs. 114/134 SE for RS 0-25 and 15/134 CNB vs 20/134 SE for RS 26-100; $p = 0.13$) or low vs. intermediate vs. high risk (85/134 CNB vs. 78/134 SE for RS 0-17 and 43/134 CNB vs. 48/134 SE for RS 18-30 and 6/134 CNB vs. 8/134 SE for RS 31-100; $p = 0.19$). No differences were observed based on age relative to 50 years or nodal status (data not shown). Cohen's Kappa statistic $k = 0.64$ (95% CI, 0.44-0.83) supports substantial agreement between the CNB and SE samples. Lin's concordance correlation coefficient (CCC) demonstrates similar agreement for the continuous RS result between paired samples (CCC = 0.86 [0.80-0.90]). Overall percent agreement was 91.8% (87.1-96.4%).

CONCLUSIONS:

Studies evaluating the level of concordance of ER, progesterone receptor, and HER2 biomarker status between CNB and SE samples have found high concordance rates, albeit varied. We now provide data demonstrating high concordance of RS results between CNB and SE specimens obtained from the same breast primary tumor without intervening systemic therapy. This supports use of either biopsy source for testing with a genomic predictor to identify those patients who will most likely benefit from chemotherapy and which patients may be spared.

PO4-08-10

Genetic mutations and associated rates of pathologic complete response among a diverse patient population with early stage triple negative breast cancer

Presenting Author(s) and Co-Author(s):

C. Taylor. Ochsner Health, United States

M. Sheen. Ochsner Clinic Foundation, New Orleans, Louisiana, United States

R. Cattie. Ochsner Health, United States

V. Chung. Ochsner Health, New Orleans, Louisiana, United States

M. Bratton. Ochsner Health, United States

M. Lakey. Ochsner Health, United States

E. Biggs. Ochsner Health, United States

Background:

Combination treatment with chemotherapy and immunotherapy remains the standard of care for high risk, early-stage triple negative breast cancer (TNBC). Although the addition of immunotherapy improves rates of pathologic complete response (pCR) and event-free survival, approximately 50% of patients achieve pCR with neoadjuvant chemotherapy alone suggesting that some patients may safely avoid the potential toxicities of immunotherapy without compromising outcomes.^{1,2} Markers of immune activation including PD-L1 expression and tumor infiltrating lymphocytes have demonstrated prognostic significance; however, identifying a predictive biomarker to aid in selecting those patients most likely to benefit from immunotherapy remains an unmet need.^{3,4} Genetic mutations are suggestive of DNA susceptibility to damage and the role they may play as a potential marker of immune response is unclear.^{5,6} This study explores genetic analysis and mutation rates among a diverse cohort of patients with TNBC to identify patterns associated with and without pCR.

Methods:

We evaluated 105 women diagnosed with Stage I-III TNBC and treated with combination neoadjuvant chemotherapy and immunotherapy at Ochsner Cancer Center between December 2019 through June 2022. Exclusion criteria included ER+, PR+, HER2+, or unknown receptor status, no pembrolizumab in the neoadjuvant setting, no definitive surgery following neoadjuvant treatment, absence of documented race and age less than 18 years of age. Data was collected utilizing Epic Slicer Dicer program, in addition to chart review. Genetic analysis was performed using a variety of DNA-based next generation sequencing analysis platforms.

Results:

91 patients met inclusion criteria. 17 patients were found to have pathogenic mutations (BRCA1/2, POLE and ATM), 38 patients had variants of undetermined significance (VUS) and 36 patients had neither. Among patients with pathogenic genetic mutations, 81.25% had a pCR following neoadjuvant treatment compared to 58.33% of those with a VUS and 47.06% of those with no known mutation (p=0.07). Before adjusting for age and stage, patients with a pathogenic mutation were 73% more likely to achieve pCR than those with no known genetic mutations (crude RR: 1.73, 95% CI: 1.13-2.65). After adjusting for age and stage, the relationship was not statistically significant (aRR: 1.15, 95% CI: 0.78-1.34). Among the 47 Black patients, 5 were found to have a pathogenic mutation and 29 had a VUS. 11 of the 39 White

patients were found to have a pathogenic mutation while only 6 had a VUS. Across all genetic mutation categories, Black patients experienced lower rates of pCR than White patients. White patients with a known pathogenic mutation had the highest rate of pCR at 90.91%, while Black patients with no identified mutation had the lowest rate of pCR at 38.46%. The generalizability of these results may be limited due to small sample size.

Conclusion:

Our results demonstrating higher rates of genetic variants among patients achieving pCR regardless of race highlight the importance of better understanding how these variants correlate with tumor mutational burden (TMB) and further, the role this may play in predicting immune-response. Larger studies are needed to assess TMB as a predictive biomarker in early-stage TNBC as this may provide opportunities to further individualize treatment and minimize toxicity among this group of patients. Additionally, given differences in the prevalence of pathogenic mutations and VUS among Black patients, better understanding the relationship between mutation status and immune response is imperative to optimize outcomes in this high-risk population.

Table 1. Log-Binomial Regression Results Predicting Pathological Complete Response (N=86)

	Pathological Complete Response	
	Crude RR (95% CI)	Adjusted RR (95% CI)
Genetic Mutation		
Pathogenic (n=17)	1.73 (1.13-2.65)	1.15 (0.84-1.56)
VUS (n=38)	1.24 (0.79-1.95)	1.03 (0.78-1.34)
None (n=36)	ref.	

PO4-09-01

Survival of patients harboring a germline ATM pathogenic/likely pathogenic variant and diagnosed with breast cancer: A case-control study

Presenting Author(s) and Co-Author(s):

M. Cruellas. Cancer Genetics Unit, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Spain, United States

A. Roqué. Cancer Genetics Unit, Girona Catalan Institute of Oncology, Spain, United States

N. Dueñas. Cancer Genetics Unit, Hospitalet Catalan Institute of Oncology, Spain, United States

I. Teruel. Medical Oncology, Institut Català d'Oncologia Badalona(ICO Badalona), Catalonia, Spain

N. Tuset Der-Abraïn. Hospital Universitari Arnau de Vilanova de Lleida, United States

A. Rezqallah. Cancer Genetics Unit, Vall d'Hebron Institute of Oncology (VHIO), United States

v. Navarro. Oncology Data Science (ODysSey) Group, Instituto de Oncología Vall d'Hebron (VHIO), Barcelona, Spain, United States

L. Joval-Ramentol. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

M. torres. Cancer Genetics Unit, Vall d'Hebron Institute of Oncology (VHIO), Spain, United States

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

J. brunet. Cancer Genetics Unit, Girona Catalan Institute of Oncology, Spain, United States

J. Balmaña. Vall d'Hebron University Hospital, Barcelona, Spain

Introduction: Patients harboring a pathogenic/likely pathogenic variant (PV/LPV) in ATM present an increased lifetime risk of developing breast cancer (BC). The survival outcomes of these patients are not well-known.

Methods: Retrospective, multicentric case-control study. Case group included patients with stage I-III breast cancer harboring a PV/LPV in ATM. Control group included patients with stage I-III breast cancer with a negative germline BC multigene panel testing including ATM gene analysis. Clinical outcomes defined as locoregional relapse-free survival (RFS), distant RFS and breast cancer specific survival were compared between cases and controls. Case group was obtained from five hereditary cancer units and control group was obtained from a sporadic clinic-based cohort. Cases and controls were matched 1:2 by stage, molecular subtype by immunohistochemistry, age at BC diagnosis and year of BC diagnosis. Baseline continuous variables were presented as mean and standard deviation and comparison was performed with Student's t-test. Baseline categorical variables were presented with number and percentage and comparison were performed using chi-square test. Survival analyses were estimated by Kaplan-Meier curves, the comparison of survival was tested by stratified log-rank testing. Cox proportional hazards model was used to estimate the hazard ratio and confidence intervals.

Results: We identified 64 patients (p) with an ATM PV/LPV and 120 controls. Median age at diagnosis was 47 years (28-84) and 46 years (25-88), respectively. The main tumoral characteristics in both groups were ductal (87.5% and 83.5%), luminal B-HER2 negative (37.5% and 45.8%) with histological grade II (54.7% and 58.5%) tumors. Majority of tumors in both groups were diagnosed at stage II (53.1% and 54.2%). Differences between groups were

observed in first-degree BC family history (39p (61.9%) vs 51p (43.6%); p=0.02); frequency of multicentric/multifocal tumors (15p (25%) vs 13p (11.1%); p=0.018); contralateral breast cancer (16p (25%) vs 8p (6.7%); p=0.0004) and type of surgery (46.8% conservative surgery in cases and 69.2% in controls; p< 0.001). The result of the germline genetic study was not available for all patients before surgery. Baseline characteristics are summarized in Table 1.

With a median follow-up of 6.7 years, we observed more locoregional recurrence and distant recurrence in the control group (ipsilateral local or lymphatic recurrence: 0p (0%) vs 15p (12.5%); p=0.078; metachronic contralateral breast cancer: 7p (12.7%) vs 3p (2.6%); p=0.02; distance recurrence 5p (7.8%) vs 24p (20%); p=0.03. No differences between groups were observed in BC-specific survival analysis, with a median BC-specific survival of 6.24y (4.67-12.1) in patients with ATM and 6.68y (6.12-7.94) in the control group (HR: 1.21 (0.88-1.65); p=0.24).

Conclusions: Patients with BC harboring a germline ATM PV/LPV had more multifocal and multicentric disease at diagnosis; and more synchronous and metachronous contralateral BC compared to controls, with no differences in BC-specific survival. Further studies in a larger cohort are warranted to analyze sensitivity to systemic therapies.

Table 1. Baseline characteristics of cases and control groups. ER (Estrogen Receptor) positive if > or equal to 1%; PR (Progesterone Receptor) positive if > or equal to 1%; HER2 (Human epidermal growth factor receptor-2); ChTh: Chemotherapy; SLNB: Sentinel Lymph Node Biopsy; AL: Axillar lymphadenectomy

	ATM PV/LPV carriers	Non carriers	p
N	54	120	
Median age BC diagnosis	47 y (28-84)	46 y (25-88)	0.759
Median year of BC diagnosis	2012 (1984-2022)	2014 (1993-2022)	0.145
Premenopausal	44 (69%)	73 (61%)	0.319
BC Family history			
BC FDR	39 (61.9%)	51 (43.6%)	0.020
BC FDR or SDR	45 (71.4%)	69 (59%)	0.101
Tumor characteristics			
Histology			
Ductal	56 (87.5%)	96 (83.5%)	0.284
Lobullilar	3 (4.7%)	13 (11.3%)	
Others	5 (7.8%)	6 (5.2%)	
ER +	61 (95.3%)	113 (94.2%)	0.745
PR +	50 (79.4%)	93 (78.8%)	0.931
HER2 +	16 (28.6%)	21 (18.6%)	0.142
Molecular subtype			
Luminal A	11 (17.2%)	21 (17.5%)	0.703
Luminal B HER2 negative	24 (37.5%)	55 (45.8%)	
Luminal NOS	18 (28.1%)	23 (19.2%)	
HER2 + luminal	8 (12.5%)	15 (12.5%)	
HER2 + non-luminal	3 (4.7%)	6 (5%)	
Triple negative	0 (0%)	0 (0%)	0.018
Multifocal/multicentric	15 (25%)	13 (11.1%)	
Histologic Grade			
1	8 (15.1%)	13 (12.3%)	0.856
2	29 (54.7%)	62 (58.5%)	
3	16 (30.2%)	31 (29.2%)	
Tumor size (TNM)			
T1	33 (52.4%)	55 (45.8%)	0.224
T2	27 (42.9%)	54 (45%)	
T3	2 (3.2%)	11 (9.2%)	
T4	1 (1.6%)	0 (0%)	
Lymph node (N)			
0	32 (50%)	68 (56.7%)	0.608
1	25 (39.1%)	45 (37.5%)	
2	5 (7.8%)	6 (5%)	
3	2 (3.1%)	1 (0.8%)	
Metastasis (M)			
0	64 (100%)	120 (100%)	0.990
1	0 (0%)	0 (0%)	
I	23 (35.9%)	42 (35%)	
II	34 (53.1%)	65 (54.2%)	
III	7 (10.9%)	13 (10.8%)	
IV	0 (0%)	0 (0%)	
Contralateral breast cancer			
Yes	16 (25%)	8 (6.7%)	0.0004
Synchronous	9 (14%)	5 (4.2%)	0.015
Metachronic	7 (12.7%)	3 (2.6%)	0.02
Treatment			
ChTh neoadjuvant	16 (25%)	37 (10.8%)	0.408
Surgery			
Conservative	30 (46.8%)	81 (69.2%)	<0.001
Unilateral mastectomy	19 (29.7%)	34 (29%)	
Bilateral mastectomy	15 (23.4%)	2 (1.7%)	
Pathologic complete response to ChTh neoadjuvant	5 (41.7%)	10 (27%)	0.338
SLNB/AL			
SLNB	31 (50.8%)	73 (64%)	0.092
AL	30 (49.2%)	41 (36%)	
Adjuvant Radiotherapy			
Yes	40 (62.5%)	91 (75.8%)	0.059
Adjuvant ChTh			
Yes	36 (58.1%)	58 (48.3%)	0.216
Adjuvant anti-HER2			
Yes	11 (17.2%)	19 (15.8%)	0.814
Adjuvant Hormonotherapy			
Yes	58 (93.5%)	103 (85.8%)	0.125

PO4-09-02

Making a Case for Access to Genetic Testing in a Low Resource Country: A review of 313 Cases of MBC

Presenting Author(s) and Co-Author(s):

A. Alabi. College of Medicine of the University of Lagos, Lagos, Nigeria

A. Lawal. Lagos University College of Medicine, Nigeria, United States

T. FALOWO. CANCERAWARE, United States

O. FATIREGUN. LAGOS UNIVERSITY TEACHING HOSPITAL, United States

Background

Breast Cancer is the most common malignancy in Nigerian Women. It is responsible for the highest mortality amongst all malignant conditions.

Breast cancer in Nigerian women typically presents at an earlier age and with a more aggressive tumour with triple negative molecular pattern in Nigerian women.

These are usually some of the criteria for Genetic testing in the NCCN Guidelines.

Due to resource challenges, Genetic testing is not readily available to Nigerian women

We believe that if we can demonstrate that a high proportion of Nigerian women with breast cancer meet the criteria for Genetic Testing for Hereditary Breast and Ovarian Cancers, a case can be made for deploying resources towards Genetic Testing in this population of Women.

Materials and Methods

We collected prospective data about Nigerian Patients with Metastatic Breast Cancer as part of a UICC MBC Grant.

We evaluated these patients for criteria for testing for breast cancer and present the result of our evaluation.

Results

Three hundred and Thirteen patients were recruited for this study. There were 2 male and 311 female. Twelve participants did not know their age, but 146 (40.3%) were younger than 45 years while 175 (55.9%) were older than 45 years. Twenty four (7.7%) had bilateral breast cancer while the 289 (92.3%) had unilateral breast cancer. One hundred and sixty two (54.8%) participants were triple negative, 124 of whom were 60 years or younger.

In total, out of 313 participants, 202 (64.5%) patients were candidates for Genetic testing in a cohort of Metastatic Breast Cancer patients in Nigeria.

Conclusion

Various Indications for Genetic Testing in a cohort of Nigerian patients with breast cancer exists in more than 60% of patients. Considering the importance of PARP inhibitors in the management of breast cancer and implications for family members of these patients. It is important that cost appropriate genetic testing is made available to this group of breast cancer patients.

Risk Factors for Genetic Testing in Nigerian Patients

Risk Factor	Total Participants	No with Risk Factor	Percentage
< 45 years	313	126	40.3%
Triple Negative < 60 years	313	124	39.6%
Bilateral Breast Cancer	313	24	7.7%
Male Breast Cancer	313	2	0.6%
Total with Risk Factors	313	202	64.5%

PO4-09-03

Environmental Metal Exposures and Breast Cancer Risk: A Prospective Study of Nationally Representative Canadian Data

Presenting Author(s) and Co-Author(s):

K. Pullella. University of Toronto, Toronto, Ontario, Canada

J. Lubinski. International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland, United States

A. Hanley. Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada

S. Harris. Occupational Cancer Research Centre & Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

S. Narod. Women's College Research Institute, Toronto, Ontario, Canada

J. Kotsopoulos. University of Toronto, Toronto, Ontario, Canada

Introduction: The impact of metal exposure on breast cancer risk remains unclear. Studies have explored metals independently with limited investigation into chronic exposures and mixture analyses. This project describes exposure to eight heavy and essential metals and evaluates the association between metals and breast cancer risk, independently and in a mixture, among Canadian women.

Methods: Demographic information and concentrations of urinary or blood metal biomarkers from 2007-2017 of the Canadian Health Measures Survey (CHMS) were analyzed. Incident breast cancers were ascertained through linkage to the Canadian Cancer Registry. Metal exposure was described using weighted percentiles and categorized by tertiles. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for metal exposure and breast cancer risk. Quantile g-computation was used to estimate the joint association between metal exposure and breast cancer risk.

Results: This analysis included 5,100 women (mean age 44.6 years) with an average follow-up of 6.6 years. Higher urinary arsenic ($> 13.0 \mu\text{g/L}$) and cadmium ($> 10.0 \mu\text{g/L}$) had a significant increased risk of breast cancer (HR_{Arsenic T3 vs. T1} = 2.05; 95%CI 1.05-3.94; HR_{Cadmium T3 vs. T1} = 1.71; 95%CI 1.01 – 5.87). Analyses into the joint association between the metal exposure mixture and breast cancer risk are ongoing, and matrix results will be presented.

Conclusion: This represents the first evaluation of metal exposure and breast cancer risk in a nationally representative cohort. Our findings suggest that arsenic and cadmium, even at low levels, may be associated with an increased risk of breast cancer. These findings can inform population-level interventions to reduce the burden of cancer in Canada.

PO4-09-06

Area Deprivation Index (ADI) among Patients with Breast Cancer in Buffalo

Presenting Author(s) and Co-Author(s):

M. Alharbi. Roswell Park Comprehensive Cancer Center, United States

A. Roy. Roswell Park Comprehensive Cancer Center, United States

A. Patel. Roswell Park Comprehensive Cancer Center, United States

K. Catalfamo. Roswell Park Comprehensive Cancer Center, United States

K. Attwood. Roswell Park Comprehensive Cancer Center, United States

A. Omilian. Roswell Park Comprehensive Cancer Center, United States

E. Bouchard. Roswell Park Comprehensive Cancer Center, United States

E. Levine. Roswell Park Comprehensive Cancer Center, United States

T. O'Connor. Roswell Park Comprehensive Cancer Center, United States

A. Early. Roswell Park Comprehensive Cancer Center, United States

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

Introduction:

Socioeconomic and racial disparities can limit access to health care. Prior studies suggest that living in a disadvantaged neighborhood results in poorer outcomes in several malignancies. ADI is an index that categorizes areas based on socioeconomic variables. In this observational study, we aimed to investigate the ADI among patients (pts) with breast cancer (BC) seen at Roswell Park Comprehensive Cancer Center in Buffalo, New York, and study its association with clinical outcomes to identify the areas with the highest unmet need for possible intervention strategies.

Methods:

We reviewed data of 187 pts diagnosed with stages 1-3 and de-novo stage 4 BC between 2014 to 2018. We obtained information on ADI using pts' home addresses via Neighborhood Atlas tool www.neighborhoodatlas.medicine.wisc.edu. ADI values were categorized into four quartiles Q1(80-100%), Q2(60-79%), Q3(40- 59%), and Q4(0-39%) from highest deprivation/poor social economic status areas to least disadvantaged areas, respectively. Demographic and clinicopathological characteristics including age, race, comorbidities, stage, type of insurance, duration on treatment were compared by ADI. Kruskal-Wallis and Chi-square was used for comparing continuous and categorical variables, respectively. Recurrence free survival (RFS), time to next treatment (TNT), and overall survival (OS) were estimated using Kaplan Meier method. Multivariate Cox regression model was used to analyze outcomes for pts with stage 4 in the most disadvantaged areas (ADI \geq 60%) adjusting for relevant covariates. Analyses were performed using SAS v9.4 at a significance level of < 0.05 .

Results:

98% pts (183/187) were females, 85% (160/187) Whites, 9% (17/187) African Americans, and 3% (6/187) Asians. 62% (116/187) lived in the most disadvantaged areas: 37% (70/187) in Q1, and 24% (46/187) in Q2, while 27% (51/187) lived in Q3, and 11% (n=20/187) in Q4. 80% (150/187) pts were diagnosed with hormone receptor positive BC, 18% (34/187) HER2 positive, and 15% (28/187) triple negative BC. 45% of pts (83/187) had de novo stage 4, the rest were diagnosed with stages 1-3. There was no difference in the distribution of age, race, employment, insurance, comorbidities, substance use, smoking, access to contraception,

screening mammogram, or adherence to anti-estrogen and radiation therapy by ADI. There was a significant difference in adherence to chemotherapy/anti HER2 therapy: 92% (36/39) in Q1, 100% (24/24) in Q2 vs. 85% (24/28) in Q3 and 67% (6/9) in Q4, $p=0.029$. Among pts with stages 1-3, there was no difference in RFS ($p=0.700$) or OS ($p=0.400$) by ADI. Among stage 4 patients, there was an association between TNT and ADI, where patients living where there was a trend towards worse survival with increasingly disadvantaged neighborhoods, $p=0.008$ (Table1). Moreover, there was a significant difference in OS by ADI, $p=0.03$ (Table 2). There was a significant association between ADI and both TNT and OS, even after adjusting to age, race, BC subtypes $p=0.004$ and $p=0.034$ respectively (Table3).

Conclusion:

Our study in the Western New York region showed that BC pts living in disadvantaged areas had worse survival and shorter TNT despite being more adherent to chemotherapy/anti HER2 therapy. Our study validates prior studies showing that ADI is an important factor impacting BC outcomes. These data will help guide our future efforts to maximize resource allocation towards these disadvantaged areas to improve BC outcomes.

Table1

Table1			
ADI	TNT in months	Confidence Interval (CI)	P-value
0-39% (Q4)	42	10.0-NR	0.008
40-59% (Q3)	15	7.0-59.0	
60-79% (Q2)	14	10.0-NR	
80-100% (Q1)	6	4.0-12.0	

Table2

Table2			
ADI	Median OS (months)	95% CI (months)	p-value
<60 (Q3-4)	30	10.0-59.0	0.030
≥60 (Q1-2)	10	6.0-14.0	

Table3

Table3	ADI	HR	CI 2.50%-97.50%	p-value
OS	ADI ≥ 60 (Q1-2)	2.701	1.362 - 5.357	0.004
	ADI < 60	Ref.		
TNT	ADI ≥ 60 (Q1-2)	1.983	1.051 - 3.742	0.034
	ADI < 60	Ref.		

PO4-09-07

Overall Survival According to Race and Socioeconomic Status Among Women Treated for Breast Cancer at Ascension Health Hospitals in Metropolitan Detroit

Presenting Author(s) and Co-Author(s):

S. Sivapalan. Michigan State University College of Osteopathic Medicine, United States

K. Berdi. Ascension St. John Hospital, Michigan, United States

A. Shamsa. Wisconsin Medical College, United States

M. Vlachaki. Ascension Macomb Oakland Hospital, Warren, Michigan, United States

A. Thet. Ascension St John Hospital, United States

J. Falk. Ascension St John Hospital, Grosse Pointe Woods, MI 48236, Michigan, United States

C. Dul. Ascension St John Hospital, Grosse Pointe Woods, Michigan, United States

P. Chuba. AMOH Webber Cancer Center, United States

Background: Despite increasing public awareness and education regarding racial inequality, African American (AA) patients continue to carry higher likelihood of death from breast cancer due to both cancer phenotype and remediable factors of access to care and socioeconomic status.

Patients and Methods: We identified 3,241 patients treated for breast cancer between 2006 and 2015 at Ascension St John Hospital (Detroit MI), Ascension Macomb Oakland Hospital (Warren MI) and Ascension Providence Hospital (Southfield MI). Of these, 2530 (78.1%) were categorized as White (W), 658 (20.3%) as African American (AA), and 53 (1.6%) as Other. We considered known risk factors of race and zip code as well as marital status and having any Medicaid insurance (7.4%). 58.55% of patients were married, 15.88% never married, 13.9% widowed, and 11.6% divorced or separated. There were 632 (19.5%) cases represented from the 50 most affluent zip codes in Michigan (median income \$83,125 to \$140,372), 400 (12.3%) from the 50 least affluent zip codes (median income \$14,909 to \$33,500), 2199 (67.8%) from the intermediate zip codes, and 10 (0.31%) unknown or out of state. Tumors subtypes were 62% Luminal A (HR+/HER2-), 9.5% Basal (HR-/HER2-), 3.74% Her2 Enriched (HR-/HER2+), and 8% Triple Positive (HR+/HER2+). There were 279 Stage T0 Receptor positive DCIS and 64 Receptor Negative DCIS. 57.3% had lumpectomy or partial mastectomy as the first course of surgery, 27.9% had some form of mastectomy and 14.7 percent mastectomy with reconstruction. SAS for Windows 9.4, Cary, NC and Tableau 2023.1 was used for descriptive and crude analysis.

Results: As expected overall survival was highly statistically associated ($p < 0.0001$) with the variables: age, race, subtype, node positivity and AJCC pathologic stage. Socioeconomic risk factors including zip code ($p < 0.0001$), marital status ($p = 0.0006$), and carrying Medicaid insurance ($p < 0.0001$) statistically influenced overall survival. When considering the 50 most affluent zip codes, just 3.79% were African American (AA), with a greater proportion diagnosed at Stage I (49.85%) as compared to the 50 least affluent zip codes (81.97% AA; 37.74% Stage I, $p = 0.022$).

Conclusions: As expected, breast cancer survival was influenced by race, tumor, and patient characteristics. This analysis allows for evaluation of the relative influence of biologic factors

(e.g. tumor subtype and cancer stage) and socioeconomic indicators including zip code (stratified by median income) and insurance status.

PO4-09-08

Perceptions and Experiences of Black Women on Family History Sharing and Genetic Testing for Hereditary Breast and Ovarian Cancer

Presenting Author(s) and Co-Author(s):

K. Riggan. Mayo Clinic, United States

J. Yap. Mayo Clinic, United States

E. Cobran. Mayo Clinic, United States

M. Halyard. Mayo Clinic, United States

S. James. Mayo Clinic, United States

M. Kelly. Mayo Clinic, United States

D. Phillips. Mayo Clinic, United States

M. Allyse. Mayo Clinic, United States

Black women experience significant disparities in morbidity and mortality related to hereditary breast and ovarian cancer (HBOC). Early identification of women with HBOC is essential for proactive screening and timely diagnosis. However, evidence suggests that Black women receive genetic testing for HBOC at lower rates than their White counterparts. We conducted in-depth qualitative interviews with 107 Black women with a personal or family history of breast or ovarian cancer, to understand their perceptions of their familial risk of HBOC and interest in genetic testing. In phase 1 of this study, participants were recruited from the networks of patient support organizations and historically Black sororities representing mostly highly educated and well insured patients. In phase 2, participants were recruited from a family medicine safety net clinic in Jacksonville, FL for socioeconomic diversity. Participants in both cohorts frequently expressed a lack of awareness about their family cancer history and identified many barriers to family disclosure of a cancer diagnosis. These include a culture of silence around medical issues and a belief that personal difficulties should be kept to oneself. Practical and cultural barriers to family history sharing were magnified among those with lower socioeconomic status. Many participants in both cohorts indicated a strong desire to understand their own risk of HBOC. They also expressed interested in genetic testing to proactively mitigate risk to themselves and future generations. Understanding of the potential relevance of HBOC testing to one's personal health and post-test actionability was variable across both groups, although perceptions of genetic testing were generally favorable. These findings suggest that culturally tailored educational materials and alternative clinical modalities to collect family health history may be beneficial to improve timely identification of Black women who meet NCCN Guidelines for HBOC testing. Specifically, greater attention should be given to addressing barriers that led to underestimation of HBOC risk among patients experiencing disparities driven by adverse social determinants of health.

PO4-09-09

Deep Immunoprofiling Demonstrates Racial Differences in the Peripheral Immune System in Women at Risk for Breast Cancer

Presenting Author(s) and Co-Author(s):

E. Ogayo. Dana-Farber Cancer Institute, United States

M. Spasic. Brigham and Women's Hospital, Boston, MA, United States

T. Rahman. Dana Farber Cancer Institute, United States

O. Kantor. Brigham and Women's Hospital/Dana-Farber Cancer Institute, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

P. van Galen. Brigham and Women's Hospital, Boston, MA, United States

S. McAllister. Harvard Institutes of Medicine, Boston, Massachusetts, United States

E. Mittendorf. Dana Farber Cancer Institute, Boston, Massachusetts, United States

Background:

Disparities in breast cancer outcomes between Non-Hispanic Black (NHB) and Non-Hispanic White (NHW) women have been attributed to NHB women presenting with more aggressive subtypes and later stage disease, differences in treatment receipt and adherence, access to care and tumor biology. However, previous work has shown that these known factors do not fully account for the observed disparities in outcomes. Systemic immune fitness is a factor not previously studied that may play a role in dictating disease progression and therapeutic responses. Numerous factors, including age and race, impact immune system function and understanding these changes is critical to address disparities in breast cancer outcomes. Here, we developed a pipeline for deep immunoprofiling of peripheral blood mononuclear cells (PBMC) at single cell resolution by full-spectrum flow cytometry. Using this pipeline, we sought to investigate whether there are differences in immune fitness between NHB and NHW women at high risk for developing breast cancer.

Methods:

PBMC were collected and processed from age-matched NHB and NHW women (n=20/cohort) identified as being at high risk for developing breast cancer through our institution's B-PREP (Breast Cancer Personalized Risk Assessment Education and Prevention) clinic. Two custom antibody panels and protocols for comprehensive immunoprofiling of T and B cell subsets (T/B Panel), as well as monocytic, NK, and dendritic cell subsets (M/N/D Panel), along with functional and exhaustion markers were designed, optimized, and implemented. Traditional gating strategies were used to quantify proportions of canonical cell populations, and unbiased high dimensionality reduction analysis was performed using the OMIQ analysis platform to assess phenotypes and functional status of various immune cell subsets.

Results:

Significant differences between cohorts in abundance as well as phenotype of various cell populations were observed. Specifically, CD4⁺ follicular helper T cells, TEMRA CD8, and CD45RA Terminal Effector CD8⁺ cells were enriched in NHB women while PD-1⁺/CD3⁺ cells and PD-1⁺/CD8⁺ cells were enriched in the NHW women (Table). Additionally, several immunosuppressive and systemic inflammatory immune cell types were enriched in NHB women (Table).

Conclusions:

Deep immunoprofiling using single-cell spectral flow cytometry revealed differences in peripheral immune cells between NHB and NHW women at high risk for breast cancer. The significant enrichment of immunosuppressive monocytes and several activated NK cell populations in PBMC samples from NHB women relative to those from NHW women indicate an altered immune environment that may influence breast cancer development. Additional analysis, including a larger sample size and patients with invasive cancer, are ongoing to further understand if differences in immune fitness between NHB and NHW women are associated with disparities in breast cancer outcomes.

Table: PBMC populations (% of CD45+) that are significantly enriched in NHB relative to NHW patients

Cell Phenotype	Cell Surface Markers	P Value	Log Fold Change (positive value enriched in NHB patients)
CD4 Follicular Helper T	CD45+/CD3+/CD8-/CD4+/CD45RA- /CD197+/CD185+/CD183all	0.0106	0.2091
TEMRA CD8	CD45+/CD3+/CD4- /CD8+/CD45RA+/CD197-	0.0193	0.2789
CD45RA Terminal Effector CD8	CD45+/CD3+/CD4- /CD8+/CD45RA+/CD197-/CD27-/CD28-	0.0232	0.3598
PD1+ (CD279) CD8s	CD45+/CD3+/CD4-/CD8+/ CD279+	0.0403	-0.1328
PD1+ (CD279) CD3s	CD45+/CD3+/CD279+	0.0436	-0.0802
CD159c+, NK	CD45+/CD3-/CD19-/CD14-/CD7+/CD159c+	0.0032	0.3593
CD336+, NK	CD45+/CD3-/CD19-/CD14-/CD7+/ CD336+	0.0033	0.2384
Intermediate Monocytes - Immunodepressed	CD45+/CD14+/CD16+/HLA-DR-	0.0058	0.9802
Intermediate Monocytes	CD45+/CD14+/CD16+	0.0068	0.1924
Intermediate Monocytes - Normal	CD45+/CD14+/CD16+/HLA-DR+	0.0091	0.1828
CD337+, Terminal NK	CD45+/CD3-/CD19-/CD14-/CD7+/CD56- /CD16+/CD337+	0.0110	-0.2984
Terminal NK	CD45+/CD3-/CD19-/CD14-/CD7+/CD56- /CD16+	0.0188	-0.3220
CD335+, Terminal NK	CD45+/CD3-/CD19-/CD14-/CD7+/CD56- /CD16+/CD335+	0.0201	-0.3761
CD94+, Terminal NK	CD45+/CD3-/CD19-/CD14-/CD7+/CD56- /CD16+/CD94+	0.0202	-0.3234
Classical Monocytes - Normal	CD45+/CD14+/CD16-/HLA-DR+	0.0218	-0.1006
CD159c+, Mature NK	CD45+/CD3-/CD19-/CD14- /CD7+/CD56+/CD16+/ CD159c+	0.0226	0.3990
CD336+, Mature NK	CD45+/CD3-/CD19-/CD14- /CD7+/CD56+/CD16+/ CD336+,	0.0272	0.3089
CD314+, Early NK	CD45+/CD3-/CD19-/CD14- /CD7+/CD56+/CD16-/ CD314+	0.0313	0.1783
CD159c+, Early NK	CD45+/CD3-/CD19-/CD14- /CD7+/CD56+/CD16-/ CD159c+	0.0356	0.1880
Tim3+, Terminal NK	CD45+/CD3-/CD19-/CD14-/CD7+/CD56- /CD16+/CD223+	0.0368	-0.3072
Classical Monocytes	CD45+/CD14+/CD16-	0.0393	-0.0843

PO4-09-10

A successful method for treatment of an uninsured underprivileged breast cancer population

Presenting Author(s) and Co-Author(s):

I. Komenaka. Ironwood Cancer and Research Centers, United States

T. Reyes. University of Arizona - College of Medicine, United States

J. Gilbert. Morehouse School of Medicine, United States

C. Hsu. University of Arizona - Tucson, United States

W. Arslan. Maricopa Medical Center/Valleywise, United States

G. Ramos. Maricopa Medical Center/Valleywise, United States

J. Dover. Integrated Medical Services, United States

H. Hitchon. Abrazo Health, United States

J. Nodora. University of California - San Diego, United States

E. Martinez. University of California, San Diego, United States

Background Improvements in breast cancer treatment and care have resulted in improved outcomes and decreased mortality. These improvements, however, come with great expense. Despite efforts from health care systems, a significant proportion of the population remains uninsured. The uninsured population is often underprivileged, undereducated and more likely to come from racial/ethnic minority groups. This combination of factors results in a delay in diagnosis, presentation at later stage, and decreased access and compliance with treatment. The goal of the current study is to describe a method for treating an uninsured, underprivileged breast cancer population and the resulting outcomes. Methods Retrospective review was performed of all breast cancer patients seen at Maricopa Medical Center, the safety net hospital in Phoenix, AZ. All breast cancer patients seen from January 1, 2000 to December 31, 2020 were included. Baseline data for every patient was compiled prospectively, supplemented by retrospective chart review. The data included sociodemographic information, health literacy assessment, and diagnostic tests. Health literacy was assessed using the Newest Vital Sign (NVS). Breast cancer treatment, follow up, and mortality were documented. Beginning on July 1, 2006 a new process was implemented to facilitate care of uninsured patients. More details will be included in the poster presentation. Briefly, however, core needle biopsies were performed in the Breast Clinic by the Breast surgeon or Physician assistant during the initial consultation. Rather than requiring full payment of the planned operation upfront, instead a down payment was made with a plan for payment in installments of the remainder of the cost. For chemotherapy and targeted therapy, a process was implemented to apply for discounted medications for appropriate regimens. There are no radiation therapy facilities at Maricopa Medical Center. An agreement was therefore made with a Radiation oncology group in Phoenix to provide discounted radiation therapy. The treatment was paid through treatment grants as well as fundraising activities by the Health Foundation of the hospital. In 2011, the Breast surgeon underwent training for genetic counseling at City of Hope Medical Center to provide genetic counseling for these patients. Results A total of 1,797 patients were included. Among them, 661 patients were seen before the process (BP) was started, while 1,136 patients were seen after the new process (NP) was implemented. Overall, the mean age of the patients was 52 years with most patients being Hispanic (56%). On average the patients had 10 yrs of education and 18% had adequate health literacy. The majority of patients were not employed (70%) and completely uninsured (56%) or underinsured (31%). Only 18% of patients underwent

screening mammography and as a result 67% of patients presented at stage II or later. Despite the barriers mentioned above, the NP group underwent a higher percentage of breast conservation procedures (75% versus 47%, $p < 0.001$). A higher percentage of the NP group received adjuvant therapy: Chemotherapy (91% vs 70%, $p < 0.001$), Radiation therapy (91% versus 70%, $p < 0.001$), and initiated endocrine therapy (87% versus 67%, $p < 0.001$). At a mean follow up of 8 years, these improvements in adjuvant therapy resulted in a lower incidence of both ipsilateral breast tumor recurrence and chest wall recurrence (2% vs 16%, $p < 0.001$ and 5% versus 8%, $p = 0.21$, respectively) and improvement in overall survival (90% vs 81%, $p < 0.001$). Conclusions Despite treatment of a population with many barriers to breast cancer management, implementation of a treatment process improved access to diagnosis and surgical therapy as well as recommended adjuvant therapy. These improvements resulted in lower local recurrence rates and improved survival in an uninsured population.

PO4-09-11

Predictors of Cardiotoxicity in Early Breast Cancer Patients Treated with Doxorubicin and/or Trastuzumab: Implications of Race/Ethnicity and Insurance Status

Presenting Author(s) and Co-Author(s):

S. Jahangier. Advocate Aurora Health, United States

R. Qamar. Advocate Aurora Health, United States

V. Thohan. Mission Health, United States

M. Singh. Advocate Aurora Research Institute, United States

Y. Liao. Advocate Health, United States

J. Weese. Advocate Aurora Health, United States

B. Khandheria. Advocate Health, United States

A. Kamke-Jordan. Advocate Aurora Research Institute, United States

Predictors of Cardiotoxicity in Early Breast Cancer Patients Treated with Doxorubicin and/or Trastuzumab: Implications of Race/Ethnicity and Insurance Status

Shahzaad K Jahangier, MD, Yunqi Liao, MS, Maharaj Singh, PhD, James Weese, MD, Bijoy Khandheria, MD, Anna Kamke-Jordan MS, Vinay Thohan, MD, Rubina Qamar, MD

Background: Approximately 4.1 million women in the United States are living with breast cancer¹. Cardiac dysfunction is a significant adverse effect of commonly used breast cancer therapies like doxorubicin (D) and trastuzumab (T). The cardiotoxicity (CTox) associated with these agents manifests as a reduction in left ventricular ejection fraction (LVEF) with or without signs and symptoms of heart failure.

Purpose: The objective of this study is to identify high-risk populations susceptible to developing CTox, with a focus on identifying individuals who could potentially benefit from the early initiation of empiric cardioprotective therapies.

Methods: We investigated the relationship of race/ethnicity, insurance status, treatment regimen and comorbidities including hypertension (HTN), hyperlipidemia (HLD), diabetes mellitus (DM), tobacco use, BMI, age, and radiation therapy on the development of CTox from D and/or T. A total of 133 newly diagnosed stage I-III invasive breast cancer patients were enrolled in a prospective clinical trial (2013-2017) and received standard of care D and/or T based systemic therapy. Echocardiogram data was collected every 6 months for two years and then based on clinical need for a total of six years. CTox was defined as a >10% drop in LVEF, and/or LVEF < 50%.

Results: Our study included a population of 133 patients comprising Black (22%), White (77%), and Hispanic (1.5%) individuals. Among these patients, 32 developed CTox (Black 41%, White 19%, Hispanic 50%). Of all patients, 29% had State insurance while 71% had Private insurance. Prevalence rates for comorbidities were as follows: HTN (41%), HLD (32%), DM (13%), and tobacco use (36%). In a univariate logistic regression model, race/ethnicity, HTN, insurance status, and tobacco use were most strongly associated with Ctox. When controlling for tobacco use and HTN, race/ethnicity was not significantly associated with Ctox. However, direct comparisons of levels of race/ethnicity showed that Black patients were more likely to develop Ctox when compared to White patients (OR 2.60, 95% CI = 1.01-6.65, P = 0.045). HTN

patients were also more likely to develop Ctox, when controlling for ethnicity and tobacco use (OR 2.62, 95% CI = 1.10-6.43, P = 0.031).

In a separate multivariate analysis, we examined insurance as a surrogate for socioeconomic status. Having State compared to Private insurance was associated with an increased risk of developing CTox when controlling for race/ethnicity and HTN (OR 3.73, 95% CI = 1.47-9.58, P = 0.006).

Furthermore, in all models, HLD, DM, BMI, age, and radiation field were not found to be significantly associated with increased CTox.

Conclusion: In our well characterized population of patients with stage I-III breast cancer, who were prospectively followed and received standard of care systemic therapy, we observed an association between insurance status with increased risk of CTox from treatment regimen.

¹Lisa Gallicchio, PhD and others, Estimation of the Number of Individuals Living With Metastatic Cancer in the United States, JNCI: Journal of the National Cancer Institute, Volume 114, Issue 11, November 2022, Pages 1476–1483

PO4-09-12

Academic-community partnership bridges disparities in African American patient representation in accelerated partial breast irradiation clinical trials

Presenting Author(s) and Co-Author(s):

E. Kakadiaris. UTSW Obstetrics and Gynecology, United States

B. Lue. UTSW Radiation Oncology, United States

Y. Kwon. UTSW Radiation Oncology, United States

P. Alluri. UTSW, United States

D. Kim. Dep of Radiation Oncology at Vanderbilt University, United States

A. Sprangler. UTSW Radiation Oncology, United States

M. Arbab. UTSW Radiation Oncology, United States

R. Timmerman. UTSW, United States

A. Rahimi. University of Texas Southwestern Medical Center, Dallas, Texas, United States

Purpose/Objectives: Clinical outcomes in African American (AA) patients diagnosed with breast cancer continue to lag behind other racial groups. Thus, AA women are 41% more likely to die from breast cancer than White women despite lower incidence of breast cancer in AA women. Some of these disparities are related to barriers in access to standard-of-care treatments such as radiation therapy (RT). The prolonged nature of radiation treatments confers disproportionate higher burden (due to lost wages, transportation costs etc.) on economically disadvantaged groups such as AA women. Accelerated partial breast irradiation (APBI), which dramatically reduces treatment time in appropriately selected patients, has the potential to mitigate financial toxicity, and improve access and treatment compliance for AA. However, underrepresentation of AA patients in APBI trials may pose a barrier to wide adoption of APBI treatments in this patient population. At our institution, we have established a unique partnership between our University Hospital and a county hospital that serves as a safety-net hospital for many economically disadvantaged groups and treats a large proportion of AA patients. The goal of this study is to determine if our unique academic-community partnership improves disparities in representation of AA patients in APBI trials. **Methods:** We performed a PUBMED search to identify 197 clinical trials involving APBI. After excluding international trials and multiple reports from the same trials, we identified 80 unique studies that were based in the United States. A total of 20 studies investigating APBI provided demographics data, comprising 1735 total patients. AA enrollment rate in these trials was compared to APBI trials completed at our institution in partnership with our county hospital partner. **Results:** Out of 1785 patients enrolled in APBI trials in the United States where demographic information was available, 1488 patients were White (85.7%), 124 were Black (7.1%), 67 were Hispanic (3.9%), and 46 were Asian (2.7%), and 10 patients were classified as multiple or unknown (0.6%). We compared these results to two APBI trials conducted at our institution investigating 5-fraction and single fraction APBI regimens. Out of a total of 104 patients treated, 17 patients (16.3%) were Black. This difference in proportion of AA patient enrollment between our institution (16.3%) versus those reported in APBI trials across the United States (7.1%) was statistically significant ($p < 0.05$). **Conclusion:** Reporting and representation of AA patients in APBI trials remains low, which may lead to lower adoption of APBI treatments in AA patients. This may lead to underutilization of APBI, a convenient treatment with lower financial toxicity, among AA patients. Our study shows that effective academic-community partnerships can bridge such disparities in AA patient representation in APBI trials. Expansion of such academic-community

partnerships across the country may bridge systemic disparities in AA patient representation in oncology clinical trials. Future studies are needed to determine if improved access to novel and convenient treatments such APBI will bridge existing disparities in clinical outcomes in patients diagnosed with breast cancer.

PO4-10-02

Implementing Just ASK™ to achieve diverse participation and representation in a RCT of chemotherapy-induced peripheral neuropathy

Presenting Author(s) and Co-Author(s):

M. Weiss. Breastcancer.org, United States

M. Giaddui. Lankenau Institute for Medical Research, Wynnewood, PA, United States

S. Kjelstrom. Lankenau Institute for Medical Research, Wynnewood, PA, United States

A. Ghaneie. Department of Hematology/Oncology at Lankenau Medical Center, Main Line Health, United States

J. Hong. Lankenau Medical Center, Main Line Health, Wynnewood, PA, United States

J. Burrell. Lankenau Institute for Medical Research, Wynnewood, PA, United States

S. Windawi. Lankenau Institute for Medical Research, Wynnewood, PA, United States

E. Erebor. Lankenau Institute for Medical Research, Wynnewood, PA, United States

B. Mann. Lankenau Medical Center, Main Line Health, Wynnewood, PA, United States

S. Roberts. Lankenau Medical Center, Main Line Health, Wynnewood, PA, United States

G. Bidas. Lankenau Medical Center, Main Line Health, Wynnewood, PA, United States

S. Meske. Breastcancer.org, United States

L. Saeed. Lankenau Institute for Medical Research, Wynnewood, PA, United States

K. Aliano Ruiz. Lankenau Institute for Medical Research, Wynnewood, PA, United States

J. Hibbs. Department of Medical Oncology, Doylestown Hospital, United States

J. Marks. Lankenau Medical Center, Main Line Health, Wynnewood, PA, United States

D. Holtz. Lankenau Medical Center, Main Line Health, Wynnewood, PA, United States

Z. Ali. Department of Hematology/Oncology at Lankenau Medical Center, Main Line Health, United States

A. Shevade. Department of Hematology/Oncology at Lankenau Medical Center, Main Line Health, United States

R. Ciocca. LMC, United States

P. Gilman. Lankenau Institute for Medical Research, Wynnewood, PA, United States

S. Larson. Center for Population Health Research, Main Line Health, Wynnewood, PA, United States

S. Shimamoto. Department of Neurology, Baylor University Medical Center, United States

D. Martinez. Department of Psychiatry, Columbia University Irving Medical Center, New York, NY, United States

F. Chino. Memorial Sloan Kettering Cancer Center, New York, New York, United States

N. Barrett. Center for Equity in Research, Duke Cancer Institute, Durham, NC, United States

Background:

Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting complication of cancer treatment which disproportionately affects Black patients, and can negatively impact survival and quality of life. Strategies to improve diverse participation and representation in clinical trials are necessary to reduce this health disparity.

Methods:

To ensure diverse representation in our RCT of CBD vs placebo in patients with grade 2-3 CIPN after treatment with taxane or platinum-based chemotherapy, key evidence-based strategies outlined in the ASCO-ACCC Just ASK™ Training Program were implemented. Eligibility criteria were as inclusive as possible, including CIPN duration up to 2 years and a range of diagnoses: nonmetastatic breast, colorectal, endometrial; and ovarian cancer. Few comorbidities were excluded. The diverse research team engaged every potentially eligible patient with the opportunity to make an informed decision to participate in the study. Using an assets-based approach, the team assessed and addressed social drivers of health (SDoH) and built trust by providing transparency, timely access to all team members, flexible study visits (including telemedicine), and study materials which were comprehensive, understandable, and accessible, within a culture of respect for patient autonomy and privacy.

Results:

Between 6/1/2020 and 8/8/2022, 230 patients were prescreened, 124 met eligibility, 54 consented and joined, and 46 completed ≥8 of the 12-week treatment phase and were included in the analysis. The study successfully enrolled a participant population that was 30% Black and 67% White (Table), reflecting community demographics of the enrolling facility. Attrition was lower than expected (15% vs 30% assumed in statistical plan) and only 5 of 425 planned study visits for the 46-patient cohort were missed.

Table. Baseline Characteristics

	Total n = 46
Age (Mean/SD)	59.6 (8.8)
Gender	
Male	5 (10.9%)
Female	41 (89.1%)
Race	
White	31 (67.4%)
Black	14 (30.4%)
Other	1 (2.2%)
Ethnicity	
Hispanic	2 (4.4%)
Not Hispanic	44 (95.6%)
Cancer Type	
Breast	29 (63.0%)
Colo-rectal	9 (19.6%)
Ovarian	7 (15.2%)
Uterine	1 (2.2%)

The most effective strategy to achieve diverse participation was prescreening the electronic medical record (EMR) with daily Epic® and OncoEMR® queries (DQ) by a research

assistant. DQ allowed all potentially eligible patients to be approached to participate and yielded about half of enrollees. Also key to success were engaged study champions among medical oncology fellows, oncology nurses, nurse navigators, clinical research coordinators, and research-oriented attending physicians. Some physician referrals were facilitated by the ease of secured texts and EMR messages, and peer recognition; however, few referrals came from non-research-oriented physicians.

Eleven of the 54 consented patients were identified to have essential needs and received facilitated social work assistance, including psychosocial support, financial assistance (for monetary grants for direct expenses or access to medical insurance and other benefits); and support for transportation, nutrition; child and eldercare. Of the 11 patients with essential needs, 4 were unable to complete the study due to either personal (3) or medical issues (1).

Conclusions:

The ASCO-ACCC Just ASK™ approach was successful for diverse clinical trial enrollment with strong protocol adherence and low attrition. Key steps included: study team diversity, a culture of respect and transparency, EMR prescreening, SDoH assessment and solutions, and engagement of research-oriented study champions. As achieving diverse participation in clinical trials is essential to reducing health disparities, the Just ASK™ approach should be considered an essential aspect of clinical trial design and implementation.

Baseline Characteristics

Table. Baseline Characteristics

	Total n = 46
Age (Mean/SD)	59.6 (8.8)
Gender	
Male	5 (10.9%)
Female	41 (89.1%)
Race	
White	31 (67.4%)
Black	14 (30.4%)
Other	1 (2.2%)
Ethnicity	
Hispanic	2 (4.4%)
Not Hispanic	44 (95.6%)
Cancer Type	
Breast	29 (63.0%)
Colo-rectal	9 (19.6%)
Ovarian	7 (15.2%)
Uterine	1 (2.2%)

PO4-10-03

Relationship Between Insurance Status and Breast Cancer Care in Young Mexican Women

Presenting Author(s) and Co-Author(s):

D. Gonzalez-Sanchez. Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, Mexico

A. Ramirez-Cisneros. Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, United States

A. Platas. Instituto Nacional de Cancerología, United States

A. Platas. Breast Medical Oncology Department, Instituto Nacional de Cancerología, Mexico

D. Vazquez-Juarez. Breast Cancer Center, Hospital Zambrano Hellion TecSalud, United States

F. Mesa-Chavez. Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, Mexico

A. Ferrigno. Hospital Zambrano Hellion - TecSalud, Tecnologico de Monterrey, United States

A. Mohar. Instituto Nacional de Cancerologia, Mexico

A. Fonseca. Breast Medical Oncology Department, Instituto Nacional de Cancerología, Mexico

C. Villarreal-Garza. Tecnologico de Monterrey, Nuevo Leon, Mexico

BACKGROUND

In Mexico, 71% of the population is covered by public health insurance, while 2% are privately insured and 27% are uninsured. Previous studies have demonstrated differences in breast cancer (BC) care according to type of healthcare coverage in the United States and Latin America. Most studies have observed that privately insured patients are diagnosed at earlier stages, have less symptom-to-diagnosis and treatment delays, and have better overall outcomes. The aim of this analysis was to evaluate whether differences in BC care exist among young women with breast cancer (YWBC), ≤40 years at diagnosis, depending on their insurance status in Mexico.

METHODS

Data was collected from the Mexican prospective cohort of YWBC Joven & Fuerte. Patient surveys and researcher follow-ups were used to collect data related to clinicopathologic features, time from symptom onset to seeking medical assistance and treatment, and perceived quality of information received and medical staff support. Results were analyzed using SPSS.

RESULTS

Information about health insurance status was available for 608 patients: 565 (93%) had public coverage and 43 (7%) had private coverage. Table 1 describes the clinicopathologic characteristics of both groups. Patients with private insurance were diagnosed at earlier stages, 0-II vs. III-IV (81% vs. 16%), than those with public insurance (50% vs. 45%) ($p < 0.001$). No difference was found on the distribution of BC subtypes among both groups. A total of 573 (94%) patients had registered information regarding the time from symptom onset to contacting a medical professional. Only 18 (3%) were diagnosed with imaging studies (5% and 3% with private and public coverage, respectively). More privately insured patients (95%) contacted a healthcare professional during the first 3 months since symptom onset than publicly insured patients (74%) ($p = 0.003$). Information regarding the time from contacting a healthcare professional to treatment start was available for 472 (78%) patients. There was no difference in

the proportion of patients who started treatment ≤ 3 months after arriving with a healthcare professional according to type of health insurance (76% private vs. 67% public coverage; $p=0.2$).

The majority of patients (96%) considered having adequate support from the medical staff (100% private vs. 94% public). Compared to those with public coverage, more privately insured patients perceived receiving adequate information about their treatment (79% private vs. 50% public; $p < 0.001$). There were no differences between groups regarding the perceived quality of information regarding their diagnosis ($p=0.06$) and continuous BC care ($p=0.6$).

CONCLUSION

Patients with private coverage were diagnosed at earlier stages, reported contacting a healthcare professional earlier, and perceived receiving adequate information regarding their treatment more often than patients with public coverage. These results coincide with previously reported differences between patients with private and public health insurance. Interestingly, there were no differences between the delays from the first visit to treatment initiation and perceived support from the medical staff depending on type of healthcare coverage. Given the observed differences between privately and publicly insured patients, population-based interventions to increase awareness of alarm signs for BC and widespread access to quality patient education resources could help decrease the disparities between these groups.

TABLE 1. Clinicopathologic features of BC depending on insurance status

Subtype	Public Insurance (n=568)		Private Insurance (n=43)	
Triple Negative	144	25%	13	30%
Hormone-sensitive/HER2 +	87	15%	4	9%
Hormone-sensitive/HER2 -	289	51%	19	44%
Hormone-negative/HER2 +	38	7%	4	9%
Stage				
Stage 0	10	2%	3	7%
Stage I	47	8%	6	14%
Stage II	225	40%	26	60%
Stage III	199	35%	6	14%
Stage IV	58	10%	1	2%

PO4-10-04

Treatment differences by race and age in metastatic hormone receptor-positive/HER2-negative breast cancer

Presenting Author(s) and Co-Author(s):

Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States

J. Ivory. UNC-Chapel Hill, United States

A. Deal. UNC Lineberger Comprehensive Cancer Center, United States

A. Wardell. UNC Lineberger Comprehensive Cancer Center, United States

A. Wheless. University of North Carolina Lineberger Comprehensive Cancer Center, United States

C. Dees. University of North Carolina, Chapel Hill, North Carolina, United States

L. Carey. UNC-Lindberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

Introduction:

Black and younger patients are more likely to have aggressive forms of breast cancer. Endocrine therapy (ET) plus a CDK4/6 inhibitor is the standard of care first-line therapy for patients with hormone receptor-positive, HER2-negative (HR+/HER2-) metastatic breast cancer (MBC). Recent data has shown better outcomes with this approach compared to chemotherapy, even for patients with aggressive disease. Our study looked at differences in first-line treatment among Black and younger women with HR+/HER2- MBC.

Methods:

Clinical characteristics, treatment, and outcomes of patients diagnosed with HR+/HER2- MBC between 2011-2022 were retrieved from the UNC Metastatic Breast Cancer Database. Log binomial regression modeling compared treatment choices by group, and Cox proportional hazards regression modeling evaluated progression-free survival (PFS) from the start of treatment.

Results:

524 patients were included in this analysis. 30% were young patients (< 50 years of age), 20% were Black patients, 62% had only 1 site of metastasis and 51% had visceral involvement. When looking at first-line treatment for metastatic disease, 21% of overall patients had received chemotherapy. The likelihood of receiving chemotherapy was higher for younger versus (vs) older patients (29% vs 18%, RR=1.63, p=0.004), for Black vs White patients (31% vs 18%, RR=1.71, p=0.002), and for those with visceral vs non-visceral involvement (26% vs 16%, RR=1.67, p=0.004). A model including age, race, and visceral involvement showed similar findings. Among patients who received ET as the first line treatment for metastatic disease, the likelihood of receiving CDK 4/6 inhibitors in addition to ET was lower for young Black patients compared to young White patients (41% vs 74%, RR=0.55, p=0.02). However, among older patients ≥ 50 , no significant difference was seen by race (Blacks 60% vs Whites 56%, RR=1.1, p=0.61). Adjusting for visceral involvement showed similar findings. Patients who received ET (with or without CDK 4/6 inhibitors) had better PFS compared to patients receiving chemotherapy as first-line therapy (HR 0.65, 95% CI 0.49, 0.88, p=0.005), this held true after adjusting for age, race, treatment group and visceral involvement (HR 0.7, p=0.02). A stratified analysis showed similar findings within Black patients (HR 0.42, p=0.003), and young patients (HR 0.55, p=0.01).

Conclusion:

Overall, Black and younger patients were more likely to receive chemotherapy as the first-line treatment for metastatic disease. Among patients who received ET as the first-line treatment for MBC, young Black patients were less likely to receive CDK 4/6 inhibitors compared to young White patients. Further studies are needed to outline the multi-level factors contributing to the identified disparities in care among patients with HR+/HER2- MBC.

PO4-10-06

Cost-effectiveness analysis of ribociclib in the treatment for premenopausal or perimenopausal women with HR+/HER2- advanced breast cancer: a public health care system perspective in Mexico

Presenting Author(s) and Co-Author(s):

S. Campos-Gomez. Centro Oncologico Estatal Issemym, Toluca de Lerdo, Mexico, United States

C. Pichardo Piña. Aditum Consulting Group, Mexico, Mexico, Mexico, Mexico

BACKGROUND: Ribociclib (RIB) an inhibitor of cyclin-dependent kinase 4 and 6 for the treatment of advanced breast cancer (ABC), has demonstrated significant efficacy in prolonging progression-free survival and overall survival when added to endocrine therapy (ET). Because of the high-cost perception of this therapeutic class, it is crucial to assess their relative value compared to existing standards of care in the local setting.

Chemotherapy is used as the first line of treatment in a conservative case in almost three-quarters of ABC patients with positive hormone receptors in the Public Health System in Mexico. Additionally, the high use of chemotherapy presents additional clinical and economic challenges for the Institute. Among the clinical challenges, the toxicity associated with chemotherapy regimens stands out.

We evaluated the cost-effectiveness of the inclusion of RIB+ ET to usual care in the treatment of premenopausal or perimenopausal ABC from the perspective of the Public Health System in Mexico. Direct medical costs were considered.

METHODS: We developed a partitioned survival model to simulate time to cancer progression and to compare lifetime clinical benefit and cost of standard alternative treatment strategies for patients with metastatic disease. Per approved indication, endocrine treatment-naïve patients were assigned to RI plus ET or usual care (different chemotherapy schemes). Costs in Mexican Pesos (MXN) were estimated from the perspective of the Public Health System in Mexico.

Costs and clinical benefits were discounted at 5% annually. The model assumptions were informed based on published clinical trial data from the randomized Phase III MONALEESA-7 trial and other peer-reviewed studies and indirect treatment comparisons. We carried out one-way and probabilistic sensitivity analyses to assess the robustness of our results to the changes in model assumptions.

RESULTS: Ribociclib reduced monthly direct medical costs associated with the administration of breast cancer treatment and the management of adverse events. Direct drug acquisition costs per month of ribociclib were in the range of the cost of current available and used therapies. Indirect treatment comparisons did not show statistical significance of the benefit of ribociclib vs. standard of care, primarily due to heterogeneity leading to a mixed evaluation vs. two comparator groups according to the statistical significance of the survival improvement.

Ribociclib is a 100% oral therapy with a manageable safety profile with dosage adjustments, so it does not require institutional resources for its administration or for managing adverse events. Its consolidated cost at 28 days of treatment is up to 40% less than combined chemotherapy regimens and up to 30% less than monotherapy schemes.

Average cost-effectiveness for progression-free survival for ribociclib is among the lowest considering chemotherapy options even though generic versions are available for many of them. For the comparators with comparable efficacy, ribociclib was cost-saving at current public market prices. For the comparators where ribociclib showed a significant benefit, the incremental cost-effectiveness ratio of ribociclib vs. standard of care is also below the threshold of 3 GDPs per capita vs. most options, leading to cost-effectiveness. A longer treatment duration due to progression delay was a main driver of incremental cost.

CONCLUSIONS: Ribociclib is cost-saving or cost-effective vs. standard of care in the Public Health System in Mexico. Other variables must be considered to inform clinical and funding decisions, such as disease burden and humanistic impact on this young, economically active population.

PO4-10-07

**Understanding Psychological distress in patients prior to breast cancer diagnosis :
Mixed Methods Study**

Presenting Author(s) and Co-Author(s):

Y. Gao. Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan,030032,China;, United States

J. Gao. Shanxi Bethune Hospital,Shanxi Academy of Medical Sciences , Tongji Shanxi Hospital,Third Hospital of Shanxi Medical University, Taiyuan,030032,China, United States

Purpose : While the association between diagnosis of breast cancer and post-diagnosis psychological distress has been well documented, data regarding pre-diagnosis psychological distress in the breast cancer population are limited. The purpose of the current study is to measure the distress levels of patients prior to breast cancer diagnosis, to identify the categories of distress they have, and describe the experience of distress of patients before diagnosis.

Methods: This study uses a mixed research method of cross-sectional survey and qualitative interviews. In the quantitative part, a cross-sectional survey of 118 patients with completed breast biopsies awaiting pathological diagnosis was conducted using the National Comprehensive Cancer Network's (NCCN's) Distress Thermometer(DT) and Problem List (PL), In the qualitative part, 15 patients were invited using convenient and purposive sampling. Data was collected using a semi-structured face-to-face interview and recorded. The transcribed text was analyzed using Colaizzi's phenomenological method.

Results: The results reveal that 63.6% of patients reported a higher level of psychological distress (n=75, scoring \geq 4).Most patients had emotional (98%) or physical (64%) problems. Among these, worry or anxiety (47.5%), fear (33.1%), finances (21.2%), sadness and depression(18.6%), and grief or loss(15.3%) were the most frequently reported problems. Multivariate logistic regression analysis showed that the factors associated with psychological distress before the diagnosis of breast cancer patients were age, education level. The experience of patients before diagnosis emerged five themes: Very high psychological distress index; Strong uncertainty; The demand of information; Guilt for the family ; Hoped for psychological support from the health care team.

Conclusions: Psychological distress is prevalent prior to breast cancer diagnosis and may merit early intervention. Understanding patients' distress may help guide future psychosocial needs assessments and interventions to promote patient quality of life.

Table 1 Sample characteristics (n=118).

Table 1 Sample characteristics (n=118).

	Women with breast cancer (n=118)			
	N(%)	Min	Max	Mean
Age		27	83	52.9 ± 12.3
Educational level				
≤9 years	72 (61.0%)			
>9years	46 (39.0%)			
Marital status				
Single	6(5.1%)			
Married	112 (94.9%)			
Occupation				
Unemployed	69 (58.5%)			
Employed	49(41.5%)			
comorbidities				
NO	70 (59.3%)			
YES	48 (40.7%)			
Family cancer history				
NO	99(83.9%)			
YES	19(16.1%)			
Childbearing status				
No	7 (5.9%)			
Yes	111(94.1%)			
BI-RADS				
4c/5	96 (81.4%)			
4b	20 (16.9%)			
4a	2(1.7%)			
age of child		1	45	26.1 ± 10.7
DT score		0	10	4.67 ± 2.1
HADS-A score		1	16	7.95 ± 3.24
HADS-D score		1	18	6.61±3.36
DT≥4	75(63.6%)			
HADS-A≥8	70(59.3%)			
HADS-D≥8	47(39.8%)			

Table 2 Univariate analysis of predictors associated with psychological distress

Table 2 Univariate analysis of predictors associated with psychological distress

	DT≥4	χ^2	p
Age	50.03 ± 10.99	3.456	0.001
Educational level		9.269	0.002
≤9 years	38 (50.7)		
>9years	37 (49.3)		
Marital status		2.494	0.114
Single	2 (2.7)		
Married	73 (97.3)		
Occupation		2.1181	<0.001
Unemployed	32 (42.7)		
Employed	43 (57.3)		
comorbidities		0.475	0.491
NO	45 (60.0)		
YES	30 (40.0)		
Family cancer history		1.168	0.280
NO	65 (86.7)		
YES	10 (13.3)		
Childbearing status		0.132	0.716
No	4 (5.3)		
Yes	71 (38.7)		
BI-RADS		0.233	0.629
4c/5	62 (82.7)		
4b	13 (17.3)		

Table 3 The binary logistic regression model of psychological distress

Table 3 The binary logistic regression model of psychological distress

	B	SE	Wald χ^2	P	OR (95% CI)
Breast cancer					
Age	-0.043	0.022	3.896	0.048	0.958 (0.919,0.999)
Educational level	1.034	0.516	4.020	0.045	2.813 (1.024,7.733)
Occupation	1.863	0.528	12.458	<0.001	6.440 (2.289,18.117)

PO4-10-08

Building a standard methodology: Early Gynecologic Consultation and Bone Mass Density Examination in Breast Cancer Patients Receiving Endocrine Therapy

Presenting Author(s) and Co-Author(s):

C. Ching-Wen. Taipei Medical University, United States

T. Ka-Wai. Taipei Medical University Shuang Ho Hospital, United States

S. Chih-Ming. Taipei Medical University Shuang Ho Hospital, United States

W. Hsueh-Chi. Taipei Medical University Shuang Ho Hospital, United States

Purpose

Hormone receptor-positive type of breast cancer is typically treated with hormone therapy (HT), including tamoxifen and aromatase inhibitors (AI). However, long-term use of HT may increase the risks of endometrial cancer, vaginal dryness, and osteoporosis. To minimize the risks, breast surgeons should schedule regular follow-up with gynecologists and arrange bone mass density (BMD) examination. Using the Plan-Do-Study-Act (PDSA) methodology, we aimed to increase cross-team care with gynecology department and to promote BMD examination for breast cancer patients receiving HT.

Methods

We formed a multidisciplinary team including breast surgery department and gynecologic department in our hospital that care for female patients with breast cancer and related side effects. We arranged a lecture for all collaborative doctors, introducing our aims, interventions, and measurement strategies to test in multiple PDSA cycles. The interventions with standardized criteria include: (1) a gynecologic consultation, triggered if a patient initially receive tamoxifen and (2) a BMD examination, triggered if a patient initially receive AI. The triggering mechanism is embedded in the ambulatory alarming system. Both the intervention rates were tracked during PDSA cycle 1 in 2023 and compared with baseline rates in 2020-2022. Adherence to the plan was maintained and measured using data analytic reports and chart audits.

Results

The gynecologic consultation rate during PDSA cycle 1 is significantly higher than the baseline, which is 40.4% and 22.4% ($p = 0.006$), respectively. In patients who received tamoxifen, 6-month-consultation rate during PDSA cycle 1 is also significantly higher than the baseline group, which is 77.77% and 42.9% ($p = 0.005$), respectively. The median time from HT therapy to first gynecologic consultation decreased from 51 days to 28 days. Furthermore, the baseline BMD testing rate before our intervention was 30.6%. This increased to 48.3% during PDSA cycle 1.

Conclusion

Standardized gynecologic consultation criteria led to earlier gynecologic consultation in breast cancer patients receiving tamoxifen and higher BMD test rates in patients receiving AI. Future PDSA cycles will focus on assessing the frequency of subsequent gynecologic encounters in patients who received a triggered gynecologic consult.

PO4-10-09

MBC Community Barriers and Patient Navigation Training Needs

Presenting Author(s) and Co-Author(s):

S. McCoy. Susan G. Komen, Dallas, Texas, United States

K. Fox. Susan G. Komen®, United States

K. Volpe. Susan G. Komen®, United States

T. Lee. Susan G. Komen, United States

J. Okamoto. Susan G. Komen, United States

J. McMahon. Susan G. Komen, United States

K. Wojtanik. Susan G. Komen®, United States

Background

Komen's mission is to save lives by meeting the most critical needs in our communities and investing in breakthrough research to prevent and cure breast cancer. One method to achieve our mission is through patient navigation. Evidence supports the role of patient navigation in improving breast health outcomes. Patient navigators identify and address barriers to equitable cancer care delivery in a fragmented healthcare system and work to ease the burdens that patients diagnosed with breast cancer experience. As a valued member of a patient's health care team, patient navigators contribute to improving the quality of cancer care and eliminating barriers throughout the continuum of care. However, not all breast cancer patients experience the same barriers.

Metastatic breast cancer (MBC) is the most advanced stage of breast cancer, and there is some evidence that suggests those diagnosed with MBC have unique experiences and needs that often determine and/or contribute to their disease trajectory. Despite this, little in-depth systematic work has been done to understand the unique challenges faced by those diagnosed with MBC or to explore strategies to address those challenges, and there have been no known efforts to equip patient navigators to specifically address the unique barriers of those diagnosed with MBC.

Methods

Susan G. Komen®'s Center for Applied Research (CfAR) designed the MBC Patient Navigation Training research study to improve the health outcomes of those diagnosed with MBC through patient navigation. The study design includes 4 phases of qualitative methodology with MBC and patient navigator communities to accomplish the following objectives:

- Examine the needs and barriers of MBC patients (Phase 1)
- Identify what needs and barriers MBC patients face that can be addressed through patient navigation (Phase 2)
- Assess the gaps in Komen's Patient Navigation Training Programs' ability to prepare navigators across the United States to address the identified needs/barriers of MBC patients (Phase 3)
- Design a new module to fill the gaps in Komen's Patient Navigation Training Program to support patient navigators serving MBC communities across the U.S. (Phase 4)

Participants were recruited through a grassroots approach to community engagement, with

members of the study team, Komen staff, and other breast health advocates contacting individuals and organizations across the U.S. Individuals were invited to attend a virtual introductory call to meet study staff and each other before consenting to participate in the virtual focus groups.

Results

Participants diagnosed with MBC (n=17) attended one of four virtual focus groups held May 2023 to share their lived experiences. The focus groups were recorded, the recordings were transcribed and checked for accuracy, and study staff analyzed data using a constant comparison approach to qualitative data analysis with NVivo data management software. Those diagnosed with MBC identified challenges of their diagnosis, barriers within the healthcare system, financial toxicity, lack of support, and health inequities as factors limiting their access to care. These participants also identified the role patient navigators could serve to help address these challenges.

Next Steps

In Phase 2, the study team will examine to what extent patient navigators feel prepared to address the barriers of MBC communities. Based on the findings from this study, the team will identify areas where more training is needed (Phase 3) and design a training module for Komen's Patient Navigation Training Program (Phase 4) to better prepare patient navigators across the U.S. to meet the needs of MBC communities and improve health outcomes and cancer care delivery.

PO4-10-10

NAVYA-AI enabled intervention to increase real-world guideline compliant care: Improving NGS testing in breast cancer

Presenting Author(s) and Co-Author(s):

R. Badwe. Tata Memorial Centre, United States

P. Thaker. Washington University St. Louis, United States

F. Begum. Navya Network, United States

M. Acherjee. Navya Network, United States

G. Srivastava. Navya Network, United States

N. Ramarajan. Navya Network, United States

S. Nag. Sahyadri Group of hospitals, United States

S. Gupta. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), United States

S. Gulia. Tata Memorial Centre, United States

J. Ghosh. Tata Memorial Centre, United States

B. Sirohi. BALCO Medical Centre, United States

BACKGROUND: Navya-AI is a validated online cancer informatics solution that combines artificial intelligence based analysis of the guidelines and evidence, along with asynchronous expert review. Navya-AI releases preliminary system-generated opinions for patients whose treatment plans fit high confidence based on NCCN Guidelines and prior expert reviews. Prior research (SABCS 2014-2018 and ASCO 2021 showed: 1) 97% concordance of Navya-AI predictions with an academic medical center in India and in the US 2) 80% of patients implement treatment concordant with Navya-AI recommendations on the ground 3) Navya's NCCN and evidence-based treatment plans reduce the patient waiting times for an expert opinion by an average by 3.5 days.

Next generation sequencing (NGS) is an expensive but necessary method for identifying patients for risk reduction and therapy selection in breast cancer (BC). NGS testing can be over-used or under-used, and compliance with NCCN guidelines on patient selection is especially important in resource-constrained settings and Low Middle Income Countries (LMIC) such as India. The aim of this study is to find the physician compliance to NCCN guidelines on NGS testing in India, and how Navya-AI can identify the opportunity for improved care, and improve compliance with guidelines for optimal care.

METHODS: From January 2022 to May 2023, Breast Cancer patients receiving Navya-AI treatment plan (based on guidelines and live expert-review) were analyzed. Patients who could afford NGS testing and targeted therapies, and who met the Enhanced tier of NCCN resource stratified guidelines for their care centers were identified. Their records were screened by Navya-AI to assess if they met NCCN criteria for NGS testing for risk reduction or for treatment selection (young age, positive family history, triple negative breast cancer etc.). Treating physicians were then analyzed if they had ordered NGS appropriately, or had missed an opportunity for NGS (undertreatment), or had over-ordered NGS (overtreatment). **RESULTS:** 521 BC patients who could afford NGS tests received a Navya-AI plan during this period. Of these, 85% were Indian patients (415/521) and were analyzed. Patients were diverse with respect to age, cancer stage, family history of cancer and histology: Age < 35: 6.7%, 35-50: 33%, 51-65: 43.76%, >65: 16.51%; early stage: 21.5%, locally advanced stage:

29.56%, metastatic stage: 47.79% and benign disease: 1%; positive family history of cancer: 37.35%, triple negative BC: 21.9%. Of 415 Indian breast cancer patients who could afford testing, NGS testing was indicated in 69.64% (289/415) as per NCCN guidelines.

The treating physician was compliant with NCCN guidelines in only 47.95% (199/415) of the cases: 19.2% (80/415) of the time, NGS was indicated and the treating physician ordered the same; 28.67% (119/415) of the time, NGS was not indicated, and the treating physician did not order NGS. The remaining 52% were not compliant with NCCN. Under-treatment was present in 50.36% (209/415) of cases, and was the vast majority of fallouts. Over-treatment was only present in 1.69% (7/415).

In all 50.63% (209/415) cases, where NGS was not ordered by the treating oncologist, but was indicated, and affordable to the patient, Navya requested the patient to discuss the risks/benefits of NGS testing with their treating oncologist.

CONCLUSION: NGS testing in BC patients has significant impact on risk-reduction, genetic counseling, choice of surgery, and treatment options for adjuvant therapy. Missed opportunities for NGS testing in more than 50% of the patients who can afford the testing and resultant therapies, points to a significant area where compliance with guidelines and expert opinions can impact outcomes. A 'Technological Earthshot' that significantly increases adoption of guideline-based care is the first and an easy step towards 'Cancer Moonshots'.

PO4-10-11

Needs of oncology nurse navigators serving young or metastatic breast cancer patients

Presenting Author(s) and Co-Author(s):

K. Owens. Facing Our Risk of Cancer Empowered, United States

M. Dean. University of South Florida, United States

E. Bourquardez Clark. University of South Florida, United States

P. Welsh. Facing Our Risk of Cancer Empowered, United States

D. Rose. Facing Our Risk of Cancer Empowered, United States

E. Kuhn. Susan G. Komen Foundation, United States

J. Conaty. University of South Florida, United States

R. Pugh-Yi. Akeso Consulting, Vienna, Virginia, United States

S. Friedman. Facing Our Risk of Cancer Empowered, United States

Oncology nurse navigators (ONN) facilitate breast cancer patients' care via information, resources, and referral services. Two important groups of breast cancer patients served by ONN are young women with breast cancer (yBC), defined as women diagnosed at age 45 or younger, and metastatic breast cancer (mBC) patients. These two groups of patients have distinct needs for clinical care and services. To better understand the needs and experiences of ONN serving these patients, we surveyed 52 active ONN in the United States via an online needs assessment survey about their familiarity with topics relevant for breast cancer patients, referral patterns, and perception of educational needs.

As expected, most ONNs saw more yBC than mBC patients. Familiarity of ONN with topics relevant for yBC and mBC differed based on their work experience. For some topics, earlier-career ONN (<5 years of work experience) reported distinct experiences from later-career ONN (more than 5 years of work experience). Earlier-career ONN were less familiar than later-career ONN with clinical trial participation (45% vs 79%; $p=0.0315$) and genetic counseling and testing (73% vs 96%; $p=0.0431$).

Most ONN referred yBC and mBC patients for financial, mental health, or genetic testing services. For many other services, referral patterns of yBC and mBC patients differed. Earlier-career ONN referred patients less often than later-career ONN to clinical trials (35% vs 89%; $p=.0014$ for yBC, and 36% vs 89%, $p=.0028$ for mBC).

Earlier-career ONN tended to refer mBC patients less often than yBC for genetic counseling and testing, healthy lifestyles, menopause management, and sexual health or intimacy services. In contrast, later-career ONN referred yBC and mBC patients at similar rates.

ONN reported substantial barriers to many services (but not to fatigue, menopause management, and pain management). The services for which ONN most frequently reported barriers were fertility preservation (predominantly financial and lack of programs/providers) and clinical trial services (patient understanding of value and medical jargon/health literacy barriers). ONN referred patients infrequently to some services despite reporting few barriers in contrast to prior reports of breast cancer patients' needs.

Most ONN were interested in continuing education for sexual health and intimacy but not

clinical trials, treatment side effects, or pain management. Most ONN cited a need for patient materials about sexual health and intimacy and mental health issues. While most ONN were confident in their ability to address questions about breast cancer in the media, they indicated additional resources would be useful.

Understanding barriers to information and referrals is necessary to develop approaches to reduce educational gaps and lower referral barriers. Adapting efforts according to ONN career stage may be an important component for continuing education. For clinical trial participation, patient-friendly materials may help reduce barriers to referral and participation.

PO4-10-12

Value of Molecular Targets and Genome-Targeted Therapies FDA-Approved for Metastatic Breast Cancer, 2006-2023

Presenting Author(s) and Co-Author(s):

A. Tibau. Program On Regulation, Therapeutics, And Law (PORTAL) Division of Pharmacoepidemiology and Pharmacoeconomics Brigham and Women's Hospital and Harvard Medical School, United States

T. Hwang. Cancer Innovation and Regulation Initiative, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, Massachusetts, United States

C. Molto Valiente. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., United States

J. Avorn. Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA, United States

A. Kesselheim. Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA, United States

Title: Value of Molecular Targets and Genome-Targeted Therapies FDA-Approved for Metastatic Breast Cancer, 2006-2023

Background: The number of FDA-approved genome-targeted cancer drugs for metastatic breast cancer has increased, providing the potential for personalized therapy. To help physicians, patients, and policymakers differentiate meaningful from trivial innovation in this field, we assessed the validity of the targets and value of the outcomes used in the pivotal trials supporting approval.

Methods: We analyzed trials supporting genome-targeted breast cancer drugs FDA-approved between 2006-2023, defined as those using a genomic test in which the drug targeted a given genomic alteration. From FDA drug labels and trial reports, we extracted characteristics of pivotal trials. For Accelerated Approvals—a special FDA program allowing approval based on unvalidated surrogate measures—if the drug later received traditional approval based on a confirmatory trial, only the latter was analyzed. Strength of evidence supporting molecular targetability was evaluated using the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT). Clinical benefit for approved indications was assessed using the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). Molecular targets qualifying for ESCAT category level I-A or I-B associated with ESMO-MCBS grade 4 or 5 were rated as high-benefit genomic-targeted breast cancer treatments.

Results: Fifteen genome-targeted drugs covered 17 indications and targeted 8 driver alterations. Among the 17 pivotal trials supporting these indications, most were randomized (11, 65%), phase 3 (11, 65%) and open-label (14, 82%). The most common primary endpoint leading to approval (10, 59%) was progression-free survival. Eleven trials (65%) had a I-A ESCAT targetability, 5 (29%) had a I-C targetability score and 1 (6%) was categorized as II-A. ERBB2 amplification, germline BRCA1/2 mutations, PIK3CA mutations, and ESR1 mutation were classified as tier I-A due to randomized trials demonstrating the effectiveness of approved

targeted therapies in patients with these alterations. RET fusions, NTRK fusions, and microsatellite instability were classified as tier I-C, while high-tumor mutational burden was categorized as tier II-A. Eighteen percent of trials (3/17) demonstrated ESMO-MCBS grades 4-5. Overall, 3 of 17 (18%) indications had high-benefit genomic-based cancer treatments.

Conclusions: Among molecular-targeted cancer therapies approved for metastatic breast cancer, fewer than a fifth demonstrated substantial patient benefits at approval. Benefit frameworks like ESCAT and ESMO-MCBS can help stakeholders identify therapies with the greatest potential.

PO4-11-01

Validation of a CARG-BC-based score for the prediction of therapy-induced toxicities in patients with metastatic breast cancer

Presenting Author(s) and Co-Author(s):

J. Zimmermann. Department of Gynecology, Obstetrics and Reproductive Medicine, Saarland university hospital, Homburg; Germany, United States

A. Aygün. Department of Gynecology, Obstetrics and Reproductive Medicine at Saarland University Hospital, United States

A. Kaya. Department of Gynecology, Obstetrics and Reproductive Medicine, Saarland university hospital, Homburg; Germany, United States

M. Radosa. Department of Gynecology, Obstetrics and Reproductive Medicine at Saarland University Hospital/Department of Gynecology and Obstetrics, Klinikum Bremen Nord, United States

C. Radosa. Institute and Policlinic of Diagnostic and Interventional Radiology, Medical University, TU Dresden, United States

E. Solomayer. Department of Gynecology, Obstetrics and Reproductive Medicine, Saarland University Hospital, Homburg, Germany, United States

J. Radosa. Department of Gynecology, Obstetrics and Reproductive Medicine, Saarland University Hospital, Homburg, Germany, United States

Introduction

Prediction of treatment-induced toxicities is important in order to tailor and adjust oncologic therapies.

As limited tools exist to predict the risk of therapy-induced toxicities in patients with metastatic cancer, we aimed to develop and to validate a score for the prediction of therapy-induced toxicities in patients with metastatic breast cancer treated with chemotherapy and immunotherapy. The score was based on the Cancer and Aging Research Group-Breast Cancer early-stage breast cancer score for prediction of chemotherapy-induced toxicities.

Methods

All patients treated for metastatic breast cancer with chemotherapy and immunotherapy at the Department of Gynecology, Obstetrics and Reproductive Medicine at Saarland University Hospital between 01/2014 and 05/2022 were included in this retrospective study. Patient characteristics and therapy-relevant oncological parameters were recorded, as well as therapy-induced toxicities (recorded according to CTC), hospitalization rates, toxicity-related dose reductions and therapy discontinuations. In the first cohort (development cohort), a new score for the prediction of therapy-induced toxicities was developed using ROC analysis and multivariate analysis based on the CARG-BC score. In the second cohort (validation cohort), this was validated using Pearson's correlation coefficient.

Results

Data from 32 patients were analyzed for the development cohort, and inclusion of 102 patients contributed to the validation cohort. The newly developed score consists of seven independent factors for the prediction of toxicities \geq CTC III° and includes the parameters "presence of visceral metastases" (yes/no), "received previous lines of therapy" (yes/no), "limited mobility/able to walk less than one kilometer" (yes/no), "a fall in the last six months" (yes/no), "social

interactions" (yes/no), "pretherapeutic change of transaminases" (yes/no) and "pretherapeutic change of hemoglobin" (hemoglobin < / > 10 g/dl).

Based on the results, three risk groups were defined (low (0-2), medium (3-5) and high (6-15) risk). 28% of patients were in the low-risk group, 37% in the intermediate-risk group and 34% in the high-risk group.

Overall, 49% of the patients had toxicities \geq CTC III°. Distributed across the subgroups, these occurred in 14% in the low-risk group, 34% in the intermediate-risk group and in 52% in the high-risk group ($p \leq 0.01$). Risk score results showed a correlation with treatment discontinuation and hospitalization rate ($p \leq 0.01$), but not with dose reduction ($p = 0.77$).

Conclusion

The available data show a correlation between the risk score results and the occurrence of systemic therapy-induced toxicities in patients with metastatic breast cancer. The results can be used to further identify risk populations and to systematically apply preventive and supportive measures in order to improve quality of life in patients with metastatic breast cancer.

PO4-11-02

Accelerating Progress and Achieving Health Equity: The American Cancer Society National Breast Cancer Roundtable

Presenting Author(s) and Co-Author(s):

A. Dedmon. American Cancer Society, United States

T. Petee. American Cancer Society Headquarters, United States

O. Olopade. Center for Clinical Cancer Genetics & Global Health, Section of Hematology and Oncology, Department of Medicine, University of Chicago, Chicago, Illinois, United States

J. Williams. Breast Cancer School for Patients, United States

A. Kamal. American Cancer Society, United States

S. Shafir. American Cancer Society, United States

Background: Breast cancer continues to be a leading cause of death among women, with disparities in mortality rates persisting, particularly for Black women and under-supported communities. In response to this urgent need, the American Cancer Society (ACS) has launched the American Cancer Society National Breast Cancer Roundtable (ACS NBCRT) to address complex challenges across the breast cancer continuum and improve access to quality care. Methods: The ACS NBCRT is a coalition of organizations committed to eliminating disparities and reducing mortality rates. By leveraging strategic partnerships and using the Collective Impact Model, the ACS NBCRT aims to ensure equitable access to screening, treatment, and comprehensive support services. The roundtable follows the proven ACS Roundtable Model, which brings together diverse contributors to drive progress on breast cancer priorities. Results: The ACS NBCRT, chaired by prominent leaders in the field, has engaged thought leaders, organizations, policymakers, and individuals with lived experiences to identify initial roundtable priorities through a community-informed process. The ACS NBCRT conducted three listening sessions, 8 focus groups, 10 community conversations, and 33 informant interviews and received 700+ responses to a nationwide survey. As a result of this work, the ACS NBCRT leadership was able to interpret the data to inform our roundtable's strategic priorities focused on risk reduction, screening, early detection, access to treatment, clinical trials, and support services. Workgroups will address cross-cutting approaches, including health equity, patient navigation, and education, to develop short- and long-term goals for the roundtable. This approach to addressing health equity through our priority areas is intentional, and it is reflected in our engagement with lived experience experts and diverse community contributors in our early planning, formative research, leadership recruitment, and our member engagement and recruitment. Conclusion: Through its Collective Impact approach, the ACS NBCRT is poised and positioned to accelerate progress, promote health equity, and reduce the burden of breast cancer. The roundtable is uniquely designed to identify and addresses gaps by providing a neutral platform to convene diverse stakeholders to establish national priorities across the cancer continuum, catalyze policy and patient care solutions, promote evidence-based strategies and translate them into practice, and leverage volunteer knowledge and experiences to inform the reduction of health disparities. The roundtable's commitment to strategic partnerships, evidence-based strategies, and health equity will drive change and allow the ACS NBCRT to lead the national dialogue on breast cancer. Implications: The establishment of the ACS NBCRT signifies a crucial step towards achieving health equity in breast cancer care. By addressing disparities and promoting collaborative solutions, the roundtable aims to improve outcomes for all people facing breast cancer.

PO4-11-03

Impact of Short Term Fasting (STF) on Fatigue developing in primary breast cancer (BC) patients receiving the Henderson or Sparano Scheme in the prospective multicentre FIT2- cohort

Presenting Author(s) and Co-Author(s):

D. Koppold. Charité Universitätsmedizin Berlin, Germany
C. Kessler. Charité Universitätsmedizin Berlin, Germany
M. Wischnewsky. University of Bremen, Germany
I. Alvarado. Charité Universitätsmedizin Berlin, Germany
N. Steckhan. Charité Universitätsmedizin Berlin, Germany
C. Kempter. Waldfriede Krankenhaus, Germany
M. Paul. Vivantes Klinikum Am Urban, Germany
B. Brückner. Waldfriede Krankenhaus, Germany
D. Fischer. Ernst-von-Bergmann Klinikum Potsdam, Germany
A. Wunschel. Waldfriede Krankenhaus, Germany
R. Stange. Charité Universitätsmedizin Berlin, Germany
E. Hanslian. Charité Universitätsmedizin Berlin, Germany
M. Jeitler. Charité Universitätsmedizin Berlin, Germany
A. Michalsen. Charité Universitätsmedizin Berlin, Germany

Background: Experimentally, it has been shown that short-term fasting (STF) induces a “protective mode” in healthy cells against chemotherapeutic toxicity while it enhances the susceptibility of tumor cells to chemotherapy. In healthy cells, fasting triggers distinct protective metabolic and gene expression changes, such as upregulation of DNA repair mechanisms, autophagy, and downshift of metabolic pathways including IGF-1-dependent signaling. This study was conducted to assess feasibility, quality of life (QoL) including chemotherapy-induced fatigue (CTF) comparing STF around each chemotherapy (4xAC or 4xEC) to a plant-based low-sugar diet (PBD).

Methods: Newly diagnosed BC-patients treated by the Henderson or Sparano scheme were included in this randomised, controlled, multicenter study. CTF was assessed by the FACIT-F questionnaire before (day 0) and after chemotherapy (day 7) as well as at months 4 (V1) and 6 (V2).

Results: Of the included n=106 patients, 52 were randomized to STF and 54 to PBD. n=90 (84.9%) patients obtained AC/EC+Pac and 16 (15.1%) AC/EC+Doc. FACIT-F showed no significant difference at baseline (STF 42.8; PBD 41.3; p=0.708). The differences between the corresponding FACIT-F Trial Outcome Index resp. Total FACIT-F at cycle 4 day 7 were 13.1 (SE 4.7) resp. 15.8 (SE 5.6), both in favor of STF (statistically significant (p < 0.007) and clinically relevant (minimal important difference (MID) > 5). This difference was visible for all breast cancer subtypes, i.e. luminal A & B, as well as HER2 overexpressed and triple negative tumors, with the STF group showing no clinically relevant fatigue after 4 cycles of chemotherapy (FACIT-F > 34), across all subtypes. The opposite was true for the PBD group (FACIT-F < 34) across all subtypes. FACIT-F (22.7) for PBD in HER2 overexpressed and triple negative tumors was significantly worse than those in luminal A and B patients (FACIT-F= 29.1;

difference 6.4 > MID=3). STF was well tolerated and there were no serious adverse effects.

Conclusion: STF during chemotherapy is well tolerated and appears to improve QoL including fatigue during chemotherapy compared to a plant-based low-sugar diet, independent of intrinsic subtypes.

PO4-11-04

Early Discontinuation of Adjuvant Chemotherapy in Older Adults with Early Breast Cancer: Results from the Prospective Multicenter HOPE Study

Presenting Author(s) and Co-Author(s):

J. Ji. City of Hope, United States

C. Sun. City of Hope, United States

R. Freedman. Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

H. Cohen. Duke University, United States

H. Klepin. Wake Forest School of Medicine, Winston-Salem, NC, Winston-Salem, North Carolina, United States

W. Tew. Memorial Sloan Kettering Cancer Center, New York, NY, United States

B. Moy. Massachusetts General Hospital, United States

A. Chapman. Thomas Jefferson University, Sidney Kimmel Cancer Center, PA, United States

T. Wildes. University of Nebraska Medical Center/Nebraska Medicine, Omaha, NE, United States

E. Dotan. Fox Chase Cancer Center, Philadelphia, PA, United States

A. Magnuson. University of Rochester Medical Center, Rochester, NY, United States

T. O'Connor. Roswell Park Comprehensive Cancer Center, United States

M. Fenton. Division of Hematology and Medical Oncology, Lifespan Cancer Institute and Legorreta Cancer Center, Warren Alpert Medical School of Brown University, Providence, RI, United States

H. Kim. City of Hope, Duarte, CA, United States

V. Katheria. City of Hope, Duarte, CA, United States

C. Gross. Yale School of Medicine, New Haven, Connecticut, United States

H. Muss. University of North Carolina, United States

M. Sedrak. University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA, Los Angeles, California, United States

Background: Older adults with early breast cancer (EBC) treated with adjuvant chemotherapy frequently experience severe toxicities. As a result of such toxicities, many older adults do not complete all planned chemotherapy cycles (i.e., discontinue chemotherapy early). Early discontinuation may increase the risk of recurrence and decrease survival. However, aging is heterogeneous and identifying which older adult is at risk of early discontinuation before starting chemotherapy remains a key knowledge gap. To fill this gap, we examined the incidence, reasons, and risk factors for early discontinuation of adjuvant chemotherapy in older adults with EBC.

Methods: This is a post-hoc analysis of 501 older adults (age>65) with EBC enrolled in the Hurria Older PatiEnts (HOPE) with Breast Cancer Study (NCT01472094, R01AG037037), a prospective multicenter study. All participants were treated with neo/adjuvant chemotherapy. Prior to initiating chemotherapy, participants completed survey measures on sociodemographic, clinical, and geriatric assessment characteristics. The primary outcome was early discontinuation (yes/no; yes, defined as failure to complete all planned chemotherapy cycles).

Multivariable logistic regression with stepwise selection was used to evaluate the association between baseline variables (demographic, clinical, geriatric assessment) and early discontinuation.

Results: A total of 501 participants (median [range] age, 70 [65-86] years and mean [SD] physician-rated KPS 93 [9.3]) were included. One hundred and thirteen (23%) had early discontinuation. Among participants with early discontinuation, 69% discontinued treatment within the last 3 cycles. In bivariate analysis, early discontinuation was associated with older age (continuous), higher stage (II/III), use of non-TC regimens (anthracycline-based or trastuzumab-based), lower albumin level (continuous), a history of diabetes, ≥ 1 fall in the last 6 months, and lower activities of daily living (ADL) score (< 85). Multivariable stepwise logistic regression analysis identified that ≥ 1 fall in the last 6 months, ADL score < 85 , and regimen were associated with early discontinuation at $p < 0.05$. In the final model, after accounting for clinically meaningful variables including age, stage, and regimen, the results for falls (odds ratio [OR] = 2.04, 95% CI: 1.10-3.78, $p=0.02$) and ADL (OR=2.10, 95% CI: 1.32-3.34, $p=0.002$) remained highly significant. Compared to participants with no falls and ADL scores >85 , participants with who reported both falls and an ADL score < 85 prior to initiation of chemotherapy had more than 4-fold increased odds of early discontinuation (Table).

Conclusion: In this cohort of older adults with EBC, nearly 1 in 4 older patients initiated neo/adjuvant chemotherapy but did not complete all planned chemotherapy cycles. Older patients at risk for early discontinuation should be identified and targeted upfront before initiating chemotherapy.

Table. Multivariable associations between falls, ADL score, and early discontinuation.

	Early Discontinuation			Multivariable ^a	
	Yes (n=113)	No (n=388)	Total** (N=501)	OR (95% CI)	p-value
≥ 1 Fall in Last 6 Mos					
No	90 (20.6%)	346 (79.4%)	436	1.00	
Yes	22 (36.7%)	38 (63.3%)	60	2.04 (1.10-3.78)	0.02
ADL Score					
≥ 85	40 (16.4%)	204 (83.6%)	244	1.00	
< 85	73 (28.6%)	182 (71.4%)	255	2.10 (1.32-3.34)	0.002
Combination of Falls and ADL Score					
No Falls/ADL Score ≥ 85	36 (16.1%)	187 (83.9%)	223	1.00	
Yes Falls/ADL Score ≥ 85	3 (16.7%)	15 (83.3%)	18	1.11 (0.29-4.21)	0.88
No Falls/ADL Score < 85	54 (25.5%)	158 (74.5%)	212	1.90 (1.16-3.13)	0.01
Yes Falls/ADL Score < 85	19 (45.2%)	23 (54.8%)	42	4.73 (2.22-10.07)	<0.001

^aAdjusted for age (continuous), stage (I vs. II/III), and regimen (anthracycline based + no trastuzumab vs. non-anthracycline based + no trastuzumab vs. anthracycline based + trastuzumab vs. platinum/CMF + trastuzumab vs. taxol only + trastuzumab vs. other).

** Five patients missing fall information. Two patients missing ADL score.

PO4-11-05

The “Couples Coping with Cancer Together Program” provides insight into individual’s distress and an opportunity to discuss prognosis in a manner that is normalized as standard of care.

Presenting Author(s) and Co-Author(s):

J. Mortimer. City of Hope, Duarte, California, United States

K. Romig. City of Hope, United States

C. Cuevas. City of Hope, United States

L. Thomas. City of Hope, United States

J. Waisman. City of Hope Comprehensive Cancer Center, United States

K. Clark. City of Hope, United States

M. Razavi. City of Hope, United States

M. Loscalzo. City of Hope, United States

Background: For both the patient and their partner, high levels of cohesion/communication are beneficial to coping with cancer. Prognosis alignment in couples has implications for medical care and end of life planning. The objectives of this study were to: assess areas of psychosocial distress endorsed by the patient and her partner and to determine each individual’s understanding of prognosis.

Methods: Women with metastatic breast cancer and their partners completed a couples’ tailored biopsychosocial screening and alignment in perception of prognosis immediately before the initial consultation with a Medical Oncologist. In addition, the couples were offered a standardized couples’ session before the medical consultation, individual couples’ counseling, and a strengths-based group intervention. As a component of biopsychosocial screening, each patient and her partner were asked individually their understanding of the patient’s prognosis as “What is your understanding of the medical situation?” They were asked their understanding of the likelihood of cure with supporting text and percentages provided: 76-100%; 51-75%; 26-50%, or 0-25%.

Results: To date 241 women and their partners are included in this analysis. All the patients had metastatic breast cancer and were being evaluated by a Medical Oncologist. The majority of the patients, 67%, were > 50 years of age (Range 18-79years), 85% had an advanced degree (> high school); 93% selected English as their preferred language, and 100% completed the prognosis question. Five of the top 10 causes of distress were shared by the patient and her partner. These included: Feeling anxious or fearful, worry about the future, sleeping, fatigue, and managing multiple demands. Additional concerns of the patient included: side effects of treatment, understanding my treatment options, how my family will cope, fear of medical procedures and physical appearance. The partners endorsed: Best help my partner, losing control, talk about end of life, feeling down and depressed, and finances. The partner understood the prognosis to be more favorable than the patient.

Conclusions: It is feasible to introduce a prognosis question for both patient and her partner as standard of care. Given the importance of open communication amongst the patient, partner, and physician regarding advanced care planning, there is the potential to decrease the devastation of decisional regret in both patient and partner.

PO4-11-06

Survey of Questionnaires on the Efficacy and Cost of Scalp Cooling Devices in Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

H. Kotani. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

N. Kureyama. Department of Breast Oncology, Aichi Cancer Center Hospital, United States

M. Kusudo. Aichi Cancer Center Hospital, United States

R. Komaki. Aichi Cancer Center Hospital, United States

A. nakakami. Aichi Cancer Center Hospital, United States

Y. Endo. Aichi Cancer Center Hospital, United States

A. Kataoka. Aichi Cancer Center Hospital, United States

A. Yoshimura. Aichi Cancer Center Hospital, United States

M. Hattori. Aichi Cancer Center, United States

M. Sawaki. Department of Breast Oncology, Aichi Cancer Center, Japan

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

< Background > Scalp cooling devices have demonstrated effectiveness in mitigating chemotherapy-induced alopecia, with an approximate reported success rate of 50% in hair preservation. Nevertheless, their utilization may lead to adverse effects and financial burdens for patients. Our institution introduced the Paxman scalp cooling system in 2021 for breast cancer patients undergoing perioperative chemotherapy, with its application extending to over 120 cases. An out-of-pocket expense of 16,000 yen (\$110) per chemotherapy session is required, separate from insurance-covered treatments. We conducted a retrospective evaluation using patient questionnaires and medical records to assess the efficacy and cost-related satisfaction concerning scalp cooling devices.

< Methods > The subjects consisted of breast cancer patients who had undergone at least one session of chemotherapy with scalp cooling devices at our institution. Objective assessment of hair preservation was performed through head photographs taken during the usage of the cooling devices and recorded in the medical charts. The evaluation was carried out using CTCAE version 4, and statistical analysis of relationships was conducted utilizing Stata version 18 and the χ^2 test.

< Results > Responses were collected from 91 patients (survey response rate: 96%). The median age of the patients was 51 years (range: 28-80). The regimens of chemotherapy included anthracycline-based (A) in 10 patients (11%), taxane-based (T) in 19 patients (21%), A-T combination in 57 patients (63%), and HER2-targeted therapy in 38 patients (42%). The results of questionnaire revealed, besides scalp cooling, patients incurred a median cost of 131,000 yen(\$922) for wigs and 10,000 yen(\$70) for hair care and other expenses. 61 individuals (67%) completed the scalp cooling treatment during the chemotherapy. The reasons for discontinuation of scalp cooling were mainly discomfort due to tightness (33%), followed by the time-consuming nature of the process (30%), hair loss (26%), and excessive cold sensation (26%) (Multiple answers allowed). Regarding the benefits and drawbacks of scalp cooling devices, 50 patients (56%) expressed satisfaction for scalp cooling, 26 patients (29%) had neutral feelings, 14 patients (16%) expressed unsatisfied, and one response was unknown. Regarding the device's cost, 14 patients (16%) were satisfied, 35 patients (40%) were neutral,

39 patients (44%) were unsatisfied, and three responses was unknown. Among the 52 patients who continued using the device until their final chemotherapy session and could assess the head photographs, the hair loss grades were as follows: grade 0 in 9 patients (17%), grade 1 in 22 patients (42%), and grade 2 in 21 patients (40%). A correlation was observed between the objective hair loss grade and satisfaction with the device's efficacy ($p < 0.01$), while no significant correlation was found between satisfaction and the cost ($p = 0.21$) (attached table).

< Discussion > Although more than half of the patients who utilized scalp cooling devices expressed satisfaction with their efficacy, merely 16% expressed satisfaction with the associated costs. Addressing patient financial burdens, including expand to insurance coverage, becomes imperative for future considerations.

The relation between hair preservation and satisfaction for efficacy and cost.

Hair preservation	Are you satisfied with the effectiveness of scalp cooling?					p	Are you satisfied with the cost of scalp cooling?					p
	satisfy	neutral	unsatisfy	unknown			satisfy	neutral	unsatisfy	unknown		
success	23 (79)	5 (17)	0	1(3)	<0.01	7(23)	10(32)	12(39)	2(6)		0.2	
fail	8 (38)	6 (29)	7 (33)	0		1(5)	12(57)	7(33)	1(5)			

A correlation was observed between the objective hair loss grade and satisfaction with the device's efficacy ($p < 0.01$), while no significant correlation was found between satisfaction and the cost ($p = 0.21$)

PO4-11-07

Early response to Adaptive Nutrition and Exercise Weight loss (A-NEW) Study for Breast Cancer Survivors with Overweight or Obesity

Presenting Author(s) and Co-Author(s):

J. Sheng. Johns Hopkins University, United States

A. Montanari. Johns Hopkins University, United States

J. Trost. Johns Hopkins University, United States

M. Lu. Johns Hopkins University, United States

J. Mahosky. Johns Hopkins Sidney Kimmel Cancer Center, United States

S. Parida. Johns Hopkins University, United States

A. Blackford. Johns Hopkins University, Baltimore, Maryland, United States

D. Sharma. Johns Hopkins University, United States

M. Laudenslager. Johns Hopkins University, United States

K. Gudzone. Johns Hopkins University, United States

J. Coughlin. Johns Hopkins University, United States

V. Stearns. Johns Hopkins University, Baltimore, Maryland, United States

BACKGROUND: Obesity is associated with inferior survival and increased risk of recurrence in breast cancer (BC) survivors. In the Look AHEAD trial, 45% of patients attained $\geq 5\%$ weight loss at 2 months, and those who lost 3-6% of weight at 2 months had higher odds of $>5\%$ weight loss at 1 year. Behavioral weight loss (BWL) studies consistently demonstrate that only half of BC survivors lose $>5\%$ weight, emphasizing the need for new approaches to aid those not benefiting from BWL alone. We hypothesized that early weight loss could identify BC survivors with excess body weight who may not benefit from BWL alone, and my benefit from the addition of a FDA-approved anti-obesity pharmaceutical agent.

METHODS: Women with stage 0-III BC and BMI >27 kg/m² who completed recommended local therapy and chemotherapy were enrolled in a 6-month BWL program consisting of remote coaching, an online curriculum, and tracking of diet, activity and weight. Patients completed demographic surveys and were weighed in clinic at baseline and 2 months. We used an adaptive design utilizing weight loss at 2 months to identify those with greater likelihood of weight loss at 6 months with BWL alone. Patients with and without $\geq 5\%$ weight loss at 2 months were stratified as FAST-BWL and SLOW-BWL, respectively. Those in FAST-BWL continued BWL alone for 4 months, while those in SLOW-BWL also receive anti-obesity medication (Contrave®) until end of study. We anticipate 55% of 55 subjects enrolled will be in the SLOW-BWL group, resulting in a sample size of approximately 30 SLOW-BWL women and 25 FAST-BWL women. Simon's two-stage minimax design was used for the SLOW-BWL group. The null hypothesis that the true rate of attaining $\geq 5\%$ weight loss is 10.9%, which is chosen based on the rate of women attaining $\geq 5\%$ weight loss in the self-directed arm in the previously conducted POWER-remote study. The null hypothesis will be rejected if 7 or more women are observed in the 30 patients who attain $\geq 5\%$ weight loss. This design yields a power of 80% at type I error rate of 5% when the true rate of attaining $\geq 5\%$ weight loss of the baseline weight for the SLOW-BWL women is 29%, a clinical meaningful rate for the SLOW-BWL women group. We performed a descriptive analysis and evaluated outcomes at 2 months.

RESULTS: Total enrollment is complete, and at time of presentation, 54 of 55 participants will

be at end of study. Mean age at enrollment was 56 [30 -73], and majority were white (73%), postmenopausal (84%), had an ECOG of 0 (77%) and were employed (69%). The median time from diagnosis to enrollment was 3.9 years [0.6-10.0]. Over half received chemotherapy (54%), radiation (73%), and current endocrine therapy (75%); only 13% received prior antiHER2 therapy. Mean baseline weight was 213 (SD 30) pounds and baseline BMI was 35.5 (4.7). Mean HbA1c, total cholesterol, LDL, and triglycerides were 5.6% (0.4), 203 (29), 120 (26), and 135 (64), respectively. After 2 months of the BWL intervention, 14 (27%) attained $\geq 5\%$ weight loss (FAST-BWL) and 38 (73%) did not (SLOW-BWL).

CONCLUSIONS: We have successfully enrolled to this novel adaptive design and will present full data at the conference. Understanding predictors of successful weight loss inform populations that may benefit from anti-obesity medication, and design future studies that allow more patients to achieve significant weight loss.

PO4-11-08

Risk of second malignancies in breast cancer patients. A population-based retrospective cohort study between 2010-2020.

Presenting Author(s) and Co-Author(s):

G. RAMA. Santiago de Compostela University, United States

M. Perez-Lopez. Hospital Universitario A Coruña, A Coruña, Spain., A CORUÑA, Galicia, Spain

S. Antolin Novoa. Complejo Hospitalario Universitario A Coruña (CHUAC). GEICAM Spanish Breast Cancer Group., Spain

C. Reboredo. Oncology Department-University Hospital A Coruña, A Coruña, Galicia, Spain

B. ALONSO. Oncology Department. University Hospital of A Coruña. Spain, United States

S. silva diaz. Oncology Department-University Hospital A Coruña, A Coruña, Galicia, Spain

B. GRAÑA. Oncology Department. University Hospital of A Coruña. Spain, United States

L. Calvo. Oncology Department-University Hospital A Coruña, A Coruña, Galicia, Spain

T. GARCIA-CABALLERO. Pathology Professor. University of Santiago de Compostela. Spain, United States

Introduction: Breast cancer survivors live longer due to early detection programs and therapeutic advances. Staging and molecular classification are important for prognosis and treatment. At the same time these patients are at increased risk for second primary cancers. Comprehensive evaluation of second cancer risk among patients treated in recent decade with early detection and prevention programs of other tumors lacking. This study aims to identify, characterize and associate breast cancers with second primary malignancies based on different variables.

Methods: We identified 3487 females with a first primary breast cancer between 2010 and 2020 in medical records at University Hospital of A Coruña in Spain. Over a median follow-up of 8 years, one hundred patients (2,9%) develop second cancer. According National Cancer Institute, second primary tumor (SPT) was defined as an invasive primary cancer after a first primary cancer. In our case a breast carcinoma. Second cancer risk was evaluated for all cancers (excluding ipsilateral breast carcinoma) which were diagnosed at least 12 months after primary breast tumor. We analyzed breast cancer subtype, family history and pathogenic genetic variants, tobacco use and second primary tumor type.

Results: Several clinical characteristics were evaluated, including breast cancer stage, histological type and subtype. The incidence of breast cancer and SPT was increased with age with peaks in the 60's and 70's, respectively. Only 13% had SPT between 40-49 years. Approximately 10 women a year, in our study, developed second cancer. 52% of SPT patients had cancer family history. Pathogenic variant study was carried in 25% of women with SPT, 46% of them no mutation were found, but in 17% was detected a germline BRCA1 deleterious variant. Other pathogenic variants were founded: 4% in BRCA2, and 33% in others genes (CHEK2, MSH2, MSH6, PMS2, CDH1, FANC1 y SMAD4) Regards tobacco use, active smokers were 13% and 12% of women had been smoking years ago. Of these 13 active smokers, 10 develop lung cancer (77%) an 5 of former smokers (42%). Luminal subtype was the most common breast cancer (33% Luminal A, 34% Luminal B Her2 negative, 10% Luminal B Her2 positive, 4% Her2-enriched, 10% Triple negative and 3% carcinoma in situ with estrogen and progesterone expression) and stage I and II were most frequent (80%). The most

usual second primary neoplasms were lung, colorectal and pancreatic carcinoma (21%, 17% and 7% respectively), and only 2% contralateral breast cancer, with an average of approximately 4 years between breast cancer and the SPT. In 11% of patients were found more than 2 tumors. At the time of the analysis, 73% of these patients are free of disease. In SPT study population few recurrences were described, 2 relapses of breast cancer and 9 of SPT. The median between breast cancer diagnosis and the SPT diagnosis was 54 months [0,7 – 129]. The median to relapse of breast cancer was 73 months [68 – 77]. The median between SPT diagnosis and relapse was 39,25 months [1 - 134]. STP recurrences were observed in colorectal and lung cancer, mainly. Data on recurrences and mutations were not significative.

Conclusion: In our breast cancer population the incidence of second primary tumors is around 3% over a 10 – year period. The diagnosis of the SPT arises several years after breast cancer and generally has a worse prognosis. Elevated risks of second cancer among breast cancer survivors treated in recent decade suggests that heightened surveillance is warranted and continued efforts to reduce second cancers are needed. It is mandatory make an effort and focusing in recommendations and advise about tobacco consumption, healthy lifestyle and adherence to Pap test and stool test in survivors.

PO4-11-09

Feasibility of physical activity behaviour change for women living with metastatic breast cancer, a randomised controlled trial

Presenting Author(s) and Co-Author(s):

M. Liu. University of Sydney, United States

S. Kilbreath. University of Sydney, United States

E. Dylke. University of Sydney, United States

J. Yee. University of Sydney, United States

J. Beith. Chris O'Brien Lifehouse, Camperdown, NSW, Australia., United States

Background

Physical activity benefits women living with metastatic breast cancer by improving outcomes such as physical function, health-related quality of life and fatigue. These findings have been reported within well-resourced trials that involve exercise equipment and supervision. Home or community-based settings, however, may be preferable and more accessible. This trial evaluated the feasibility of a remotely delivered behaviour change intervention for increasing physical activity for women living with metastatic breast cancer, and evaluated the program's efficacy.

Methods

A 12-week randomised controlled trial was conducted in which 20 women living with metastatic breast cancer were recruited from a metropolitan outpatient cancer clinic. Inclusion criteria were over 18 years old, English speaking, ambulatory, and not regularly active at time of recruitment. Participants were randomised 1:1 to an intervention or attention control group. Both groups received a recommendation for 150 minutes of physical activity, a wrist-worn activity monitor, a physical activity diary, and nine phone or video call sessions (six weekly, three fortnightly). The intervention group received individualised behaviour change advice on topics such as physical activity benefits, motivation, barriers and social support; the attention control group received a recurring symptom questionnaire and no behavioural advice. Feasibility outcomes included recruitment, dropout and session adherence rates, and acceptability of methods was evaluated with an interview at trial completion. Baseline and 12-week outcomes included: i) physical activity minutes measured with a 5-day Actigraph wear, ii) 6-minute walk distance, iii) 30-second sit-to-stands, iv) questionnaires for self-reported physical activity, health-related quality of life, fatigue, behavioural factors (stage of change, self-efficacy, decisional balance, processes of change, social support), and patient-specific function. Questionnaires were measured again at 18 weeks.

Results

Recruitment, baseline measures and within-trial sessions are completed; 12 and 18-week measures will conclude late August. Thirty-two women were approached to enrol the target sample of 20, with exclusion reasons being disinterest (n=5), health problems (n=4), loss of contact (n=2) and already physically active (n=1). Median age was 62 years (IQR: 60-69), and median time since metastatic diagnosis was 4 years (IQR: 1-5). Twelve women had bone metastases, and ten had a musculoskeletal comorbidity. Session delivery through video or phone calls were equally preferred (n=10 each). Participants completed 84% of the sessions, with reasons for missed sessions consisting of forgetting (55%), feeling unwell (24%), IT problems (7%), holiday (7%), and work commitments (7%). Median session duration for the intervention group was 23 minutes (IQR: 20-28), and control group was 17 minutes (IQR: 14-

21). The preferred type of physical activity was predominantly walking, and no adverse events were reported. Four women dropped out after loss of contact. Compared to age-matched normative values, baseline outcomes varied: actigraphy-measured physical activity was low (median: 68 minutes/day, IQR: 45-88), self-reported physical activity was high (median: 289 MET-minutes/day, IQR: 52-728), 6-minute walk distance was equal (median: 529m, IQR: 416-579), 30-second sit-to-stands were low (median: 11, IQR: 8-14), health-related quality of life was high (median: 80, IQR: 70-100), and fatigue was equal (median: 30, IQR 20-40).

Conclusions

Women living with metastatic breast cancer were generally receptive of the trial, and recruitment, dropout and session adherence rates were positive. The women who dropped out were more physically active, physically functional and/or rated higher on the questionnaires, indicating that the trial may be more suited to those with limited physical activity experience.

PO4-11-10

Comparison of frozen embryo transfer cycle (FET) outcomes between young women with breast cancer (YWBC) with and without pathogenic variants (PV), and breast cancer-free PV carriers

Presenting Author(s) and Co-Author(s):

M. Sharon-Weiner. CReATe Fertility Centre/University of Toronto, Toronto, Ontario, Canada

A. Kauffman. Temerty Faculty of Medicine, University of Toronto/ CReATe Fertility Centre, Toronto, Ontario, Canada

A. Tanen. Temerty Faculty of Medicine, University of Toronto, United States

S. Yee. CReATe Fertility Centre, United States

S. Madjunkova. CReATe Fertility Centre, Toronto, Ontario, Canada

K. Glass. CReATe Fertility Centre/ University of Toronto, Toronto, Ontario, Canada

BACKGROUND: In vitro fertilization (IVF) and preimplantation genetic testing for aneuploidy (PGT-A) and monogenic disorders (PGT-M) are valuable tools for YWBC with or without PV such as BRCA1/2, ATM, CHEK2, PMS2 to prevent variant transmission to offspring. However, to date, there is scarce data on the usability of these cryopreserved, tested embryos and on the outcomes of FET cycles within the cancer population. It has been suggested that PV may influence endometrial thickness which is associated with embryo implantation and ultimately FET success rates. Thus, this study aimed to compare reproductive outcomes of FET cycles between YWBC with an identified PV, breast cancer (BC) patients without a PV, and cancer-free PV-carriers who returned to use their cryopreserved oocytes or embryos derived from IVF ± PGT-A/M cycles.

METHODS: Patients that underwent either fertility preservation (FP) prior to BC therapy or preventative IVF/PGT-A/M cycles from 2009-2023 were included. All IVF & PGT-A/M was performed at academic IVF centre. Genetic testing was conducted using high resolution next generation sequencing on the Illumina platform. We compared reproductive outcomes between 3 groups: 1) YWBC with a known PV (BCPV), 2) YWBC without a PV (BCNV), 3) Cancer-free patients who had a PV (CFPV). Primary outcomes measured were endometrial thickness, and FET success rates (i.e., ongoing pregnancy or live birth) analyzed by chi-square, t-tests and ANOVA.

RESULTS: 185 patients underwent 202 cycles for either oocyte or embryo freezing.

Mean age was 33.8 ± 4.6 years (range 21-45) and mean BMI was 24.6 ± 5.0 kg/m² (range 15.7-42.7). 64 patients had a PV including BRCA1 (n=22), BRCA2 (n=20) and others (n=22): ATM, BARD1, BRIP1, CHEK2, MLH1, P53, PALB2, PDL2, PMS2, PTCH1, & RAD51D.

When comparing the BCPV, BCNV & CFPV groups, no significant differences were found in the mean age (33.7 ± 4.9 vs. 36.8 ± 4.3 vs. 34.3 ± 4.4 years, $p=0.52$), mean BMI (26.2 ± 4.9 vs. 24.3 ± 4.8 vs. 24.3 ± 4.8 kg/m², $p=0.13$), and the proportion of smokers (23.1% vs. 35.0% vs. 36.4%, $p=0.72$). Only 60% of BCNV performed PGT-A due to their lack of PV.

As of June 2023, 44 patients (12 in BCPV, 20 in BCNV, and 12 in CFPV) returned to undergo 81 FET cycles (range 1-5/patient). 12/81 (14.8%) FETs involved a surrogate. When comparing the BCPV, BCNV & CFPV who had FET, a significant difference was found in the mean age at

oocyte retrieval between BCPV & BCNV (32.9±4.4 vs. 37.0±4.0 years, p=0.001) but not with CFPV (33.5±4.4 years). The endometrial thickness at the time of FET between the BCPV, BCNV, and CFPV groups was similar (10.2±1.6 vs. 10.6±2.6 vs. 9.3±1.9 mm, p=0.12), as was the proportion of smokers (25.0% vs. 36.8% vs. 33.3%, p=0.79). YWBC had a mean delay from egg retrieval to their first FET of 37 months. Estrogen receptor positive (ER+) YWBC had a longer delay than ER- patients (40.1±23.8 months vs. 29.6±11.6 months, p=0.25).

29/44 (65.9%) had at least one successful FET and another 5 YWBC conceived naturally or with intrauterine insemination (IUI); the cumulative pregnancy rate was 77.3% (34/44). The clinical pregnancy rate of 81 FETs was 44.4%. The BCPV group (73.7%) had a significantly higher successful outcome than the BCNV (35.3%) and CFPV (35.7%) groups (p=0.01).

CONCLUSIONS: FP done at the time of a BC diagnosis is an effective tool to preserve fertility potential. 77% of patients had at least one baby from either IVF, IUI or conceived naturally. We did not find a difference in endometrial thickness in PV carriers. While all YWBC had a delay to their first FET from the time of their retrieval, those who were ER+ had a longer delay than ER- because of their need for endocrine therapy. The BCPV group had the highest FET success rate which is likely due to their younger age and use of PGT-A/M thereby eliminating FETs of abnormal embryos that would fail to implant. The BCNV were older with more untested embryos. The CFPV group transferred euploid embryos and thus the lower success rate is puzzling and needs further investigation.

PO4-11-11

Provider perceptions of the POSITIVE trial, endocrine therapy interruption, and fertility preservation

Presenting Author(s) and Co-Author(s):

B. Leon. Cardinal Health Specialty Solutions, United States

R. Bone. Cardinal Health Specialty Solutions, United States

Y. Jeune-Smith. Cardinal Health Specialty Solutions, United States

S. Hallmeyer. Advocate Lutheran General Hospital, United States

B. Feinberg. Cardinal Health Specialty Solutions, United States

Background: Fertility preservation and family planning are pressing survivorship concerns for many young, reproductive-aged women with hormone receptor-positive (HR+) early-stage breast cancer. Following primary treatment, patients typically receive 5-10 years of adjuvant endocrine therapy (ET), during which pregnancy is contraindicated and fertility may decrease. The first-of-its-kind POSITIVE trial (NCT02308085) sought to challenge this archetype by prospectively evaluating the impact of temporary ET interruption to allow patients to attempt conception. Participants (n=516) received 18-30 months of ET followed by a 3-month washout period prior to initiating a 2-year break from therapy to attempt pregnancy. Results demonstrated that short-term disease outcomes were not impacted by temporarily pausing therapy to allow women who desire conception to attempt pregnancy. This survey-based study aimed to evaluate community oncologists' perceptions of the POSITIVE trial data, ET interruption, and fertility preservation efforts.

Methods: US-based oncologists convened at three live meetings in March and April 2023 to review clinical updates presented at SABCs 2022. Participant characteristics and demographic data were collected via an online survey prior to the respective meetings. Perceptions/reactions to clinical updates were captured using audience response system technology. Data were summarized using descriptive statistics.

Results: Among 157 respondents, 82.8% identified as community providers, with 17.9 mean years of clinical experience. On average, participants reported that 85.4% of their time is allocated towards direct patient care, with approximately 21 patients seen per clinic day. Most respondents (85.8%) indicated that they only refer patients to a fertility specialist if the patient initiates fertility preservation discussions and nearly half (45.7%) reported that within the last year, 20% or less of their patients have discussed fertility concerns with them prior to initiating therapy. Additionally, over three-quarters of respondents (79.9%) indicated that 10% or less of their patients with breast cancer underwent fertility preservation within the last year. Prior to reviewing the POSITIVE trial data, 51.3% of respondents reported that they would be most likely to offer therapy interruption to patients with low- or intermediate-risk disease, while 19.8% would do so for all patients regardless of risk status. After reviewing the POSITIVE trial data, 59.3% of respondents would offer therapy interruption to patients with low- or intermediate-risk disease, while 30% would do so for all patients regardless of risk status. Notably, a majority of respondents (54.8%) indicated that they would recommend a therapy interruption of 12 months or less, while 11.1% would opt for 19-24 months.

Conclusions: Findings demonstrate that the onus of initiating discussions surrounding fertility and reproductive topics is often placed on patients, and many patients do not proactively address these matters or undergo fertility preservation prior to initiating treatment. Overall,

respondents viewed the POSITIVE trial favorably, as evidenced by their increased willingness to consider temporary ET interruption for all patients following their review of the study data. Although the POSITIVE trial allowed up to 2 years of therapy interruption, respondents preferred a treatment break of 12 months or less. With the adoption of the POSITIVE strategy into routine clinical practice, younger women with HR+ breast cancer may no longer be faced with the difficult choice of pursuing potentially life-saving therapy or starting/expanding a family, thereby addressing a current unmet survivorship need among this patient population. However, it remains to be seen how many physicians will offer this approach, who is the ideal candidate, and what the appropriate ET interruption length will be.

PO4-11-12

Patient Reported Outcomes from a multi-site, prospective Pivotal study evaluating pegulicianine fluorescence guided surgery (pFGS) for breast cancer lumpectomy procedures using the Lumicell Direct Visualization System (DVS)

Presenting Author(s) and Co-Author(s):

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

I. Wapnir. Stanford Cancer Institute/Stanford University, Stanford, California, United States

E. Hwang. Duke University, Durham, North Carolina, United States

D. Carr. Novant Health, Winston-Salem NC, United States

P. Blumencranz. Baycare Medical Group, United States

K. Smith. Lumicell, Inc, United States

M. Chang. Lumicell, United States

J. Ferrer. Lumicell, Inc, United States

B. Smith. Massachusetts General Hospital, United States

Background: In pegulicianine fluorescence guided surgery (pFGS), a standard of care lumpectomy procedure is performed, and additional tissue is taken from cavity walls at sites of high pFGS signal. This approach has been shown to reduce 2nd surgeries and remove additional tumor left by standard surgery, but may remove more tissue, potentially worsening cosmetic outcomes. Patient breast satisfaction surveys were used to assess cosmesis after pFGS.

Methods: A prospective Pivotal trial of pFGS in women undergoing lumpectomy surgery for stage 0-III breast cancer was conducted at 14 US sites (NCT03686215). We assessed the safety and efficacy of the Lumicell DVS in identifying and removing residual cancer from the lumpectomy cavity in real time. Patient Reported Outcome Measures (PROM) data was collected as an exploratory endpoint. The BREAST-Q, a validated tool that measures patient perspectives after different breast procedures, was used to collect PROM data. An 11-question BREAST-Q survey was used to measure patients' breast satisfaction at baseline (pre-surgery) and at multiple timepoints through 6-months post lumpectomy.

Descriptive statistics of participating patients' responses were collected and analyzed. Survey results were analyzed by the distribution of patient ratings for each question and the change in the distribution of ratings over time, with comparison of baseline to post-lumpectomy. Comparison of patient satisfaction with or without additional pFGS-directed tissue removal was performed with Item Response Theory assuming all items equally discriminative of responding patients. For each timeframe, responses to BREAST-Q items were used to create a response score for each patient. Scaled factor scores (0-100) were compared between groups with and without additional tissue removed during pFGS.

Results: Of the 357 patients evaluated for efficacy in the primary Pivotal study analysis, 255 patients agreed to participate in the PROM surveys (71%). Approximately 60% of the participating respondents completed a pre- and initial post-lumpectomy survey while only 34% of the participating patients completed a pre- and 6-month post-lumpectomy survey. Most patients responded either "Very Satisfied" or "Somewhat Satisfied" across all surveyed timeframes. No significant difference in patient breast satisfaction was found at any time point between the groups with and without additional pFGS-guided shaves removed ($p > 0.05$). There

were 4 patients with scores of 3 or higher pre-surgery but 2 or lower post-surgery. Among these, 1 had no pFGS-guided shaves taken. The remaining 3 had had pFGS-guided shaves taken, but 2 required a second lumpectomy surgery and 1 underwent mastectomy, these additional surgeries likely accounting for decreased cosmetic outcomes.

Discussion: Patient perspective of breast satisfaction was not decreased by the amount of extra tissue removed by pFGS. These data suggest that pFGS using the Lumicell DVS does not significantly decrease breast cosmesis. Three of 4 patients with decreased satisfaction had 2nd surgeries, confirming the importance of finding approaches to decrease 2nd surgeries.

This data was collected during the COVID-19 pandemic, which may have adversely impacted the compliance rate of survey completion.

Studies in larger cohorts with longer follow up are required to better assess the relative impact of 2nd surgeries, radiation, and systemic therapy on breast satisfaction PROM scores after lumpectomy.

PO4-12-01

Navigation program for timely needs assessment and referral to appropriate services among young breast cancer patients in Mexico

Presenting Author(s) and Co-Author(s):

F. Mesa-Chavez. Breast Cancer Center, Hospital Zambrano Hellion, Tecnológico de Monterrey, Mexico

L. Labra. Instituto Nacional de Cancerología, United States

A. Rodriguez. Breast Medical Oncology Department, Instituto Nacional de Cancerología, Mexico

A. Fonseca. Breast Medical Oncology Department, Instituto Nacional de Cancerología, Mexico

M. Cruz-Ramos. Instituto Nacional de Cancerología, United States

A. Platas. Breast Medical Oncology Department, Instituto Nacional de Cancerología, Mexico

P. Cabrera-Galeana. Instituto Nacional de Cancerología, CDMX, Distrito Federal, Mexico

C. Villarreal-Garza. Tecnológico de Monterrey, Nuevo Leon, Mexico

Background: International guidelines on young women with breast cancer (YWBC) endorse patient navigation (PN) and education interventions to reduce barriers that hinder early access to information and healthcare. In Mexico, the first PN program for YWBC was created by Joven & Fuerte in 2020 for the systematic identification of patients' medical and support needs and their referral to the appropriate services. This study aims to evaluate whether the PN program facilitates referral and timely access to specialty or supportive care services, to identify the associated barriers, and to assess patients' satisfaction.

Methods: This prospective cohort included women ≤ 40 years, recently diagnosed with BC (≤ 3 months [m]), treated at Instituto Nacional de Cancerología from Nov-20 to Jun-23. Participants were exposed to a PN program in which a series of target questions and validated surveys were applied at baseline, 3 m and 6 m to systematically identify their needs. At each timepoint, the navigator had an in-person or remote meeting with each patient to provide general BC information, share the detected needs, and provide referral to the required services. Patients' attendance to referrals and related barriers at baseline and 3 m were assessed at 3 m and 6 m, respectively.

Results: 207 patients had completed baseline navigation at the time of the analysis, while 138 (67%) and 123 (59%) had completed 3 m and 6 m navigation, respectively. Median age at diagnosis was 36 years (21-40). Most patients had \geq high school education (57%), were unemployed (67%), were single/divorced (52%), had ≥ 1 child (72%), and had public (79%) or no (21%) health insurance.

The services patients were referred to according to their needs and their rates of attendance are detailed in the Table. The most mentioned barriers for attendance to referrals at both baseline and 3 m were patient-physician miscommunication (n=36 and n=32), personal decision not to attend (n=18 and n=8), and forgetfulness (n=6 and n=8). Moreover, attendance to referrals made in 2022-2023 was significantly higher than in 2020-2021, when COVID-19 restrictions were in place (72% vs 48%; $p < .001$).

Feedback on the PN program was provided in 172/207 (83%), 96/138 (70%), and 123/123 (100%) cases at baseline, 3 m and 6 m, respectively. At all timepoints, nearly all patients were

very satisfied/satisfied with the program (98-99%); believed the needs detection survey had explored aspects they deemed relevant at the moment (91-98%); affirmed the program had eased their referral to all (73-80%) or some (19-27%) of the services they believed they needed; and stated the program aided them to better cope with their illness (97-99%). Most (82-88%) rated their satisfaction with the information provided by the program $\geq 90/100$.

Conclusion: The main needs observed in this YWBC cohort comprised access to support groups, nutritional counseling, psychological care, and wig providers. The vast majority of patients were highly satisfied with the information and guidance provided by the PN program. Although PN timely identified patients' health needs and informed them on their individual referral recommendations, attendance rates to the required services were suboptimal in most cases. Factors for non-attendance included possibly the COVID-19 pandemic, as well as personal and health system aspects, which should be further explored to effectively address them and increase timely access to comprehensive, patient-centered care.

Patients' referral and attendance to specialty and supportive care services

Referral services	Baseline - Patients referred N=207 (100%)	Baseline - Patients who attended (% of attendance)	3 m - Patients referred N=138 (100%)	3 m - Patients who attended (% of attendance)	6 m - Patients referred N=123 (100%)
Support groups	185 (88%)	112 (61%)	15 (11%)	15 (100%)	5 (4%)
Nutritionist	165 (79%)	44 (27%)	67 (49%)	30 (45%)	50 (41%)
Psychology	137 (65%)	35 (26%)	44 (32%)	25 (57%)	25 (20%)
Wig provider	116 (55%)	41 (35%)	23 (17%)	22 (96%)	9 (7%)
Fertility preservation	50 (24%)	23 (46%)	5 (4%)	5 (100%)	2 (2%)
Genetics	41 (20%)	26 (63%)	13 (9%)	7 (54%)	6 (5%)
External prostheses	22 (10%)	7 (32%)	4 (3%)	4 (100%)	25 (20%)
Palliative care	10 (5%)	1 (10%)	3 (2%)	1 (33%)	3 (2%)
Psychiatry	8 (4%)	2 (25%)	2 (1%)	1 (50%)	2 (2%)
Rehabilitation	6 (3%)	3 (50%)	3 (2%)	0 (0%)	10 (8%)
Pain clinic	3 (1%)	1 (33%)	1 (1%)	1 (100%)	3 (2%)
Sexuality counseling	NA	NA	16 (12%)	4 (25%)	28 (23%)

PO4-12-02

Screening adherence for second primary malignancies in breast cancer survivors: a cross-sectional study assessing behaviors, facilitators, and barriers to enhance quality care

Presenting Author(s) and Co-Author(s):

F. Mesa-Chavez. Hospital Zambrano Hellion - TecSalud, Tecnológico de Monterrey, Nuevo Leon, Mexico

M. Salazar-Alejo. Breast Cancer Center, Hospital Zambrano Hellion, Tecnológico de Monterrey, Mexico

C. Villarreal-Garza. Tecnológico de Monterrey, Nuevo Leon, Mexico

Background: Continuous advancements in medical care have significantly increased the life expectancy of breast cancer (BC) patients. Due to this increased lifespan, combined with genetic, hormonal and environmental factors, BC patients have an increased risk of developing a 2nd primary malignancy. Therefore, regular screening for other types of cancer is of utmost importance for comprehensive care of BC survivors (BCS). The aim of this study was to evaluate the level of compliance with screening for cervical, lung, and colorectal cancer among BCS. Additionally, the study aimed to identify the facilitators and barriers influencing cancer screening (CS) adherence.

Methods: An online survey for BCS was developed to assess sociodemographic data, risk perception of developing a 2nd primary malignancy, attitudes towards CS, and compliance with CS. It was distributed through the social media of Mexican oncology-related NGOs.

Results: In total, 52 BCS (median age: 44 years, range: 28-67 years) answered the survey. Most were diagnosed with stage III (38%) or II (29%) BC. The majority had completed at least high-school education (90%), had public health insurance (60%) or no insurance (25%), and reported a monthly income < 500 USD (52%). A total of 3 (6%) cases of 2nd primary malignancies were reported, including 2 cases of contralateral BC and 1 cervical carcinoma. Among 50 participants with an indication for cervical CS, 37 (74%) had a pap smear within the past 3 years. Only 7/24 (29%) eligible participants underwent colorectal CS within the last 10 years. Screening modalities included 6 colonoscopies and 1 occult blood test. The primary reason for non-compliance in both cervical and colorectal CS was the absence of a physician's recommendation, accounting for 79% and 88% of the cases, respectively. None of the participants had an indication for lung CS, thus no low-dose computed tomographies were performed for this purpose.

Participants demonstrated a mean knowledge score of 72/100 (SD=19) regarding CS. Most respondents mentioned that, compared to the general population, they considered themselves to be at no/very low/low risk of developing cervical (75%), colon (73%), or lung cancer (75%).

In terms of attitudes towards CS, an overwhelming majority of participants (98%) affirmed that BCS should undergo screening for other types of cancer. Most stated that, if recommended by a physician, they would agree/strongly agree (96%) to undergo screening for other neoplasms. Nearly all agreed/strongly agreed (98%) that being screened for other types of cancer would be beneficial for their own health; and agreed/strongly agreed (98%) that CS is the most effective way to approach other types of cancer. Additionally, most agreed/strongly agreed (96%) their CS would benefit their family members.

On univariate analysis, no sociodemographic or clinical factors were associated with CS adherence. However, it is important to note that the study may have been underpowered to detect significant associations due to the limited sample size.

Conclusion: In conclusion, even though most BCS acknowledge its importance, screening for 2nd primary malignancies in this group exhibits suboptimal rates. This study highlights the potential role that BC oncologists could play on increasing CS uptake by reminding patients of their corresponding recommendations to detect other types of cancer. Further research is crucial to enhance our understanding of the key factors influencing these outcomes and to contribute to the development of targeted strategies aimed at enhancing CS adherence.

PO4-12-03

PATIENT REPORTED OUTCOMES IN TERMS OF ARM AND SHOULDER FUNCTIONS AND QUALITY OF LIFE AND LYMPHEDEMA ARE AFFECTED BY THE STAGE, AND EXTENT OF AXILLARY SURGERY IN THE EARLY POSTOPERATIVE PERIOD OF PATIENTS WITH BREAST CANCER

Presenting Author(s) and Co-Author(s):

H. Kilic. Department of Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, United States

S. Emiroglu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey

E. Ozgorgu. Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey., United States

M. Tukenmez. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey

A. Bozdogan. Department of Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, United States

M. Muslumanoglu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey

V. Ozmen. Florence Nightingale Sisli Hospital, Department of Surgery, Istanbul, Turkey

D. Sindel. Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey., United States

A. İgci. American Hospital, Department of Surgery, Istanbul, Turkey

A. Oral. Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey., United States

N. Cabioğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Bakırköy, Istanbul, Turkey

This study evaluated whether lymphedema, patient-reported arm and shoulder morbidity and quality of life one year after axillary surgery are affected by stage or axillary surgery type between early stage patients and patients with locally advanced breast cancer who underwent surgery following neoadjuvant therapy. By determining the risk factors associated with severe lymphedema and deterioration of patient-reported outcomes, lymphedema could be prevented by early intervention to improve the prognosis of lymphedema and quality of life. Material and Methods: Between January 2021 and May 2022, a total of 253 breast cancer patients, 128 early stage and 125 locally advanced stage who underwent surgery including sentinel lymph node biopsy (SLNB) with/without axillary lymph node dissection (ALND) following neoadjuvant therapy were included in this study. The patients who underwent upfront surgery were defined as early-stage, and those who underwent surgery following neoadjuvant chemotherapy were considered as having locally advanced breast cancer (LABC) who have also participated in the prospective MF18-03 registry trial. Patients were prospectively evaluated by the SF-12 quality of life and QUICK-DASH hand, arm, and shoulder range of motion questionnaires and circumferential tape measurements of the arm width to evaluate the lymphedema before surgery, and 6 month- and 12-month assessments. The volume difference of 10% or more in the operated arm compared to the healthy arm was considered as lymphedema.

Results: In the assessment of SF-12 quality of life questionnaire, there was a decrease in physical function scores at the 6th month despite recovery at the 12th month in both groups compared to the initial preoperative scores ($p < 0,001$). Moreover, patients with locally advanced breast cancer were found to have decreased SF-12 general health ($p=0.024$), vitality ($p=0.034$),

and mental health scores in one year after surgery ($p=0.004$).

Patients with mastectomy and locally advanced breast cancer were more likely to have a diminished arm and shoulder function as assessed with the QUICK-DASH questionnaire at the 6th and 12th months compared to those with breast conservation (6. month, $p=0.009$, 12. month, $p=0.004$), and early breast cancer, respectively (6. month, $p=0.014$, 12. month, $p<0.001$)

In the present cohort, lymphedema was detected in 19 (7.5%) patients including 16 cases with mild (11-20%), 2 cases with moderate (21-40%), and one case with severe (41-80%) lymphedema one year after surgery. Axillary dissection was found to be associated with an increased risk of lymphedema (SLNB, 5.0% vs ALND, 17.6%; $p=0.005$). Similarly, removal of >6 lymph nodes was also associated with an increased risk of lymphedema that was not statistically significant (<6 LNs, 6.4% vs >6LNs, 10.8%; $p=0.277$). Among those with LABC, however, patients with removal >6 LNs were more likely to have lymphedema (>6 LNs, 15.4% vs <6 LNs, 5.8%; $p=0.096$). Conclusion: These findings suggest that only an extensive axillary surgery was associated with an increased risk of breast cancer-related lymphedema. Patients with a mastectomy were more likely to have diminished arm and shoulder function compared to those with breast conservation. Furthermore, patients with locally advanced breast cancer were more likely to have a dispaired quality of life score and a limited arm and shoulder function regardless of the presence of lymphedema. Early prompt diagnosis and therapy of lymphedema can therefore potentially improve quality of life.

PO4-12-05

Immediate breast reconstruction is associated with reduced incidence of ipsilateral lymphedema in breast cancer patients undergoing mastectomy

Presenting Author(s) and Co-Author(s):

J. Byeon. Department of Surgery, Seoul National University Hospital, United States

I. Shin. Department of Surgery, Seoul National University Hospital, United States

H. Lee. Department of Surgery, Seoul National University Hospital, United States

E. Kang. Seoul National Univ. Hospital, Surgery, Republic of Korea

J. Jung. Seoul National Univ. Hospital, Surgery, Korea, United States

C. Lim. Seoul National Univ. Hospital, Surgery, Korea, United States

W. Han. Seoul National University Hospital, Seoul, Republic of Korea

H. Kim. Seoul National Univ. Hospital, Surgery, Korea, United States

H. Lee. Seoul National University Hospital, United States

H. Moon. Seoul National University, Republic of Korea

Purpose: The number of patients undergoing immediate breast reconstruction after mastectomy is increasing. A study of ipsilateral lymphedema after immediate breast reconstruction is also needed. This retrospective study aimed to identify the risk factors associated with lymphedema incidence after mastectomy in breast cancer patients, particularly focusing on the impact of the immediate breast reconstruction.

Methods: A retrospective analysis was conducted on 6,105 patients who underwent mastectomy for breast cancer with or without immediate breast reconstruction from Jan 2012 to Dec 2022 at Seoul National University Hospital to identify the potential risk factors for developing ipsilateral lymphedema.

Results: A total of 6,105 breast cancer patients with a mean age of 50.1 years were included in this study, with a median follow-up period of 52.0 months. In univariate analysis, the incidence of lymphedema was significantly lower in the immediate breast reconstruction group (4.47%) compared to the no reconstruction group (9.15%) ($p < 0.001$). Other significant risk factors included the number of dissected axillary lymph nodes, number of metastatic lymph nodes, body mass index (BMI) over 25 kg/m², the use of neo-adjuvant chemotherapy or adjuvant radiation therapy, and older age at the time of operation. In multivariate analysis, the immediate breast reconstruction remained to be an independent predictor of developing lymphedema (OR: 0.71, 95% CI: 0.55-0.91, $p = 0.008$), along with the number of dissected lymph nodes (OR: 1.06, 95% CI: 1.05-1.08, $p < 0.001$), neoadjuvant chemotherapy (OR: 1.83, 95% CI: 1.44-2.33; $p < 0.001$), adjuvant radiation therapy (OR: 6.77, 95% CI: 5.16-8.96, $p < 0.001$), BMI >25 kg./m² (OR: 1.58, 95% CI: 1.26–1.97, $p < 0.001$) and older age at surgery (OR: 1.01, 95% CI: 1.00-1.02, $p = 0.007$).

Conclusion: Our data demonstrates significantly lower rates of ipsilateral lymphedema for the patients undergoing immediate reconstruction after mastectomy when compared to that of the mastectomy alone. While these observations require further validation, our study provides useful information for the surgical decision making in patients who are considering the option of immediate reconstruction after mastectomy.

PO4-12-06

Interstitial Lung Disease (ILD) in Sequential Antibody Drug Conjugate (ADC) use in patients with Metastatic Breast Cancer (MBC): A Multi-Institutional experience

Presenting Author(s) and Co-Author(s):

S. Premji. Department of Oncology, Mayo Clinic, Rochester, Minnesota, United States
L. Huppert. University of California, San Francisco, Oakland, California, United States
R. Mahtani. Miami Cancer Institute, Plantation, Florida, United States
S. Fisch. University of California, San Francisco, United States
N. Dempsey. Miami Cancer Institute, Baptist Health of South Florida, United States
A. Raimonde-Taylor. Rush, United States
S. Jacob. University of California, San Francisco, California, United States
L. Quintal. University of California, San Francisco, United States
J. Chien. University of California, San Francisco, San Francisco, California, United States
M. Melisko. University of California at San Francisco, San Francisco, California, United States
A. Sandoval-Leon. Miami Cancer Institute, Miami, Florida, United States
L. Carcas. Miami Cancer Institute, United States
M. Ahluwalia. Miami Cancer Institute, United States
N. Harpalani. Baptist Health, United States
J. Hoppenworth. Mayo Clinic, United States
D. Idossa. University of Minnesota, United States
R. Rao. Rush, United States
H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States
K. Giridhar. Mayo Clinic, Rochester, Minnesota, United States

Introduction: Interstitial Lung Disease (ILD) is a known adverse event associated with Antibody Drug Conjugates (ADCs), causing fibrosis of the lung. In the DESTINY-Breast 04, TROPICS-02, and ASCENT trials the rate of ILD/Pneumonitis was 12.1%, 0.4%, and 0% respectively. In these studies, the time to first cross-sectional imaging after initiation of ADC was 6 weeks. However, prior treatment with a topoisomerase-1 inhibitor ADC was not permitted in these studies, so the influence of sequential ADC treatments remains unknown. Here, we aimed to characterize the frequency and management of ILD in sequential use of ADCs in a multi-institution retrospective analysis.

Methods: We identified patients (pts) with HR+/HER2-low and HR-/HER2-low MBC who had received both Trastuzumab-deruxtecan (T-DXd) and Sacituzumab govitecan (SG) monotherapy (in either order, with or without intervening therapies) who were treated at five academic centers between 2020-2023. Patients had received treatment with the ADC in either routine clinical treatment or as a prior participant on a clinical trial with ADC monotherapy. Information regarding ILD diagnosis, imaging, timing of onset, peak and resolution along with management information was collected and analyzed. Retrospective assessment of ILD toxicity was graded using CTCAE v5.0, based on available clinical and radiographic reports.

Results: 10/60 pts who received ADC therapy in this multi-institutional cohort were diagnosed with ILD (all grades). No differences in age or BMI were observed in those who developed ILD versus those who did not, and 9/10 pts were White, 1 was Asian, with a median age of 59 years (47-79 years). Pertinent history in these pts included 3/10 had a prior smoking history, 8/10 had a prior cardiac or pulmonary comorbidity (including sleep apnea, lung cancer, hypertension, hyperlipidemia, thrombosis, or stroke). Prior to receiving their first ADC, 7/10 patients had metastatic disease to the lung. All 10 patients were diagnosed with ILD during treatment with T-DXd. 4 pts initially received T-DXd, then developed ILD and then upon recovery, subsequently received SG. The remaining 6 pts initially received SG (with no reports of ILD), and then received T-DXd and subsequently developed ILD. In the entire cohort, the median time from ADC initiation to first CT scan was 8 weeks (range 1-22 weeks). Within the cohort that developed ILD, the median time from initiation of T-DXd to first CT scan was also 8 weeks (range 6-13 weeks).

The median time to diagnoses of ILD was 3 months after initiation of T-DXd (range 0.4-14.5 months). Dyspnea was the most common presenting symptom in 9/10 pts and at diagnosis of ILD, dyspnea was graded as III in 6/10 pts, II in 3/10 pts, and I in 1/10 pts. Diagnostic evaluation included CT chest (9/10), pulmonary consultation (8/10), pulmonary function testing (2/10), and bronchoscopy (1/10). 4/10 patients presented at their highest-grade toxicity at diagnosis. All patients stopped T-DXd treatment, 7 were hospitalized, 7 required supplemental oxygen, and 8 were prescribed steroids for treatment. Of those receiving steroids, the most common starting dose was prednisone 1 mg/kg and doses ranged from 0.5 mg/kg to 9mg/kg prednisone equivalents. No patient received a secondary immunosuppressive agent. The steroid treatment duration ranged from 1-4 months. None of the 10 pts underwent re-challenge with T-DXd and 3/10 developed grade V ILD (death).

Conclusion: We observed a 16.6% incidence of all grade ILD (5% grade V ILD) with T-DXd and 0% with SG. In this small cohort study, we did not observe a clear increased risk for ILD with sequential treatment of ADCs. Practice patterns were consistent with recommended diagnostic evaluation and steroid management. Additional strategies are needed to characterize pts most at risk for developing ILD and to identify situations where re-challenge may be safe.

PO4-12-07

INSTITUTIONAL EXPERIENCE IN PATIENTS WITH EARLY BREAST CANCER WHO RECEIVED CARDIOTOXIC THERAPY IN CARDIONCOLOGY UNIT

Presenting Author(s) and Co-Author(s):

T. martos. Medical Oncology. Hospital del Mar. Barcelona. Spain, United States

L. Belarte-Tornero. Hospital del mar, United States

M. Ble. Hospital del mar, United States

E. Gimeno. Hospital del mar, United States

L. Sanhauja. Hospital del mar, United States

F. Martines-Medina. Hospital del mar, United States

M. Martinez-García. Hospital del mar, United States

M. Castro-Henriques. Hospital del Mar Passeig Marítim 25, 08003 Barcelona, United States

J. Albanell. Hospital del mar, United States

S. Servitja. Hospital del Mar, Barcelona, Spain, United States

Introduction: Early breast cancer (eBC) is the most frequent malignancy diagnosed in women worldwide; fortunately, survival is increasing related to early diagnosis and the incorporation of new drugs. In this scenario, preventing long-term toxicities become essential. Cardiac adverse events related to anthracyclines or trastuzumab such as reduction in left ventricular (LV) systolic function and clinical heart failure (HF), are well known and are the leading cause of morbidity in breast cancer survivors. Cardioprotective strategies and early diagnoses of asymptomatic cardiac dysfunction are essential to optimized management and prevention of overt cardiovascular (CV) disease. We made a specific cardiac assessment within an Oncocardiology multidisciplinary Unit in patients receiving anticancer therapies. We present the experience in patients with eBC treated with anthracyclines, trastuzumab or both in the past five years.

Materials and Methods: We conducted an institutional, interventional, prospective study in patients who received anthracyclines, trastuzumab or both according to the standard of care (SoC) in eBC. Basal CV risk stratification included lipid profile, glycated haemoglobin, high-sensitive troponin T (hs-TnT) and N-terminal ProB-type natriuretic peptide (NT-ProBNP) was done. Image assessment was done by echocardiogram (echo), including myocardial deformation assessed by speckle tracking (STRAIN).

Follow-up was done according to anthracycline or trastuzumab therapy with echo and cardiac biomarkers during the systemic therapy and at the end of anticancer treatment, 1, 2 and 5 years after. Patients with uncontrolled CV risks factors according to local protocol, asymptomatic cardiac dysfunction defined as decreased strain (>15% compared with baseline) or increased cardiac biomarkers (Hs-TnT >14 at baseline or x3 basal value during the follow-up; NT-ProBNP > 300 in patients with < 50y; > 600 in patients between 50-75-y or >900 in patients > 75 years or older) or patients who develop heart failure during the treatment or follow-up were referred to cardiologist.

Results: between 2018 and 2022, 1125 patients were diagnosed with eBC in our institution, and 435 patients received systemic treatment with anthracyclines, trastuzumab or both. During the study period, 165 of these patients were referred to the cardio-oncologist. 60% received

treatment with anthracyclines, 36% with trastuzumab and 4.1% with both. The median age was 58(\pm 23.2), 60% had previous CV risk factors. The main reason to refer patients to the cardio-oncologist was asymptomatic cardiac dysfunction and uncontrolled CV risk factors. (Table 1). 60% of patients initiated angiotensin-converting-enzyme inhibitors or Beta-blockers, and only two patients stopped anticancer therapy due to severe cardiac dysfunction. The period of high risk of developing cardiotoxicity was the first year after the end of treatment.

Conclusion: multidisciplinary evaluation within a cardio-oncology unit is useful to optimize CV risk factors and to detect asymptomatic cardiac dysfunction in patients receiving cardiotoxic drugs.

Table 1. Main reasons to refer patients to cardiologist.

Causes of Cardiotoxicity	(%)
Increased Cardiac biomarkers	25.4
Decreased Strain	11.5
Both (1, 2)	23
FEVI<50	2.3
Symptomatic Cardiac dysfunction	1.9

PO4-12-08

Changes in peripheral immune cell composition in women who do and do not develop breast cancer

Presenting Author(s) and Co-Author(s):

J. Kresovich. H. Lee Moffitt Cancer Center and Research Institute, United States

K. O'Brien. National Institute of Environmental Health Sciences, United States

Z. Xu. National Institute of Environmental Health Sciences, United States

C. Weinberg. National Institute of Environmental Health Sciences, United States

D. Sandler. National Institute of Environmental Health Sciences, United States

J. Taylor. National Institute of Environmental Health Sciences, United States

Background: Breast cancer survivors have higher age-specific rates of hypertension and other chronic diseases than women without a history of breast cancer. We and others have shown that alterations to the immune system are associated with risk of these conditions in the general population, leading to the hypothesis that the increased chronic disease risk in breast cancer survivors may be driven, in part, by lasting changes in immunity. Peripheral immune cell composition appears to become altered years before a breast cancer diagnosis, but little is currently known about the influence of different breast cancer treatments on subsequent changes to leukocyte composition and the persistence of these associations over time.

Methods: Among 410 women enrolled in the Sister Study, paired blood samples collected an average of 7.6 years apart were analyzed for DNA methylation (DNAm). Deconvolution methods were applied to these DNAm data to estimate circulating percentages of 12 leukocyte subsets. Approximately half the women sampled were diagnosed and treated for breast cancer between the blood draws (n= 185) whereas the other half remained breast cancer-free (n= 225). Breast tumor characteristics and treatment information were abstracted from medical records. Mixed-effect linear regression models were used to estimate changes in leukocyte composition over time comparing women with breast cancer to those who remained breast cancer-free. A case-only analysis of breast cancer survivors was performed to examine the persistence of changes over time and to explore whether changes in leukocyte composition were associated with the types of therapies received (endocrine therapy, radiation therapy, chemotherapy). All models were adjusted for age and self-reported race. In the treatment analysis, because tumor characteristics can guide clinical decisions, tumor estrogen receptor status and stage at diagnosis were additionally included as model covariates.

Results: At baseline, women who developed breast cancer between the blood draws had lower mean circulating percentages of CD8+ cytotoxic T cells than women who remained breast cancer-free (3.8% vs 4.6%; P-diff= 0.04). After accounting for differences in leukocyte composition at baseline, compared to women who remained breast cancer-free, women diagnosed and treated for breast cancer between the blood draws had decreases in total circulating CD4+ helper T cell percentage (adjusted mean difference [β]= -1.50, 95% CI: -2.56, -0.44, P= 0.006) and alterations to both naïve and memory B cell percentages (naïve B cells, β = 0.46, 95% CI: 0.17, 0.75, P= 0.002; memory B cells, β = -0.22, 95% CI: -0.34, -0.09, P= 0.001). Although associations did not vary by tumor characteristics or participant race, the changes in leukocyte composition appeared to persist over time as changes were not associated with time since diagnosis. In the case-only analysis of different breast cancer therapies, radiation was associated with decreases in CD4+ T cells (β = -2.56, 95% CI: -4.26, -0.88, P= 0.003) and

chemotherapy was associated with increases in B cells ($\beta = 0.62$, 95% CI: 0.07, 1.16, $P = 0.03$). Surgery and endocrine therapy were not meaningfully associated with changes in leukocyte composition.

Conclusions: Breast cancer survivors have lasting changes in peripheral leukocyte composition that may be related to the types of treatments received. These findings add to our understanding of the biological changes that underlie the long-term health of breast cancer survivors.

PO4-12-09

National Physical Activity Guidelines and It's Association with Fatigue in Patients with Breast Cancer Pre- and Post-Chemotherapy in a Prospective, Nationwide Study.

Presenting Author(s) and Co-Author(s):

L. Mattick. University of Rochester, Rochester, New York, United States

H. Sun. University of Rochester, United States

K. Mustian. University of Rochester School of Medicine and Dentistry, United States

L. Peppone. University of Rochester School of Medicine and Dentistry, United States

A. Williams. University of Rochester, United States

P. Lin. University of Rochester, United States

E. Arana. University of Rochester, United States

J. McGuire. University of Rochester, United States

A. Curtis. Spartanburg Regional Healthcare System, United States

A. Conlin. Providence Cancer Institute, United States

L. Weiselberg. Zucker School of Medicine at Hofstra/Northwell, United States

M. Janelins. University of Rochester School of Medicine and Dentistry, United States

Background: Cancer-related fatigue (CRF) is one of the most pervasive side effects of cancer and its treatment, reported by nearly 90% of patients. Physical activity (PA) during treatment may prevent or lessen CRF burden. Current aerobic PA guidelines for cancer patients recommend at least 150 minutes of moderate PA or 75 minutes of vigorous PA or some equivalent combination of moderate and vigorous PA (MVPA). Many patients have difficulty meeting these guidelines during treatment, however, meeting these guidelines may not be necessary to alleviate CRF. This study evaluated patterns of PA below the recommended guidelines and their association with CRF in cancer patients during treatment.

Methods: In a nationwide, prospective cohort study of patients with stage I-IIIc breast cancer (n=580) we assessed the relationship between self-reported PA (Aerobics Center Longitudinal Study PA) and CRF (Multidimensional Fatigue Symptom Inventory, MFSI) pre- and post-chemotherapy. Spearman correlations were utilized to evaluate the association of all PA (MET hr/wk) and MVPA (MET hr/wk) with overall CRF (total MFSI) and 5 CRF subdimensions (general, physical, emotional, mental CRF and vigor) at pre- and post-chemotherapy. ANCOVA estimated mean CRF score according to whether patients weekly MVPA (1) met 100% of the PA guidelines, (2) met 50%-99% of the PA guidelines (75-149 minutes), or (3) did not meet 50% of the PA guidelines (< 75 minutes).

Results: Pre-chemotherapy, only 34% of participants met the PA guidelines, post-chemotherapy, only 21% of patients met the PA guidelines. At both time points, we observed small to moderate inverse correlations of MVPA with overall CRF and several subdimensions of CRF (Table 1; $r = -0.11, -0.19$). Pre-chemotherapy, those who did not meet 50% of the PA guidelines report significantly higher total CRF compared to those who met the PA guidelines (12.5 ± 1.2 vs 5.3 ± 1.5 ; $p < 0.001$). However, those who met only 50%-99% of the PA guidelines, had comparable total CRF to those who fully met the PA guidelines (7.2 ± 2.2 ; $p = 0.474$). A similar pattern was observed for the subdimensions general, mental, and physical CRF. Those who met 50% of the guidelines also had significantly lower vigor compared to those who met the guidelines (11.9 ± 0.3 vs 13.8 ± 0.4 ; $p < 0.001$), while those who met 50%-

99% of the guidelines had comparable vigor to those who fully met guidelines (13.1 ± 0.6 ; $p=0.278$). Post-chemotherapy CRF was higher among all patient's, again there was no significant difference in total, general, physical CRF and vigor between those who met the PA guidelines and those who met 50%-99% of the PA guidelines.

Conclusions: All PA was consistently inversely associated with CRF pre- and post-chemotherapy for patients with breast cancer. Current minimum aerobic PA guidelines for patients with cancer are difficult to achieve during treatment. Lower doses of MVPA than the current PA guidelines suggest may provide equal benefit and represent a more achievable goal for patients with cancer.

Table 1: Spearman correlations of CRF and physical activity in patients with breast cancer pre- and post-chemotherapy.

	Pre-Chemo (n=580)		Post-Chemo (n=537)	
	All PA (MET hr/Wk)	MVPA (MET hr/Wk)	All PA (MET hr/Wk)	MVPA (MET hr/Wk)
	r	r	r	r
MFSI Total	-0.13**	-0.15***	-0.15**	-0.19**
MFSI Emotional	-0.08	-0.05	-0.03	-0.11*
MFSI General	-0.12**	-0.16***	-0.16***	-0.16***
MFSI Mental	-0.12**	-0.09*	-0.02	-0.02
MFSI Physical	-0.06	-0.17***	-0.06	-0.10*
MFSI Vigor	0.13**	0.16***	0.17***	0.19***

MVPA = moderate to vigorous physical activity
 * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
 Higher MFSI scores indicate more fatigue except for the vigor subscale where a higher score indicates less fatigue

Table 2: ANCOVA; Mean CRF score according to the PA guidelines.

Mean (SE)	Pre-Chemo (n=580)					Post-Chemo (n=537)				
	<75 min MVPA (n=304)	75-149 min MVPA (n=90)	>150 min MVPA (n=186)	p- value ¹	p- value ²	<75 min MVPA (n=324)	75-149 min MVPA (n=101)	>150 min MVPA (n=112)	p- value ¹	p- value ²
	MFSI Total	12.5 (1.2)	7.2 (2.2)	5.3 (1.5)	<0.001	0.474	19.7 (1.2)	15.9 (2.2)	10.2 (2.1)	<0.001
MFSI Emotional	6.5 (0.3)	6.3 (0.5)	5.8 (0.4)	0.111	0.413	4.8 (0.3)	4.9 (0.5)	3.3 (0.4)	0.002	0.010
MFSI General	8.3 (0.4)	7.0 (0.7)	6.4 (0.5)	0.001	0.424	12.7 (0.4)	10.9 (0.7)	9.4 (0.6)	<0.001	0.118
MFSI Mental	5.1 (0.3)	4.1 (0.4)	4.1 (0.3)	0.007	0.867	6.7 (0.3)	6.9 (0.5)	6.1 (0.1)	0.315	0.270
MFSI Physical	4.5 (0.3)	2.7 (0.5)	2.9 (0.3)	<0.001	0.807	7.5 (0.3)	6.4 (0.5)	5.6 (0.5)	0.002	0.302
MFSI Vigor	11.9 (0.3)	13.1 (0.6)	13.8 (0.4)	<0.001	0.278	12.0 (0.3)	13.3 (0.5)	14.2 (0.5)	<0.001	0.192

p-value¹ – Comparison of >150 minutes MVPA weekly to <75 minutes MVPA weekly
 p-value² – Comparison of >150 minutes MVPA weekly to 75-149 minutes MVPA weekly
 Higher MFSI scores indicate more fatigue except for the vigor subscale where a higher score indicates less fatigue

PO4-12-10

Sacituzumab Govitecan Toxicity Outcomes In Arab Patients with Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Altarturi. King Faisal Specialist Hospital and Research Center, United States

K. Suleman. King Faisal Specialist Hospital and Research Center, Riyadh, Ar Riyad, Saudi Arabia

A. AlSayed. King Faisal Specialist Hospital and Research Center, Saudi Arabia

H. Al-Shamsi. Department of Medical Oncology - Burjeel Cancer Institute - Abu Dhabi - UAE, United Arab Emirates

A. Alawadhi. Tawam Hospital, United States

B. Basuliamn. KFMC, United States

S. Alaklabi. King Faisal Specialist Hospital & Research Center, RIYADH, Saudi Arabia

Background:

The Arab population is often underrepresented in clinical trials, which limits our knowledge of drug safety and efficacy in this population due to genetic variability that can affect drug metabolism and adverse events (AEs). Sacituzumab govitecan (SG) is approved for metastatic triple negative breast cancer (mTNBC), and recently hormone receptor positive metastatic breast cancer (HR+ MBC). Here we report toxicity outcomes and RDI in Arab population.

Methods:

A multi-center retrospective study of patients with mTNBC and HR+ MBC treated with SG from January 2021 until May 2023 was conducted. Demographics and clinical variables including site of metastases, prior lines of therapy, relative dose intensity (RDI), adverse events (AEs) were collected. For continuous variables, Mann-U Whitney and Kruskal Wallis tests were used to compare mean, median, standard deviation, and range. For categorical variables, Fisher's exact tests and Pearson Chi-square tests were used. SAS v9.4 was used to perform statistical analysis at a significance level of 0.05.

Results:

A total of 35 patients was enrolled. The median age at diagnosis of metastatic breast cancer was 39 years interquartile range (IQR) (35, 44). The median age at starting SG was 44.5 years IQR (38,50). The majority of patients (65%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1, (21%) of the patients had an ECOG PS of 0, and (15%) had an ECOG PS of 2. 48.6% received 3 or more lines of prior therapy in the metastatic setting while 51.4% received less than 3 lines of prior therapy in the metastatic setting. 77.1% of patients had 3 or > organs involved with metastatic disease, while 22.9% of patients had < 3 organ involved. The most common metastatic sites were the lung (54.3%), liver (62.9%), bone (68.6%), and brain (45.7%). The median RDI of SG was 100% for a sample of 34 individuals, with one missing value IQR (94%,100%). The rate of overall AEs was (77.1%), with the most common AEs being; neutropenia (44.4%), diarrhea (37.0%), anemia (22.2%), thrombocytopenia (22.2%), nausea (14.8%), and vomiting (7.4%). Grade 3 AEs rate was 34.3%. The most common grade 3 adverse events were diarrhea (11.4%), fatigue (5.7%), and alopecia (2.9%). The rate of treatment interruption and dose reduction due to AEs was 31.4%. Only one patient (2.9%) had to discontinue SG treatment due to adverse events.

Conclusion:

The study suggests that SG is safe and well-tolerated in young Arab patient population. The sample consisted of relatively young patients, which may reflect a reluctance to prescribe SG to older Arab patients. Caution should be exercised when generalizing the findings due to limitations of the study. Further studies with larger sample sizes are needed to validate these findings and to explore the efficacy of SG in Arab patients with mTNBC and HR+ MBC.

PO4-12-11

Patient (pt) time burden with IV vs subcutaneous (SC) administration of trastuzumab/pertuzumab (HP): A time and motion (T+M) substudy of a single arm phase II trial of adjuvant endocrine therapy plus HP for stage I HER2+ breast cancer

Presenting Author(s) and Co-Author(s):

A. Waks. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
N. Graham. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
E. Chen. Brigham and Women's Hospital, United States
A. Frey. Dana-Farber Cancer Institute, United States
V. Attaya. Dana-Farber Cancer Institute, United States
I. Abbass. Genentech, United States
A. Fung. Genentech, United States
J. Sussell. Genentech, Inc., South San Francisco, California, United States
P. Cortazar. Genentech, Inc., South San Francisco, United States, United States
C. Harvey. Dana-Farber Cancer Institute, United States
K. Almeida. Dana-Farber Cancer Institute, United States
D. Leth. Dana-Farber Cancer Institute, United States
W. Chen. Dana-Farber Cancer Institute, United States
J. Leone. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
S. Schumer. Dana-Farber Cancer Institute, United States
N. Tayob. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: The time required for in-clinic drug administration may have a substantial detrimental impact on breast cancer patients' quality of life. SC drug administration, as opposed to IV, may reduce this time commitment. The purpose of this study was to estimate the relative difference in time and logistical burden between IV and SC administration of HP.

Methods: We prospectively enrolled a pre-specified sub-cohort of pts participating on the ADEPT trial (NCT04569747) to this T+M substudy. The ADEPT trial is an ongoing single arm prospective phase II trial of adjuvant SC HP (for 1 yr) plus endocrine therapy for pts with hormone receptor-positive (HR+) and HER2+ stage I (pT1N0 or pT1N1mi) breast cancer. Pts eligible for ADEPT have completed primary breast surgery and are systemic therapy-naïve. Pts who received cycle 1 of loading SC HP at Dana-Farber Cancer Institute and tolerated SC drug administration were eligible and enrolled consecutively to the T+M substudy until the T+M accrual goal; accrual to the T+M substudy was mandatory for eligible pts. The T+M substudy was a single arm crossover design in which pts received 2 cycles of IV HP, followed by 2 cycles of maintenance dose SC HP. During those 4 treatment (tx) cycles, timepoints in the drug preparation and administration process were captured from the electronic medical record or flowsheets filled out by infusion nurses. The primary endpoint of the T+M substudy was total pt chair time in the infusion area (measured from start of first drug administration to end of final post-drug observation period). Exploratory endpoints included total drug preparation time and total pt tx experience time. A sample size of 22 pts was estimated to provide 86% power with 2-sided alpha 0.05 to detect a difference of 70 mins in the primary endpoint by tx arm (IV vs SC).

For all endpoints, the average time across both tx cycles was calculated for each pt, and the overall mean across pts for each of IV and SC administration was computed (with standard deviation). Average times for IV vs SC administration were compared via paired Wilcoxon signed rank tests. Adjustments for multiple comparisons were not included.

Results: 22 pts participated on the T+M substudy, and each had timepoints captured during 4 tx cycles (2 IV and 2 SC cycles), for a total of 88 patient-cycles analyzed overall. Pts had median age 58 yrs (range 42-83), and were 96% female, 82% White, 9% Black, 9% Asian; and 100% non-Hispanic. Comparison of time intervals for IV vs SC drug administration is shown in the Table. Mean total pt infusion chair time was 84.3 mins with IV HP, vs 22.5 mins with SC HP, for a difference of 61.8 mins shorter pt time commitment in favor of SC administration ($p < 0.0001$). The mean total drug preparation time was significantly decreased in favor of SC administration (by 78.2 mins; $p < 0.0001$); and the total pt tx experience time was significantly decreased in favor of SC administration (by 81.8 mins; $p < 0.0001$).

Conclusions: This prospective T+M study demonstrated that pt infusion chair time is significantly decreased with SC as compared to IV administration of HP, shortening this pt time burden by approximately one hour. SC drug administration is an approach that may help to improve and shorten the pt breast cancer therapy experience and decrease pharmacy burden.

Time description (interval measured)	Time spent, IV cycles (mean and [SD] in minutes)	Time spent, SC cycles (mean and [SD] in minutes)	Mean difference between IV and SC cycles (minutes)	p value
Total pt infusion chair time (first drug administration start to final post-drug observation period end)	84.3 [11.9]	22.5 [2.6]	61.8	<0.0001
Total drug administration time (first drug administration start to final drug administration end)	61.6 [6.5]	7.4 [2.3]	54.2	0.0001
Total drug preparation time (order receipt by pharmacist to drug leaving pharmacy)	119.2 [35.5]	41 [15.7]	78.2	<0.0001
Total pt treatment experience time (infusion room check-in time to final post-drug observation period end)	177.8 [34]	96 [17.5]	81.8	<0.0001

SD, standard deviation

SD, standard deviation

PO4-12-12

An Updated analysis of risk factor identification and Hyperglycemia prevention with alpelisib + fulvestrant in PIKC3A-mutated , hormone-receptor positive, human epidermal growth factor-2 negative advanced breast cancer

Presenting Author(s) and Co-Author(s):

H. Moore. Duke Cancer Institute, Durham, North Carolina, United States

S. Burnette. Department of Pharmacy, Atrium Health Wake Forest Baptist, United States

E. Poehlein. Department of Biostatistics and Bioinformatics, Duke University, United States

H. Lee. Department of Biostatistics and Bioinformatics, Duke University, United States

K. Westbrook. Duke Cancer Institute, Duke University, United States

T. Bagwell. Mercer University School of Medicine, United States

K. Novido. Duke University, United States

S. Dent. Duke University, Durham, North Carolina, United States

Background:

SOLAR-1 investigated use of alpelisib (ALP) + fulvestrant (FLV) in patients (pts) with hormone-receptor positive (HR+)/human epidermal growth factor-2 negative (HER2-), PIK3CA-mutated advanced breast cancer (ABC) after progression on endocrine-based therapy and demonstrated a clinically significant increase in all-grade (G) and G3-4 hyperglycemia (HG) compared to placebo + FLV. Current guidance recommends an insulin sensitizer (metformin, thiazolidinedione, SGLT2i) at HG onset. Given high rates of HG, a preventative protocol and identification (ID) of associated risk factors (RFs) was implemented to minimize HG, dose reductions and discontinuation. Although METALLICA investigated the implementation of metformin for hyperglycemia prophylaxis, there is limited data for alpelisib use and hyperglycemia prevention in high risk or controlled type 2 diabetic patients. Duke Breast Oncology Clinic (DBOC) implemented a preventive strategy to minimize HG and treatment disruptions in patients receiving alpelisib, including pre-diabetic and controlled-diabetic patients.

Methods:

This single-center, retrospective study included pts receiving at least one 28-day cycle of ALP+FLV between June 2019 and April 2023. One week prior to ALP initiation, pts initiated an insulin-sensitizer. Pts had fasting plasma glucose (FPG) levels drawn on day 8, 15, 28, and monthly while on ALP. The primary outcome was incidence of G2-4 HG. Descriptive statistics were used to summarize results. Number of RFs for HG (age \geq 65 years, BMI \geq 25 kg/m², baseline FPG \geq 100 mg/dL, and A1c \geq 5.7%) were compared between pts with and without HG using Wilcoxon rank-sum test.

Results

A total of 30 pts (29 females; 1 male) were included with a median age of 60 years. The cohort was 70% White, 23% Black, while 67% were overweight/obese, and 50% had a history of type 2 diabetes mellitus (T2DM), gestational diabetes, or pre-diabetes. 29 pts received a CDK4/6 inhibitor prior to starting ALP. By day 28, 13 pts (43%) had G2-4 HG, with only 4 (13%) having G3 HG and zero having grade 4. Pts with G2-4 HG had a median of 2 RFs compared to only 1 RF if no HG. 8 pts (27%) required a temporary hold of ALP and 5 pts (17%) required a dose reduction in ALP due to HG. 25 pts permanently discontinued ALP; 14 due to disease progression and 8 due to an adverse event with only 3 due to HG. Median duration of ALP was 86 days (range 24-442), with 5 pts continuing to receive ALP at time of analysis. Patients with

grade 2-4 HG by day 28 after ALP initiation had an older median age (66 years), higher BMI (median 28.1 kg/m²), higher baseline FPG (median 100 mg/dL), and higher baseline HbA1c (median 5.6%) compared to those without grade 2-4 HG (Table).

Conclusions:

Implementation of a HG prevention protocol with ALP in the real-world setting demonstrated fewer G3-4 HG events compared to that seen in SOLAR-1 (13% vs 36.6%) but slightly higher than METALLICA (6%) although we included a higher risk patient population. An increase in HG-associated RFs correlated with a higher incidence of G2-4 HG. Early risk identification and optimization of prophylactic antihyperglycemics can reduce ALP dose reductions and discontinuations secondary to HG. ALP use in higher-risk patients can be considered with a HG prevention protocol.

Table 1. Hyperglycemia outcomes

Hyperglycemia Outcomes	Patients (N=30)	
Number of patients who had all-grade hyperglycemia by day 28 (%)	13 (43.3)	
Highest grade of hyperglycemia occurrence by day 28		
2	9 (30.00)	
3	4 (13.3)	
4	0 (0)	
None of the above	8 (26.7)	
Patient-specific risk factors for all-grade hyperglycemia		
	All-grade hyperglycemia (N=13)	No all-grade hyperglycemia (N=17)
Age ≥65 years	7 (53.8%)	4 (23.5%)
BMI ≥25 kg/m ²	12 (92.3%)	8 (47.1%)
Baseline FPG ≥100 mg/dL	7 (53.8%)	5 (29.4%)
Baseline HgA1c ≥5.7%	6 (46.2%)	6 (35.3%)

PO4-13-01

A randomised trial comparing 6-monthly dosing of adjuvant zoledronate with a single one-time dose in patients with early breast cancer (REaCT-ZOL): Quality of life and toxicity outcomes

Presenting Author(s) and Co-Author(s):

I. Machado. Ottawa Hospital, Ottawa, Ontario, Canada
L. Clemons. Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
C. Stober. Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
G. Pond. McMaster University, United States
A. Awan. The Ottawa Hospital Cancer Centre, Canada
H. Conter. William Osler Cancer Centre, United States
D. Simos. Stronach Regional Cancer Center, United States
S. Dhesy-Thind. Juravinski Cancer Centre at Hamilton Health Sciences, United States
M. Mates. Cancer Centre of Southeastern Ontario, Canada
V. Kumar. Markham Stouffville Hospital, Shakir Rehmatullah Cancer Clinic, United States
J. Hilton. The Ottawa Hospital Cancer Centre, United States
L. Vandermeer. Ottawa Hospital Research Institute, Ontario, Canada
M. Clemons. Ottawa Hospital, Ottawa, Ontario, Canada

Background: While adjuvant 6-monthly zoledronate is widely used in patients with early-stage breast cancer (EBC), questions remain around optimal scheduling of adjuvant bisphosphonates. We reviewed quality of life and bisphosphonate-related toxicities observed within a prospective randomised trial.

Methods: Patients with EBC were randomised to either a single infusion of adjuvant zoledronate (4mg IV) or to 6-monthly treatment for 3 years. Quality of life was measured using the EQ-5D-5L questionnaire (before and after each infusion and 6-monthly thereafter in the single infusion arm). Acute phase reaction (APRs) data was collected after each infusion and data on other bisphosphonate-related toxicities (hypocalcaemia, renal impairment, ONJ and atypical fractures) was collected 6-monthly for 3 years.

Results: Between 21-Nov-2018 and 02-Apr-2020, 211 patients were randomized to either a single infusion (n=107) or 6-monthly (n=104) adjuvant zoledronate. While each zoledronate infusion was associated with a worsening QoL, the overall QoL was the same in the two study arms. APRs occurred in 75% of patients after receiving zoledronate. Other bisphosphonate-related toxicities were uncommon in either arm. Significantly more patients discontinued study treatment in the 6-monthly arm (30/104, 28.8%) compared with the single infusion arm (3/107, 2.8%) ($p < 0.001$). The most common reason for study discontinuation was the occurrence of APRs, pain and malaise. Disease-free and overall survival rates were not significantly different in the study arms.

Discussion: A single infusion of adjuvant zoledronate may offer patients a more convenient and better tolerate regimen than repeat infusions. APRs remain an important toxicity with repeat infusions of zoledronate, leading to increased rates of treatment discontinuation. Larger, definitive, trials comparing a single infusion with repeat treatments are required.

PO4-13-02

Molecular Expression Assays Improve the Prediction of Local and Invasive Local Recurrence after Breast Conserving Surgery for DCIS

Presenting Author(s) and Co-Author(s):

E. Hahn. Princess Margaret Cancer Centre, United States

R. Sutradhar. Institute for Clinical Evaluative Sciences, United States

L. Paszat. Institute for Clinical Evaluative Sciences, United States

L. Nguyen. Institute for Clinical Evaluative Sciences, United States

D. Rodin. University Health Network - Princess Margaret Cancer Centre, United States

S. Nofech-Mozes. Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

S. Trebinjac. Sunnybrook Health Sciences Center, United States

C. Fong. Institute for Clinical Evaluative Sciences, United States

E. Rakovitch. Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Introduction

Ductal carcinoma in situ (DCIS) is routinely treated with adjuvant radiotherapy (RT) after breast conserving surgery (BCS) in order to reduce the risk of local recurrence (LR) and invasive LR. Nomograms based on clinicopathological features (CPF) and molecular expression assays have been developed in an effort to provide individualized risk estimates and personalize decision-making. However, molecular assays are costly and it remains unclear if they provide more accurate recurrence risk estimates compared to algorithms based on CPF alone. We examined the impact of the 12-Gene DCIS Score (DS) and the 21-Gene Recurrence Score (RS) molecular expression assays, in addition to CPF, on the accuracy of predicting 10-year LR and invasive LR risk compared to predicted estimates based on CPF alone. In addition, we examined if a model including the 21-Gene RS improves the 10-year predicted risks of invasive LR after BCS for DCIS compared to estimates based on the DS+CPF or CPF alone.

Methods

We used a population-based cohort diagnosed with pure DCIS treated with BCS +/- RT from 1994-2003. All cases had expert pathology review providing contemporary assessment of diagnosis, margin status, margin width, multifocality, presence and extent of comedo necrosis, subtype, nuclear grade, and tumor size. For each case, a representative tissue block or unstained slide was sent to measure the 12-Gene DS and 21-Gene RS. Predictive models were developed using multivariable Cox regression analyses with backward selection and included all CPF, treatment with RT, and interactions. The performance of each model was evaluated based on c-statistic, -2log likelihood estimate (-2LLE), and Akaike information criterion (AIC). Calibration was performed using bootstrap resamples, with replacement. We compared the performance of the best model derived from CPF alone, the 12-Gene DS with CPF, and the 21-Gene RS with CPF on their ability to predict the 10 year risks of LR and invasive LR measured against outcomes observed in the cohort.

Results

The population-based cohort includes 1226 women, 514 were treated with BCS alone and 712 were treated with BCS + RT. Median age was 56 years. Median follow-up was 10 years. Fifty-two percent of tumors were between 1 and 2.5 cm, 35% were ≤ 1 cm, and 13% were > 2.5 cm.

Comedo necrosis was present in 68%, and nuclear grade was low, moderate, and high in 7%, 54%, and 39%, respectively. Margins were negative in 90.5% of cases (N=1109). The 12-Gene DS was low, intermediate, and high in 53.5%, 20.9%, and 25.6% and the 21-Gene RS was >25 in 30% of patients. 194 women (15.8%) experienced ipsilateral LR as a first event; 112 were invasive LR.

Models including either the DS or RS expression assays performed better in predicting the 10-year risk of LR after BCS compared to the model based on CPFs alone, demonstrating higher c-statistics (0.705, 0.699, and 0.662, respectively), lower AIC and lower -2LLE. The two molecular-based predictive models also performed better in predicting the risk of invasive LR compared to CPF model, although with smaller differences in c-statistics (0.684, 0.683, and 0.667, respectively), AIC or -2LLE. The predictive model based on the 21-Gene RS with CPF did not perform better in the prediction of the 10 year risk of invasive LR compared the 12-Gene DS + CPF model. All models were well calibrated.

Conclusion

The predictive model based on the 12-Gene DS with CPF more accurately predicted the 10-year risk of LR and invasive LR after BCS compared to model based on CPF alone. Inclusion of the 21-Gene RS with CPF did not improve the prediction of the 10-year risk of LR or invasive LR. This suggests that nomograms that include the 12-Gene assay with CPF provide more accurate individualized estimates of recurrence risk after BCS and can help improve personalized decision-making in the management of DCIS.

PO4-13-04

Added Value from Patient Advocates in a Translational Working Group: the COMET Study

Presenting Author(s) and Co-Author(s):

- D. Collyar. Patient Advocates in Research, United States
- D. Basila. Alliance Foundation Trials, United States
- T. Lynch. Duke University, United States
- S. Schnitt. Harvard Medical School, United States
- J. Marks. Duke University, United States
- S. Strand. Stanford, Stanford, California, United States
- T. Hyslop. Thomas Jefferson University Hospitals, United States
- S. Badve. Emory University School of Medicine, United States
- M. Watson. Washington University School of Medicine, United States
- H. Le-Petross. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
- L. Grimm. Duke University, United States
- R. West. Stanford University Medical Center, Stanford, California, United States
- A. Weiss. Division of Surgical Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States
- A. Rapperport. Alliance Foundation Trials, United States
- L. King. Duke University, United States
- R. Factor. Duke University, United States
- M. Ryser. Duke University, United States
- A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
- E. Hwang. Duke University, Durham, North Carolina, United States
- A. Thompson. Baylor College of Medicine, Houston, Texas, United States

Introduction: A phase III multicenter prospective randomized clinical trial called “Comparing an Operation to Monitoring, with or without Endocrine Therapy (COMET)” (NCT02926911) assesses the risks/benefits of active monitoring (AM) versus surgery for women with low-risk ductal carcinoma in situ (DCIS). It is funded by the Patient-Centered Outcomes Research Institute and enrolled 997 women between 06/30/17 and 01/13/23. Research Patient Advocates (PAs) have been embedded from the study design stage and continue to provide guidance as part of the COMET leadership team. The COMET biobank is funded by independent foundations and is managed through monthly Translational Working Group (TWG) meetings. The TWG includes PAs, clinicians, pathologists, radiologists, and researchers from multiple institutions who discuss topics like categorization of biospecimens into discovery/validation sets; development of a pathology workflow/sample tracking process; use of small samples; and potential areas of future research/technologies that may improve DCIS diagnostics, prognostics, and care management. Methods: The TWG leveraged the existing Alliance Foundation Trials, LLC biobank infrastructure and facilitates the collection, submission, storage and analysis/use of blood, tissue, and breast images collected at specified timepoints and stored in central tissue/image repositories. PAs are active and integral in the TWG, assisting

with logistical issues (contracts, transfer agreements, resource requests); communicating with sites; identifying study topics and biomarkers relevant to diverse patients; providing guidance on commercial predictive/prognostic tests; promoting effective stewardship of samples; ensuring overall focus remains on advancing clinical utility; and reporting translational study results to trial participants who agreed to donate samples/images. Results: Over 90% of requested samples/images have been submitted by >85 sites. Each patient's biospecimens and pathology images are linked and de-identified for research. Use of artificial intelligence (AI) is being considered to assist in sample review. TWG members have complementary areas of expertise/experience and promote active stewardship for effective management of these scarce resources. PAs have played key roles concerning equitable data-sharing and acceleration of data and material transfer agreements. They have also been active in development of standards for discovery/training sets, validation test sets; communication procedures for patient cases that progress to future breast events; ways to catalog technologies (e.g., multi-omics, AI); and in research proposal review. Consensus has been achieved regarding major issues such as authorship, biospecimen custodianship, intellectual property, and criteria relevant to patient needs. Logistical barriers, including data sharing and technicalities of biospecimen release, have been resolved. The TWG also played an integral role in resolving recruitment challenges to COMET by creating standard pathology eligibility criteria, resulting in evidence-based protocol amendments that increased accrual. A retrospective review of biospecimens has been performed to determine adequacy for ensuing correlative molecular and spatial profiling studies. Conclusion: PAs help the COMET TWG set policy, and oversee biospecimen/image collection, and biobank use and sharing. PA input also facilitates equitable, transparent research studies and technology development that can improve personalized decisions for surgery versus AM in women with low-risk DCIS. PAs in the TWG aim to integrate the diagnostic and prognostic tools developed as part of the COMET study into future patient care.

PO4-13-05

Spotlight on PSMA as a new theranostic biomarker for breast cancer

Presenting Author(s) and Co-Author(s):

S. Bravaccini. IRCCS Istituto Romagnolo Per lo Studio dei Tumori, Meldola, Italy, United States

S. Cortecchia. Azienda Unità Sanitaria Locale (AUSL) Imola, United States

F. Foca. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

G. Martinelli. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

S. Ravaioli. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

M. Tumedei. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

F. Matteucci. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

R. Maltoni. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

G. Paganelli. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", United States

F. Poli. Azienda Unità Sanitaria Locale (AUSL) Imola, United States

M. Puccetti. Azienda Unità Sanitaria Locale (AUSL) Imola, United States

Breast cancer patients are risk-stratified on the basis of the subtype classification. However, this parameter is not completely accurate in discriminating between high- and low-risk disease, creating a need for a reliable marker to determine aggressiveness. Prostate-specific membrane antigen (PSMA) could fulfill this need given that it has been reported to be expressed by breast cancer tumor cells and the endothelial cells of tumor vessels. We analyzed 68 breast cancers (BC) of whom 14 luminal A, 28 Luminal B, 15 HER2 positive and 11 triple negative BC to assess whether PSMA expression by immunohistochemistry was different in the several tumor subtypes and was related to ki67 expression and stromal TILs. PSMA positivity was calculated as the number of positive vessels on 10 fields at 40X magnifications. Kruskal Wallis's test was used to assess difference in PSMA positivity among BC subgroups and Dunn's test was performed for post-hoc comparisons; Spearman's rho coefficient was calculated to analyze the correlation among PSMA, Ki67 and TILs. Our results show that median PSMA was higher both considering the number of positive vessels and the staining intensity in TNBC compared to Luminal A and B tumors ($p < 0.001$). Ki67 was higher in TNBC compared to Luminal A tumors ($p < 0.001$). We saw a correlation between PSMA and ki67, especially in HER2+ tumors ($p = 0.002$), while a correlation between PSMA and TILs was observed in TNBC ($p = 0.014$). The analysis of PSMA expression on the lymph nodes showed the same trend observed for the primary tumors given that it was higher in TNBC compared to HER2 positive and luminal cancers.

Our results suggest that PSMA could be used as theranostic biomarker in BC considering that it is highly expressed in more aggressive tumors and the possibility to treat PSMA-expressing patients for anti-angiogenesis and/or radionuclide treatment.

PO4-13-06

Effect of neoadjuvant dose-dense dose-intense chemotherapy timing infusion on complete histological response rate among patients with triple negative breast cancer (SIMCLOCK)

Presenting Author(s) and Co-Author(s):

C. Bouchez. Department of Breast Disease, Hôpital Saint Louis, Paris, France., United States

S. Catozzi. Institut Curie, Inserm U900, MINES ParisTech, CBIO - Centre for Computational Biology, PSL Research University, Saint-Cloud France, United States

C. Cuvier. Department of Breast Disease, Hôpital Saint Louis, Paris, France., United States

L. Someil. Department of Breast Disease, Hôpital Saint Louis, Paris, France., United States

C. De Bazelaire. Department of radiology, Hôpital Saint Louis, Paris, France, United States

C. Miquel. Department of pathology, Hôpital Saint Louis, Paris, France., United States

N. Mhamdi. Department of pathology, Hôpital Saint Louis, Paris, France., United States

L. Teixeira. APHP Hôpital Saint Louis, France

M. Espie. Centre des Maladies du Sein, Hôpital Saint-Louis, United States

E. Moati. Department of Breast Disease, Hôpital Saint Louis, Paris, France., United States

L. Droin. Department of Breast Disease, Hôpital Saint Louis, Paris, France., United States

A. Ballesta. Institut Curie, United States

S. Giacchetti. Hôpital Saint Louis, Paris, France

Effect of neoadjuvant dose-dense dose-intense chemotherapy timing infusion on complete pathological response rate among patients with triple negative breast cancer (SIMCLOCK)

Background:

Triple-negative breast cancers (TNBC) exhibit major responses to dose-dense, dose-intense (DD-DI) neoadjuvant chemotherapy (NAC) (1). Although chronomodulated chemotherapy has shown efficacy and reducing toxicity in other cancers, there are no data in breast cancers (2). We report here a series of patients with TNBC treated with DD-DI NAC and analyzed the association between chemotherapy time infusion and pathological complete response rate (pCR) and residual tumor burden (RCB).

Patients and Methods:

Patients with non-metastatic TNBC treated at breast cancer disease center, St Louis hospital (Paris, France), with neoadjuvant DD-DI cyclophosphamide (1200 mg/m² d1) – epirubicin (75 mg/m² d1) q2w (SIM regimen) followed by 12 injections of paclitaxel (80 mg/m²) qw were included. Starting time of each chemotherapy infusion were systematically recorded. Primary endpoint was pCR defined as no residual invasive tumor in breast and in lymph nodes. Patients were dichotomized into “morning” and “afternoon” infusion groups, independently for “SIM” and “paclitaxel” regimens. Two timing cut-offs were defined according to: 1) median time of all infusions 2) cut-off maximizing morning/afternoon differences of RCB. Statistical differences between the two patient groups were assessed for metabolic response at 2 courses at Pet scan (breast delta SUV_{max}), RCB class (0-1 vs 2-3), pCR, dose reduction rate and 24-months event-free survival (24-months EFS).

Results:

Between January 2018 and January 2022, 93 patients were included. Median age was 51 (28-74). Majority of SIM administrations occurred between 12:00 and 15:00 and Paclitaxel administrations between 11:20 and 14:30. Median follow-up was 32.4 months. Main characteristics between “morning group” or “afternoon” groups in the SIM or paclitaxel were similar. pCR was obtained in 48.9% of the whole population. Regardless of cut-offs defined, no difference in pCR rate was observed. Similarly, no differences were observed between morning and afternoon groups in terms of either metabolic response, dose reduction rate or 24-months EFS (table 1).

Conclusion:

Time of DD-DI NAC infusion is not associated with differences in pCR rate nor in RCB, toxicity and EFS in patients with early TNBC. As immunotherapy combined with NAC is a new standard in TNBC, the impact of immunotherapy infusion time combined with NAC is under evaluation.

References:

1. Giacchetti S et al. Long-term survival of advanced triple-negative breast cancers with a dose-intense cyclophosphamide/anthracycline neoadjuvant regimen. *Br J Cancer*. 2014;110(6):1413-9.
2. Printezi MI et al. Toxicity and efficacy of chronomodulated chemotherapy: a systematic review. *The Lancet Oncology*. mars 2022;23(3)

	“SIM morning” Group	“SIM afternoon” Group	p-value	“SIM morning” Group	“SIM afternoon” Group	p-value	“Paclitaxel morning” Group	“Paclitaxel afternoon” Group	p-value	“Paclitaxel morning” Group	“Paclitaxel afternoon” Group	p-value
	Median time infusion			RCB differences			Median time infusion			RCB differences		
Chosen cut-off time	13:38			12:09			12:55			13:33		
Number of patients	n=48	n=45		n=22	n=71		n=47	n=46		n=56	n=37	
pCR rate (%)	48.9	48.9	p=1.000	45.5	50.0	p=0.899	46.8	51.1	p=0.838	50.0	47.2	p=0.963
RCB class 0-1 vs 2-3	63.8 vs 36.2	62.2 vs 37.8	p=0.822	59.1 vs 40.9	64.3 vs 35.8	p=0.870	61.7 vs 38.3	64.4 vs 35.5	p=0.748	66.1 vs 33.9	58.3 vs 41.7	p=0.531
Metabolic response (%)	-54.9	-54.3	p = 0.919	-54.7	-54.6	p = 0.981	-53.9	-55.3	p = 0.809	-52.8	-57.5	p= 0.415
Dose reduction rate (%)	20.8	37.8	p=0.116	27.3	29.6	p=1.000	25.5	32.6	p=0.601	25.0	35.1	p=0.412
24-months EFS (%)	92.9	87.7	p=0.76	97.9	82.6	p=0.34	84.5	92.1	p=0.15	94.2	84.4	p=0.53

Table 1: Differences between “morning” and “afternoon” groups in SIM and paclitaxel regimen, with two timing infusion cut-offs.

Differences between “morning” and “afternoon” groups in SIM and paclitaxel regimen, with two timing infusion cut-offs.

	“SIM morning” Group	“SIM afternoon” Group	p-value	“SIM morning” Group	“SIM afternoon” Group	p-value	“Paclitaxel morning” Group	“Paclitaxel afternoon” Group	p-value	“Paclitaxel morning” Group	“Paclitaxel afternoon” Group	p-value
	Median time infusion			RCB differences			Median time infusion			RCB differences		
Chosen cut-off time	13:38			12:09			12:55			13:33		
Number of patients	n=48	n=45		n=22	n=71		n=47	n=46		n=56	n=37	
pCR rate (%)	48.9	48.9	p=1.000	45.5	50.0	p=0.899	46.8	51.1	p=0.838	50.0	47.2	p=0.963
RCB class 0-1 vs 2-3	63.8 vs 36.2	62.2 vs 37.8	p=0.822	59.1 vs 40.9	64.3 vs 35.8	p=0.870	61.7 vs 38.3	64.4 vs 35.5	p=0.748	66.1 vs 33.9	58.3 vs 41.7	p=0.531
Metabolic response (%)	-54.9	-54.3	p = 0.919	-54.7	-54.6	p = 0.981	-53.9	-55.3	p = 0.809	-52.8	-57.5	p=0.415
Dose reduction rate (%)	20.8	37.8	p=0.116	27.3	29.6	p=1.000	25.5	32.6	p=0.601	25.0	35.1	p=0.412
24 months EFS (%)	92.9	87.7	p=0.76	97.9	82.6	p=0.34	84.5	92.1	p=0.15	94.2	84.4	p=0.53

Table 1. Differences between “morning” and “afternoon” groups in SIM and paclitaxel regimen, with two timing infusion cut-offs.

PO4-13-07

Association of clonal hematopoiesis (CH) with clinical outcomes among survivors of breast cancer (BC)

Presenting Author(s) and Co-Author(s):

- D. Soldato. Gustave Roussy, Villejuif, France, United States
- A. Della Noce. Centrale Supelec, United States
- A. Di Meglio. Gustave Roussy, Villejuif, France, Paris, France
- C. Marzac. Gustave Roussy, Villejuif, France, United States
- B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France
- A. Martin. Unicancer, Paris, France, United States
- S. Everhard. Unicancer, Paris, France, United States
- M. Breckler. Gustave Roussy, United States
- S. Boyault. Centre Léon Bérard, Lyon, France, United States
- M. Rousseau. Centre Léon Bérard, Lyon, France, United States
- O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France
- C. COUTANT. Centre Georges-François Leclerc, France
- P. Cottu. Institut Curie, United States
- O. Rigal. Centre Henri Becquerel, Rouen, France
- C. Levy. Centre François Baclesse, United States
- C. Jouannaud. Institut Godinot, Reims, France
- B. Sauterey. Institut de cancérologie de l'Ouest, Angers, France
- N. Droin. Gustave Roussy, Villejuif, France, United States
- B. Job. Gustave Roussy, United States
- A. Bertaut. Centre Georges François Leclerc, Dijon, France, United States
- F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France
- I. Vaz Luis. Gustave Roussy, Villejuif, France
- J. Micol. Gustave Roussy, Villejuif, France, United States

Background: Clonal hematopoiesis (CH) refers to the identification of clonal expansion of hematopoietic cells due to somatic mutations in leukemia-associated genes without evidence of hematologic anomalies. CH, particularly with variant allele frequency (VAF) $\geq 10\%$, has been associated with adverse outcomes, including reduced survival in advanced malignancies and higher risk of cardiovascular events. The aim of this study was to evaluate the biological and prognostic relevance of CH in survivors of breast cancer (BC).

Methods: CANTO (NCT01993498) is a prospective, multicenter cohort enrolling patients diagnosed with stage I-III BC. CANTO collects clinical, tumor and treatment-related characteristics at diagnosis (dx). Follow-up visits are scheduled at 1, 2, 4 and 6 years after dx and data on disease status, type of recurrence, and survival status are collected. We assessed CH among pts ≥ 40 years, without previous solid or hematological cancer, with blood samples available at dx and year 4 or experiencing death or disease recurrence before year 4. CH was determined using Next-Generation Sequencing with unique molecular identifiers (HaloPlexHS,

Agilent Technologies) for 17 genes (including DNMT3A, TET2, ASXL1, PPM1D, ATM, JAK2 and TP53) on blood samples obtained at dx. Outcomes of interest included invasive disease-free survival (iDFS), distant disease-free survival (DDFS) and overall survival (OS) defined according to STEEP criteria. Kaplan-Meier estimator, log-rank test and multivariate Cox models assessed prognostic role of CH.

Results: In the cohort with available CH data (N=1219) mean age (SD) was 57.5 (10.1) years, 62% of pts were postmenopausal, 40.9% were current or former smokers, 46.2% had stage I BC, 77.7% had HR+/HER2- BC, 53.5% received chemotherapy and 80.8% hormonal therapy. CH was detected with a VAF $\geq 1\%$ in 306 pts (25.1%) including 207 pts (67.6%) with DNMT3A mutation, $\geq 2\%$ in 186 (15.3%) and $\geq 10\%$ in 45 (3.7%) pts. Pts with CH $\geq 10\%$ were more frequently older (65.3 vs 57.2 years, $p < .0001$) and with a previous history of cardiovascular disease (53.3% vs 37.3%, $p < 0.02$). At a median (IQR) follow-up of 7.0 (6.2-7.8) years 246 iDFS, 161 DDFS and 118 OS events were observed. Only 8 cases of new hematological malignancies were observed. Pts harboring CH with a VAF $\geq 10\%$ had worse OS (log-rank $p=0.04$) and CH with a VAF $\geq 10\%$ was associated with higher risk of death (HR= 2.4, 95%CI 1.04-5.6); presence of CH with lower VAF was not associated with worse OS. Table displays complete results for all tested associations.

Conclusions: CH at dx was identified in 25% of pts with stage I-III BC aged ≥ 40 years in the CANTO cohort, including 4% with a VAF $\geq 10\%$. In a large, prospective cohort of survivors of BC, we confirmed known associations of CH with older age and cardiovascular history. We observed few secondary hematological malignancies. CH with a VAF $\geq 10\%$ was significantly associated with higher risk of death while adjusting for other relevant prognostic factors. Furthermore, a trend towards higher risk of DDFS events was observed among pts harboring CH with a VAF $\geq 10\%$.

Multivariate Cox models for iDFS, DDFS and OS*						
Variable	iDFS		DDFS		OS	
	HR	95%CI	HR	95%CI	HR	95%CI
CH, VAF $\geq 10\%$ vs $< 10\%$	1.56	0.79-3.08	2.14	0.99-4.64	2.41	1.04-5.60
CH, VAF $\geq 2\%$ vs $< 2\%$	0.85	0.56-1.29	0.87	0.51-1.47	0.70	0.37-1.34
CH, VAF $\geq 1\%$ vs absent	0.85	0.60-1.18	0.99	0.66-1.50	0.77	0.47-1.28

iDFS: invasive disease-free survival, DDFS: distant disease-free survival, OS: overall survival, HR: hazard ratio, 95% CI: 95% confidence interval, CH: clonal hematopoiesis, VAF: variant allele frequency, DNMT3A: DNA methyltransferase 3 alpha.

* All models included and were adjusted for: age (continuous), BMI (continuous), smoking status (never vs former smoker and never vs current smoker), stage at diagnosis (stage I vs stage II and stage I vs stage III), Charlson comorbidity index (≥ 1 vs 0), receipt of chemotherapy (yes vs no), radiotherapy (yes vs no), hormonal therapy (yes vs no) and antiHER2 therapy (yes vs no).

PO4-13-08

Mechanical conditioning (MeCo) score is higher in circulating tumor cells (CTCs) compared to primary tumors in early-stage breast cancer and even higher in metastases compared to CTCs in metastatic breast cancer

Presenting Author(s) and Co-Author(s):

G. Mouneimne. MeCo Diagnostics, United States

A. Watson. MeCo Diagnostics, California, United States

A. Grant. UGenome Biotech, United States

D. Campo. Next Bioinformatics, United States

A. Ring. University Hospital, Zurich, United States

P. Bains. University of Southern California, United States

J. Lang. Cleveland Clinic, Cleveland, Ohio, United States

Background: The mechanical conditioning (MeCo) score is a gene expression signature that is acquired early by cancer cells in the primary breast tumor and is reflective of their responsiveness to matrix stiffness (fibrotic-like matrix rigidity). Further, chromatin remodeling in response to stiffness allows cancer cells to retain their aggressive features even in the absence of mechanical stimulation by the primary tumor microenvironment, for instance, during their dissemination through the circulation in metastasis. Importantly, patients who have high MeCo score tumors are at higher risk of developing metastatic breast cancer, compared to low MeCo scores ($p < 0.0001$; HR=2.2, 95%CI 1.7-2.7; Watson et al 2021, PMID: 34192535). Moreover, circulating tumor cells (CTCs) are associated with higher rate of metastatic dissemination, making CTC detection in the circulation of breast cancer patients a significant prognostic biomarker for breast cancer metastasis. Beyond their enumeration per blood volume units, specific prognostic features of CTCs are not fully explored. We sought to determine whether, compared to primary tumors, CTCs retain high MeCo scores and whether these scores are maintained during late-stage breast cancer in the metastatic sites.

Methods: CTCs were isolated from peripheral blood of two patient cohorts: stage II-III breast cancer patients using immunomagnetic enrichment/FACS methodology (Lang et al 2018, PMID: 29868978) and of metastatic breast cancer patients using ANGLE Parsortix microfluidics system (Ring et al 2022, PMID: 35000083). Gene expression profiling using RNA-seq was performed in CTCs and in matching primary tumors (PT) and metastases (MET) for the early-stage and late-stage cohorts, respectively. A quantile normalization approach was used to allow comparison across cohorts. MeCo scores were computed for all samples as per Watson et al 2021. Wilcoxon matched-pairs signed rank test was performed for comparison of MeCo scores from matching samples within each cohort; Mann-Whitney unpaired test was used to compare MeCo scores of CTCs across cohorts.

Results: In 12 pairs of early-stage breast cancer patient CTCs and PT, MeCo scores of CTCs were significantly higher than their matched PTs ($p=0.026$). Furthermore, in 26 pairs of metastatic patient's CTCs and MET, MeCo scores of METs were significantly higher than matching CTCs ($p=0.0004$). MeCo scores of CTCs were similar between early- and late-stage breast cancer despite differing CTC isolation strategies (epitope-dependent and microfluidics size gradient). 98% of genes in the MeCo score were present in the evaluable CTC, MET and PT samples.

Conclusions: Our results show that the MeCo score is higher in CTCs compared to PTs and in METs compared to CTCs in early- and late-stage breast cancer, respectively. Therefore, the MeCo score is progressively higher throughout the metastatic cascade in breast cancer. These findings demonstrate that mechanical conditioning is retained during metastatic progression, even as cancer cells transition through the circulation where the initial induction by matrix stiffness is lost. Further, these findings support that cancer cells with higher MeCo scores are more competent with—and potentially selected for by—metastatic progression. Importantly, these findings provide a novel feature of CTCs, mechanical conditioning (MeCo), which is associated with higher capacity for metastasis. Further, since the CTC MeCo score is elevated even in early-stage breast cancer, it could provide, in addition to CTC enumeration, a potential prognostic tool to predict metastatic risk in breast cancer patients.

PO4-13-09

Paclitaxel affects the efficacy of PD-1 blockade by interfering with lipid metabolism reprogramming in patients with breast cancer.

Presenting Author(s) and Co-Author(s):

H. Mo. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

J. Han. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

J. Zhai. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

X. Sun. Cancer Hospital of Huanxing Chaoyang District Beijing, Beijing, China

X. Guan. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

H. Qian. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

F. Ma. Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background:

The question of how chemotherapeutic drugs affect the efficacy of PD-1/PD-L1 antibodies in patients with breast cancer is still pending. In a previously single-cell sequencing study, we have demonstrated that paclitaxel reduces the level of CXCL13+ T cells and other immune cells critical for atezolizumab to work, leading to inferior efficacy of atezolizumab in triple negative breast cancer (TNBC). How paclitaxel affects these important immune cells remains obscure. Recently, plasma metabolomic and proteomics analysis have shown that patients' systemic metabolic signatures is correlated with the response of PD-1/PD-L1 antibody. As such, understanding the differential metabolic influences of the diverse chemotherapeutic drugs that comprise an immune response to TNBC offers an opportunity to appropriately select chemotherapeutic backbones for ICIs.

Methods:

We collected pre- and post-treatment plasma samples from breast cancer patients for metabolomic and proteomic analysis, including four patient cohorts: two independent cohorts (discovery cohort and validation cohort) in which patients were treated with ICIs, one cohort in which patients were treated with paclitaxel, and one cohort of patients treated with nab-paclitaxel. Patients were divided into responder group (R, tumor shrinkage) or non-responder group (NR, tumor increase) according to the change in tumor size after treatment relative to baseline. This was followed by integrating metabolomics and proteomics with single-cell transcriptome, along with in vitro experiments, to shed light on the mechanisms of action leading to ICIs resistance in breast cancer patients.

Results:

In the discovery cohort, the metabolites that mostly differed between the R and NR groups at baseline were lysoglycerophospholipids. These results were further validated in the validation cohort of patients. The dynamic changes of lysoglycerophospholipids were still significantly different between the R and the NR groups after ICIs treatment in the discovery cohort. It's worth noting that the level of lysophosphatidylcholines (LPCs), the most prominent

lysoglycerophospholipids, increased significantly in the R group, while no significant changes among LPCs were found in the NR group after ICIs treatment. In the validation cohort, the median PFS of LPC^{low} patients was 1.8 months versus 6.8 months in the LPC^{high} group (P = 0.0068).

After one cycle of paclitaxel treatment, the metabolic status of patients changed dramatically, especially the levels of lipids. It is notable that most LPCs were significantly downregulated after paclitaxel treatment. However, in patients who received nab-paclitaxel, few significantly changed lipids were detected after one cycle nab-paclitaxel treatment compared with their baseline conditions. Interestingly, the levels of LPCs were upregulated after one cycle nab-paclitaxel treatment, but decreased after paclitaxel treatment.

Single-cell omics results showed that in patients' PBMCs, CXCR4+ NK cells were the most closely related to plasma LPC levels, while FGF2+ NK cells were in the tumor microenvironment. We isolated and expanded NK cells from PBMCs for in vitro experiments, and found that LPC stimulation can significantly upregulate the expression of CXCR4+ in NK cells, and further increase the chemotaxis and cytotoxicity of NK cells.

Conclusions:

In breast cancer patients receiving ICIs, the systemic lipid metabolism status, especially lysoglycerophospholipids, is closely related to the efficacy of immunotherapy. The key molecule LPC, the most prominent lysoglycerophospholipids, may promote the efficacy of immunotherapy by activating NK cells in breast cancer patients. Paclitaxel may impair the efficacy of immunotherapy by affecting the systemic lipid metabolism status, especially by reducing plasma LPC levels, so it is not a suitable partner for ICIs.

PO4-13-10

The anti-metastatic role of BMP4 through cholesterol biosynthesis inhibition and consequent interaction with statin benefit in breast cancer.

Presenting Author(s) and Co-Author(s):

L. Chi. Olivia Newton-John Cancer Research Institute, Heidelberg, Victoria, Australia

A. Redfern. University of Western Australia, Perth, Western Australia, Australia

A. Burrows. La Trobe University, Victoria, Victoria, Australia

S. Roslan. St. Vincent Hospital Melbourne, Melbourne, Victoria, Australia

L. Oh. Fiona Stanley Hospital, Perth, Western Australia, Australia

L. Spalding. Harry Perkins institute for Medical Research, Perth, Western Australia, Australia

R. Anderson. Olivier Newton-John Cancer Research Institute, Melbourne, Western Australia, Australia

We have previously identified a role for bone morphogenic protein 4 (BMP4) in reducing distant relapse risk after early breast cancer (BrCa) (1). We therefore set out to identify mechanisms underlying the protective effect of BMP4, looking to translate this finding for patient benefit.

A highly metastatic variant of the triple negative MDA-MB-231 human BrCa line (231-HM-turboGFP) was transduced with BMP4, leading to sustained BMP4 secretion. These modified tumours were established in NSG mice, resected at a given size and turboGFP-positive cancer cells were recovered from primary tumours for RNA sequencing analysis. Gene set enrichment analysis (GSEA) was completed to identify signalling pathways that were significantly modulated by BMP4. The four most significantly downregulated gene sets were associated with cholesterol synthesis, with the overwhelming majority of genes in this pathway being downregulated. BMP4 downregulation of 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1, involved in cholesterol biosynthesis) was confirmed at the protein level by western blotting on whole tumour lysates. Forced expression of BMP4 also led to a significant reduction in the levels of free and total cholesterol. In a confirmatory analysis of the METABRIC human BrCa dataset, the expression of cholesterol biosynthesis-related genes inversely correlated with the expression of BMP4. Further, for the majority of these genes, expression was elevated in high-grade breast tumours, and predicted worse overall survival of patients. Finally, we tested the effect of a lipophilic statin, lovastatin, on the growth and metastasis of 231-HM-turboGFP tumours. Treatment did not affect the growth of primary tumours but significantly less metastases were observed in the lungs of treated mice, at least partially replicating the anti-metastatic effect of BMP4.

Having identified inhibition of cholesterol biosynthesis as a potential mechanism of protective BMP4 action we then asked if BMP4 status interacted with any protective effect of co-administered statins. We therefore returned to the cohort initially employed to demonstrate BMP4 benefit (1) and looked at the interaction between BMP4 protein levels and statin usage with regards to recurrence. BMP4 protein and statin usage data were available on a cohort of 417 patients with early BrCa. Statin use compared to none led to a reduced risk of distant relapse (8 v 22%, 0.0029) at 15 years. BMP4 led to borderline reduction in distant relapse (16 v 24%, $p=0.052$). In BMP4 negative tumours, statin protected against any relapse ($p=0.0025$) whereas in BMP4 positive disease no significant risk reduction was not significant ($p=0.074$). Absence of BMP4 expression may be a biomarker of both higher relapse risk and statin benefit in early BrCa.

1. Eckhardt et al, Cancer Res. 2020;80(6):1304-1315

PO4-13-11

Epigenetically defined sub-clonal heterogeneity drives therapy resistance in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

F. Ahmadimoghari. The Institute of Cancer Research, London, England, United Kingdom

Y. Zhang. The Institute of Cancer Research, United States

I. Mavrommati. The Institute of Cancer Research, London, UK, United Kingdom

S. Thakur. The Institute of Cancer Research, United States

C. Starling. The Institute of Cancer Research, United States

I. Roxanis. The Institute of Cancer Research, United States

S. Haider. Breast Cancer Now Toby Robinsons Research Centre, The Institute of Cancer Research, London, United States

R. Natrajan. The Institute of Cancer Research, London, UK, London, United Kingdom

Background

Triple-negative breast cancer (TNBC) is a highly aggressive and heterogeneous disease with an average survival of less than 50%. Although immunotherapy is showing promising results in early TNBC, many patients do not respond, and chemotherapy remains the main treatment. High recurrence rates in TNBC are in part due to its inherent molecular heterogeneity and sub-clonal diversity, whereby cells present in minority sub-populations escape therapeutic pressure. Recurrent genomic alterations are not selected for upon therapy resistance in neoadjuvant chemotherapy (NAC) resistant TNBC, however sub-clonal transcriptionally defined cells are “primed” to drive resistance and are pre-existing, suggesting phenotypic heterogeneity is governed by inheritable activation of epigenetically defined regulatory regions.

Here, we sought to characterise the sub-clonal and spatial diversity of chemotherapy resistant TNBC to identify the epigenetic hallmarks of lethal sub-populations of cells that may induce cell state transition, therapy resistance and ultimately metastatic progression.

Methods

Sixteen primary untreated triple-negative breast tumours (eight chemotherapy sensitive (Chemo^S) and eight chemotherapy resistant (Chemo^R, who died of their disease within three years)) were subjected to cell-matched high-depth multiome single nuclei RNA- and ATAC-sequencing. Driver DNA mutations and copy number alterations (CNA's) were identified using a clinically validated targeted capture panel. Four tumours were subject to spatial RNA and ATAC profiling. Fourteen TNBC PDX models generated from patients with residual disease post NAC were subjected to single nuclei sequencing and used for validation. Meta-clustering of epithelial cells from the RNA profiles was used to identify sub-populations of cells harbouring distinct epigenetic and transcriptomic features enriched in Chemo^R patients. Findings were validated in the BrightNess TNBC NAC clinical trial and in chemotherapy treated TNBC patients from the SCAN-B study.

Results

Unsupervised meta-clustering (MC) of epithelial cells in G₁ phase of the cell cycle identified nine meta-clusters across the dataset. A distinct immune-like MC was contributed by epithelial G₁ cells, suggesting a cross-talk of epithelial cells with spatially proximal immune cells. Two

MCs were dominated by cells from Chemo^R patients and were defined by pathways related to hypoxia, EMT, and extra-cellular matrix signalling. Using scATAC profiles, we identified that the sub-populations of cells in the Chemo^R dominant MCs were underpinned by both promoter and distal differential chromatin accessibility, that mapped to H3K27ac enhancer sites, suggesting a role of distal enhancer chromatin modification in regulating MC transcription. None of the meta-clusters were dominated by tumours with specific genetic mutations or CNA's.

Spatial ATAC and RNA profiling of a subset of tumours identified spatial epigenetically defined regions that showed distinct chromatin profiles, suggesting that the epigenetic regulation of genes that define the MCs are spatially distinct.

Chemo^R clusters were independently reproduced in a cohort of fourteen residual disease TNBC PDXs. Genes pertaining to the immune-like MC were associated with a good prognosis in independent cohorts of contemporary treated TNBC (SCAN-B) and associated with response to NAC in the BrightNess trial. Marker genes from Chemo^R dominant MCs were associated with poor prognosis and significant levels of residual disease following NAC.

Conclusions

Our multi-modal integrative analysis reveals unprecedented insight into the role of epigenetically defined spatially distinct, sub-clonal populations that pre-exist in treatment naïve TNBC and predict therapy response. This suggests pre-existing populations of cells have already acquired the epigenetic footprints and hence transcriptomic features to allow them to evade therapy.

PO4-13-12

PIK3CA mutational status in tissue & plasma as a prognostic tool in HR+/HER2- breast cancer (BC)

Presenting Author(s) and Co-Author(s):

E. Terán Brage. IBSAL - University Hospital of Salamanca, United States
R. Lozano Mejorada. IBSAL - Hospital Universitario de Salamanca, Spain, United States
A. Rodrigues Françoso. University Hospital of Salamanca, United States
J. Muñoz Leon. University Hospital of Salamanca, United States
□. López Gutiérrez. IBSAL - University Hospital of Salamanca, United States
L. Figuero-Pérez. Medical Oncology Department, Complejo Asistencial Universitario de Salamanca, Castilla y Leon, Spain
D. Morchón Araujo. IBSAL - University Hospital of Salamanca, United States
M. Garijo Martínez. IBSAL - University Hospital of Salamanca, United States
J. Roldán Ruiz. IBSAL - University Hospital of Salamanca, United States
M. Abad Hernández. IBSAL - University Hospital of Salamanca, United States
M. Sancho de Salas. IBSAL - University Hospital of Salamanca, United States
E. Fonseca Sánchez. IBSAL - University Hospital of Salamanca, United States
C. Rodríguez Sánchez. IBSAL - University Hospital of Salamanca, United States

Background: Activating mutations of PIK3CA gene are described in about 30-40% of BC. They confer overall worse prognosis and resistance to endocrine and chemotherapeutic therapy. Concordance between testing methods (tissue & plasma) are not widely studied. We aim to correlate tissue & plasma assays and to analyze the discordant cases and prognostic value of PIK3CA mutations (PIK3CAm) in HR+/HER2- BC.

Methods: We performed a retrospective and unicentric analysis of PIK3CA mutational status in tissue & plasma samples in patients (pts) with HR+/HER2- BC from February/21 to April/23. PIK3CA test: Cobas®PIK3CA Mutation Kit. We correlated both diagnostic methods. Kaplan-Meier and Cox models were used to analyze progression-free survival (PFS) and comparison outcomes in PIK3CAm vs wild-type (wt).

Results: We analyzed 225 samples from 161pts with HR+/HER2- BC (149 in tissue & 76 in plasma). PIK3CA mutations were detected in 62pts (38.5%), of which 39.6% (59pts) were detected in tissue and 11.8% (9pts) in plasma. Hotspot mutations: H1047X (45.7%), E545X (20%) and E542K (12.8%).

In advanced disease, metastatic BC (mBC), tissue & plasma concordance was conducted in 64 cases, with overall correlation rate of 70.3%. We found PIK3CAm in 28pts: by both methods in 9pts (32.1%) and exclusively tissue detection in 19 cases (67.8%). Plasma detection was correlated with the presence of ≥3 metastatic sites (66.7% vs 31.6%; p=0.08) and with collection of samples during disease progression (66.7% vs 47.4%; p=0.43).

80pts received treatment with CDK4/6 inhibitors + endocrine therapy. PFS was slightly shorter in PIK3CAm vs wt (24m vs 30m; HR=1.39 [95%CI,0.7-2.4], p=0.26). A sub-analysis was performed based on exons 9 & 20, showing a significantly lower PFS in PIK3CAm exon 9 vs 20

population (9.7m vs 30.3m; HR=2.84 [95%CI,1.1-7.4], p=0.02). In addition, plasma detection of PIK3CAm was associated with worse PFS compared with PIK3CAm detected only in tissue (12.4m vs 29.3; HR=2.4 [95%CI,0.8-6.5], p=0.08). Although we observed a trend towards a poorer PFS in pts with visceral involvement in PIK3CAm (21.9m vs 30.1m; HR=2.82 [95%CI,0.6-12.3], p=0.14), in a multivariate analysis, mutations in exon 9 were an independent poor prognostic factor regardless visceral involvement and detection in plasma; p=0.05.

Conclusions: Our results support the PIK3CA determination in tissue as the diagnostic method of choice, although further studies could better define the role of liquid biopsy in the detection of PIK3CAm. In our population, the presence of PIK3CAm confers poorer prognosis in luminal BC, being significantly worse in mutation carriers in exon 9 regardless visceral involvement and plasma mutation detection.

Table. Tissue & plasma correlation in patients with PIK3CA mutational status tested in our population (mBC).

		Tissue		
		Mutated	WT	Total
Plasma	Mutated	9 (32.1%)	0 (0%)	9 (14.1%)
	WT	19 (67.8%)	36 (100%)	55 (85.9%)
Total		28 (100%)	36 (100%)	64 (100%)
Positive agreement:		9/28 (32.1%)		
Negative agreement:		36/36 (100%)		
Overall agreement:		45/64 (70.3%)		

PO4-14-01

Synergistic Activity of CDK8/19 Inhibitor RVU120 and MEK Inhibitors in Hormone-Negative Breast Cancer: Implications for Targeted Therapy

Presenting Author(s) and Co-Author(s):

U. Pakulska. Ryvu Therapeutics S.A., United States

A. Moszynska. Ryvu Therapeutics S.A., United States

J. Martyka. Ryvu Therapeutics S.A., United States

J. Woznicki. Ryvu Therapeutics S.A., United States

E. Adamczyk. Ryvu Therapeutics S.A., United States

M. Obacz. Ryvu Therapeutics S.A., United States

K. Keska Izvorska. Ryvu Therapeutics S.A., United States

K. Wiklik. Ryvu Therapeutics S.A., United States

A. Stachowicz. Ryvu Therapeutics S.A., United States

H. Nogai. Ryvu Therapeutics S.A., United States

M. Mazan. Ryvu Therapeutics S.A., United States

T. Rzymiski. Ryvu Therapeutics S.A., United States

Breast cancer (BC) is a complex disease with distinct subtypes, including triple-negative breast cancer (TNBC), which lacks targeted therapies. CDK8 and CDK19, components of the mediator complex involved in transcriptional regulation, have emerged as potential therapeutic targets in BC. Transcriptomic analysis revealed that elevated CDK8 expression was associated with poor prognosis across all BC subtypes. Furthermore, previous studies demonstrated that sensitivity to CDK8/CDK19 inhibition correlated with high STAT3 phosphorylation and enrichment of TNF/NF- κ B and STAT target genes in responder cells.

In this study, we evaluated the responsiveness of TNBC cell lines to RVU120, a highly selective and potent CDK8/CDK19 inhibitor currently undergoing clinical trials for acute myeloid leukemia (AML), high-risk myelodysplastic syndrome (HR-MDS), and solid tumors. Notably, the sensitivity of TNBC cell lines to RVU120 varied depending on the culture conditions, with the presence of epidermal growth factor (EGF) identified as a major determinant of response variability. Considering the role of EGFR in activating downstream signaling pathways, including MAPK and STAT, and previous observations of synergy between small molecule CDK8 inhibitors and MEK inhibitors in neuroblastoma, we investigated MEK inhibitors as potential combination partners in hormone-negative BC.

Among the 15 tested BC cell lines, a synergy between CDK8/CDK19 inhibitors and MEK inhibitors was observed in 5 cell lines, antagonism in another 5 cell lines, and no synergy in the remaining 5 cell lines, based on the analysis with Combobenefit software (Loewe additivity model). Importantly, cell lines where synergy of the combination therapy has been observed, exhibited EGFR amplification and markers of activated RAS pathway. This pattern of response was consistent across different MEK and MEK/RAF inhibitors, including selumetinib, trametinib, and avutometinib. These findings highlight the synergistic potential of combining RVU120 with MEK inhibitors in hormone-negative BC, particularly in TNBC with EGFR amplification and an active RAS pathway.

Ongoing studies involving RNAseq analysis and organoid screening aim to further elucidate the

underlying mechanisms and confirm the efficacy of this combination therapy. Furthermore, in vivo efficacy experiments are necessary to validate in vitro activity of both compounds. Successful development of this therapeutic concept relies on the validation and implementation of selected partner drugs targeting RAS pathway, as well as the identification of suitable biomarkers such as EGFRamp or RAS-score. Promising findings of this study provide a rationale for exploring the combination of CDK8/CDK19 inhibitor RVU120 and MEK inhibitors as a potential targeted therapy strategy for hormone-negative BC.

PO4-14-02

Enhancing Informative Outcomes with Liquid Biopsy in a Real-World Population of Patients with Advanced Breast Cancer: Analysis of the SOLTI-1903 HOPE Study

Presenting Author(s) and Co-Author(s):

T. Pascual. SOLTI Cancer Research Group, Barcelona, Spain /Department of Medical Oncology, Hospital Clínic de Barcelona, Spain / Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain., United States

E. Seguí. SOLTI Cancer Research Group; Hospital Clínic Barcelona; IDIBAPS, Barcelona, Catalonia, Spain

R. Olivera-Salguero. SOLTI Cancer Research Group, United States

J. Cejalvo. Hospital Clínico Universitario de Valencia, Valencia, Spain

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

P. Tolosa. SOLTI Cancer Research Group, Barcelona, Spain/Medical Oncology Department, Hospital 12 de Octubre, Madrid., Madrid, Madrid, Spain

M. Vidal. Medical Oncology Department, Hospital Clínic of Barcelona ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; SOLTI Breast Cancer Research Group ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Catalonia, Spain

M. Malumbres. Vall d'Hebron Institute of Oncology, Barcelona; Spanish National Cancer Research Centre (CNIO), Madrid, Spain; Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain., United States

J. Gavilá. Medical Oncology Department, Fundació Instituto Valenciano de Oncología, Valencia, Spain; SOLTI Cancer Research Group, United States

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

S. Pernas. SOLTI Cancer Research Group, Barcelona, Spain Institut Catala d'Oncologia; IDIBELL, L'Hospitalet, Barcelona, Spain

R. López. SOLTI Cancer Research Group; Clinical University Hospital and Health Research Institute of Santiago de Compostela (IDIS)- CIBERONC, United States

M. Margelí. SOLTI Cancer Research Group. Medical Oncology Department, ICO Badalona, B-ARGO Group. GEICAM Spanish Breast Cancer Group., Catalonia, Spain

J. Balmaña. Vall d'Hebron University Hospital, Barcelona, Spain

M. Muñoz. SOLTI Breast Cancer Research Group, Hospital Clínic of Barcelona, Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, Catalonia, Spain

I. Blancas. Medical Oncology Dept, University Hospital San Cecilio, Granada, Spain

V. Boni. NEXT Madrid, University Hospital Quironsalud, Madrid, Spain, United States

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

E. Galve. Hospital Universitario de Basurto, United States

A. Perelló. Hospital Son Espases, Palma, Illes Balears, Spain, United States
R. Sánchez-Bayona. Medical Oncology Department, Hospital 12 de Octubre, Madrid. SOLTI Cancer Research Group, Barcelona, Spain
S. de la Cruz. SOLTI Cancer Research Group; Complejo Hospitalario de Navarra, Pamplona, United States
M. de la Hoya. Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, United States
A. Blanch-Torras. SOLTI Cancer Research Group, United States
R. Sposito. SOLTI Cancer Research Group, United States
J. Canes. SOLTI Cancer Research Group, Barcelona, Spain, United States
H. Masanas. SOLTI Cancer Research Group, United States
R. Olmos. Asociación Española de Cáncer de Mama Metastásico, Spain, United States
M. Forns. Asociación Española de Cáncer de Mama Metastásico, Spain, United States
M. Prieto. Asociación Española de Cáncer de Mama Metastásico, Spain, United States
A. Casas. SOLTI Cancer Research Group; Fundación Actitud Frente al Cáncer, Sevilla, Spain, United States
A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

Background: The integration of next-generation sequencing (NGS) into routine clinical practice is often hindered by financial and logistical challenges, resulting in diagnostic and therapeutic disparities among patients. Addressing these issues, the SOLTI-1903 HOPE study (NCT04497285) seeks to evaluate the feasibility of implementing a molecular screening program that actively involves patients with advanced breast cancer (ABC) in the management of their disease. By empowering patients, this study aims to gain a comprehensive understanding of the genomic landscape of ABC and to facilitate patient access to matched targeted therapies in Spain

Methods: In the SOLTI-1903 HOPE study, a patient-centric approach was adopted, allowing patients living anywhere in Spain, and diagnosed with ABC, to actively lead their inclusion, participation, and follow-up using a digital tool (DT). Patients signed an informant consent, and then provided clinical information and underwent a liquid biopsy (LBx) using the Guardant360 panel at a local laboratory. LBx samples could be obtained at the moment of progressive disease (PD), when a new line of treatment was started < 8 weeks before extraction (PT), or during treatment with stable disease or partial response lasting more than 8 weeks (SD/PR). Clinical and molecular findings were evaluated by a Molecular Advisory Board (MAB), which generated a comprehensive report explaining the observed alterations and listing potentially beneficial matched targeted treatments. The primary endpoint of this subanalysis was to compare the genomic outcomes between LBx samples obtained at SD and those obtained at PD or PT. In the study, tissue samples were also collected and analysed by Foundation but this analysis will be reported in other communications.

Results: From October 2020 to May 2023, a total of 273 blood samples were obtained from 253 patients diagnosed with ABC, with the majority being HR+/HER2- (81%), followed by HER2-positive (13%) and triple-negative (6%). Mean turnaround time was 10.9 days from blood collection to final result.

Despite nearly 40% of patients being SD or PR, in 79.9% of the LBx (n=218), one or more genomic alterations were detected, and among these, 74.0% (n=202) were classified as

pathogenic. Among the 74 genes analyzed by the Guardant360 panel, 8 genes were classified as tiers I-III according to the ESCAT levels of clinical relevance. In 150 LBx samples (54.9%), one or more pathogenic alterations were associated with ESCAT levels I-III, while only the remaining 52 LBx samples (19.1%) with pathogenic alterations were not associated with any ESCAT levels I-III.

Among the analyzed LBx samples, a total of 928 distinct gene alterations were identified. Of these, 650 alterations (70.1%) were classified as pathogenic, while 278 (29.9%) were categorized as variants of unknown significance or lacked a reported impact. Notably, 25% (n=323) of the pathogenic gene alterations were further classified as ESCAT I-III.

Out of the 273 LBx samples, 140 were obtained at PD, 30 at PT, and 103 at SD/PR. Circulating tumor DNA (ctDNA) was detected in 91.4% of PD samples, 86.7% of PT samples, and 62.1% of SD/PR samples ($p < 0.001$). Alterations classified as ESCAT levels I-III were observed in 70% of PD samples, 60% of PT samples, and 33% of SD/PR samples ($p < 0.001$).

In 20 patients, LBx was repeated, with 16 of them having the first LBx obtained during SD/PR and the second LBx collected during PD or PT. The detection rate of ctDNA increased significantly from 18.7% (n=3) to 87.5% (n=14) ($p < 0.001$). The number of LBx samples with ESCAT levels I-III alterations also showed a significant increase from 12.5% (n=2) to 68.7% (n=11) ($p = 0.0032$).

Conclusions: Our findings highlight the importance of obtaining LBx samples during disease progression -compared to SD/PR- to gain greater genomic informativeness and better guide personalized treatment approaches for patients with advanced breast cancer.

PO4-14-03

Results of Comprehensive Genomic Profiling of Metastatic Breast Cancer Patients at a Single Institute in Japan

Presenting Author(s) and Co-Author(s):

T. Kon. Tohoku University Hospital, Sendai, Miyagi, Japan

H. Tada. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

M. Miyashita. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

A. Ebata. Department of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

N. Shoji-Harada. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, Japan

Y. Hamanaka. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

M. Sato. Tohoku University Hospital, United States

M. Yanagaki. Tohoku University Hospital, United States

S. Tsunokake. Tohoku University Hospital, United States

T. Motonari. Tohoku University Hospital, United States

A. Yamazaki. Tohoku University Hospital, United States

T. Ishida. Division of Breast and Endocrine Surgical Oncology, Tohoku University Graduate School of Medicine, Miyagi, United States

BACKGROUND. Comprehensive genomic profiling (CGP) was officially approved by the Japanese National Health Insurance System in June 2019. Currently, three CGP tests are available: FoundationOne CDx (F1CDx), OncoGuide NCC Oncopanel (NCC), and FoundationOne Liquid CDx (F1LCDx). This study examines the clinical significance of CGP testing in patients with metastatic breast cancer (mBC) in Japan. **METHODS.** The subjects were 105 patients (pts) who underwent CGP testing at our hospital from June 2019 to July 2023. Of these, 64 pts received tissue panels for F1CDx, 25 pts for F1LCDx, and 16 pts for others. Based on the reports from the testing companies and the expert panel committee's review, we evaluated the percentage of patients for whom matched therapy (MT) was recommended, whether MT was performed, and the prognosis of the group of patients for whom MT was performed. Overall survival was analyzed with the log-rank test. **RESULTS.** Of the 105 patients who underwent CGP testing, 47 pts (44.8%) were recommended MT corresponding to ESCAT (ESMO Scale for Clinical Actionability of molecular Targets) ranking I/II or clinical trials due to genetic alterations, and only 7 pts (6.7%) reached those treatments. Three HER2-negative patients were prescribed anti-HER2 therapy for ERBB2 amplification, one patient was prescribed entrectinib for NTRK fusion, and three patients participated in clinical trial for ERBB2 mutation and FGFR1 rearrangement. If ESCAT ranking beyond I/II and recommended therapy from FoundationOne report (e.g. Abemaciclib for CCND1 amplification, Everolimus for PTEN loss) are added, 64 pts (60.1%) were considered these treatments, and 19 pts (18.1%) actually received these treatment. Among these 19 pts, overall survival was significantly improved that of patients who did not reach treatment (21.1 m vs 6.2 m, $p=0.0097$). **CONCLUSIONS.** We examined the rate of MT attainment by CGP in mBC at a single institute. We found that the rate of MT attainment with ESCAT ranking I/II, or clinical trials corresponding

to genetic mutations, was low. The overall survival of patients who underwent MT, which can be performed by Japanese insurance, was significantly different from that of patients who did not undergo MT. Low accessibility of ESCAT ranking I/II MT may be because, in Japan, CGP testing is available only for patients who have completed or are expected to complete standard therapy. Early use of CGP testing and an increase in clinical trials will be desirable in Japan.

PO4-14-04

Comprehensive genomic profiling results in patients with metastatic breast cancer due to germline BRCA1/2 status and their HER2-low status

Presenting Author(s) and Co-Author(s):

H. Tada. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

M. Miyashita. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

N. Shoji-Harada. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, Japan

Y. Hamanaka. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

M. Sato. Tohoku University Hospital, United States

M. Yanagaki. Tohoku University Hospital, United States

S. Tsunokake. Tohoku University Hospital, United States

T. Motonari. Tohoku University Hospital, United States

t. Kon. Tohoku University Hospital, United States

A. Yamazaki. Tohoku University Hospital, United States

T. Ishida. Division of Breast and Endocrine Surgical Oncology, Tohoku University Graduate School of Medicine, Miyagi, United States

Objective: To determine the usefulness of comprehensive genomic profiling testing and the percentage of HER2-low in patients with germline BRCA1/2 (gBRCA1/2) variants metastatic breast cancer.

Methods: We included 3404 patients with metastatic recurrent breast cancer who underwent CGP testing from June 2019 to June 2023 in Japan. We examined the proportion of patients with or without recommended therapy, the proportion of patients who received matched therapy, and the proportion of patients with HER2 low by gBRCA1/2 variant due to CGP testing. **RESULTS.:** Of the 3404 patients, 69 (2.0%) had gBRCA1, 136 (4.0%) had gBRCA 2, 5 (0.1%) had gBRCA1 & gBRCA2, 1807 (53.1%) were negative, and 1388 (40.1%) were untested or unknown. The overall percentage of patients who recommended targeted therapy due to CGP testing was 37.4%(1272/3404), with gBRCA1 at 31.9%(22/69), gBRCA2 at 43.4%(59/136), and gBRCA1&gBRCA2 at 50%(2/4). The percentage of matched therapy performed in the 1st line after the expert panel was 8.3% overall, 2.9% for gBRCA1, 14.0% for gBRCA2, and 0% for gBRCA1&gBRCA2. The rate of tumor mutation burden (TMB) high was 7.4% overall, and gBRCA1 at 2.9%, gBRCA2 at 9.6%, and gBRCA1&gBRCA2 at 50%. On the other hand, the percentage of HER2-low was 38.3% overall, 29% for gBRCA1, 58.1% for gBRCA2, and 25% for gBRCA1 & gBRCA2.

Conclusion.: Germline BRCA2 variants had a higher rate of reaching matched therapy based on CGP test results. The higher rate of TMB high was suggested to be the reason for this. The high percentage of patients with HER2-low is also expected to improve the prognosis.

PO4-14-05

Germline and acquired genetic variants and long-term cancer-related fatigue among survivors of early-stage breast cancer (BC)

Presenting Author(s) and Co-Author(s):

A. Di Meglio. Gustave Roussy, Villejuif, France, Paris, France
E. Thomas. Centre Léon Bérard, Lyon, France
Y. Drouet. Centre Léon Bérard, Lyon, France
J. Micol. Gustave Roussy, Villejuif, France, United States
D. Soldato. Gustave Roussy, Villejuif, France, United States
M. Franzoi. Gustave Roussy, Villejuif, France, France
M. Pagliuca. Gustave Roussy, Villejuif, France, United States
J. Havas. Gustave Roussy, Villejuif, France, United States
A. Martin. Unicancer, Paris, France, United States
S. Everhard. Unicancer, Paris, France, United States
C. Besse. CNRGH-CEA, Évry-Courcouronnes, France, United States
A. Boland. CNRGH-CEA, Évry-Courcouronnes, France, United States
C. Marzac. Gustave Roussy, Villejuif, France, United States
N. Droin. Gustave Roussy, Villejuif, France, United States
S. Boyault. Centre Léon Bérard, Lyon, France, United States
M. Rousseau. Centre Léon Bérard, Lyon, France, United States
O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France
P. Cottu. Institut Curie, Paris, Paris, Ile-de-France, France
C. Jouannaud. Institut Godinot, Reims, France
M. Fournier. institut Bergonié, Bordeaux, France
L. Vanlemmens. Centre Oscar Lambret, Lille, France
C. COUTANT. Centre Georges-François Leclerc, France
A. Dhaini Merimeche. Institut de cancérologie de Lorraine, Nancy, France, United States
B. Sauterey. Institut de cancérologie de l'Ouest, Angers, France
F. Joly. Centre François Baclesse, Caen, France, United States
M. Campone. Institut de Cancérologie de l'Ouest, René Gauducheau, Saint-Herblain, France
F. Lerebours. Institut Curie, United States
M. Mouret-Reynier. Centre Jean Perrin, Clermont Ferrand, United States
O. Rigal. Centre Henri Becquerel, Rouen, France
T. Petit. Centre Paul Stauss, Strasbourg, France
S. Guillermet. Centre Eugène Marquis, Rennes, France
A. Arnaud. Institut Sainte Catherine, Avignon, France
M. Ibrahim. CHU La Source, Orléans, United States
S. Giacchetti. Hôpital Saint Louis, Paris, France

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France
J. Wassermann. CHU Pitié Salpêtrière, Paris, France
O. Arsène. Centre Hospitalier de Blois, Blois, France
A. Darut-Jouve. Institut de Cancérologie de Bourgogne, Dijon, France, United States
A. Bertaut. Centre Georges François Leclerc, Dijon, France, United States
F. André. Faculté de Médecine Paris-Sud XI, Gustave Roussy, Villejuif, France
J. Deleuze. CNRGH-CEA, Évry-Courcouronnes, France, United States
A. Viari. INRIA, France, United States
I. Vaz Luis. Gustave Roussy, Villejuif, France

BACKGROUND: Previous studies suggested that bio-behavioral models explain part of the variability of cancer-related fatigue, and pro-inflammatory and age-related processes emerged as contributors to persistent fatigue. However, the biological underpinnings of this complex symptom, including its relevant genomic correlates, are still poorly understood. We aimed to comprehensively explore the association of genetic variants with long-term cancer-related fatigue.

METHODS: We used the prospective, multicenter, longitudinal CANcer TOxicity cohort, enrolling patients at diagnosis of stage I-III BC (NCT01993498). Outcomes included severe ($\geq 40/100$) global (EORTC QLQ-C30) as well as physical, emotional, and cognitive (FA12) fatigue at year (Y)1, Y2, and Y4 after BC diagnosis. Applying a hypothesis-driven approach, we investigated (i) germline genetic variants in a pre-specified Genetic Risk Index (GRI) assaying expression-regulating single nucleotide polymorphisms (SNPs) in the promoter regions of 3 pro-inflammatory cytokine genes (IL1B [rs16944], IL6 [rs1800795], and TNF [rs1800629]; Bower J, JCO 2013; N=9035), and (ii) age-related expansions of hematopoietic clones carrying recurrent acquired mutations, commonly defined as clonal hematopoiesis of indeterminate potential (CHIP; NGS with unique molecular identifiers for 17 genes [including DNMT3A, TET2, ASXL1, PPM1D, ATM, JAK2, and TP53]; N=1219). The contribution of GRI and CHIP to fatigue was assessed by multivariable logistic regression models. Taking an agnostic approach, we then performed a genome-wide association study (GWAS) of fatigue and 1,894,511 germline SNPs (Illumina InfiniumExome24 / Illumina GSA24; N=9056). All genetic variants were assessed at BC diagnosis. Tested associations were adjusted by validated clinical predictors (Di Meglio A, JCO 2022).

RESULTS: In the overall cohort (N=9056) mean age was 56.5 years (SD 11.2), 51.0% had stage II or III BC, 52.6% received chemotherapy, and 82.1% endocrine therapy. The prevalence of severe fatigue was 26.1% at diagnosis and increased to 36.5%, 34.3%, and 32.6% at Y1, Y2, and Y4 after diagnosis, respectively. Most patients (77.4%) had 3-6 high-frequency alleles across the 3 SNPs in the pro-inflammatory GRI. Among patients with available CHIP data, 15.2% and 3.7% had a Variant Allele Frequency (VAF) $>2\%$ and $>10\%$, respectively. The pro-inflammatory GRI was not associated with fatigue outcomes. We found significant associations between CHIP and severe long-term global fatigue at Y4 (adjusted OR [95%CI]: VAF $\geq 2\%$ vs $< 2\%$, 1.64 [1.08-2.51], $p=0.021$; VAF $\geq 10\%$ vs $< 10\%$, 2.22 [1.00-4.94], $p=0.050$). The GWAS identified several regions (each including ≥ 2 SNPs) as associated with severe fatigue outcomes (suggestive p -value cut-off $< 5 \times 10^{-5}$; see Table for number of identified regions by outcome and respective nearby genes). Overlap in biological pathways was observed in some of the gene regions associated with global and physical fatigue, but not for emotional or cognitive fatigue. Common biological processes that were associated (FDR < 0.05) with such genes included synaptic transmission, hemoglobin-oxygen binding, and

response to stress.

CONCLUSIONS: This study provides suggestive association data between gene variants and long-term cancer-related fatigue. While previously reported associations with pro-inflammatory GRI were not confirmed, some biological processes that may inform the mechanistic understanding of this symptom emerged, including associations with aging and response to stress that warrant further exploration.

Genes in proximity of regions associated with severe fatigue outcomes

Outcome	N. regions	Genes
Severe global fatigue at Y1	14	CTC-359M8.1; RP11-146I2.1; LRFN2; LINC00841; SAMD4A; CTD-2130013.1
Severe global fatigue at Y2	8	VAV3-AS1; THRB; RP1-209A6.1; PLXDC2; NALCN
Severe global fatigue at Y4	12	ROBO2; NRPI; DOCK1; AC104389.28 // HBG2 /// HBE1; FGF14; SHISA9; RP11-35G9.3 /// RP11-35G9.5 /// ATP8B1
Severe physical fatigue at Y1	19	TCF7L1; GPR156; SERP1 /// EIF2A; SLC2A9; CTD-3118D11.3; PTPRD; ERCC6L2; CAMSAP1; CCDC34; DSCAM
Severe physical fatigue at Y2	9	PPARGC1A; PDOD4; BBIP1; SHOC2; PRR5L; AL035610.2
Severe physical fatigue at Y4	7	FIN2; PARK2; CELF2; UNC13C

///: marks different regions.

All association analyses were adjusted by age, body mass index, smoke behavior, pre-treatment fatigue, pain, insomnia, and anxiety, and by the first ten axes of principal component analysis of the genetic data to control for population stratification.

There was no overlap in biological pathways for the gene regions associated with emotional or cognitive fatigue (gene regions not shown).

PO4-14-06

Impact of Serum HER2 Extracellular Domain in Metastatic Breast Cancer Patients Treated with Trastuzumab Deruxtecan (T-DXd)

Presenting Author(s) and Co-Author(s):

K. Nozawa. Aichi Cancer Center Hospital/Department of Breast Oncology, Nagoya, Aichi, Japan

M. Kusudo. Aichi Cancer Center Hospital, United States

N. Kureyama. Department of Breast Oncology, Aichi Cancer Center Hospital, United States

A. nakakami. Aichi Cancer Center Hospital, United States

R. Komaki. Aichi Cancer Center Hospital, United States

Y. Endo. Aichi Cancer Center Hospital, United States

A. Kataoka. Aichi Cancer Center Hospital, United States

H. Kotani. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

A. Yoshimura. Aichi Cancer Center Hospital, United States

M. Hattori. Aichi Cancer Center, United States

M. Sawaki. Department of Breast Oncology, Aichi Cancer Center, Japan

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Background: Trastuzumab deruxtecan (T-DXd) is a standard of care as 2nd line and after prior chemotherapy for HER2 positive and low metastatic breast cancer (MBC), respectively, based on Destiny Breast03 and 04 results. However, biopsies over time during treatment have shown that HER2 expression is variable. The predictive factors of trastuzumab deruxtecan (T-DXd) for MBC with HER2 positive and low are unclear. The HER2 extracellular domain (HER2-ECD) has been confirmed as a prognosis marker and predictive marker of treatment for HER2-positive MBC. Especially, HER2-ECD is considered a promising biomarker in cases where HER2 expression in metastases is unconfirmed. We hypothesized that HER2-ECD could serve as a biomarker for T-DXd.

Patients and methods: A retrospective study of consecutively treated patients in a single center between 2019-2023 with HER2-low and HER2-positive MBC was performed using chart review. HER2 status was diagnosed according to 2020 ASCO-CAP guidelines. HER2-ECD high was defined as >15.0 ng/ml. HER2-ECD was collected prior to T-DXd treatment. We compared overall response (ORR), progression-free survival (OFS), overall survival (OS), and disease control rate (DCR) at HER2-ECD high and low groups. Cox regression analyses were performed to assess the ORR. We used the Kaplan-Meier method to estimate the PFS and OS and the log-rank test to compare each treatment group.

Results: A total of 41 MBC patients were included in this study. Patients with HER-positive and HER2-low were 34 and 7, respectively. Among HER2 positive (n=34), HER2-ECD high and low are 14 (41%) and 20 (59%) patients, respectively. Among HER2 low (n=7), HER2-ECD high and low are 3 (43%) and 4 (57%) patients, respectively. Twenty-six patients received T-DM1 prior to T-DXd treatment for MBC with HER2 positive, but no patients received CPT-11 before T-DXd for MBC with HER2 positive and low. The ORR of T-DXd was 89% and 52% in the HER2-ECD high and low groups, respectively (p< 0.001). All 6 cases with CR were HER2-ECD high. Among HER2 low group (n=7), ORR of T-DXd was 67% (2/3) and 25% (1/4) in HER2-ECD high and low groups, respectively. The median PFS in the HER2-ECD high group showed

longer than the HER2-ECD low group, 21.8 vs. 8.0 months (HR 0.31; 95%CI, 0.13-0.78, p=0.012). Although there were no significant differences in OS, HER2 ECD high group tended to show longer OS (HR 0.23; 95%CI, 0.04-1.16, p=0.07). The DCR was 100% in the HER2 ECD high group and 87% in the low group.

Conclusion: T-DXd showed significantly better response and prolonged PFS in the group with high HER2-ECD. HER2-ECD has the potential to become a biomarker for T-DXd. Further study is warranted to assess the HER2-ECD as a biomarker, especially for HER2 low MBC patients treated with T-DXd.

Association between the response and the HER2 status or HER2-ECD status

	CR	PR	SD	PD	ORR (%)	DCR (%)
ALL (n=41)	6	22	10	3	68%	92%
HER+ (n=34)	6	19	6	3	74%	91%
HER2-low (n=7)	0	3	4	0	43%	100%
HER2-ECD high (n=18)	6	10	2	0	89%	100%
HER2-ECD low (n=23)	0	12	8	3	52%	87%

PO4-14-07

Genomic and immune profiling of breast cancer brain metastases

Presenting Author(s) and Co-Author(s):

A. Van Swearingen. Duke Center for Brain and Spine Metastasis, United States

M. Lee. Duke University, United States

L. Rogers. Duke University, United States

A. Sibley. Duke University, United States

P. Shi. Duke University, United States

X. Qin. Duke University, United States

M. Goodin. Duke Center for Brain and Spine Metastasis, United States

K. Owzar. Duke University, United States

C. Anders. Duke Cancer Institute, Durham, North Carolina, United States

BACKGROUND: Brain metastases (BrM) arising from breast cancer (BC) are an increasing consequence of advanced disease, with up to half of patients (pts) with metastatic HER2+ or triple negative breast cancer experiencing central nervous system (CNS) recurrence. The genomic alterations driving CNS recurrence, along with contribution of the immune microenvironment, particularly by BC subtype remains unclear.

METHODS: We characterized BrM from a cohort of n=42 BC pts by sequencing whole-exome DNA and total RNA libraries from frozen (n=31) and FFPE (n=34) BCBrM, FFPE extracranial (ECT, n=12) and blood DNA (n=26) tissues from the Duke Brain Tumor Biorepository. Analyses conducted and planned include inference of PAM50 intrinsic subtypes, somatic mutations, copy number alterations, immune cell type decompositions by CIBERSORTx, differential RNA expression, driver analysis, and associations with clinical outcomes.

RESULTS: PAM50 subtypes across 31 frozen BrM were 23% Luminal (Lum) A, 13% LumB, 33% HER2-enriched, 27% Basal-like, 3% Normal-like. For 34 FFPE BrM, 15% were LumA, 24% LumB, 33% HER2-enriched, 24% Basal-like, 3% Normal-like. Across 26 paired FFPE and frozen BrM, subtype discrepancy was seen in 23% (6) cases of which frozen to FFPE classification differed: 3 LumA to LumB, 1 LumB to LumA, 1 Normal to LumB, and 1 Basal to LumB. Among 10 paired FFPE BrM and ECT, subtype concordance was observed in 70%. Discordance was seen in 1 case each for ECT to BrM: LumB to HER2, LumB to LumA, Basal to Normal-like. WES demonstrated frequent copy number alterations (CNA) in clinically-relevant genes including TGFB1, NOTCH1, CDK4, and ERBB3, in both BrM and ECT. For pts with matched blood, ERBB3 CNA (gain and loss) were more commonly found in FFPE BrM (7/19, 37%) compared to ECT (1/8, 13%). Among BrM, the most frequently altered clinically-relevant genes included TP53 (~75%), PTEN, EGFR, RB1, PIK3CA, NF1 and ESR1 (all $\leq 15\%$); in ECT, TP53 (67%), BRCA2, FBXW7, and ATM (all $\leq 33\%$). PI3K pathway genes (e.g. PTEN, PIK3CA) alterations were exclusive to BrM. One pt's ECT showed an ATM mutation that was not observed in the paired BrM. Conversely, BRAF and CCND2 mutations were observed in BrM, but not ECT for 1 pt each. Inferring the relative abundance of immune populations in frozen BrM illustrated that 23% were CD4+ resting memory T cells, 25% M2 tumor-permissive macrophages, 13% M0 macrophages; M1 tumor-inhibiting macrophages were only 2%. When comparing immune cell populations between FFPE BrM and ECT, ECT had more M1 macrophages (Chi-sq 4.23, P = 0.04), while other immune cell populations were of similar

relative abundance. Immune cell fractions did not vary by subtype in BrM or ECT with one exception: M2 macrophages were lower in Basal compared to LumB tissues (frozen BrM: Chi-sq = 9.28, P = 0.05; FFPE BrM: Chi-sq = 4.61, P = 0.33; FFPE EC: Chi-sq = 9.78, P = 0.04). In n=8 pt-matched FFPE BrM/ECT, hallmark pathways upregulated in BrM included MYC and E2F targets and oxidative phosphorylation, while those with lower expression in BrM included epithelial-mesenchymal transition, interferon gamma response, and JAK-STAT signaling.

CONCLUSION: This analysis showed moderate discrepancy in subtype call of BrM by tissue preparation (frozen vs. FFPE), with LumB classification showing the highest discrepancy, and more commonly called in FFPE tissues. Subtype concordance between ECT and BrM was relatively high. Analysis of CNA illustrated deletions and amplifications in targetable genes, notably ERBB3 preferentially in BrM compared to ECT. Mutational analysis identified targetable alterations exclusive to BrM; this knowledge could lead to BrM-targeted treatments. Inferred immune cell populations illustrated a tumor permissive microenvironment in BrM. Therapeutic strategies repolarizing macrophages toward a tumor-inhibiting phenotype in BrM are warranted. Analyses of associations between genomic data and clinical outcomes, as well as driver analyses, are ongoing.

PO4-14-08

A gene expression-based classifier for HER2-low breast cancer

Presenting Author(s) and Co-Author(s):

S. Di Cosimo. Biomarker Unit, Department of Applied Research and Technological Development, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

S. Pizzamiglio. Unit of Bioinformatics and Biostatistics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, United States

C. Ciniselli. Unit of Bioinformatics and Biostatistics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, United States

V. Duroni. Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, United States

V. Cappelletti. Biomarkers Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, United States

L. de Cecco. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, United States

M. De Santis. Radiation Oncology 1, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy, United States

R. Orlandi. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, United States

M. Iorio. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, United States

M. Silvestri. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, United States

G. Pruneri. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, United States

P. Verderio. Unit of Bioinformatics and Biostatistics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, United States

Background: The definition of HER2-low breast cancer from clinical trials of antibody-conjugated drugs (ADCs) relies on immunohistochemistry scoring (IHC). However, in daily-practice the accuracy of IHC is hindered by inter-observer variability in assessing HER2 non-overexpressing status. Here, we aimed to identify breast cancer primary tumors with low HER2 expression by leveraging gene expression profiling.

Materials and methods: A discovery approach was applied to gene expression profile of internal INT1 (n= 125) and INT2 (n= 84) datasets. We identified specific differently expressed genes (DEGs) according to HER2 IHC categories 0, 1+, 2+ and 3+. Principal Component Analysis (PCA) was used to generate a HER2-low signature whose performance was confirmed in the independent INT3 (n= 95), and TCGA and GSE20194 publicly available datasets. The association between the HER2-low signature and HER2 IHC categories was evaluated by non-parametric Kruskal-Wallis (KW) test with post hoc pair wise comparisons (i.e. contrasts); the HER2-low signature discriminatory capability was assessed by estimating the area under the receiver operating characteristic (ROC) curve (AUC) with its corresponding 95% Confidence Interval (CI). Gene Ontology and KEGG analyses were performed to enrich the DEGs for functional information.

Results: A 20-gene HER2-low signature, consisting of both up-regulated (n=11) and down-regulated (n=9) genes, was computed based on the DEGs according to HER2 IHC categories as follows: 11 genes specific for the 1+ category, 8 genes for the 2+ category, and 1 gene for the HER2-low category. HER2-low signature genes were significantly enriched with lipid and steroid metabolism pathways, peptidase regulation, and humoral immune response. The HER2-low signature levels demonstrated a significant association with HER2 IHC categories (KW p-value < 0.001) and were distributed in a bell-shaped pattern across IHC categories (low values 0 and 3+; high values 1+ and 2+), effectively distinguishing HER2-low from 0 (contrast

p-value < 0.001) and 3+ (contrast p-value < 0.001). Notably, the signature levels were significantly higher in tumors scored with 1+ as compared to 0 (contrast p =0.002). The HER2-low signature association with IHC categories and discriminatory capability was confirmed in the independent INT3 and TCGA datasets with higher values in HER2-low compared to both 0 and 3+. The HER2-low signature achieved an AUC value of 0.72 (95%CI 0.62-0.83) in differentiating HER2 0/3+ from HER2 1+/2+ categories, which is worth noting in light of the individual ERBB2 mRNA AUC value of 0.48 (95%CI 0.34-0.62).

Conclusions: The 20-gene HER2-low signature was generated by maximizing the differences in gene expression between tumors with different HER2 status according to IHC. In contrast to the previously published single ERBB2 gene expression assessment, our data presents compelling evidence for effectively distinguishing HER2-low tumors, including those scored as 1+ from HER2-0 tumors. Our signature holds potential in selecting novel candidates for ADC therapy.

PO4-14-09

A computational model of the mechanisms of action of combined endocrine therapy and CDK4/6 inhibition predicts outcome in patients with Luminal B breast cancer

Presenting Author(s) and Co-Author(s):

L. Schmiester. University of Oslo, Oslo, Norway

F. Brasó-Maristany. Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), United States

V. Kristensen. Oslo University Hospital, United States

A. Frigessi. University of Oslo, Oslo Centre for Biostatistics and Epidemiology (OCBE), University of Oslo, Norway, Norway

A. Prat. Hospital Clinic, Barcelona, Catalonia, Spain

A. Köhn-Luque. University of Oslo, Oslo, Norway

Background: Hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer (BC) is clinically and biologically heterogeneous. CDK4/6 inhibitors (CDK4/6i) are proven to be effective in different molecular subtypes of HR+/HER2- BC, including the PAM50 luminal B. However, not all patients benefit to the same extent and new biomarkers for response are needed. The aim of this study was to develop a computational workflow to predict the response of patients with luminal B BC to treatment with CDK4/6i in combination with endocrine therapy (ET).

Methods: The main part of the workflow is a computational model representing the mechanisms of action of the drugs and their influence on protein signaling and cell proliferation in the tumor. The model was trained on publicly available data from BC cell lines (Western blot time courses and viability dose-response data). The model was then used to predict response in patients by incorporating gene expression profiles obtained at baseline. The output of the model was a score indicating how strongly the tumor responded to the treatment.

Gene expression data determined using the nCounter BC360 panel was available at baseline from two patient cohorts: 1) the CORALLEEN phase II trial which evaluated neoadjuvant ribociclib plus letrozole vs multi-agent chemotherapy in postmenopausal patients with luminal B by PAM50, HR+/HER2- early BC (Prat et al. *Lancet Oncology*. 2020), 2) a retrospective study of postmenopausal patients with HR+/HER2-/Luminal B advanced BC treated with CDK4/6i plus ET in the first line setting at Hospital Clinic Barcelona (hereafter CDK cohort). PAM50 risk of relapse (ROR) and Ki67 levels were considered as outcome for the CORALLEEN patients. Progression free survival (PFS) was available in the CDK cohort. Area under the ROC Curve (AUC) was used to estimate the discrimination performance of the model. Differences were tested for statistical significance using Wilcoxon rank-sum test. Hazard ratios were estimated using Cox regression to investigate the association with PFS.

Results: The computational model used here describes the dynamics of relevant protein-protein and drug-protein interactions to the treatment of CDK4/6i plus ET. The model showed high agreement with the training data obtained from cell lines (Pearson correlation of 0.88 and 0.95). The ability of the trained model to predict treatment outcome in patients was validated in baseline samples of the CDK4/6i arm (n=51) and the chemotherapy arm (n=52) of the CORALLEEN trial, and baseline Luminal B primary tumors of the CDK cohort (n=19). For each patient, a response score was calculated by the model using the expression of 6 genes at baseline as input. This response score was significantly associated with patient response in

both cohorts. The model identified patients with high Ki67 (AUC of 0.80 (95% CI 0.64 - 0.92)) and high ROR (AUC of 0.78 (95% CI 0.64 - 0.89)) after treatment in the CDK4/6i arm of the CORALLEEN cohort and was used to stratify patients into different response groups. The AUC in the chemotherapy arm of CORALLEEN for identifying high Ki67 was 0.44 (95% CI 0.29 - 0.58), indicating that the predictions are specific to CDK4/6i plus ET treatment. Additionally, stratification of patients in the CDK cohort into either two or three groups based on the response score was linked to PFS (HR=3.71 (95% CI 0.97 - 14.16), p=0.055 and HR=2.92 (95% CI 1.08 - 7.86), p=0.034, respectively).

Conclusion: A mechanistic model was developed, trained on cell line data, and then used to predict treatment outcome of patients with HR+/HER2-/PAM50 Luminal B BC treated with CDK4/6i plus ET. This approach showed significant association with observed outcome and could be used to assign patients to different response groups, indicating the usefulness of the model as a potential marker for response.

PO4-14-10

Circulating Tumor DNA as a Biomarker for ADCs in Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

H. Chang. University of Texas at Southwestern, Dallas, Texas, United States

I. Anawate. University of Texas at Southwestern, United States

A. Low. University of Texas at Southwestern, United States

S. Huang. University of Texas at Southwestern, United States

J. Maues. GRASP, Washington, District of Columbia, United States

C. Hodgdon. Grasp Cancer, United States

I. Chan. University of Texas Southwestern Medical Center, United States

Background: Breast cancer is a complex disease characterized by heterogeneity, and the analysis of circulating tumor DNA (ctDNA) holds promise for capturing this heterogeneity. Recently, ctDNA testing has been employed in clinical practice to guide targeted therapies for metastatic breast cancer, particularly in cases of hormone receptor-positive disease with mutations in PIK3CA and ESR1. This approach becomes necessary when traditional tumor biopsies are inadequate for next-generation sequencing (NGS) testing or fail to capture the full extent of the cancer's heterogeneity. Moreover, the utilization of antibody-drug conjugates (ADC) in addressing tumor heterogeneity continues to expand. However, there has been no biomarker, outside of HER2 protein expression, to predict ADC response. In this project, we test the hypothesis that ctDNA can be utilized as a biomarker to predict response to novel therapies such as ADCs.

Methods: We analyzed a subset of patients from the Dallas Metastatic Breast Cancer Study comprised of patients with metastatic breast cancer (n= 109) who underwent ctDNA testing using the Tempus xF liquid biopsy ctDNA sequencing panel. This panel detects 105-genes that are known oncogenic drivers and resistance mutations. The data was collected from a single academic medical center between the initial year of ctDNA collection in 2019 and 2023.

Results: Among these patients, 85 (77.9%) had hormone receptor-positive disease, 13 (11.9%) had triple-negative breast cancer, and 11 (10.0%) had HER2-positive disease (including 3 (2.75%) patients with triple-positive disease). Only 22 of these patients had tissue biopsies that underwent NGS testing. Analysis of all patients revealed that the most common gene alteration was PIK3CA, which was identified in 70 patients. Specifically, the most frequently observed alteration was PIK3CA p.545K, found in 25 patients. Table 1 further details the frequency of each gene in this subset of patients.

Among the patients, 34 out of 109 (31%) received an ADC, while only 8 out of 109 (7%) received immunotherapy. Patients with CDKN2A achieved the longest progression-free survival (PFS) on an ADC, with a median PFS of 7 months, whereas patients carrying mutations in TP53, PIK3R1, PIK3CA, PTEN, NF1, BRAF, RHOA, FGFR4, KRAS, TERT, GATA3, HNF1A, FB1, STOP had median PFSs of 2 months or less. Table 2 provides additional information on the response of patients with specific mutations to ADCs. Notably, only one patient received sequential ctDNA testing, and in that case, there was a gain of TP53 p.N239S following sacituzumab govitecan administration compared to the baseline ctDNA test, followed by a gain of PIK3CA p.P449_L455del after trastuzumab deruxtecan administration.

Conclusions: As we observe changes in subtypes following treatment progression, researchers are actively seeking biomarkers to better characterize real-time changes in tumor biology that can predict response and resistance to treatments. Further studies are needed to identify additional genes present in ctDNA that can provide mechanistic insights into why certain patients respond favorably to ADCs while others do not. We are currently enrolling patients for a prospective study that aims to assess baseline ctDNA levels and monitor changes in variant allele frequency following treatment with ADCs and immunotherapy.

Table 2

Gene	Frequency (%)
PIK3CA	23.41%
TP53	23.08%
ESR1	13.04%
PTEN	4.35%
ERBB2	4.01%
NF1	4.01%
GATA3	2.34%
RB1	2.01%
ARID1A	2.01%
ATM	2.01%
PIK3R1	1.67%
CDH1	1.67%
AKT1	1.67%
BRCA1	1.34%
KRAS	1.34%
CDKN2A	1.34%
GNAS	1.00%
TERT	1.00%
BRCA2	0.67%
EGFR	0.67%
PALB2	0.67%
FGFR4	0.67%
HNF1A	0.67%
MYC	0.67%
CTNNB1	0.67%
MSH3	0.33%
SPOP	0.33%
PMS2	0.33%
MTOR	0.33%
BRAF	0.33%
MLH1	0.33%
RHOA	0.33%
NOTCH1	0.33%

Median PFS on ADC by Gene

Gene	mPFS on ADC (month)
CDKN2A	7
BRCA1	6
PALB2	4
ERBB2	3
ESR1	3
TP53	2
PIK3R1	2
PIK3CA	2
PTEN	2
NF1	2
BRAF	2
RHOA	2
FGFR4	2
KRAS	1.5
TERT	1.5
GATA3	1
HNF1A	1
RB1	1
SPOP	1
AKT1	
MYC	0
CDH1	
ARID1A	0

PO4-14-11

Findings of clinically significant variants (Tier IA) with OmniSeq INSIGHT ® in a breast cancer cohort of 987 patients

Presenting Author(s) and Co-Author(s):

H. Ko. Labcorp Oncology, United States

D. Dash. Labcorp (Omniseq Inc.), United States

E. Severson. Labcorp Oncology, United States

K. Strickland. Labcorp Oncology, United States

Z. Bliss. Labcorp Oncology, United States

P. DePietro. Labcorp Oncology, United States

J. Conroy. OmniSeq, Inc., Buffalo, New York, United States

S. Ramkissoon. Labcorp Oncology, United States

S. Zhang. Labcorp Oncology, United States

Background:

There were an estimated 2.3 million new breast cancer cases worldwide in 2020, with breast cancer now the most diagnosed type of cancer representing 25% of cancer cases and 17% of cancer deaths (1). The GLOBOCAN Cancer Tomorrow prediction tool estimates that incidence will increase by > 45% by 2040 (2). Optimal treatment for breast cancer is increasingly dependent upon knowing a patient's somatic and germline genomic alteration status. To highlight the importance of these genomic alterations, we provide an overview of the genomic findings in 987 consecutive breast cancer patients tested in the course of routine clinical care.

Methods:

Comprehensive Genomic and Immune Profiling (CGIP) was performed on 987 qualified breast cancer samples at a CAP/CLIA and NYS CLEP certified reference laboratory with the OmniSeq INSIGHT ® test (3). OmniSeq INSIGHT ® is a next generation sequencing-based laboratory developed test for the detection of genomic variants, signatures, HLA Class I genotypes, and immune gene expression in formalin-fixed paraffin-embedded (FFPE) tumor tissue. DNA is sequenced to detect small variants in the full exonic coding region of 523 genes, copy number alterations in 59 genes (gains and losses), as well as analysis of microsatellite instability (MSI) and tumor mutational burden (TMB). RNA is sequenced to detect fusions and splice variants in 55 genes, in addition to mRNA expression in 64 immune genes. The resultant information, along with PD-L1 protein expression by immunohistochemistry (IHC), is intended for use by qualified health care professionals in accordance with professional guidelines in oncology for management of patients with solid neoplasms. Tier IA variants include variants with strong clinical significance as per AMP–ASCO–CAP recommendations (4).

Results:

There were 384 Tier IA variants detected in 370 of 987 breast cancer patients (~37.5%) with 251 in PIK3CA (65.3%), 60 in ERBB2 (15.6%), 46 in BRCA2 (11.9%), 19 in BRCA1 (4.9%), 4 in NTRK3 (1.0%), 1 in NTRK1 (0.26%) and 1 in PALB2 (0.26%) including copy number variations (CNV), gene fusion and single nucleotide variants (SNV).

At the individual gene level for Tier IA variants, PIK3CA had 251 SNVs detected, ERBB2 had 55 CNVs, 1 gene fusion and 4 SNVs detected, BRCA2 had 39 SNVs and 8 CNVs detected,

BRCA1 had 19 SNVs, NTRK3 had 4 gene fusions, NTRK1 had 1 gene fusion and PALB2 had 1 SNV detected.

At the variant class level, there were 63 CNVs, 6 gene fusions and 315 SNVs observed.

Conclusions:

CGIP for breast cancer patients identified one or more clinically significant Tier IA genomic alterations that directs targeted therapy in ~ 37.5% of patients in a cohort of real world patients tested during the standard course of clinical care. This highlights the need for comprehensive genomic testing in breast cancer patients to drive therapeutic decision making.

References:

1. Sung H et al.; Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries; *CA Cancer J Clin*, 2021 May;71(3):209-249.

2. Heer E et al.; Global burden and trends in premenopausal and postmenopausal breast cancer: a population-based study; *Lancet Glob Health*, 2020

3. Conroy JM et al.; A scalable high-throughput targeted next-generation sequencing assay for comprehensive genomic profiling of solid tumors; *PLoS One*. 2021

4. Li MM et al.; Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the association for molecular pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagnost*. 2017;19(1):4–23.

PO4-14-12

Predicting Response to HER2 Tyrosine Kinase Inhibitors and Antibody Drug Conjugates in HER2 Mutant Invasive Lobular Carcinoma Using CRISPR/Cas9 Knock-in Cell lines and Patient-derived Organoids

Presenting Author(s) and Co-Author(s):

J. Liu. University of Pittsburgh, United States

D. Tseng. University of Pittsburgh, United States

J. Hooda. University of Pittsburgh, United States

D. Brown. University of Pittsburgh, Pittsburgh, Pennsylvania, United States

A. LEE. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

S. Oesterreich. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

Background: Activating mutations in ERBB2 (HER2) are enriched >4-fold in invasive lobular carcinoma (ILC) with a rate of up to 19% in metastatic ILC. ILC is a histologic subtype of breast cancer characterized by loss of E-cadherin (CDH1), suggesting a potential interaction between loss of CDH1 and mutations in ERBB2. Recent trials have demonstrated promising single agent efficacy using the irreversible pan-HER tyrosine kinase inhibitor (TKI), neratinib, in patients with metastatic ERBB2 mutant ILC. However, further studies on combination therapies with other anticancer agents are needed to increase response rate and progression free survival for these patients. HER2-targeted antibody drug conjugates (ADC), particularly trastuzumab deruxtecan (T-DXd), have shown great promise in HER2-low metastatic breast cancer. Yet, their efficacy as a single agent or with HER2 TKIs in HER2-low and -mutant ILC is unknown and warrants investigation.

Methods: Past studies analyzing ERBB2 mutations used overexpression of ERBB2 mutant cDNA, but this approach does not faithfully recapitulate the human disease. To model ERBB2 missense mutations as found in human breast cancers, we used CRISPR-based prime editing to generate a panel of isogenic ILC cell lines and patient-derived organoids (PDO) harboring ERBB2 wild-type (WT) or ERBB2 mutations (S310F or V777L). Both of these ERBB2 mutations have been previously characterized and are known to be activating mutations. We then used them to test neratinib and other TKIs with ADCs, including T-DXd and trastuzumab emtansine (T-DM1).

Results: We successfully introduced single copy, heterozygous activating ERBB2 mutations (S310F or V777L) into two ERBB2-nonamplified metastatic ILC cell lines (MDA-MB-134 and SUM44PE) and one ERBB2-nonamplified metastatic ILC PDO (IPM-BO-053). Positive clones carrying the mutations were verified by Sanger sequencing and droplet digital PCR and subsequently pooled together. We further demonstrated that these mutations hyperactivated HER2 and downstream signaling pathways. ILC cell lines harboring these mutations showed enhanced sensitivity to HER2 TKIs but not ADCs. In contrary, ERBB2 mutations did not alter responses of IPM-BO-053 PDOs to HER2 TKIs but significantly increased responses to ADCs. Interestingly, we also observed accelerated HER2 protein degradation upon heregulin stimulation in ERBB2 mutant ILC PDOs, suggesting activating ERBB2 mutations may enhance ADC/HER2 complex internalization, degradation, and release of payloads. Lastly, we explored drug synergy between HER2 TKIs and ADCs in isogenic IPM-BO-053 PDOs and found that combination of T-DXd and neratinib or afatinib showed synergy (Combination Index < 1).

Conclusions: Although the reason for the discrepancies in drug response between ILC cell lines and PDOs is not clear, we hypothesize that response in 3D PDOs might be more faithfully representing response seen in patients. We will generate additional ILC PDOs with knock-in ERBB2 mutations to validate our findings. Irreversible HER2 TKIs, such as neratinib and afatinib, showed synergy with T-DXd in ERBB2 mutant ILC PDOs. This holds important therapeutic implications in light of current treatment options for ILC. In future experiments, we will test if neratinib or afatinib increases endocytic uptake of T-DXd using a fluorescently labeled endocytosis tracker. Further, an in-depth molecular characterization of our isogenic cell lines and PDOs models is ongoing to gain mechanistic insights into how activating ERBB2 mutations increase HER2 internalization and degradation. Our in vitro studies provide a strong foundation for in vivo testing of neratinib or afatinib with T-DXd for ERBB2 mutant ILC.

PO4-15-01

A multi-center prospective cohort study to evaluate the presence of circulating tumor cells using the Epic Sciences platform among women with metastatic breast cancer

Presenting Author(s) and Co-Author(s):

K. Jerzak. Sunnybrook Health Sciences Centre, United States

P. Goodwin. University of Toronto, United States

M. Ennis. Self employed, United States

C. Brezden-Masley. Mount Sinai Hospital, Canada

N. Bouganim. Medical Oncology, McGill University Health Centre, Montreal, QC, Canada, United States

M. Basik. Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada, United States

A. Jain. Synnybrook Research Institute, United States

G. Di Caro. Epic Sciences, United States

R. Wenstrup. Epic Sciences, United States

N. Hartmann. EPIC SCIENCES, United States

M. Slade. Epic Sciences, California, United States

A. Lohmann. London Health Sciences Centre, United States

Background: The presence of tumor cells (or their components) in the blood of women with a history of early breast cancer has the potential to herald the development of metastatic recurrence at its earliest stages. Such early detection could potentially lead to novel prevention strategies, but it requires a sensitive assay.

Objective: To use the Epic Sciences platform to detect and enumerate CTCs in blood samples from patients with an established diagnosis of metastatic breast cancer (MBC), prior to initiation of 1st line systemic therapy in the metastatic setting.

Methods: We conducted a multi-center prospective cohort study to evaluate the presence of CTCs using the Epic Sciences platform among patients with a new diagnosis of MBC. Men or women age 18 to 85 were included, irrespective of breast cancer subtype. Patients with a prior or concurrent malignancy whose natural history or treatment had the potential to interfere with the detection of MBC in a liquid biopsy were excluded.

A one-time blood draw was performed before patients received any local or systemic therapy in the metastatic setting. In addition, those with recurrent disease must have been off any systemic adjuvant therapy for ≥ 3 weeks prior to blood collection. Two 5 mL blood samples were obtained for CTC identification and enumeration. CTC identification was based on immunofluorescence analysis using Epic Sciences platform as previously described (Ueno et al 2017). The presence of CTCs was correlated with clinical and pathological features, which were abstracted from medical records and pathology reports. The association between the presence of CTCs and clinical/pathologic characteristics was tested using Fisher's exact test for categorical variables and t-test or Wilcoxon rank sum tests for numerical variables. All analyses were performed using the R software package.

Results: 100 patients were recruited between February 2021 and January 2023 at five

academic oncology centres in Ontario and Quebec, Canada. 95 patients had evaluable blood for analysis and 5 did not due to blood age and/or insufficient blood volume. Six patients were excluded after providing a blood sample because tissue biopsy ultimately revealed a 2nd primary tumor (n=4) or benign tissue (n=2). Hence, 89 patients with a clinical diagnosis of MBC and with evaluable blood for CTC analyses were ultimately included in our cohort.

The average age of patients was 61 years. Most patients (n=49, 55%) had a prior history of early breast cancer, 38 (43%) had de-novo metastatic disease and prior breast cancer history was unknown for 2 patients. 50 (66%) of patients had visceral metastatic disease. The most common sites of metastases included bone (62%), lung (30%), liver (29%) and lymph nodes (17%).

63 of 89 patients (71%) had detectable CTCs at baseline, prior to any local or systemic treatment in the metastatic setting. The median number of detectable CTCs per 5mL sample was 2 (IQR 8.5) and the range was 0 – 12,798. Twenty nine of 89 (33%) patients had 5 or more CTCs detected per 5ml blood. The proportion of patients with detectable CTCs was numerically highest (n=39/51, 76%) among patients with hormone receptor (HR)+/HER2-ve breast cancer, followed by HER2+ (n=16/22, 73%) and triple negative (n=8/13, 62%) disease. Associations between CTC detection with prior history of early breast cancer, sites of metastatic disease and disease burden will also be presented.

Conclusions: Approximately 3 in 4 women with newly diagnosed metastatic breast cancer have detectable CTCs using the Epic Sciences platform prior to initiation of first line systemic therapy. CTCs may be a promising tool for the monitoring of breast cancer recurrence and will be investigated in an ongoing Canadian prospective observational study that aims to elucidate biomarkers of late breast cancer recurrence.

PO4-15-02

ApoE polymorphism is associated with aggressive tumor phenotypes for breast cancer patients

Presenting Author(s) and Co-Author(s):

M. Luciano. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

R. Sant'Ana. Instituto do Câncer do Ceará, FORTALEZA, Ceara, Brazil

V. Lima. Instituto do Câncer do Ceará-ICC, Fortaleza, Ceara, Brazil

P. Silva. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

C. Albuquerque. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

F. Bitencourt. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

M. Bezerra. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

F. Oliveira. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

J. De Moura. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

I. Fernandes. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

F. Leite. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

Introduction: Apolipoprotein E (APOE) is implicated in several biological processes, such as protein synthesis, cell growth and differentiation, cholesterol transport, lipid metabolism, and tissue repair. APOE has different isoforms (E2, E3, and E4) that combine conflicting relations with cancer risk. This study aimed to evaluate the distribution of different isoforms of APOE among suspected HBOC (Hereditary Breast and Ovarian Cancer Syndrome) patients.

Methodology: DNA was extracted from the blood cells of 108 patients. The detection was performed using qPCR after amplifying specific regions containing the polymorphisms. It was considered that all the amplicons containing Cq amplification < 35. The melting curve for each patient was analyzed to determine the frequency of the isoforms E2, E3, E4, and genotypes E2/E2, E2/E3, E2/E4, E3/E3, and E3/E4. The allele and genotype were also correlated with hereditary variants previously identified by genetic tests for germline mutations and with tumoral phenotype. The data were expressed in frequency and associated using chi-square tests or Fisher's exact test (SPSS v20.0, $p < 0.05$). Results A total of 108 patients filling criteria for HBOC syndrome were evaluated. Among them, 15 (13.9%) had a mutation in BRCA1, 5 (4.6%) in BRCA2, and 2 (1.9%) in TP53. Most patients were under 45 years old ($n=76$, 70.4%), female ($n=104$, 96.3%), had a high school education ($n=44$, 44.0%), were non-smokers ($n=79$, 80.6%) or drinkers ($n=76$, 78.4%), and had no comorbidities ($n=66$, 64.1%). Overweight at diagnosis was observed in 61 (68.5%) individuals. The most frequent tumor phenotype and stage were luminal B ($n=46$, 43.4%) and stage IIIA ($n=22$, 26.2%), respectively. Neoadjuvant chemotherapy was performed in 40 (47.1%) with a high rate of complete and partial response 18 (36.7%) and 22 (44.9%), respectively. Regarding ApoE polymorphisms, the E2 allele showed the lowest frequency ($n=7$, 6.5%), E3 was present in 103 (95.4%) cases, while E4 was present in 39 (36.1%). The most frequent genotype was E3/E3 ($n=64$, 58.3%), followed by E3/E4 ($n=34$, 31.5%), E2/E3 ($n=6$, 5.6%), E4 ($n=4$, 3.7%), and E2/E4 ($n=1$, 0.9%). No cases of E2/E2 genotype were observed. The presence of E2 was inversely associated with comorbidity frequency ($p=0.040$) but directly associated with TP53 mutation ($p=0.012$) and triple-negative tumor phenotype ($p=0.027$). E3 was not associated with clinical characteristics, but E4 was associated with low Ki-67 immunoreactivity ($p=0.033$). The E2/E3 phenotype was directly associated with triple-negative tumors ($p=0.044$) and heterozygous tumors ($p=0.011$).

Conclusion: The ApoE polymorphism, particularly the presence of the E2 allele in heterozygosity, is associated with TP53 mutation and a more aggressive tumor phenotype.

PO4-15-03

Quantitative Measurement of TROP2 via Chromogenic Immunohistochemistry in Breast Cancer

Presenting Author(s) and Co-Author(s):

M. He. Yale University, New Haven, Connecticut, United States

M. Liu. Yale University, New Haven, Connecticut, United States

T. Aung. Yale University, New Haven, Connecticut, United States

S. Burela. Yale University, United States

K. Bates. Yale School of Medicine, United States

C. Robbins. Yale, United States

D. Rimm. Yale University, New Haven, Connecticut, United States

Sacituzumab govitecan (SG) is an antibody-drug conjugate that targets human trophoblast cell-surface antigen 2 (TROP2), which is expressed in over 90% of breast cancer cases (Zaman et al, 2019). By delivering the cytotoxic SN-38 (topoisomerase I inhibitor) to TROP2 expressing breast cancer cells, SG showed promising antitumor activities in clinical trials and is now an approved treatment for triple-negative breast cancer (TNBC) and hormone receptor (HR)-positive HER2-negative breast cancer in the metastatic setting. Despite the prevalent expression of TROP2 in breast cancer, the objective response rates reported from clinical trials were about 30%, indicating the need for a diagnostic test that can identify which patients are likely to benefit from therapy. Although the drug is approved without a companion diagnostic assay, recent data from the TROPiCS-02 trial has shown that TROP2-low (H-score < 100) showed a non-significant hazard ratio for benefit from SG. In the same study, patients treated with SG with H-score >100 showed a significant hazard ratio for benefit compared to physician's choice (Tolaney et al, ASCO 2023). This suggests that TROP2 expression level is associated with SG response and that a threshold for TROP2 expression level may aid patient selection. Although over 90% of breast cancer patients were considered TROP2-positive by IHC, the expression level of TROP2 was never quantitatively assessed in large breast cancer cohorts. Here we describe a quantitative chromogenic immunohistochemistry (IHC) assay with a cell line standard. Mass spectrometry was used to measure TROP2 peptide concentrations in the six standard cell lines, and the correlation between the mass spectrometry and IHC data for each cell line was then used to convert chromogenic signals to concentrations of TROP2 protein (fmol/mm²). The antibody used in this assay was rigorously validated, and the antibody concentration was optimized for the best signal-to-noise ratio. The optical density (OD) of chromogenic staining was measured using QuPath 0.4.3 (Qymia extension) by identifying the tumor area via object classifiers and manual editing and then calculating the area-normalized sum of OD. Collectively, this assay can measure up to 29.1 fmol/mm² of TROP2. By applying this assay to two serial retrospective primary breast cancer cohorts from Yale University, we quantitatively measured TROP2 expression levels in 332 clinical cases. Not surprisingly, over 90% of cases showed some chromogenic signal, with a median TROP2 concentration of 2.1 fmol/mm² and a maximum of 10.5 fmol/mm². TROP2 expression levels showed no significant association with clinicopathologic characteristics including race, stage, BRCA mutation status, molecular subtype, HER2 IHC levels, and outcome. Further work is underway to optimize the assay toward the goal of determination of whether there is a quantitatively definable threshold for TROP2 expression below which patients are unlikely to benefit from SG or other TROP2-targeted therapies.

PO4-15-04

Differential genomic profiling of progesterone receptor (PR) negative, estrogen receptor (ER) positive HER2-negative metastatic breast cancer (MBC) through circulating tumor DNA

Presenting Author(s) and Co-Author(s):

L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

A. Davis. Washington University in St Louis School of Medicine, United States

A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States

C. REDUZZI. Weill Cornell Medicine, United States

K. Clifton. Washington University in St Louis School of Medicine, United States

E. Podany. Washington University in St. Louis, St. Louis, Missouri, United States

W. Hensing. St. Luke's Cancer Institute, United States

M. Velimirovic. Cleveland Clinic, United States

A. Shah. Northwestern University, United States

L. Foffano. Department of Medicine, University of Udine, United States

L. Munoz Arcos. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, New York, United States

E. Nicolò. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

C. Dai. MGH Cancer Center, United States

J. Keenan. Cancer Center, Massachusetts General Hospital, United States

A. Behdad. Pathology and Laboratory medicine, Cleveland Clinic, United States

S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States

W. Gradishar. Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

F. Puglisi. National Cancer Institute, Centro di Riferimento Oncologico (CRO), IRCCS, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

M. Cristofanilli. Weill Cornell Medicine, United States

Background: MBC is usually classified based on ER and HER2 status. Although the absence of PR expression is commonly associated with a poorer response to endocrine therapy (ET) and an unfavorable prognosis, data regarding the underlining molecular features that occur in this subgroup are still unclear. The aim of this study was to investigate genomic differences between ER/PRpos HER2neg (PRpos) and ERpos PR/HER2neg (PRneg) MBC through circulating tumor DNA (ctDNA) profiling in a large multicenter consortium.

Methods: This retrospective study analyzed a cohort of 1089 patients at Weill Cornell Medicine,

Northwestern University, Massachusetts General Hospital, and Washington University in St. Louis with HER2neg MBC and ctDNA testing by Guardant360. Oncogenic pathway status (i.e., RTK, RAS, RAF, MEK, NRF2, ER, WNT, MYC, P53, cell cycle, notch, and PI3K) was defined based on previous research (Sanchez-Vega et al. Cell, 2018). Associations across single nucleotide variations (SNVs), copy number variations (CNVs), pathway classification, and ER/PR status were tested by multinomial logistic regression and corrected for significant clinical characteristics (i.e., lines of treatment, metastatic sites). Prognosis was analyzed through Cox regression for overall survival (OS) defined from time of ctDNA collection.

Results: Among the 1089 analyzed patients, PRpos was the most represented subtype (N:580, 53%), followed by PRneg (N:300, 28%) and Triple Negative (TNBC) (N:209, 19%). In the hormone receptor positive subgroup, bone (N:663, 75%), liver (N:323, 37%) and lymph nodes (N:314, 36%) were the main sites of distant involvement. The TNBC group was exposed to significantly fewer lines of therapy (RRR:0.37, $P = 0.005$ for ≥ 5 lines). As compared to PRneg, TNBC had less frequent and PRpos had more frequent bone involvement (RRR:0.44, $P < 0.001$ and RRR:1.80, $P < 0.001$, respectively) and less frequent liver involvement (RRR:0.64, $P = 0.019$ and RRR:0.71, $P = 0.020$, respectively for TNBC and PRpos). After multivariable analysis, a significant difference with respect to PRneg was observed in SNVs for the PI3K and P53 pathways for TNBC (RRR 0.49 $P = 0.013$ and RRR 4.06 $P < 0.001$, respectively) but not for PRpos. On a single gene level, a lower incidence in CDH1 SNVs (RRR 0.09 $P = 0.036$) and a higher incidence of ESR1 SNVs (RRR 0.09 $P = 0.036$) was present in PRpos compared to PRneg. TNBC, on the other hand, was characterized by a lower prevalence of KRAS SNVs (RRR 0.09 $P = 0.036$) and PIK3CA SNVs (RRR 0.25 $P < 0.001$) and a higher prevalence of TP53 SNVs (RRR 0.09 $P < 0.001$). No ESR1 mutations were detected in TNBC. Median OS was 15 months (mo) for TNBC, 21 mo for PRneg and 31 mo for PRpos ($P < 0.001$). The differential prognostic impact of ctDNA features on OS was then analyzed across the PRpos and PRneg subpopulations. ESR1 SNVs was prognostic for both subgroups in univariable analysis (HR 2.19 $P < 0.001$ and HR 1.96 $P = 0.001$ for PRpos and PRneg, respectively). In multivariable analysis corrected for lines of therapy, ESR1 SNVs retained its significance only in the PRpos subgroup (HR 1.41 $P = 0.021$) together with NF1 SNVs (HR 2.04 $P = 0.034$). On the other hand, TP53 SNVs had a significant impact on OS in the PRneg subgroup (HR 2.02 $P = 0.014$).

Conclusions: Our study confirmed the prognostic impact of PR status in ER positive, HER2 negative MBC. Moreover, it suggested a differential profile in terms of ctDNA-detectable genomic features and their impact on survival, including well-established markers such as ESR1 SNVs, with a potential relevance for disease subtyping and future algorithms for drug development trials.

PO4-15-05

Genomic characterization and molecular predictive biomarkers for chemotherapy in a real-world population with metastatic triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

E. Olsson. Uppsala University Hospital, Uppsala University, Uppsala, Uppsala Lan, Sweden

H. Lindman. Uppsala University Hospital, Uppsala, Sweden

E. Digkas. Uppsala University Hospital, Uppsala University, United States

V. Thurfjell. Uppsala University Hospital, United States

H. Mir Ali. Kalmar Hospital, United States

U. Krüger. Kalmar Hospital, United States

A. Wennstig. Sundsvall Hospital, Umeå University, United States

M. Sundqvist. Kalmar Hospital, United States

A. Valachis. Örebro University Hospital, Örebro, Sweden

Background: The genomic landscape of metastatic triple-negative breast cancer (mTNBC) in a real-world population is poorly defined and despite recent advances in precision oncology, molecular biomarkers for chemotherapy are largely lacking. The presence of specific genomic alterations and alterations in oncogenic pathways have the potential to provide prognostic as well as predictive information for chemotherapy, which remains the backbone treatment strategy for mTNBC.

Methods: We conducted next-generation sequencing (NGS) with the FoundationOne CDx panel on tissue from the primary tumor and/or metastasis of 112 consecutive patients with mTNBC that were treated between 1998 and 2019 at 4 different Swedish hospitals. Every genomic alteration was, if applicable, subdivided into 1 of 10 canonical oncogenic pathways and noted for its involvement in the homologous recombination pathway (HRP). Frequently altered genes and pathways were then correlated with overall survival (OS) and evaluated regarding their association with progression-free survival (PFS) and response rate (RR) in patients treated with different chemotherapy agents. Tumor samples of patients with rapid progression or exceptional response to chemotherapy underwent exploratory comparison with regards to frequently altered genes and pathways and known clinical prognostic factors were compared between the two patient groups.

Results: After excluding 15 patients due to insufficient quantity/quality of tumor tissue or absence of clinical data, 97 patients were analyzed. The median age at diagnosis of metastatic disease was 61 (range: 28-90), 80 % had visceral disease and 26 % received platinum-based chemotherapy in the first line setting. The most frequently altered genes were: TP53 (82 %), RAD21 (25 %), PIK3CA (23 %), MYC (22 %) and BRCA 1 or 2 (16 %). The most frequently altered pathways were TP53 (86 %), PI3K (60 %), RTK/RAS (47 %) and cell cycle (36 %). In total, 26 % of patients had an alteration in the HRP. None of the most frequently occurring genomic alterations were associated with OS. Variants of clinical significance in the HRP and BRCA1/BRCA2 genes were associated with a longer PFS in patients treated with platinum-based chemotherapy in the first line setting (HR 0.12-0.84 and 0.12-0.92). Exceptional responders to chemotherapy exhibited a more favorable clinical profile than rapid progressors (median age 51.5 vs 66.5, median Charlson comorbidity index 0.5 vs 3) whereas some numerical difference in the genomic profiling in terms of genomic alterations in MYC and

RAS/RTK pathways (more often in exceptional responders) could be observed.

Conclusions: We found no genomic alteration with prognostic significance in a cohort of mTNBC patients treated with chemotherapy in a real-world setting. Somatic variants of clinical significance in BRCA 1 and 2 and other HRP-related genes seem to define subgroups of patients with mTNBC that respond favorably to platinum-based chemotherapy. Further research into the genomic landscape of tumors from patients with rapid progression or exceptional response to specific treatment strategies can provide insights into mechanisms of resistance and identify new predictive biomarkers.

PO4-15-06

Genomic landscape characterization after exposure to cyclin dependent kinase 4/6 inhibitors: a retrospective multi-institutional consortium analysis.

Presenting Author(s) and Co-Author(s):

L. Pontolillo. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, United States

C. REDUZZI. Weill Cornell Medicine, United States

A. Davis. Washington University in St Louis School of Medicine, United States

L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States

K. Clifton. Washington University in St Louis School of Medicine, United States

W. Hensing. Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA., United States

M. Velimirovic. Cleveland Clinic, United States

A. Shah. Northwestern University, United States

J. Donahue. Weill-Cornell, New York, New York, United States

L. Munoz Arcos. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, New York, United States

C. Dai. MGH Cancer Center, United States

J. Keenan. Cancer Center, Massachusetts General Hospital, United States

A. Behdad. Pathology and Laboratory medicine, Cleveland Clinic, United States

W. Gradishar. Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, United States

E. Bria. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

M. Cristofanilli. Weill Cornell Medicine, United States

Background: Limited data are available to determine the best therapeutic strategy for hormone-receptor positive (HR+) HER2 negative (HER2-) advanced breast cancer (ABC) after progression on cyclin dependent kinase 4/6 inhibitors (CDK4/6i). The aim of this study was to characterize the genomic and prognostic profile of patients (pts) that experienced disease progression after first-line therapy with a CDK4/6i. Methods: The study retrospectively analyzed a multi-institutional cohort of 75 patients (pts) with HR+/HER2- ABC after experiencing progression on first-line endocrine therapy (ET) with CDK4/6i and characterized by circulating tumor DNA (ctDNA) next-generation sequencing (Guardant 360). Oncogenic pathways (i.e., RTK, RAS, RAF, MEK, NRF2, ER, WNT, MYC, p53, cell cycle, notch, and PI3K) were defined based on previous research (Sanchez-Vega et al. Cell, 2018). Associations across single

nucleotide variations (SNVs), copy number variations (CNVs), and pathway classification were tested by uni- and multivariable logistic regression with respect to a CDK4/6i naïve group comprising 247 patients with HR+/HER2- ABC (control). Prognosis was analyzed through Cox regression for overall survival (OS). Result: Our study cohort included 75 ABC pts who experienced progression after first line CDK4/6i plus ET: 43 pts (57.3%) were treated with ET while 31 (41.3%) with a non-ET- second line therapy. The most common histology was invasive ductal carcinoma (70.6%), 37.3% of pts were negative for progesterone expression and 26.7% had de novo metastatic disease. The PI3K (33.3%), p53 (28%) and ER (25.3%) pathways were the most mutated in the CDK4/6i-treated cohort. Comparing our population with a CDK4/6i naïve cohort (N=247), the multivariate analysis showed a higher prevalence in the study cohort of SNVs mutations in: i) ESR1 gene [Odds ratio (OR) 2.93; p=0.005]; ii) cell-cycle pathway (OR 4.24; p=0.033); iii) ER pathway (OR 2.04; p= 0.034). Moreover, in the study cohort a numerical but not significant increase of RB1 SNVs was also observed. Multivariable analyses of the 43 pts that received ET second line therapy showed a negative prognostic impact with TP53 SNVs in both progression-free survival (PFS) [Hazard ratio (HR) = 3.34; 95% CI: 1.15-9.66, p=0.026] and OS (HR = 3.85; 95% CI: 1.52-9.77, p=0.005). The prognostic role of p53 pathway mutations was also confirmed for both PFS (HR = 4.71, 95% CI: 1.64-13.50; p=0.004) and OS (HR = 3.25; 95% CI: 1.27-8.3; p=0.014). The potential interaction between the prognostic oncogenic pathways and the outcome was investigated according to the treatment strategy (ET vs non-ET). A consistent impact was observed across the above prognostic pathways both for PFS and OS. A numerical difference was observed in terms of PFS in pts with p53 pathway mutations that underwent non-ET second line. Conclusions: The genomic landscape of progressive disease after CDK4/6i exposure is significantly different from the genomic alterations detectable in treatment-naïve pts, which could potential impact future treatment strategies for patients with disease progression after adjuvant CDK4/6i exposure. Our data suggest that the choice of second-line treatment could potentially be guided by the identification of actionable mutation by ctDNA, although further prospective studies are needed to validate the clinical utility of this approach.

PO4-15-07

ESR1 mutations emerging during neoadjuvant endocrine therapy in postmenopausal ER+/HER2- early breast cancer patients: prevalence and prognostic impact

Presenting Author(s) and Co-Author(s):

J. Sandoval. Geneva University Hospitals, Geneva, Switzerland

H. Salaun. Institut Curie, United States

S. Renault. Institut Curie, United States

M. Carausu. Institut Curie, United States

A. Rampanou. Institut Curie, United States

C. Hego. Institut Curie, United States

m. Carton. institut curie, United States

L. Cabel. Institut Curie, France

J. Pierga. Institut Curie & Université Paris Cité, Paris, France

R. Geiss. Institut Curie, United States

F. Bidard. Institut Curie, Paris, France

F. Lerebours. Institut Curie, United States

Background

Neoadjuvant endocrine therapy (NET) is currently used in several clinical trials to select patients for chemotherapy de-escalation. However, exposure to NET may induce/select endocrine-resistant tumor cell clones harboring ESR1 mutations (ESR1_{mut}), which are well known to confer poor prognosis and ET resistance to aromatase inhibitors in the metastatic setting. In this study, we sought to determine the frequency and prognostic significance of ESR1_{mut} after NET in postmenopausal patients with HR+/HER2- early breast cancer.

Materials and methods

We conducted a retrospective study in postmenopausal patients with ER+/HER2-early breast cancer diagnosed between 2000 and 2012 and treated with NET for at least three months at Institut Curie Hospitals (Paris and Saint Cloud, France). Exclusion criteria were: stage IV breast cancer, no surgery of the primary tumor, neoadjuvant radiation therapy, chemotherapy or targeted therapies.

DNA from post-NET surgical samples was extracted using the phenol-chloroform DNA isolation method. ESR1_{mut} were detected with multiplex drop-off ddPCR assay previously used in the PADA-1 trial (targeting clustered hotspot mutations in exon 8 and 5, using a BioRad QX100 system and analyzed with QuantaSoft v.1.7.4 software). Associations between ESR1_{mut} detection and patient outcomes, distant relapse-free interval (DRFI) and overall survival (OS) were analyzed using the Kaplan-Meier method and Cox proportional hazards models.

Results

N=143 patients treated with NET were eligible for this study, of whom N=136 had interpretable ESR1_{mut} detection results. Median age at NET initiation was 75.4 (IQR 66.6-81.3) years. The median duration of NET was 6.6 months (IQR 5.8 – 7.6). Most patients were treated with aromatase inhibitors (n=107, 75.9%), while 24.1% (n=34) received tamoxifen. The median time

between diagnosis and surgery was 7.6 (IQR 6.4 – 8.7) months.

ESR1_{mut} were detected in post-NET surgical samples in N=7 patients (5.2%). Baseline clinicopathological characteristics were not associated with post-NET ESR1_{mut} detection status. The median follow-up for DRFI and OS was 11.0 (IQR 7.7 – 13.8) and 18.7 (IQR 13.3 – 18.7) years, respectively. The median DRFI was 6.7 (95%CI [4.9-NR]) vs 14.0 [10.7-NR] years in ESR1_{mut} and ESR1_{wt} patients, respectively (HR=1.9 [0.6-6.2], p=0.29). Similarly, median OS was numerically shorter in patients with post-NET ESR1_{mut} (6.8 [3.7-NR] vs 9.8 [8.5-NR]; HR=2.0 [0.9-4.7], p=0.09).

Conclusions

Post-NET tumors are enriched in ESR1_{mut} subclones, which represent a potentially lethal threat in the context of aromatase inhibitor-based adjuvant endocrine therapy. Although the limited sample size of our study did not allow reaching statistical significance, our results suggest, for the first time, worse survival outcomes for patients with a ESR1_{mut} detected in post-NET primary tumors. The role of next-generation oral SERDs as neoadjuvant or adjuvant endocrine therapy to prevent ESR1_{mut}-related relapses remains to be determined.

PO4-15-08

Comprehensive genomic profiling of HER2-low advanced breast cancers

Presenting Author(s) and Co-Author(s):

A. Kahn. Yale Cancer Center, Yale University, United States

E. Sokol. Foundation Medicine Inc, United States

J. Ross. Foundation Medicine Inc., United States

M. Pelletier. Foundation Medicine Inc., United States

N. Fischbach. Yale University, United States

L. puzstai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

m. lustberg. Yale Cancer Center, New Haven, Connecticut, United States

Background:

With the recent approval of the HER2-targeted antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-Dxd) for the treatment of HER2-low advanced breast cancers (aBC), [defined as HER2 immunohistochemistry (IHC) 1+, or 2+ with negative in-situ hybridization (ISH)], there is interest to understand whether this population represents a distinct molecular entity and if there are additional biomarkers that can improve patient selection for these therapies. Here, we examined 2086 aBC cases profiled with comprehensive genomic profiling (CGP) stratified by HER2 status (negative, low, and positive) and hormone receptor (HR) status (positive and negative).

Methods:

Hybrid-capture CGP targeting 324 genes was performed on advanced BC samples (FoundationOne@CDx). HER2 IHC status was abstracted from pathology reports while HER2 amplification status was abstracted from CGP.

Results:

We examined 2086 samples of aBC patients distributed as HER2-negative (n=657; IHC 0), HER2-low (n=1012, IHC 1+, 2+ ISH non-amplified), and HER2-positive (n=417; HER2 IHC 3+). HER2-low patients were significantly older than HER2-negative patients (median 60 v 57 years, p=0.0006). HER2-low cases were more common in HR-positive than in HR-negative disease (67% vs 46%, respectively).

Overall, characteristics were generally similar for genetic ancestry and TMB-H frequency across all HER2-statuses. MSI-H was rare across all HER2-statuses groups. HER2-low cases were more likely to have alterations in GATA3 (12.6% v 6.5%), ESR1 (12.4% v 7.8%), FGFR2 (4.0% v 1.8%), AR (1.1% v 0.2%), and CDH1 (15.3% v 11.6%) and less likely to harbor alterations in TP53 (44.0% v 62.4%), RB1 (6.8% v 12%), NF1 (5.5% v 9.3%), and BRCA1 (3.0% v 5.2%) when compared to HER2-negative. Some genes showed a consistent pattern of decreased frequency as HER2-IHC expression decreased from HER2-positive to HER2-low and to HER2-negative (e.g. AR alterations seen in 2.6%, 1.1% and 0.2%, respectively) while others had a increasing frequency pattern (e.g. RB1 alterations observed in 2.4%, 6.8% and 12.0%; BRCA1 seen in 1.7%, 3% and 5.2%, respectively). However, some genomic characteristics were unique to the HER2-low population (e.g. TP53 seen in 69.5% of HER2-positive and 62.4% of HER2-negative, but at a lower frequency of 44% in HER2-low cases) [Table 1].

Within the HR-positive subgroup, a lower frequency of NF1 (4.4% v 10.4%), TP53 (30.6% v 41.1%), and RB1 (4.4% v 8.0%) and a higher frequency of AR (1.0% v 0.0%) and GATA3 (16.2% v 10.9%) were observed in HER2-low vs HER2-negative cases, while within the HR-negative subgroup there was a higher frequency of GATA3 (1.2% v 0.7%) and AR (1.2% v 0.4%) and trending lower frequency of TP53 (85.7% v 90.8%) and RB1 (14.3% v 17.4%) in the HER2-low vs. HER2-negative cases. Mutations in homologous recombination repair genes (BRCA1, BRCA2, PALB2) were less frequent in HER2-low cases vs. HER2-negative cases overall (8.4% v 10.7%) and in the HR-positive (3.6% v 5.6%) and HR-negative subgroups (10.6% v 17.4%). Consistent with this, the rate of scar-based HRD signature (HRDsig) was lower in the HER2-low vs. HER2-negative subgroup (15.9% v 20.4%, p=0.02).

Conclusions:

These data suggest the HER2-low aBC has distinct genomic alterations before and after stratification by HR-status when compared to HER2-negative and HER2-positive aBC cases. Higher prevalence of some potentially actionable alterations in HER2-low cases, including FGFR2, AR, and ESR1, may aid in patient selection and drug development considering new combination approaches.

Table 1

	HER2-low		HER2-negative
	<i>Genomic alterations more common in HER2-low</i>		
GATA3	12.6%		6.5%
ESR1	12.4%		7.8%
FGFR2	4.0%		1.8%
AR	1.1%		0.2%
CDH1	15.3%		11.6%
	<i>Genomic alterations less common in HER2-low</i>		
TP53	44.0%		62.4%
RB1	6.8%		12%
NF1	5.5%		9.3%
BRCA1	3.0%		5.2%
	HER2-positive	HER2-low	HER2-negative
	<i>Decreasing frequency of genomic alterations as HER2-IHC expression decreases</i>		
AR	2.6%	1.1%	0.2%
	<i>Increasing frequency of genomic alterations as HER2-IHC expression decreases</i>		
RB1	2.4%	6.8%	12%
BRCA1	1.7%	3%	5.2%
	<i>Unique pattern of genomic alterations to HER2-low</i>		
TP53	69.5%	44%	62.4%

Summary of comprehensive genomic profiling alterations observed in HER2-low aBC compared to HER2-positive and HER2-negative cases

PO4-15-09

Unraveling the influence of progesterone receptor status on endocrine therapy sensitivity: insight from epigenetic and fragmentomics ctDNA profiling in estrogen receptor positive, HER2 negative metastatic breast cancer (MBC)

Presenting Author(s) and Co-Author(s):

L. Foffano. Department of Medicine (DAME), University of Udine, Udine, Italy., United States

E. Molteni. Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

A. Dri. Department of Medicine, University of Udine, Italy; Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy., United States

A. Franzoni. Institute of Human Genetics, University of Udine, United States

L. Cucciniello. Unit of Medical Oncology and Cancer Prevention, Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, United States

I. da Ros. IRCCS CRO, United States

S. Buriolla. Department of Medicine, University of Udine, Italy; Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

s. bolzonello. IRCCS CRO, United States

C. Noto. Department of Medicine, University of Udine, Italy; Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy., United States

S. Russo. Department of Medical Oncology, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC) Udine, Italy, Italy

S. Spazzapan. Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

E. Nascimbeni. Clinical Trial Office, CRO di Aviano, National Cancer Institute, IRCCS, 33081 Aviano, Italy, Italy

B. Pastò. IRCCS CRO, United States

G. Targato. Department of Medicine, University of Udine, Italy; Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

S. Della Rossa. Department of Medicine, University of Udine, Italy; Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy., United States

M. Bonotto. Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

A. Minisini. Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

G. Damante. Ospedale Santa Maria della Misericordia, Azienda Sanitaria Universitaria Friuli Centrale, United States

B. Belletti. Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, United States

L. Gerratana. Medical Oncology and Cancer Prevention, Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy., United States

F. Puglisi. Department of Medicine (DAME), University of Udine, Udine, Italy and Department of Medical Oncology - CRO Aviano, National Cancer Institute, IRCCS, Aviano, Friuli-Venezia Giulia, Italy

Background: In patients (pts) with estrogen receptor (ER) positive (pos), HER2 negative (neg) MBC, the absence of progesterone receptor (PR) expression is generally associated with a poorer endocrine therapy (ET) response and an unfavorable prognosis. However, real-time molecular changes during ET according to PR status are still not fully understood. The aim of this study was to examine the prognostic impact of PR and its association with the methylation levels of ESR1 promoters A (promA) and B (promB) at different timepoints in pts with ERpos HER2neg MBC who received first-line ET.

Methods: Pts were enrolled in the prospective multicenter MAGNETIC.1 trial (CRO-2018-56) between January 2018 and January 2023. As first-line ET, pts received either fulvestrant or AIs with or without CDK4/6 inhibitors (CDK4/6i) as first-line ET. ctDNA samples were collected at baseline (T0) and at 3-month intervals (T3 and T6) and analyzed through methylation-specific (MS) droplet digital PCR (ddPCR), ddPCR fragmentomics and next generation sequencing (NGS). Clinico-pathological differences across the PR expression spectrum were analyzed using Fisher's exact test. Matched pairs variations across timepoints (T0, T3, T6) of ACTBfragments distribution and ESR1 promA and promB were tested through Wilcoxon signed rank test.

Results: Out of the 111 enrolled pts, 28 had PRneg MBC, of which 20 had an invasive ductal carcinoma (IDC) histotype, and 10 were diagnosed as de novo disease. Bone was the most common metastatic site both in the PRpos and PRneg subgroups (75% vs 73%), most pts received ET+CDK4/6i (96% vs 95%).

ESR1 and PIK3CA mutations were respectively detected in 8% and 6%, and in 23% and 25% pts respectively for PRpos and PRneg. The prognostic impact of PR status was evident for both PFS (median 38 mos and 14 mos respectively for PRpos and PRneg, $P = 0.0048$) and OS (median not reached and median 33 mos respectively for PRpos and PRneg, $P = 0.001$). A significant increase in promB was observed at T3 vs T0 and at T6 vs T3 in the PRpos subgroup (respectively $P=0.0158$ and $P < 0.001$) but not in the PRneg. When comparing T6 to T0, no significant differences were observed regardless of PR status. At T3, significant decreases were observed in both the PRpos and PRneg populations for ACTBshort ($P < 0.001$ and $P=0.03$, respectively), ACTBmedium ($P=0.0049$ and $P= 0.035$, respectively) and ACTBlong ($P < 0.001$ and $P < 0.001$, respectively), compared to T0. In the comparison of T6 to T3, a significant variation in ACTBshort levels was observed in both subgroups ($P < 0.001$ for PRpos and $P=0.012$ for PRneg). while a significant reduction in ACTBmedium levels was observed only in the PRpos population when comparing T6 to T0 ($P < 0.001$).

Conclusions: PRneg status was confirmed as an unfavorable prognostic factor with respect to PRpos both for PFS and OS, potentially due to different ET sensitivity. Epigenetic ctDNA profiling revealed different dynamics of ESR1 promB between PR-positive and PR-negative MBC, suggesting a distinct role of ESR1 in the onset of ET resistance within the two subgroups.

PO4-15-10

HER2-low Status among Patients with Li-Fraumeni Syndrome and Breast Cancer

Presenting Author(s) and Co-Author(s):

L. Auresco. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

R. Colombo Bonadio. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

V. Petry. Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil, United States

L. Testa. Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil, United States

C. Moniz. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

J. Dos Santos. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

M. Del Pilar Estevez-Diz. Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil

R. Santa Cruz Guindalini. Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil, Brazil

Background:

The HER2-low status has gained significance as a target for HER2-directed antibody drug conjugates in breast cancer. It is observed in approximately 60% of hormone receptor-positive (HR+) tumors and 30% of hormone receptor-negative (HR-) tumors. Some studies suggest that the HER2-low status by itself does not influence tumor biology or prognosis. Breast cancer in the context of Li-Fraumeni (LFS) syndrome has been characterized by an enrichment in HER2-positive (HER2+, defined as +3 in the immunohistochemistry [IHC] or +2 in the IHC with positive in situ hybridization [ISH]) disease. Considering this, we aimed to evaluate whether LFS patients with breast cancer also exhibit a higher frequency of HER2-low status.

Methods:

This retrospective-prospective cohort study included patients diagnosed with breast cancer who had a pathogenic/likely pathogenic TP53 germline variant and were treated at two cancer institutions between 1999 and 2023. The primary objectives were to determine the overall proportion of HER2-low status and its distribution according to hormone receptor status. HER2-low was defined as IHC +1 or IHC +2 with negative ISH.

Results:

Fifty-three patients (52 female and 1 male) were included in the study. The most common germline TP53 variant was the TP53 R337H (71.7%). The median age at breast cancer diagnosis was 39 years (range 21–62). The majority of patients had breast cancer of no special type (79%) or lobular carcinoma (11.3%), grade 2 (54.7%) or grade 3 (24.5%), and stage I-II (67.9%). Breast cancer subtypes would classically be classified as HER2+ in 34%, HR+HER2- in 58.5%, and triple-negative breast cancer (TNBC) in 7.5% of the patients. Biopsy samples were obtained from the primary tumor in 96.3% of the cases and from lymph nodes in 3.7%. Overall, 15.1% of the cases exhibited HER2-low status, 34% were HER2-negative, and 17% were HER2-negative without IHC details (Table). In a hypothetical scenario assuming all cases without IHC details were HER2-low, the maximum estimated frequency of HER2-low status would be 32.1%. Among HR+ patients, 25.8% had HER2-low status, 45.2% were HER2-negative, and 29% were HER2-negative without IHC details. All four patients with TNBC exhibited HER2-zero status.

Conclusion:

Contrary to our initial hypothesis, the frequency of HER2-low status in this cohort of LFS patients with breast cancer was lower than anticipated. These results suggest that while breast cancer developing in the context of germline TP53 variants appears to be associated with HER2 amplification, it does not impact lower expressions of HER2. This observation reinforces the concept that HER2-low status does not seem to play a significant role as a driver of tumorigenesis. Further expansion of the study cohort and pathology analysis is planned to confirm these findings.

Table

	HER2-positive n (%)	HER2-low n (%)	HER2-zero n (%)	HER-negative without IHQ detail n (%)
Overall cohort (n=53)	18 (34%)	8 (15.1%)	18 (34%)	9 (17%)
HR+HER2- BC (n=31)	-	8 (25.8%)	14 (45.2%)	9 (29%)
TNBC (n=4)	-	0 (0%)	4 (100%)	0 (0%)

HER2 status overall and according to hormone receptor-status (for HER2-negative patients). Abbreviations: IHQ, immunohistochemistry; HR+HER2- BC, hormone receptor-positive HER2-negative breast cancer; TNBC, triple-negative breast cancer.

PO4-15-11

**HER2 STATUS AND TUMOR HETEROGENEITY IN INVASIVE BREAST CARCINOMAS:
CLINICAL PATHOLOGICAL IMPACT**

Presenting Author(s) and Co-Author(s):

K. Prigenzi. São Paulo Federal University, United States

L. Gonzalez Porta Nova. São Paulo Federal University, United States

A. Filho. São Paulo Federal University, United States

A. da Cruz. São Paulo Federal University, United States

L. Barbosa. São Paulo Federal University, United States

A. Waitzberg. Universidade Federal de São Paulo, São Paulo, Sao Paulo, Brazil

Human epidermal growth factor receptor 2 (HER2) is a major player in breast carcinogenesis with a range of 15-20% of cases harboring gene amplification and overexpression turning the tumor eligible to over eight anti-HER2 drugs in the past 15 years. Recently, novel anti-HER2 antibody-drug conjugates (ADCs) treatment was recently approved to metastatic breast cancer bearing some HER2 expression albeit not due to gene amplification. Immunohistochemically classified, by ASCO-CAP Guidelines (2018), as 1+ cases were enrolled in clinical trials and benefited by the addition of ADCs to chemotherapy. Despite being classified as HER2 negative, most tumors exhibit detectable levels of HER2 protein, reinforcing the importance of HER2 expression evaluation. HER-2 intratumoral heterogeneity (ITH) is reported in up to 40% of breast cancers and is defined as the coexistence of subpopulations of tumor cells with different HER2 gene or protein expression. In this scenario, it becomes very important to evaluate the spectrum of HER-2 expression in correlation with pathological factors as ITH is associated with poor prognosis and anti-HER2 resistance. We designed a retrospective linear study to reanalyze all HER2 immunohistochemical core biopsy slides of patients with primary invasive breast carcinomas (IBC) diagnosed and treated at São Paulo Federal University Hospital between 2019 and 2023. Clinical variables (age, laterality, tumor size by ultrasound imaging, BI-RADS) were collected from clinical files. HER2 slides were reviewed by three observers and reported regarding status by ASCO-CAP 2018 guidelines, HER2 heterogeneity and patterns. Statistical analyses were performed with Chi-Square test of independence, Fisher's exact test and Mann-Whitney U test using IBM® SPSS® Statistics (26.0) software. 353 cases were included; the mean age of the patients at the time of diagnosis was 58 years old. 191 cases (54,1%) were left sided and 162 cases (45,9%) were right sided. Regarding BI-RADS report, the major category was 4 (140 cases), followed by 5 (119 cases). Out of the 164 patients who underwent clinical follow-up at our institute, 14 deaths were reported. Concerning pathological features, IBC of no special type was the prevalent histological subtype with 304 cases (86,1%), followed by invasive lobular carcinoma, with 26 cases (7,4%). 296 cases (83,9%) were HER2 negative and 42 (11,9%) were HER2 positive; 15 cases were HER2 2+ (4,2%). Amongst negative cases, 235 were HER2 0+ and 61 were HER2 1+. Considering ITH, 287 cases (81,3%) were HER2 homogenous with 0+ score as the most prevalent, presenting with 232 cases (80%). 66 cases (18,7%) had ITH, with 1+ as the most prevalent primary score, with 34 cases (51,5%), followed by 3+, with 17 cases (25,8%). Not only HER2 positive carcinomas, but also the presence of heterogeneity in HER2 expression was associated with death outcome ($p=0,003$ and $p=0,001$, respectively). Also, HER2 positive IBC had larger tumor size compared to HER2 negative carcinomas (mean size of 25,6 mm x 31,3 mm, respectively; $p=0,012$); HER2 heterogeneity showed no statistical significance when associated with tumor size ($p=0,165$). We conclude that ITH is prevalent in HER2 expression and should be addressed in pathology

reports since it may play an additional role in tumor progression and drug response, especially in the ADCs scenario.

PO4-15-12

Personalized circulating tumor DNA monitoring to predict response to neoadjuvant therapy in patients with early-stage breast cancer

Presenting Author(s) and Co-Author(s):

M. George. Rutgers Cancer Institute of New Jersey, United States

T. Meghal. RWJBH-Monmouth, United States

C. Omene. Rutgers Cancer Institute of New Jersey, United States

E. Kalashnikova. Natera, San Carlos, California, United States

J. Fielder. Natera INC, United States

N. Ohri. Rutgers Cancer Institute of New Jersey, United States

S. Kumar. Rutgers Cancer Institute of New Jersey, United States

V. Burkovskaya. Advent Health, United States

P. Patel. Advocate Health, United States

A. Young. Advent Health, United States

M. Racenstein. Burrell College of Osteopathic Medicine, United States

T. Bauman. Advocate Health Good Shepherd, United States

W. Mchayleh. Advent Health, United States

D. Toppmeyer. Rutgers Cancer Institute of New Jersey, United States

S. Ganesan. Rutgers Cancer Institute of New Jersey, United States

B. Rosen. Advent Health, United States

A. Rodriguez. Natera, United States

M. Liu. Natera, United States

Introduction

Longitudinal ctDNA testing offers a minimally invasive approach for monitoring treatment response in patients with breast cancer (BC). In this study, we evaluated whether serial ctDNA testing during neoadjuvant therapy (NAT) can provide an early indication of treatment response or resistance and disease progression.

Methods

In this real world study, longitudinal blood samples collected from 159 patients with stage I-III BC were analyzed using a personalized, tumor-informed ctDNA assay (Signatera™ bespoke mPCR-NGS assay). Of the 159 patients, 157 received standard of care NAT; the remaining 2 patients were treated with endocrine therapy only in the neoadjuvant setting. Blood samples were collected at the time of diagnosis from 71 patients (baseline) and longitudinally during treatment from 159 patients (median time between time points: 1.5 months). ctDNA status and dynamics were correlated with clinicopathological features and surgical outcomes available at the time of data cut off.

Results

At baseline, ctDNA was detected in 72% (51/71) of patients. Baseline ctDNA detection rates varied based on histologic subtypes: 82% (28/34) in patients with triple negative breast cancer, 88% (15/17) in patients with HER2+ disease and 40% (8/20) in patients with ER+HER2- BC.

ctDNA was detectable at baseline in 72% (26/36) of patients with clinical T1-2 disease and 92% (11/12) of patients with T3-4 disease. ctDNA was detected in 64% (16/25) of patients with clinical N0, whereas among patients with at least one positive lymph node, ctDNA was detected in 92% (22/24). At baseline, 65% (31/48) of patients with low/intermediate-grade disease were ctDNA-positive, while 81% (25/31) of patients with high-grade disease were ctDNA-positive. Similarly, 83% (24/29) of patients with high levels (>20%) of Ki67 expression had detectable ctDNA prior to treatment initiation, while only 22% (2/9) of those with low level (< 20%) of Ki67 expression had ctDNA detected.

Surgical outcomes were available for 22 patients of whom 16 had achieved pathologic complete response (pCR). While 3/16 pts were ctDNA negative at baseline, all of the remaining cases except one patient with baseline ctDNA detection and serial measurements (11/12) became ctDNA negative by the end of two months of treatment. Despite achieving pCR, one patient with inflammatory ER+HER2+ BC remained ctDNA positive before and after the surgery, which informed a change in the adjuvant treatment strategy. Among those with residual disease (pT1c-T3), 28% (7/25) remained ctDNA positive after two months of NAT. Association between ctDNA dynamics and surgical outcomes of the remaining 137 patients will be presented at the time of the conference.

Conclusions

This real world study demonstrates the prevalence of ctDNA detection and dynamics in patients with eBC treated with NAT. ctDNA monitoring during NAT can facilitate real-time assessment of treatment response and serve as an early indicator of subsequent pCR to NAT.

PO4-16-01

EZH2 is Overexpressed in Invasive Carcinoma and DCIS in both BRCA1 and BRCA2 Mutation Carriers

Presenting Author(s) and Co-Author(s):

T. Domingos. Department of Pathology, Brigham and Women's Hospital, United States

R. Bonfim Pimenta Peixoto. Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA, United States

R. Fonseca Abreu. Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA, United States

A. Patel. Department of Pathology, Brigham and Women's Hospital, United States

K. Taneja. Department of Pathology, Brigham and Women's Hospital, United States

M. Moore. Dana-Farber Cancer Institute, United States

C. Kleer. Department of Pathology, University of Michigan, Ann Arbor, Michigan, United States

D. Dillon. Brigham and Women's Hospital, Breast Oncology Program, Susan F. Smith Center for Women's Cancers, Dana-Farber Brigham Cancer Center; Harvard Medical School, United States

Background

The transcriptional repressor EZH2 (Polycomb Group Protein Enhancer of Zeste Homologue 2) is overexpressed in multiple neoplasms including breast cancer where it associates with high proliferation, aggressive features and poor prognosis and is of interest as a potential therapeutic target. EZH2 nuclear expression in breast cancer has been shown to correlate specifically with high tumor grade and basal-like histologic features but has not been well studied in cancers from BRCA carriers. Here we evaluate the expression of EZH2 protein in BRCA-associated invasive breast carcinomas and precursor lesions.

Methods

Eighteen cases of invasive breast cancer in consented BRCA carriers (8 BRCA1 and 10 BRCA2) treated at Dana Farber Cancer Institute from 2001-2019 were reviewed by two pathologists (TAD and RBPP). Histopathologic features (histologic subtype, nuclear grade, mitotic score) and presence of precursor lesions were recorded. Immunohistochemistry for EZH2 was performed on freshly cut formalin-fixed paraffin-embedded tissue sections (1-3 sections/case) using a monoclonal antibody against EZH2 (D2C9, Cell Signaling). Nuclear EZH2 expression was scored as negative (score=1, no staining); weak (score 2, < 25%); moderate (score=3, 25–75%); and strong (score=4, >75%), of any intensity following published criteria. EZH2 overexpression was defined as scores 3 and 4.

Results

The majority of the invasive carcinomas showed grade III histology (13/18, 72%), as expected. Of 8 BRCA1 cases, 6 were classified as grade III (75%), 1 as grade II, and 1 as grade I (7 cases of invasive ductal carcinoma and 1 case of invasive tubular carcinoma). Of 10 BRCA2 cases, 7 were classified as grade III (70%) and 3 as grade II (30%) (5 cases of invasive ductal carcinoma and 5 cases of invasive carcinoma with ductal and lobular features). The majority of cases (13 of 18, 72%) showed high expression of EZH2 in the invasive carcinoma (6 BRCA1 and 7 BRCA2 cases; 2 grade II and 11 grade III). Of 13 cases with EZH2 overexpression, 6 were ER+/PR+/HER2- and 7 were triple negative, with 9 invasive ductal carcinomas and 4 invasive carcinomas with ductal and lobular features. Of 5 cases with no/low EZH2

overexpression, 1 was ER+/PR+/HER2-, 3 were ER+/PR-/HER2- and 1 was triple negative, with 3 invasive ductal carcinomas, 1 invasive carcinoma with ductal and lobular features and 1 invasive tubular carcinoma. In all cases with adjacent ductal carcinoma in situ (DCIS) (n=14), the pattern of EZH2 expression in the DCIS was identical to that seen in the invasive carcinoma (11 high and 3 low expression). Overexpression of EZH2 was not observed in any other precursor lesions (LCIS, ADH, ALH) or in normal tissue.

Conclusion

EZH2 protein overexpression is seen in the majority of invasive carcinomas in BRCA carriers, both in BRCA1 and in BRCA2. In all cases, the associated DCIS shows the same pattern of expression as the invasive carcinoma, suggesting that overexpression occurs early in tumorigenesis, while tumor cells are still confined within the ducts. The high rate of overexpression of EZH2 in BRCA1- and BRCA2-associated tumors suggests a potential role for EZH2 as a target and/or a biomarker in these cancers.

PO4-16-02

Can high progesterone receptor (PgR) expression identify tumours with low-risk tumour gene expression scores?

Presenting Author(s) and Co-Author(s):

R. Stein. National Institute for Health Research University College London Hospitals, London, England, United Kingdom

R. Wirtz. STRATIFYER Molecular Pathology GmbH, Germany, Germany

A. Marshall. Warwick Clinical Trials Unit, University of Warwick, Coventry, England, United Kingdom

J. Bayani. Diagnostic Development, Ontario Institute for Cancer Research Toronto, Ontario, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto. Toronto, Ontario, Canada, United States

S. Eidt. Institut für Pathologie am St. Elisabeth Krankenhaus Köln-Hohenlind, Germany, Germany

C. Schumacher. St. Elisabeth Hospital, Cologne, Germany

H. Sinn. Pathologie, Universitätsklinikum, Heidelberg, Germany

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

A. Makris. Mount Vernon Cancer Centre, Northwood, England, United Kingdom

I. Macpherson. University of Glasgow - Institute of Cancer Sciences, United Kingdom

L. Hughes-Davies. N/A, Cambridge, United Kingdom

T. Piper. University of Edinburgh, Edinburgh, United Kingdom, United States

M. Sobol. University of Edinburgh, UK, Scotland, United Kingdom

G. Dotchin. University of Warwick, Coventry, England, United Kingdom

H. Higgins. University of Warwick, United States

S. Pinder. School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom

A. Shaaban. Queen Elizabeth Hospital, Birmingham, United States

J. Dunn. University of Warwick, Coventry, England, United Kingdom

J. MS Bartlett. University of Edinburgh, Scotland, United Kingdom, United Kingdom

Background

Strong PgR expression predicts favorable outcomes for ER+ve HER2-ve breast cancer and has been proposed as a surrogate marker to distinguish between IHC-defined luminal A and luminal B subtypes. It is therefore possible that strong PgR expression may be able to predict tumor gene expression test results and independently identify tumors that are unlikely to be chemotherapy sensitive. PgR expression is traditionally determined by immunohistochemistry (IHC). Several validated RNA-based PGR expression tests have been developed that may outperform IHC.

Methods

We compared Oncotype DX RS with Oncotype DX reported PGR in 4 independent datasets which included 407 cases from the OPTIMA prelim trial. We further analyzed 251 OPTIMA

prelim cases which had additional tumor gene expression data. All gene expression assays were performed by the test vendor, including PGR gene expression determined using the Mammatyper assay. PgR IHC was determined in a single laboratory on triplicate tissue micro-arrays using quantitative image analysis including a 10% manual quality control check. We analyzed PGR expression using cutoffs that correspond to approximately 20% staining; the standard Oncotype DX PGR assay is reported as positive if the score is >5.4, corresponding to approximately 1% staining by IHC. We used Spearman's rank correlation coefficient to compare PGR data.

Results

The four Oncotype DX datasets consistently demonstrated that high Oncotype PGR expression was associated with a low RS (table). Combining the 3 validation data sets consisting of 633 cases, 70.9% had high PGR expression of which 92.7% had a an Oncotype RS ≤25. Approximately 50% of cases with low Oncotype PGR expression had an Oncotype RS >25.

Mammatyper and Oncotype PGR were highly correlated ($R_s = 0.9258$, $P < 0.001$) in the OPTIMA prelim dataset ($n=251$), with only 8.4% of tumors having discordant high/low Mammatyper and Oncotype PGR scores. 93.2% of 176 Mammatyper high PGR expression cases had an RS ≤25. The Mammatyper PGR and PgR IHC correlation was weaker ($R_s=0.763$, $P < 0.001$); 87.2% of 211 cases with >20% staining had RS ≤25. PgR IHC staining had a bimodal distribution and there was little effect on the prediction of low RS score up to a 67% cut-off. Mammatyper and Oncotype PGR scores both appear to have a normal distribution. We took advantage of this to perform an exploratory analysis using a higher Mammatyper PGR cutoff . We were able to show superior prediction of a low RS (96.8%) but with a reduced proportion (50.2%) of high PGR score tumors.

High PGR gene expression was weakly associated with low (≤60) Prosigna ROR_PT score and MammaPrint low risk (72.2% and 65.9% respectively) and with Prosigna and MammaPrint luminal A subtype (both 64.8%).

Conclusion

High progesterone receptor gene expression measured using locally performed RNA-based assays may allow the reliable prediction of Oncotype DX low-risk tumours. This analysis provides additional information for the clinical utility of PGR measurement. Additional data will be presented on the optimal PGR cutoff.

OPTIMA prelim is registered as ISRCTN42400492 and funded by the UK NIHR Health Technology Assessment Programme, award number 10/34/01. Views expressed are those of the authors and not those of the HTA Programme, NIHR, NHS or the Department of Health.

Oncotype DX RS and PGR in 4 datasets

Dataset	Cologne (discovery)			OPTIMA			Cologne			Heidelberg		
	RS ≤25	RS>25	n	RS ≤25	RS>25	n	RS ≤25	RS>25	n	RS ≤25	RS>25	n
n	86	22	108	334	73	407	85	28	113	94	19	113
<6.4	51.5%	48.5%	33	50.4%	49.6%	113	50.0%	50.0%	32	61.5%	38.5%	39
≥6.4	92.0%	8.0 %	75	94.2%	5.8%	294	85.2%	14.8%	81	94.6%	5.4%	74

Distribution of RS according to %cases with high or low PGR

PO4-16-03

Ectopic expression of lineage-specific transcription factors in Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Badve. Emory University School of Medicine, United States

J. Hu. Emory University, Atlanta, United States

Y. Zhang. Emory University, Atlanta, United States

Y. Gokmen-Polar. Emory University School of Medicine, United States

Background: Lineage-specific transcription factors (LTFs) are purported to define cellular lineages and their expression could be used to identify subtypes of cancer. In many cancers, tuft cell differentiation appears to have prognostic impact. However, such differentiation has not been documented in breast cancer.

Methods: We sought to study the fidelity of LTFs (MYOG, POU2F3, FOXA1, FOXA2, FOXA3, FOXJ1, HNF4A, HNF4G, SPIB, SOX8, GRHL1, GRHL2, and GRHL3) for their presence and prognostic impact in breast cancer. Single cell RNA data from GSE 161529, which contains 421,761 single cells, was downloaded and analyzed for the expression and co-expression of LTFs. The data was first subdivided based on ER+ and TNBC status. Analysis was performed using cells from 10ER+ samples and 4 TNBC samples. Cell clustering using Louvain's method was run using all genes. Cell type assignment was then performed using well-known markers for both tumor and lymphocyte marker from existing publications. Further analysis was restricted to keratin expressing cells and to study the presence and co-expression of LTFs in the epithelial cells. KM-Plotter was employed to determine the prognostic value of these LTFs. The analysis was further stratified by expression of estrogen receptor positive and negative status. The endpoint of relapse free survival was used, as it provided data on the largest number of patients.

Results: Single-cell analysis pipeline successfully identified distinct populations of tumor epithelial cells accompanied by various lymphocytes, including B cells, CD8+ T cells, CD4+ T cells, dendritic cells, and macrophages, in both ER+ tumors and TNBC tumor samples. We further confirmed the expression of the LTFs in the epithelial (keratin+) compartment. Expression of all LTFs (except MYOG, and FOXA2) was scattered in the different epithelial clusters. Further analysis of single LTFs showed differentially co-expression based on ER+ status. POU2F3+/ER+ cells also co-expressed FOXA1 and GRHL1 while POU2F3+/ER- cells were GRHL1+ and (weak) SPIB+. The analysis of LTFs using KM-Plotter tool revealed their expression documenting multiple cell lineages in breast cancer; this was noted in ER+, HER2+ cancers and TNBCs. The directionality of the outcome (good or bad prognosis) varied with the specific TFs and subtype of breast cancer. High expression of POU2F3, and FOXA1, and SPIB were associated with better relapse-free survival (RFS) in ER+ breast cancer. POU2F3, FOXA2, FOXA3 were associated with worse RFS, whereas SPIB was with prognosis in ER- breast cancers.

Conclusions: We for the first time document the expression of LTFs in breast cancer and their prognostic relevance based on ER+ and ERneg status. Expression of POU2F3, a marker of tuft cells which are known to regulate immune response, was noted to be associated with improved outcomes in ER+ tumors. Further characterization of the relevance of LTFs and their co-expression with respect to therapeutic response is ongoing.

PO4-16-04

Decoding the immune landscape of breast cancer (BC) during pregnancy (PrBC): Impact of hormone receptors (HR) and tumor-infiltrating lymphocytes (TILs) phenotype on gene expression signatures

Presenting Author(s) and Co-Author(s):

- K. Venetis. European Institute of Oncology, Milan, Italy, United States
- E. Sajjadi. European Institute of Oncology, Milan, Italy, United States
- C. Frascarelli. European Institute of Oncology, Milan, Italy, United States
- M. Ivanova. European Institute of Oncology IRCCS, Milan, Italy, United States
- M. D'Ercole. European Institute of Oncology, United States
- C. Blundo. Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, United States
- M. Giroda. Ospedale Maggiore Policlinico, Milan, Italy, United States
- E. Di Loreto. Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, United States
- G. Scarfone. Ospedale Maggiore Policlinico, Milan, Italy, United States
- S. Ferrero. Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico , and University of Milan, Milan, Italy, United States
- P. Veronesi. 1. Division of Breast Cancer Surgery, European Institute of Oncology, IRCCS, Milan, Italy/University of Milan, Milan, Italy, United States
- V. Galimberti. European Institute of Oncology, Milan, Italy
- F. Peccatori. Fertility and Procreation Unit, IEO European Institute of Oncology IRCCS, Milan, Italy
- N. Fusco. European Institute of Oncology, IRCCS, University of Milano, Milan, Italy, United States
- E. Guerini-Rocco. Division of Pathology, IEO European Institute of Oncology IRCCS, Milan, Italy, United States

Introduction: PrBC is an uncommon malignancy with aggressive behavior. Its pathogenesis involves distinct immune mechanisms associated with maternal-fetal tolerance and tumor-host immunoediting. PrBC displays specific patterns of TILs with increased CD8+ cells. Gaining a comprehensive understanding of the molecular processes underlying this immune synergy is crucial for enhancing PrBC patients' clinical management. Here, we sought to identify dysregulated immune-related genes in PrBC and explore their association with HR status and TILs.

Methods: A total of n=75 PrBC (age range 26-43 years) and n=67 age-matched early-onset breast cancer (EOBC) in non-pregnant women (controls; age range 28-43 years) were selected from our Institutional registry. For all cases TILs were quantified according to the International TILs Working Group recommendations and profiled by IHC for CD4 and CD8. RNA was extracted from representative FFPE tissue blocks to perform the expression analysis of 395 genes involved in tumor-immune interactions using a targeted NGS panel (OncoPrint™ Immune Response Research Assay, ThermoFisher). Samples with >1,000,000 mapped reads and >800,000 valid reads were considered adequate. R package DESeq2 software 1.38.3 was used for sequencing depth differences normalization and differential gene expression analysis. Differentially expressed genes (DEGs) were identified based on a significant p-value ($p < 0.05$).

Results: The comparison between PrBC and EOBC revealed a total of n=7 DEGs. All of these genes were upregulated and belonged to distinct superfamilies, including Cancer/Testis (CT) Antigen (MAGEA1/3, XAGE1B), Interferons/Cytokines (IFNA17, IFNB1), Chemokines (CXCL13), and Immunoglobulin (PECAM1/CD31). Notably, the upregulation of Chemokines in respect to EOBC was observed exclusively in HR+ PrBC, whereas triple-negative (TN) PrBC did not exhibit this pattern compared to the control group. Hence, the upregulation of ALOX15B, an enzyme involved in fatty acid peroxidation, was specific to TN PrBC. The immune signatures showed significant variations between PrBC and EOBC also based on TILs density and subpopulations. Indeed, the upregulation of CT genes (MAGEA1, XAGE1B) was exclusively observed in PrBC cases characterized by low TILs levels and prevalence of CD8+ or CD4+ cells. Finally, CD4+ TILs were absent or low in PrBC with upregulated Interferons, Cytokines, Chemokines, and Immunoglobulin genes, but present in cases with increased expression of CT and KLRF1 (NK cells).

Conclusion: These findings highlight the heterogeneity and distinct molecular characteristics of PrBC and EOBC. The upregulation of specific immune-related gene families, such as CT and Chemokines, in different PrBC subtypes may suggest their potential role as actionable biomarkers (e.g. MAGEA, a well-known oncogene and potential immunotherapy target). The differences in immune signatures and TILs subpopulations further emphasize the importance of the immune microenvironment in PrBC biology and behavior. Future studies could delve deeper into the clinical implications of these gene expression patterns and explore their relevance in personalized treatment strategies for PrBC.

PO4-16-05

Identification of functional HLA-A*11:01-restricted driver gene PIK3CA mutation specific T-cell receptors

Presenting Author(s) and Co-Author(s):

M. shen. Department of Breast and Thyroid Surgery, The First Affiliated Hospital of Chongqing Medical University, United States

X. han. Department of Immunology, School of Basic Medical Sciences, Chongqing Medical University, United States

s. chen. Department of Immunology, School of Basic Medical Sciences, Chongqing Medical University, United States

a. jin. Department of Immunology, School of Basic Medical Sciences, Chongqing Medical University, United States

S. Liu. Chongqing Medical University, United States

The adoptive transfer of genetically engineered T-cell receptors (TCR-T) has emerged as a promising therapeutic strategy for the treatment of solid tumors. Recent clinical trials have demonstrated the safety and efficacy of TCR-T cell therapies against certain types of metastatic solid cancers. In our study, we aimed to investigate the potential of TCR-T cell therapies targeting neoantigens, which are exclusively expressed in cancer cells, with a focus on metastatic breast cancer (MBC). Specifically, we identified four driver missense mutations (PIK3CA E542K, E545K, H1047L, and H1047R) frequently observed in MBC patients and utilized computational tools to predict the generation of neoantigens. Utilizing NetMHCpan V.4.1, we performed screening of peptides spanning the mutation region and predicted a neoantigen epitope, PIK3CA_H1047L, to bind with HLA-A*11:01. To validate the presentation and stability of the neoantigen epitope, we employed TAP1-deficient K562 cells and observed stable expression of the mutant peptide-major histocompatibility complex (MHC) complex on the cell membrane. Subsequently, we isolated T cells from healthy donors possessing the HLA-A11:01 genotype, and subjected them to successive stimulations with neopeptide-pulsed dendritic cells. T cells stimulated with neopeptide were examined for neoantigen specificity using an IFN- γ ELISpot assay. Employing pMHC tetramer staining and single-cell sorting via flow cytometry, we successfully isolated five HLA-A11:01-restricted PIK3CA_H1047L-specific TCRs. Through lentivirus transduction of these TCRs into T cells, we achieved the generation of TCR-T cells that exhibited potent and specific activity exclusively against the PIK3CA_H1047L neoantigen. The functionality of the TCR-T cells was confirmed through assessments of CD137 expression, IFN- γ secretion, and cytotoxicity assays. In conclusion, our study demonstrates T cell responses towards neoantigens derived from PIK3CA, a commonly observed driver mutation in MBC. Furthermore, we successfully isolated five distinct neoantigen-specific TCRs that specifically recognized the PIK3CA_H1047L mutation and were restricted to the prevalent HLA-A*11:01 allele. The transfer of these TCRs into T cells resulted in the generation of TCR-T products exhibiting remarkable activity against the PIK3CA_H1047L neoantigen. These findings strongly encourage further investigation into TCRs targeting driver mutations in MBC, with the aim of advancing neoantigen-targeted TCR-T therapies into clinical trials. Additionally, the PIK3CA_H1047L neoantigen holds great promise as a potential candidate for the development of effective cancer vaccines.

PO4-16-06

From Real-World Data to Improved Outcomes: Examining the Impact of Trastuzumab Disparities on Pathological Complete Response and Long-Term Survival in HER-2 Positive Breast Cancer Patients within the Brazilian Public Health System

Presenting Author(s) and Co-Author(s):

M. ANTONINI. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, Sao Paulo, Sao Paulo, Brazil

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

G. PANNAIN. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

F. BAUK RICHTER. Hospital Pérola Byington, São Paulo, Sao Paulo, Brazil

A. Amorim. Perola Byington Hospital, United States

M. Diogenes. HOSPITAL PEROLA BYINGTON, SÃO PAULO, Sao Paulo, Brazil

O. FERRARO. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

L. Gebrim. Womens' Health Hospital, São Paulo Brazil, Sao Paulo, Brazil

R. COELHO LOPES. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

J. REAL. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

Introduction: Equitable access to healthcare is a fundamental principle of public health, aiming to ensure that all individuals have the opportunity to receive effective treatments. However, disparities in access to healthcare still persist in many countries, including Brazil. These disparities can have significant impacts on the health and well-being of patients, particularly in the case of breast cancer treatment. Neoadjuvant chemotherapy (NAC) has been increasingly used for the treatment of breast cancer, encompassing conditions ranging from locally advanced tumors to early-stage triple-negative and HER-2 positive tumors.

Objectives: The aim of this study is to evaluate the impact of disparities in the use of trastuzumab (Herceptin) within the Brazilian public health system on pathological complete response (pCR), overall survival (OS), and disease-free survival (DFS). We aim to investigate whether variations in access to trastuzumab treatment influence the achievement of pCR and impact long-term survival outcomes in breast cancer patients.

Methods: This retrospective, multicenter cohort study included female patients over 18 years of age with a diagnosis of non-metastatic breast cancer undergoing NAC. pCR was defined as the absence of residual invasive or in situ tumor in the breast and axilla. As an exploratory real-world data study, no confirmatory hypothesis was established, thus no corrections for multiple comparisons were necessary. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method, calculated at five years. The study was approved by the Research Ethics Committee with registration number CAAE 64633422.4.0000.5463.

Results: Between 2011 and 2020, a total of 1,891 patients were included in the study, of whom 454 (22.9%) were HER-2 positive. The pCR rate was 25.7%. Trastuzumab was accessed by 291 (64.1%) patients ($p < 0.001$). Among those who received trastuzumab, pCR was observed in 105 (36.1%) patients, compared to 12 (7.6%) in those who did not have access to trastuzumab ($p < 0.001$). OS in HER-2 positive patients was 90.1% with pCR and 64.5% without pCR (log-rank $p < 0.001$), while DFS was 89.2% with pCR and 68.2% without pCR (log-rank $p = 0.003$). Evaluating OS and DFS in patients who received trastuzumab versus those

who did not, OS with trastuzumab and pCR was 94.3% and without pCR was 89.5% (log-rank $p < 0.001$); OS without trastuzumab and pCR was 83.3% and without pCR was 58.2% (log-rank $p < 0.001$). DFS in patients who received trastuzumab and achieved pCR was 94.5% and without pCR was 90.5% (log-rank $p = 0.05$), whereas without trastuzumab and pCR was 79.9% and without pCR was 62.1% (log-rank $p = 0.001$).

Conclusion: These findings underscore the significant impact of disparities in trastuzumab utilization within the Brazilian public health system on pCR rates and long-term survival outcomes in HER-2 positive breast cancer patients. Access to trastuzumab was associated with higher pCR rates and improved overall and disease-free survival rates. Ensuring equitable access to targeted therapies is crucial for improving treatment response and long-term outcomes in breast cancer patients.

Table 1 Clinicopathological characteristics of patients

Characteristics	pCR (n=117)		non-pCR (n=337)		p-value
	N	%	N	%	
Mean Age years [standard deviation]	49,93	[10,80]	50,5	[10,76]	0.184
Status menopausal					
Pre-menopausal	70	59,8%	154	45,7%	0.003
Menopausal	47	40,2%	183	54,3%	0.002
Family history					
Yes	28	23,9%	47	13,9%	0.018
No	89	76,1%	290	86,1%	0.003
Histological type					
IDC	100	85,5%	301	89,3%	0.078
IDC with ILC	14	12,0%	24	7,1%	0.210
Others	3	2,6%	12	3,6%	0.720
Histological grade					
G1	3	2,6%	12	3,6%	0.720
G2	26	22,2%	36	10,7%	0.048
G3	88	75,2%	289	85,8%	0.019
KI-67					
<14	26	22,2%	36	10,7%	0.011
>14	91	77,8%	301	89,3%	0.011
Hormonal Receptor					
HR +	18	15,4%	102	30,3%	0.014
HR -	99	84,6%	235	69,7%	0.005
Tumor size (T)					
T1	8	6,8%	7	2,1%	0.008
T2	35	29,9%	95	28,2%	0.172
T3	42	35,9%	143	42,4%	0.065
T4	32	27,4%	92	27,3%	0.087
Lymphnode involvement (N)					
N0	12	10,3%	5	1,5%	0.004
N1	36	30,8%	196	58,2%	0.002
N2	47	40,2%	126	37,4%	0.278
N3	4	3,4%	10	3,0%	0.360
Clinical staging (TNM) AJCC					
I	8	6,8%	5	1,5%	0.015
IIA	11	9,4%	12	3,6%	0.001
IIB	20	17,1%	75	22,3%	0.569
IIIA	42	35,9%	143	42,4%	0.162
IIIB	32	27,4%	92	27,3%	0.087
IIIC	4	3,4%	10	3,0%	0.450

Legend: AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR hormonal receptor.

Table 2 - NAC schemas and correlation with pCR.

HER-2	pCR (n=117)		non-pCR (n=337)		p-value
	N	%	N	%	
AC-T	12	10,3%	151	44,8%	<0,0001
AC-TH	105	89,7%	186	55,2%	

AC-T, doxorubicin + cyclophosphamide – taxane; AC-TH, doxorubicin + cyclophosphamide – taxane+herceptin.

PO4-16-07

Cyclin-dependent kinase inhibitor plus endocrine therapy in HR+/HER2- invasive breast cancer with bone marrow and pancytopenia: a new standard of care? Collaborative multicentric Argentinean real-world study (SUMA-02)

Presenting Author(s) and Co-Author(s):

- A. OSTINELLI. Alexander Fleming, United States
- P. Mandó. CEMIC, Centro de Educación Médica e Investigaciones Clínicas, Buenos Aires, Argentina, United States
- C. Almada. Instituto Roffo, United States
- M. Winocur. Clinica Universitaria Reina Fabiola, United States
- M. Ipiña. Hospital Aleman, United States
- V. Paez. SUMA, United States
- S. Aparicio. SUMA, United States
- s. Rivero. Alexander Fleming, United States
- F. Waisberg. Medical Oncologist, Caba, Buenos Aires, Argentina
- L. Lapuchesky. Instituto Alexander Fleming, Ciudad Autónoma de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina
- C. Micheri. SUMA, United States
- M. Montenegro. SUMA, United States
- C. Rusz Maidana. FENIX, United States
- C. Reinhardt. SUMA, United States
- E. Rovera. Instituto de Oncología Ángel H. Roffo, United States
- G. Gómez Abuin. Hospital Alemán Buenos Aires, Argentina, United States
- S. Bella. SUMA, United States
- F. Perazzo. CEMIC, Centro de Educación Médica e Investigaciones Clínicas, Ciudad Autónoma de Buenos Aires, Argentina
- A. Nervo. Instituto Alexander Fleming, Ciudad Autónoma de Buenos Aires, Argentina
- A. Aguilar. Instituto de Oncología Ángel H. Roffo, United States
- M. Chacón. Instituto Alexander Fleming, Ciudad Autónoma de Buenos Aires, Argentina
- V. Costanzo. Instituto Alexander Fleming, Buenos Aires, Argentina, United States
- V. Caceres. Roffo Institute, United States
- J. Nadal. Instituto Alexander Fleming, Ciudad Autónoma de Buenos Aires, Argentina

Introduction

Bone marrow involvement is a rare occurrence in patients with advanced breast cancer (ABC), and the prognosis in this context is generally poor. Prompt initiation of treatment to improve the patient's hematological status is crucial. However, this condition is often excluded from clinical trials, making it challenging to determine the effectiveness of new drugs. Limited data and evidence are available to guide treatment decisions, but guidelines recommend starting with chemotherapy for the need of a rapid response. This study aims to analyze the real-world efficacy of cyclin-dependent kinase inhibitors (CDKis) in HR+/HER2- ABC with bone marrow infiltration.

Methods

Retrospective multicenter cohort study including HR+/HER2- ABC patients from public and private facilities in Argentina. Patients with confirmed bone marrow involvement (blood smear or histological biopsy analysis) and treated with CDKi were eligible. Bone marrow response was defined as an increase in at least one of the previously abnormal blood series to Hb >10.0, platelets >100,000, and leukocytes >4,000.

Results

A total of 22 patients from different medical centers in Argentina were included. The median age was 55.5 (IQR 46.25-65). Histological confirmation of bone marrow involvement was reported in 81.8% (18) of patients. Among them, 54.5% (12) had initial diagnosis at an early stage, and 13.6% (3) experienced relapse during or within 1 year of completing adjuvant hormonal treatment. Bone-only metastasis was observed in 50% (11) of patients, while the remaining 50% (11) had both visceral and bone disease. Anemia, thrombocytopenia, and leukopenia were present in 95.5% (21), 90.9% (20), and 40.9% (9) of patients, respectively. In 68.2% (15) of patients, bone marrow involvement was detected at the first-line treatment setting. The selected CDKis were palbociclib in 40.9% (9) of patients, ribociclib in 31.8% (7), and abemaciclib in 27.3% (6). The bone marrow response rate was 68.2% (15), with a median of 2 cycles (range 1-5) required for a response. Dose reduction was necessary in 31.8% (7) of patients.

Discussion

Managing patients with uncommon sites of metastasis, such as bone marrow, poses significant challenges for oncologists. Bone marrow infiltration leads to hematopoietic alterations that adversely affect the quality of life, resulting in increased risk of infections, bleeding, and other comorbidities with fatal consequences. While chemotherapy is the standard treatment in such cases, our study demonstrates that CDKis are a safe and effective option for managing these complications.

Conclusion

The findings of this study support the evaluation of CDKis as a standard treatment for HR+/HER2- ABC patients. Our results are in line with the recently published phase 2 clinical trial RIGHT CHOICE, which showed a prolonged progression free survival in patients treated with ribociclib and HT with HR+/HE2- ABC and visceral crisis.

PO4-16-08

Prognostic factors for tumor recurrence after breast-conserving and radiotherapy treatment for early invasive breast cancer: ten years of results in a referral center in Mexico City

Presenting Author(s) and Co-Author(s):

N. Ortega-Avila. Instituto Mexicano del Seguro Social, United States

Y. Remolina-Bonilla. Instituto Mexicano del Seguro Social, United States

J. Caballero-Jasso. Instituto Mexicano del Seguro Social, United States

Background: Breast cancer is the most common malignancy in the world, reporting more than 2 million new cases in 2020. In early stages, patients undergo primary surgery. Breast-conserving surgery (BCS) has generally been accepted as a treatment for invasive breast cancer, findings at 20 years still show that lumpectomy and breast irradiation, as compared with mastectomy, have no significant difference in overall survival among the treatment groups. Approximately 10-15% of patients will develop local or systemic recurrence in 5 to 10 years. Factors such as young age (< 45 years), close/positive margins, no breast radiation, are associated with ipsilateral breast tumor recurrence. High grade has been related to distant metastasis. The mortality trend is upward due to a higher incidence of the disease and earlier detection.

Methods: This is an observational and retrospective cohort study, which included patients with early breast cancer, who were treated with conserving surgery and received radiotherapy, at the Breast Oncology Service at the UMAE Gineco 4 "Luis Castelazo Ayala" during the period from January 2012 to December 2022. The aim of our study was to describe the prognostic factors associated with disease-free survival (DFS) and overall survival (OS) in patients with localized breast cancer treated with BCS. DFS was defined as time from surgery to recurrence event (local recurrence, distant recurrence, contralateral breast cancer, second primary cancer, or death from any cause) whichever occurred first. For statistical analysis, Kaplan Meier and Log-rank methods were used for survival analysis. Cox proportional hazard model was used for multivariate analysis.

Results: We included 399 patients, the median follow-up was 88 months (95%CI 86-91). Median age was 59 years. The most common pathological stage was IA in 44.9%, the predominant immunophenotype was luminal A in 56.1% of patients, follow by luminal B in 19.3% and 13% were triple negative. Management of axilla with sentinel node biopsy occurred in 50.1% and 49.9% underwent to lymph node dissection. Regarding surgery outcomes 40.4% of the patients required widening of the margins, 5% of the patients remained with close surgical margins ≤ 2 mm, 7.5% had complications associated with the surgery, and none related death occurred. All patients received adjuvant radiotherapy, the median time to initiation was 32 weeks (range 3-70) and 65.4% received adjuvant chemotherapy. Recurrence events occurred in 15.5% of patients, local 2.8%, systemic 8.8%, contralateral breast cancer 1.7%, and second primary 2.2%. Estimated disease-free survival at 5 and 10 years were 86.6% and 74.2%, respectively. In the multivariate analysis independent prognostic factors for DFS were: lobular histology HR 2.95 (95%IC 1.5-5.7), tumor size ≥ 2 cm HR 1.95 (95%IC 1.1-3.6), close surgical margins HR 2.62 (95%IC 1-6.6), and ER low expression (1-10%) HR 4.39 (95%CI: 1.6-12.4). Estimated OS at 5 and 10 years for patients who experienced recurrence were 78.4% and 47.4% and for patients without recurrence were 96.8% and 93.5%, respectively (adjusted HR: 10.4, 95%CI: 5.2-20.6).

Conclusion: These results suggest that patients with early breast cancer treated with conserving surgery and radiotherapy with risk factors such as lobular carcinoma, tumor size $\geq 2\text{cm}$, close margins, and low expression of estrogen receptors have a high risk of recurrence and significantly decreased overall survival at 5 and 10 years.

PO4-16-09

Enhancing Research on Inflammatory Breast Cancer through Count Me In: Assessing the Accuracy of Self-Reported Diagnoses

Presenting Author(s) and Co-Author(s):

E. Troll. DFCI, United States

S. Ryan. DFCI, United States

V. Mason. Inflammatory Breast Cancer Research Foundation, Broadway, Virginia, United States

M. D. Powell. Dana-Farber Cancer Institute, United States

A. Hazra. Harvard Medical School, United States

N. Wagle. Genentech Oncology, United States

M. McGillicuddy. Broad Institute, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

M. Regan. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer that relies on clinical identification of specific breast changes for diagnosis, in addition to pathological confirmation of invasive breast cancer. There is a clear need to increase participation of patients with IBC in research to better understand its clinical course and optimal treatment strategy. Count Me In (CMI) is a nonprofit research initiative that enables patients across the United States and Canada to accelerate cancer research by sharing their clinical data and biospecimens. The Metastatic Breast Cancer Project (MBCProject) was the first CMI initiative and is a prospective longitudinal cohort designed to capture these data from patients with metastatic breast cancer.

Methods: We reviewed available medical records of patients participating in the MBCProject and who self-reported as having IBC. Records were reviewed by a study team member to identify documentation by a provider of an IBC diagnosis. For records without a documented IBC diagnosis, the clinical symptoms were assessed using a novel quantitative IBC scoring system (Mason G et al. BCRF 2022) currently being validated. Finally, records were also assessed by a physician for final determination of an IBC diagnosis. Records were classified as “concordant” or “not concordant”. Concordant is defined as “review of medical records confirms IBC using the unifying set of specific diagnostic criteria”. We desired the rate of concordant cases to be $\geq 90\%$; if $\leq 85\%$ it would be considered as unacceptable to rely solely on patient self-report of IBC diagnosis in future research.

Results: We reviewed records of 79 patients participating in the MBCProject who self-identified as having IBC and had medical records collected. Of these, 51 (64.5%) had IBC stated in providers' notes. Of the remaining 28 patients, 6/28 met criteria for IBC using the new IBC diagnostic criteria, 17/28 didn't have evidence of IBC based on the records available and 6/28 we were unable to make a final determination due to lack of records at the time of initial diagnosis. In total, 57/79 (72%; 95% CI 61-82%) patients had a concordant diagnosis.

Conclusion: Patient self-report registries such as CMI are invaluable for the collection of clinical information and biospecimens for research of patients with rare diseases, however, a self-reported diagnosis of IBC may not be reliable. To improve the accurate identification of IBC,

optimization of the questions asked to patients on these registries is warranted. This may include additional screening questions such as specific skin findings and timing of onset of symptoms. Focusing on patients with stage III IBC may also provide a better patient population to test this strategy.

PO4-16-10

Overall survival in sentinel node biopsy and axillary dissection: a real-world data.

Presenting Author(s) and Co-Author(s):

R. Pares. Womens' Health Hospital, São Paulo Brazil., United States

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

J. de Lima. Womens' Health Hospital, São Paulo Brazil., United States

M. Antonini. Hospital Servidor Publico estadual, United States

F. Pimentel Cavalcante. Hospital Geral Fortaleza (HGF), United States

L. Gebrim. Perola Byington Hospital, United States

Background: Information about the status of the axilla (presence or absence of lymph node disease) is important for breast cancer (BC) treatment decision-making. Axillary dissection (AD) has been gradually substituted by sentinel node biopsy (SLNB) in clinical node negative patients and intraoperative evaluation became a routine. Most of the patients with a positive node in an intraoperative evaluation were submitted to AD, and when a negative intraoperative evaluation but a positive paraffin evaluation was found a new axillary surgery was a routine. Both approaches were gradually abandoned with the publication of the ACOSOG Z011 study showing no difference in local recurrence or overall survival (OS). Objective: To evaluate the number of patients with BC who meet the criteria of Z011 trial and could be spared of AD and compare the outcomes of the SLNB only and those that had AD. Methods: Patients with BC that were submitted to upfront surgery and had at least one positive node in SLNB were included in these retrospective analyses at Pérola Byington Hospital database, diagnosed between 1992 and 2019. Clinical and pathological characteristics were extracted from the database and patient medical records. T-test or chi-square test was used to individually analyze the association of each variable between the groups. Multivariate analysis was used to calculate odds ratio (OR) and 95% confidence intervals (CI) for independent variables correlated with positive AD. Cox regression was used for survival analysis, and survival curves were plotted using the Kaplan-Meier method, analyzing the difference between curves using the Log-rank test. R software version 4.1.1 was used for all analyses, with a p-value < 0.05 considered statistically significant. Results: A total of 729 patients were analyzed, with a mean age of 54.1 (\pm 11.6) years at diagnosis. Most patients (n=633, 86.8%) underwent AD after a positive SLNB and 40,3% of the patients that were submitted to AD the only positive node was the sentinel node. After AD, 63,3% of these patients had 1 or 2 lymph nodes positive and met the Z011 criteria trial. The mean number of lymph node in AD was 12.2. Most patients (72.7%) were diagnosed at clinical stage II, 62% had nuclear grade 2 tumors, 52.9% had Luminal B subtype, and 63% were postmenopausal. Furthermore, 58.5% of patients underwent breast-conserving surgery, and 5.2% of patients experienced recurrence. The chance of AD was observed 2,2 times for the luminal B (OR 2.163, 95% CI 1.104-4.239, p=0.025), 2,1 times HER2-positive with receptor positive (OR 2.125, 95% CI 1.160-3.893, p=0.015), and 2,8 times for triple-negative (OR 2.806, 95% CI 1.013-7.757, p=0.047) compared to Luminal A. Patients that were submitted to AD had worse outcome when compared to SLNB, the overall survival showed a 94.4% higher risk of death with a median survival of 11 years (HR 1.944, 95% CI 1.20-3.14, p=0.006). Conclusion: These retrospective analyses showed 63,3% of the patients that had a positive node in a SLNB could be spared from AD (based on Z011 trial). Patients submitted to AD had worse outcome and these findings needs to be clarified.

PO4-16-11

De-escalation of anthracyclines during adjuvant therapy based on Oncotype RS: A single institution experience in Mexico City.

Presenting Author(s) and Co-Author(s):

C. González Núñez. Instituto Nacional de Cancerología, Tlalpan, Distrito Federal, Mexico

P. Cabrera-Galeana. Instituto Nacional de Cancerología, CDMX, Distrito Federal, Mexico

J. Bargalló Rocha. Instituto Nacional de Cancerología (INCAN), Mexico City, Mexico, United States

R. Vazquez-Romo. Instituto Nacional de Cancerología, United States

S. Aguilar-Villanueva. Instituto Nacional de Cancerología, United States

A. Garcilazo. INSTITUTO NACIONAL DE CANCEROLOGIA, United States

A. Velazquez-Martinez. Instituto Nacional de Cancerología, United States

A. Maliachi. Instituto Nacional de Cancerología, United States

R. Rodriguez. Instituto Nacional de Cancerología, United States

E. Romero-Bañuelos. Hospital ABC Observatorio, United States

Introduction:

In Mexico, hormone positive HER2 negative breast cancer is the most frequent subtype, accounting for 76.6% of cases. For patients undergoing local control management through surgery; adjuvant chemotherapy is usually followed depending on different risk factors. In order to avoid overtreatment, different genomic firms have been approved aiding in a more objective decision. One of these genomic firms is the Oncotype Recurrence score.

The TAILORx and RxPONDER trials have provided guidance in determining which patients are candidates for chemotherapy depending on their menopausal status. However, it has not yet been determined whether patients requiring chemotherapy can receive an anthracycline-free regimen. In the Plan B clinical trial, a non-inferiority analysis was conducted on early-stage breast cancer patients who received anthracycline-based or non-anthracycline-based chemotherapy, with the non-anthracycline regimen being non-inferior, including patients with a RS > 25. We intend to reevaluate these findings in our Mexican population.

Methods:

We evaluated 217 patients with early stage hormone sensitive HER2 negative breast cancer who had an Oncotype Recurrence score (RS) result. This retrospective cohort study took place by analyzing electronic records from January 2011 to December 2017 with patients treated at the National Cancer Institute in Mexico City.

We included patients 18 years of age or older, any sex with an Oncotype RS ≥ 16 in premenopausal patients or ≥ 26 in postmenopausal patients who received adjuvant chemotherapy with or without anthracyclines.

Our primary endpoint was iDFS comparing TC vs AC-T. Overall survival was set as a secondary endpoint.

Results:

Of the 217 patients with an Oncotype recurrence score, only 46 patients received adjuvant

chemotherapy of which 71.7% were premenopausal with a median age of 45 years. Stage II was the most common stage with 91.3% of the population, as well as ductal carcinoma with 82.6%. All patients had positive lymph nodes, 54.3% at least 1 lymph node. Most patients received AC-T adjuvant chemotherapy (60.9%), and only 39.1% received TC. Of the 46 patients analyzed, only 19.6% (9) had a recurrence upon follow-up (Table 1). Median time of follow up was 87.5 months. Difference in Disease free survival could not be established between patients receiving AC-T with 105 months (CI 95% 94.36-117.43 months) vs TC with 94.09 months (CI 95% 83.85-104.34 months, $p < 0.918$) (Figure 1). Overall survival did not have a statistical difference between both chemotherapy regimens, $p < 0.649$ (Figure 2A), when comparing Oncotype RS, overall survival was better in those with Oncotype OS < 26 , $p < 0.023$ (Figure 2B).

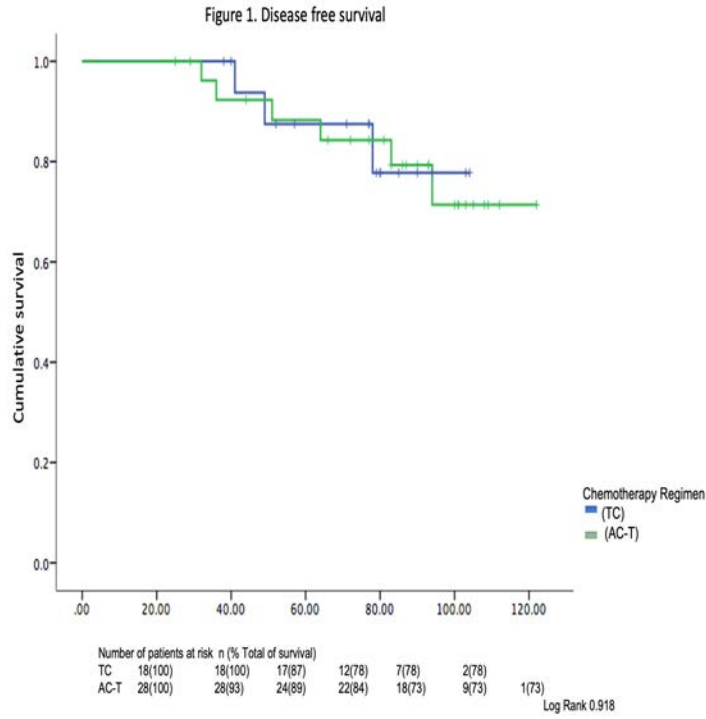
Discussion

As described previously in the Plan B trial, TC was non inferior to the conventional adjuvant regimen of AC-T in Hormone positive HER2 negative early-stage breast cancer. Our results tend to show similar results when compared to the Plan B. An important aspect to our study was that 71.7% of our patients were premenopausal, where in the Plan B trial only 35% were premenopausal, considered a higher risk group of patients. Although a statistical difference couldn't be established due to our small sample size, in DFS or OS when comparing the chemotherapy regimen. Premenopausal patients with an Oncotype RS < 26 could receive an anthracycline free regimen, without impact in their overall survival. Larger prospective studies are necessary to assure this conclusion.

Table 1 (Baseline characteristics)

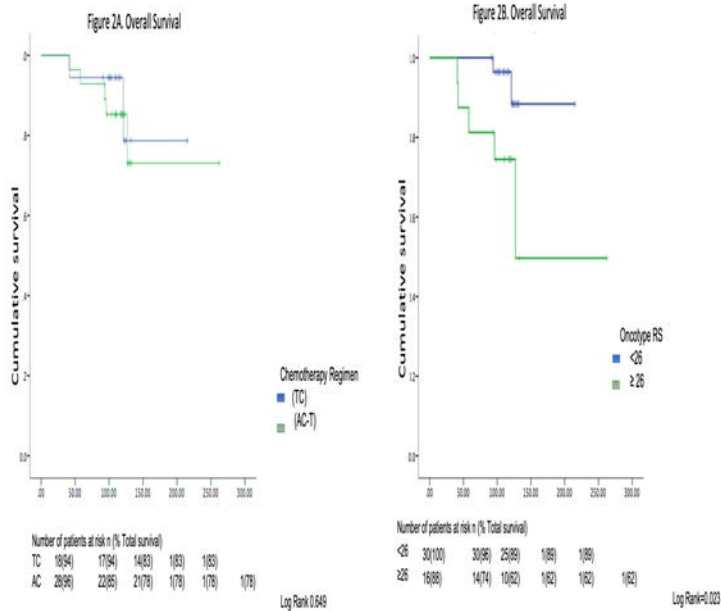
Table 1 (Baseline characteristics) (N=46)		
Variable	n	%
Age		
Median (range)	45 (35-79)	
<50 years	33	71.7%
≥50 years	13	28.3%
Hormonal status		
Premenopausal	33	71.7%
Postmenopausal	13	28.3%
Clinical Stage		
I	01	2.2%
II	42	91.3%
III	03	6.5%
Histology		
Ductal carcinoma	38	82.6%
Lobular carcinoma	05	10.9%
Other	03	6.5%
Grade		
G1	11	23.9%
G2	08	17.4%
G3	27	58.7%
Ki67		
<20	21	45.7%
≥20	25	54.3%
Positive Lymph Nodes		
1	25	54.3%
2	16	34.8%
3	04	8.7%
4	01	2.2%
Tumor Size		
<2cm	18	39.1%
≥2cm	28	60.9%
Chemotherapy regimen		
TC	18	39.1%
AC-T	28	60.9%
Hormonal therapy		
Tamoxifen	32	69.6%
Aromatase Inhibitors	14	30.4%
Type of Surgery		
Lumpectomy	19	41.3%
Mastectomy	27	58.7%
Recurrence		
No	37	80.4%
Yes	09	19.6%

Figure 1



DFS (TC vs AC-T)

Figure 2 A and B



Overall Survival

PO4-16-12

Patient initiated centricity towards improved communication, side effect management and follow-up care by Real World Evidence Survey from patients for patients – Preview of the Breast BRIDGister Platform

Presenting Author(s) and Co-Author(s):

C. Stuewe. Kontakt und InformationsStelle für Selbsthilfegruppen KISS, Germany

R. Wirtz. STRATIFYER Molecular Pathology GmbH, Germany, Germany

C. Gress. Breast BRIDGister, Germany

L. Schmidt. Cliemedo Health GmbH, Germany

V. Schweighart. Cliemedo Health GmbH, Germany

S. Eidt. Institut für Pathologie am St. Elisabeth Krankenhaus Köln-Hohenlind, Germany, Germany

C. Schumacher. St. Elisabeth Hospital, Cologne, Germany

J. Habraschka. Clinical Trial Unit, St Elisabeth Krankenhaus Köln-Hohenlind, Germany

H. Lehmann. Breast BRIDGister, Germany

K. Schuere. Breast BRIDGister, Germany

Background

Treatment adherence is crucial for outcome improvement. Still up to 50% of patients interrupt e.g. endocrine treatment or other effective treatment choices due to side effects or miscommunication. Reasons may include limited time spent for patient information in daily routine and the intrinsic barriers to frankly tell the truth to the attending physicians. Therefore, a patient initiated survey has been compiled to comprehensively address all clinical, diagnostic and critical aspects of importance for patients by decentral data capture from patients at home via smart devices in a pseudonymized & interactive fashion to refocus on challenges regarding patients needs, fears and wishes to support evidence based statistical analysis of Real World Data.

Materials and Methods

Establishing a cloud-based IT Platform enabling nationwide, decentral data entry using Climedo clinical trial software tools without the need of any commercial app utilities and therefore obeying GDPR conform standards to create an interconnected online platform integrating 36 interconnected surveys comprising >1.200 singular questions has been set up between 2020 and 2022 based on patients content elaboration & wishes. The questionnaires address all Real World experiences e.g. at initial diagnosis, during primary treatment and all subsequent lines as well as side effect management with complementary medicine and follow up care realities. After 100 patients a preplanned statistical analysis has been performed to evaluate the feasibility of the patient oriented ePRO approach and demonstrate relevance of proof-of-concept results before entering international trial expansion. Descriptive analysis by Excel as well as Correlation analysis; Chi square and Partitioning tests using the SAS JMP® 9.0.0 software were performed.

Results

Despite in depth complexity > 85% of patients completed the whole survey. Age distribution of the pilot cohort revealed comparably younger patient age (28% between 30-39 years, 40% between 40-49 years, 24% between 50-59 and 10% being above 60 years) and dominance of

Triple Negative Patients (~39%) participating the online survey in the pilot cohort. 97% of patients were treated in certified breast centers (50% in larger centers of bigger towns, 15% in central clinics, 23% in university sites, 5% in local hospitals and 7% at office based doctors). Interestingly, 25% of patients did not or only partially understand their diagnosis and upcoming treatment. Time spent for communicating initial breast cancer diagnosis was less than 10 minutes for 25% of patients, while 13% did not remember. Exclusively one treatment option was discussed with 86% of patients. 78% have been informed about their initial breast cancer diagnosis in personal meetings, while 21% were informed by phone calls. 37% of patients had been informed about their patient rights. At preplanned interim analysis 38% of patients were lymphnode positive and 6% metastasized at initial diagnosis. 56% of patients were satisfied with their guideline conform follow-up-care, while 42% did pay for additional follow up care on their own. 85% of patients wished to have a risk-adopted, more individualized follow-up care.

Conclusion

Despite complexity and lengthiness > 85% of patients did complete the survey. There is an apparent need to have more time for initial confrontation with diagnosis and treatment options. Patients are frequently not informed about alternative treatment options as well as patient rights. Patients frequently feel under pressure in their life threatening situation and suffer substantial lack of information as well as appropriate personal communication. Patient centricity should focus on elaborated communication and information systems that support treatment decision acceptance and adherence. Further details analysis will become available in upcoming subanalysis of the Breast BRIDGister platform survey.

PO4-17-01

Patient Perception and Decision-Making in HER2+ Early Breast Cancer Management: Insights from the ASKHER2 European Survey

Presenting Author(s) and Co-Author(s):

M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy

C. Jackisch. Department of Obstetrics and Gynecology, Sana Klinikum Offenbach, Germany, Germany

O. Trédan. Medical Oncology Department, Centre Léon Bérard, Lyon, France

M. Vidal. Medical Oncology Department, Hospital Clínic of Barcelona ; Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain ; SOLTI Breast Cancer Research Group ; Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Catalonia, Spain

M. Fontes-Sousa. CUF Tejo, Portugal, Lisboa, Portugal

A. Valachis. Örebro University Hospital, Sweden, Sweden

R. D'Antona. Europa Donna Italia, Italy, Italy

M. Ruz. Asociación Mama Ovario Hereditario (AMOH), Spain, Spain

E. Krone. Mamazone, Germany, Germany

M. brice. Careca Power, Portugal, United States

E. Berjonneau. Cerner Enviza, France

S. Matos. Pierre Fabre, Portugal

O. Dialla. Pierre Fabre, France

L. Guérault-Accolas. Patients en Réseau, France, France

Background

Breast cancer remains the most prevalent cancer in women globally, with Human Epidermal Growth Factor Receptor 2 positivity (HER2+) observed in 15-30% of initial breast cancer cases. Adjuvant treatment for HER2+ early breast cancer has notably reduced mortality and recurrence rates. However, the heterogeneity of the disease and in conveying risk information by healthcare providers (HCPs) leaves many women uncertain about their individual risk of recurrence and potential treatment (tx) options. Evidence shows that fear of recurrence, uncertainty about prognosis, and inadequate risk/benefit information can affect patients' decisions during their tx phase. Therefore, it is important to better understand the perceptions, attitudes, and behaviors regarding the risk of recurrence in women with HER2+ early breast cancer.

Methods

A protocol-driven, direct-to-patient online survey (30 questions total) was administered in France, Germany, Italy, Portugal, Spain, and Sweden via patient advocacy groups and panels. Women aged 18 years and above with either early-stage (eBC) (stages I-III) or metastatic (mBC) (stage IV) as the result of recurrence from an initial diagnosis of locally advanced HER2+ breast cancer were eligible to participate. The implementation of soft quotas ensured a representative sample size. This abstract presents the results of the survey.

Results

A total of 622 participants completed the survey between July 2022 and February 2023.

Majority of participants (70%) were between 40 and 65 years of age. Almost 85% had eBC (N=527), 62% had been diagnosed with HER2+ eBC for ≥ 2 years, and 68% were undergoing breast cancer tx at the time of the survey.

The main worries and concerns that were reported by participants when asked about their tx plan were risk of recurrence (27%), fear of dying (22%) and risk of tx failure (14%). Among eBC participants, 40% perceived their personal risk of recurrence to be moderate, 18% perceived it to be high, while 21% did not know their personal risk. Most eBC participants (72%) preferred short and simple explanations from the medical team about the risk of cancer recurrence, while 4% preferred not to receive this information. Overall, 30% of participants said they had fully discussed the risk of recurrence with their doctor, while 20% had no discussion. Almost all participants (97%) wanted to be involved in their tx decision, 49% completely and 48% partially. To reduce this risk of recurrence, participants with eBC were willing to change their diet habits (77%), exercise more frequently (74%), take additional tx (65%) or undergo surgery (60%). Most participants (69%) were willing to take additional tx even if it would reduce their risk of recurrence by less than 50%. Participants were most willing to tolerate fatigue (53%), followed by hot flashes (51%) and joint pain (44%), as the most acceptable side effects if they had to take additional treatments with the potential benefit of reducing risk of recurrence.

Conclusion

The multinational large direct-to-patient ASKHER2 survey reflects participants' experience and highlights concerns of patients with HER2+ breast cancer, notably on their recurrence risk. To mitigate this risk, patients exhibited a willingness to modify lifestyle habits and consider additional tx. A fraction of participants considered they had thoroughly discussed these risks with their HCPs, while the vast majority desired active involvement in their treatment decisions. These results underscore the ongoing need for HCPs to discuss the risk of recurrence in a clear way, addressing the full potential of treatment options in eBC and mBC, to enable patients to participate in this patient-centered approach of the decision-making process.

PO4-17-02

A multicenter, prospective, observational study of patients receiving trastuzumab deruxtecan for the treatment of HER2-positive and HER2-low unresectable and/or metastatic breast cancer: DESTINY-Breast-RESPOND

Presenting Author(s) and Co-Author(s):

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

R. Basho. The Lawrence J. Ellison Institute for Transformative Medicine, Los Angeles, USA, Los Angeles, California, United States

m. lustberg. Yale Cancer Center, New Haven, Connecticut, United States

G. Lyman. Fred Hutchinson Cancer Center, Seattle, Washington, USA, Seattle, Washington, United States

M. Prahlanan. AstraZeneca Pharmaceuticals, Cambridge, UK, United States

G. James. AstraZeneca Computational Pathology, Early Oncology Translational Medicine, Munich, Germany, United States

D. Varghese. AstraZeneca Pharmaceuticals LP, Gaithersburg, MD, USA, United States

F. Lujan. Global Medical Affairs, OBU, AstraZeneca, Cambridge, UK, Cambridge, England, United Kingdom

H. Tesch. Oncology Practice at Bethanien Hospital Frankfurt, Frankfurt, Germany, Germany

Background: Approximately 20% of breast cancer (BC) cases are human epidermal growth factor receptor 2-positive (HER2+; immunohistochemistry [IHC] 3+, IHC 2+/in-situ hybridization [ISH]+), and up to ~50% of patients with primary or metastatic BC (mBC) have HER2-low tumors (IHC 1+, IHC 2+/ISH-), a new therapeutically targetable subset of BC. Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate approved in the USA, EU, and other countries for the treatment of adult patients with unresectable or metastatic HER2+ BC who have received a prior anti-HER2-based regimen, or with unresectable or metastatic HER2-low BC who have received a prior chemotherapy (CTx) in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant CTx. Approvals followed positive results from the DESTINY-Breast03 and DESTINY-Breast04 clinical trials. In DESTINY-Breast03, T-DXd improved median progression-free survival (mPFS) compared with trastuzumab emtansine (28.8 vs 6.8 months, respectively; $P < 0.0001$) in previously treated (prior trastuzumab and taxane) patients with HER2+ mBC. In DESTINY-Breast04, T-DXd significantly improved mPFS vs physician's choice of CTx (9.9 vs 5.1 months, respectively; $P < 0.001$) in all randomized patients with HER2-low mBC who were previously treated with one or two lines of CTx. Alongside these efficacy benefits, T-DXd has demonstrated an acceptable and generally manageable safety profile. To optimize care and maximize treatment benefit, insights into real-world T-DXd use and safety events of interest, including patient management and experience, are needed. This study aims to describe the effectiveness and tolerability of T-DXd in patients with HER2+ or HER2-low unresectable and/or mBC in a real-world setting.

Trial design: DESTINY-Breast-RESPOND (NCT05592483) is a multicenter (120 sites planned as of June 2023), multi-country (HER2+ cohort: several regions globally; HER2-low cohort: North America only), prospective, observational study characterizing real-world clinical use, effectiveness, tolerability, and patient experience among adults who initiated T-DXd monotherapy, per standard of care, for HER2+ (second line or earlier) and HER2-low

unresectable and/or mBC (T-DXd not provided by study sponsor). The decision to initiate T-DXd will be made by the physician prior to, and independent from, participation in this study. Approximately 750 patients with HER2+ and 250 patients with HER2-low disease will be enrolled. Patients must have received prior treatment with a trastuzumab-containing regimen in the metastatic setting or have evidence of disease progression within 6 months of neoadjuvant or adjuvant treatment (HER2+ cohort), or prior CTx in the metastatic setting or have evidence of disease progression within 6 months of adjuvant CTx (HER2-low cohort). Data will be collected via chart abstraction, patient-reported outcome questionnaires on tolerability and safety (PGI-TT, NCI PRO-CTCAE, and EORTC IL19), and a daily patient nausea/vomiting symptom diary. Endpoints will be analyzed separately for HER2+ and HER2-low cohorts. The primary endpoint of interest is time to next treatment from T-DXd initiation, a measure of real-world effectiveness. Other important endpoints include treatment patterns, safety events of interest (nausea/vomiting, fatigue, alopecia, interstitial lung disease / pneumonitis, left ventricular ejection fraction decrease) and their management, time to T-DXd discontinuation, and patient-reported tolerability. Patients will be observed until end of study (~60% of patients receive subsequent treatment or have died), withdrawal from study, or loss to follow up, whichever occurs first.

PO4-17-03

Neoadjuvant chemotherapy in invasive lobular carcinoma of the breast: A retrospective study on survival outcomes

Presenting Author(s) and Co-Author(s):

V. Gauthier. CHU de Québec - Université Laval, United States

A. Simard. CHU de Québec - Université Laval, United States

C. Desbiens. CHU de Québec - Université Laval, United States

B. Poirier. CHU de Québec - Université Laval, United States

J. Lemieux. Centre des maladies du sein du CHU de Québec-Université Laval, Hôpital St-Sacrement, Québec, Quebec, Canada

D. Boudreau. CHU de Québec - Université Laval, United States

D. Leblanc. CHU de Québec - Université Laval, United States

C. Morin. CHU de Québec - Université Laval, United States

J. Hogue. CHU de Québec - Université Laval, United States

□. Poirier. CHU de Québec - Université Laval, United States

Background: Neoadjuvant chemotherapy (NAC) is a well-established component of breast cancer management. Invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) are often treated similarly, but many studies are demonstrating a major difference in treatment responses according to the histopathological type of cancer.

Aim: To evaluate the overall survival of patients with ILC after NAC compared with adjuvant chemotherapy.

Methods: This retrospective cohort study included patients treated for breast ILC between 1998 and 2016 at the Center for Breast Diseases of de CHU de Québec – Université Laval, a tertiary breast cancer center. The primary outcomes were the overall survival (OS) and the recurrence-free survival (RFS) of ILC patients receiving NAC compared with patients who received only adjuvant chemotherapy. The follow-up was censored at the last hospital contact. The secondary outcomes were the locoregional recurrence, pathological complete response (pCR), and pCR impact on survival.

Results: During the study period, 265 women were treated for ILC, of which 72 had NAC, and 193 had adjuvant therapy. No significant differences were observed regarding the patient's characteristics (age, BMI, smoking, menopausal status, and use of hormonal replacement therapy). A T4 disease was found in 29.2% of the NAC group (vs. 0 in the adjuvant group), but the N2-3 rate was lower in the NAC group (5.6% vs. 22.3%, $P=0.011$). More patients in the NAC group underwent mastectomy (65.3% vs. 29.5%, $P<0.0001$) and axillary dissection (80.6% vs. 50.8%, $P<0.0001$). Three (4.2%) patients in the NAC group achieved a pCR. The rates of radiotherapy ($P=0.851$) and hormonal therapy ($P=0.694$) were similar between the two groups. The mean follow-up was 8 years. After adjustment for age, T, N, surgery type, radiotherapy, and hormonal therapy, the NAC group showed significantly lower 10-year OS (56.2% vs. 80.7%, $P<0.0001$) and RFS (51.8% vs. 72.7%, $P=0.0004$) compared with the adjuvant group. There were no differences in the 10-year local recurrence rate (90.6% vs. 93.5%, $P=0.11$). In a Cox regression analysis of RFS considering the previously mentioned covariables, more events in the NAC group (OR=2.52, 95%CI: 1.39-4.58, $P=0.002$) and

patients with N2-N3 (OR=3.68, 95%IC: 2.00-6.80, P< 0.01).

Conclusion: Despite the general belief that ILC and IDC should be treated similarly, this study strongly suggests that ILC seems to have a poorer response to NAC. Patients diagnosed with ILC might benefit from a more aggressive surgical approach followed by adjuvant chemotherapy, no matter the severity of the disease. Additional long-term prospective comparative studies are needed to support this statement and improve the management of these patients.

PO4-17-04

CDK 4/6 inhibitor switching patterns in Swedish patients with metastatic breast cancer: 5-year update from the SIRI study

Presenting Author(s) and Co-Author(s):

H. Lindman. Uppsala University Hospital, Uppsala, Sweden

A. Valachis. Örebro University Hospital, Örebro, Sweden

R. Lauppe. Quantify Research AB, Sweden, United States

M. Lilja. Quantify Research AB, Sweden, United States

D. Nyqvist. Pfizer, United States

M. Jakobsson. Pfizer, United States

Background: CDK 4/6 inhibitors (CDK 4/6i) combined with endocrine therapy is a well-established treatment option in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC). However, there is limited evidence on switching patterns within this class of drugs. The Swedish Ibrance Registries Insights (SIRI) study investigated CDK 4/6i switching patterns in real-world setting using a nationwide cohort of MBC patients.

Methods: This was a retrospective study utilizing population-based Swedish Health Data Registers. The overall cohort included all breast cancer patients ≥ 18 years with ≥ 1 dispensation of palbociclib from January 2017 – June 2022. This subgroup analysis focused on patients with ≥ 1 dispensation of either ribociclib or abemaciclib in addition to palbociclib. Minimum follow-up was 3 months. CDK 4/6-i sequencing patterns in total and over time as well as time from the first CDK 4/6i to the subsequent, was investigated. No information on the reason for switching was available.

Results: Out of a total 2314 patients with ≥ 1 dispensation of palbociclib, 256 patients (11%) had ≥ 1 dispensation of either ribociclib or abemaciclib, either prior to (60% of cases) or following (40 % of cases) palbociclib treatment. The share of patients with dispensation of > 1 CDK 4/6i increased over the study period from 7% of the patients initiating treatment in 2017 to 15% in 2021. Of the total 2161 patients initiating CDK 4/6i treatment on palbociclib, about 5% were subsequently prescribed another CDK 4/6i. The median age at treatment initiation in patients with > 1 dispensed CDK 4/6-i was similar to the overall study cohort (67.1 vs 68.4 years). Half of the patients identified with > 1 CDK 4/6i were initiated on ribociclib and prescribed palbociclib subsequently. The second and third most common switches were palbociclib to abemaciclib (25%) and palbociclib to ribociclib (10%), respectively. Seven patients received all three CDK 4/6i.

In terms of time to subsequent CDK 4/6i, 108 patients (42%) were prescribed a subsequent CDK 4/6i within three months of treatment initiation with ribociclib-palbociclib being the most common sequence in 74 patients whereas 17%, 8%, and 4% of switches happened 4-6, 7-9, and 10-12 months after treatment initiation, respectively. Seventy-two patients (28%) had a dispensation of a subsequent CDK 4/6i more than 12 months after initiation of the first CDK 4/6i, with palbociclib-abemaciclib being the most common switch.

Conclusions: A relatively high proportion of Swedish patients treated with CDK4/6i is switched from one to another CDK 4/6i soon after treatment initiation, implying that this strategy might be

applied mainly, but not solely, due to adverse events. The increased trend over time might be associated with the regulatory approval of new CDK4/6i over time. Future studies should focus on the potential impact of switching CDK 4/6i on treatment effectiveness and toxicity as these issues have yet not been clarified.

Declaration of Interest: This study is sponsored by Pfizer. AV has reported receiving research funding from Roche. HL has reported receiving consultant/advisory fees from Lilly, Novartis, Daichii, Pfizer, MSD, Pierre Fabre, Astra-Zeneca and research funding from Roche. MJ and DN are employees of Pfizer. RL and ML are employees of Quantify Research and were paid consultants to Pfizer for this research.

Number of patients per observed CDK 4/6 inhibitor sequence	
Sequence	Number of patients
ribociclib – palbociclib	128
palbociclib – abemaciclib	69
palbociclib – ribociclib	23
abemaciclib – palbociclib	18
palbociclib - ribociclib – abemaciclib	7
ribociclib - palbociclib – abemaciclib	6
palbociclib - abemaciclib – ribociclib	3
abemaciclib - palbociclib – ribociclib	1
abemaciclib - ribociclib – palbociclib	1
Total	256

Time from initiation of first CDK 4/6 inhibitor to subsequent (number of patients)						
	Total	0-3 months	4-6 months	7-9 months	10-12 months	>12 months
palbociclib to ribociclib	30	11	4	5	3	7
palbociclib to abemaciclib	72	11	11	7	1	42
ribociclib to palbociclib	134	74	27	8	6	19
abemaciclib to palbociclib	19	11	2	1	1	4
abemaciclib to ribociclib	1	1	0	0	0	0
	256	108	44	21	11	72

PO4-17-05

Patterns of care: radiotherapy after breast conserving surgery and the use of endocrine therapy for screen-detected ductal carcinoma in situ (DCIS) in the UK

Presenting Author(s) and Co-Author(s):

P. A van Dam. Multidisciplinary Oncologic Centre Antwerp [(MOCA)], Antwerp University Hospital, Edegem, Belgium Center for Oncological Research (CORE), University of Antwerp, Wilrijk, Belgium, United States

D. Dodwell. University of Oxford, Oxford, England, United Kingdom

E. Sawyer. Guy's and St.Thomas' NHS Foundation Trust/King's College London, United States

R. Cutress. University of Southampton, United States

N. Sharma. Leeds Teaching Hospitals NHS Trust, United States

A. Shaaban. Queen Elizabeth Hospital, Birmingham, United States

A. Thompson. Baylor College of Medicine, Houston, Texas, United States

Background

The use of adjuvant radiotherapy (RT) and endocrine therapy (ET) in the management of pure ductal carcinoma in situ (DCIS) remains controversial. We investigate how the use of adjuvant RT after breast conserving surgery (BCS) and use of adjuvant ET (in BCS and mastectomy patients) has changed over time.

Methods

A prospective cohort SQL database of 11,284 patients (the Sloane Project) diagnosed 2003-2012 with screen-detected DCIS in the UK was interrogated for use of adjuvant RT and ET over time and association with factors reported to be predictive of recurrence (patient age, DCIS nuclear grade, size, comedo necrosis, resection margins), as well as institution of surgery, travel time to radiotherapy facility, Index of Multiple Deprivation and outcome (provided by the National Disease Registration Service, NDRS). RT data by site were confirmed with more recent data from the National Audit of Breast Cancer in Older Patients (NABCOP), which looked at patterns of care and outcomes for women aged 70 years and over, compared with those aged 50-64 in England and Wales.

Results

Among the 7,949 women (70.6%) treated by BCS, post-operative adjuvant RT was given to 4,939 (62.1%); RT use after BCS increased over time ($R^2 = 0.92$; $p < 0.01$). RT use was associated with year of diagnosis ($p < 0.01$), younger age at diagnosis ($p < 0.01$), larger DCIS size ($p < 0.01$), presence of comedo necrosis ($p < 0.01$), higher nuclear grade ($p < 0.01$) and presence of microinvasion ($p < 0.01$). Adjusted analyses showed the most significant factor for RT after BCS was the surgery institution. Travel time to RT facility, Index of Multiple Deprivation and final radial margin were not associated with RT use. When compared with the more recent data from the NABCOP, a marked variation in radiotherapy use across hospitals remains. Ipsilateral recurrence rate varied significantly by hospital, with some of the difference associated with RT utilisation. ET was prescribed in 1313 women (12%), more often following BCS than mastectomy ($p < 0.001$), with significant variation by institution and a decline in the use of ET over time.

Conclusion

Marked geographic variation in the use of RT and ET after surgery for DCIS persists in the UK

and is likely due to physician choice rather than other factors such as travel times to RT facilities. This is contributing to geographic variation in ipsilateral recurrence rates, suggesting the need for adoption of more authoritative guidelines to support clinical decision-making. Consistent national practice could provide auditable performance standards for adjuvant therapy of screen detected DCIS and contribute to more uniform patient care.

PO4-17-06

Real World Data: A single institute experience with neoadjuvant endocrine therapy for ER+ breast cancer — clinical response rates, clinical predictors of response and long-term outcomes following breast conserving surgery.

Presenting Author(s) and Co-Author(s):

A. Turnbull. The University of Edinburgh, United States

C. Martinez-Perez. The University of Edinburgh, Edinburgh, Scotland, United Kingdom

C. Kay. The University of Edinburgh, United States

R. Swan. NHS Lothian, Edinburgh, Northern Ireland, United Kingdom

L. Renshaw. NHS Lothian, Edinburgh, Scotland, United Kingdom

J. Dixon. The University of Edinburgh / Edinburgh Breast Unit, United States

Background: Neoadjuvant endocrine therapy (NET) in postmenopausal women (PMW) with large or locally advanced oestrogen receptor (ER)-rich breast cancer allows more women to be treated by breast-conserving surgery (BCS). A comprehensive analysis of the factors affecting clinical response to NET and the long-term safety of this strategy has been studied.

Patients: A retrospective cohort was studied of 435 PMW (median age: 77 years; range: 50-98) with ER-positive breast cancer treated with NET (aromatase inhibition) (median duration: 6.8 months; range 3-43 months), between 2001-15. Clinical response was monitored throughout NET treatment with periodic 3D ultrasound measurements of the primary tumour. All patients went on to have surgery, 55% had adjuvant radiotherapy and all had adjuvant ET for at least 5 years. All patients had routine follow-up (median follow-up 12.3 years). To-date, this represents the largest cohort of patients treated with >3 months NET.

Results: Clinical response to NET was excellent, with only 3.2% of tumours progressing on-treatment based on RECIST 1.1 criteria. Mean percentage reduction in tumour on NET was 71%. Response rate (partial/complete response) was 59% and response continued until 12 months and then levelled off. Following NET, over 92% of patients were suitable for BCS and 61% achieved clinical TNM down-staging. Multivariate analysis revealed that only ER level (response highest in patients with Allred scores 7 and 8), and percentage change in tumour volume by 6 weeks were significant predictors of overall clinical response to NET. Clinical response to NET was not associated with node status or tumour grade.

BCS following NET had a local disease control rate of 89% (95%CI±0.06) at 10 years, but actuarial local recurrence at 10 years was only 7% in those having radiotherapy compared with 30% in the group who did not receive radiotherapy (P< 0.0001). In addition, the overall recurrence rate (P=0.028) was improved by radiotherapy irrespective of nodal status. Radiotherapy did not improve overall breast cancer-specific survival (BCSS). Systemic recurrence and BCSS was higher with greater nodal involvement. Most patients in this study died of other causes (14-year crude all-cause mortality was 71%).

Conclusion: NET followed by BCS is an effective strategy in PMW with ER-rich breast cancer. Excellent clinical response rates are seen even in women with node-positive or high-grade disease. Less than 5% showed evidence of progression. Early response to NET predicts for long-term tumour volume reduction and NET can achieve continued tumour shrinkage for up to

1 year. NET followed by BCS appears a safe treatment approach and offers good long-term outcomes when BCS is followed by adjuvant radiotherapy.

PO4-17-07

RELATE 2: A real-world observational study assessing feasibility, acceptability, perceived impacts of digital apps for patients receiving olaparib or trastuzumab deruxtecan (T-DXd) as part of routine clinical practice.

Presenting Author(s) and Co-Author(s):

S. McGrath. The Royal Marsden NHS Foundation Trust, Department of Medicine, Breast Unit, United Kingdom

P. Hall. University of Edinburgh, Edinburgh, United Kingdom

M. Acquadro. Evidera, London, England, United Kingdom

S. Skovlund. Evidera, London, England, United Kingdom

P. Jayia. Astrazeneca, London, England, United Kingdom

S. McIntosh. Queen's University Belfast, United States

D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom

Background: Safe and effective use of two new treatments, T-DXd or olaparib, in breast cancer (BC) requires awareness, education and co-ownership by patients and care teams. It is hypothesized that a patient-centered digital app that provides disease and treatment-specific guidance and symptom reporting functionality while collecting specific data could positively impact patients' confidence, self-monitoring of symptoms and experience of care. This study will develop and assess two new treatment-specific versions of the accredited OWise app to evaluate how BC patients accept and use the app and how use in routine care appears to impact patients and their experience of care in relation to monitoring symptoms. As a novel element, this study will explore the feasibility of combining treatment-specific real-world data collection with digital health support to understand how treatment patterns and characteristics in the real-world setting.

OWise is a specific BC app that has been endorsed by NHS digital and is widely available through NHS app library in UK and in Netherlands. It currently has over 18K registered users.

Trial Design: The study involves two workstreams which include several sources for data collection. Workstream 1 involves collection of participants OWise data (including patient entered data as well as usage statistics) and a brief survey for participants to provide feedback on their experience using OWise every three months for up to 18 months. Survey questions are focused on their perceptions of the usefulness of the app for monitoring their health changes and communicating with their care team. Workstream 2, will launch approximately three months after the launch of Workstream 1 and will include qualitative interviews with two groups of people: 1) a small number of participants who are already enrolled in Workstream 1 and 2) clinicians (and multidisciplinary team / nurses) to further understand the perceived benefits of the app. The study's duration will be 21 months

Eligibility Criteria: The patients must be prescribed either T-DXd or Olaparib and be at least 18 years of age, be able to create an OWise account (e.g., mobile or web application) and have activated the unique study code for the treatment specific version of OWise and be able to provide online consent for study participation

Aims: Primary objectives are to evaluate the feasibility, acceptability, and perceived impacts on

patient experience, treatment use, and quality of care of two treatment specific Owise apps in routine BC care. Secondary objectives will focus on prescribing patterns, concomitant medicine use in UK practice, understanding strategies used in the real-world setting to manage AE and demographic and clinical characteristics of patients treated in the UK

Statistical methods: Aggregated Participant-level quantitative data and usage data will be analyzed for response frequencies, means, standard deviations (SD), medians, ranges, and confidence intervals (CI). Descriptive statistics and advanced statistics will be used to identify core variables and trends, investigate data distribution links between data, test significant differences between datasets according to profile/status.

Target Accrual: 300 patients T-DXd and 150 olaparib using the Owise app and being part of the real-world study. The prescription decision is independent of the study enrolment.

Contact: Dr Sophie McGrath. sophie.mcgrath@rmh.nhs.uk

PO4-17-09

Epidemiological Analysis and Overall Survival of Male Breast Cancer in a Developing Middle Eastern Country Over 18 Years

Presenting Author(s) and Co-Author(s):

Z. Abdulelah. St Bartholomew's Hospital, London, England, United Kingdom

A. Abdulelah. University of Jordan, Jordan

A. Alhajajeh. King Hussein Cancer Center, United States

A. Ghazzawi. King Hussein Medical City, United States

L. El-Amayreh. University of Jordan/ School of Medicine, United States

H. Abdel-Razeq. King Hussein Cancer Center, Amman, Jordan

Background: Despite the profound rarity of breast cancer in males, it remains of importance given the associated morbidity and mortality, including the association with worse prognosis than female patients. Nonetheless, male breast cancer epidemiology remains poorly studied in middle eastern populations.

Methodology: This retrospective cohort study examined male patients aged 15 to 85 years who were diagnosed with breast cancer between 2000 and 2018, using data from the Jordan Cancer Registry. Kaplan-Meier analysis was performed to assess the 5-year overall survival of the patients over time.

Results: A total of 22,600 patients were diagnosed with breast cancer since 2000 in Jordan, of which 362 (1.6%) patients were males. 39.8% of male breast cancer cases occurred in the right breast, while the left breast was affected in 43.4% of the cases, and 3.3% of the cases were bilateral. Meanwhile, laterality was not mentioned in 13.5% of registry records.

All male breast cancer cases were malignant in origin with the breast being the primary cancer. Most male patients had grade II (N=112, 30.9%) followed by grade III breast cancer (N=88, 24.3%).

Among the male breast cancer cohort, 224 (62.2%) were treated with surgical intervention, 103 (28.8%) patients were given chemotherapy, 84 (23.4%) patients had radiotherapy and 24 (6.70%) patients had hormonal therapy.

27 patients died during the follow up period. The 5-year overall survival rate for the patients was 92.5% (95% CI, 89.9% to 95.3%).

Conclusion: Breast cancer in middle eastern males tends to more commonly present in the left breast, and at a more advanced stage in comparison to females.

PO4-17-10

Epidemiological Analysis and Overall Survival of Female Adolescent and Young Adults Breast Cancer in a Developing Middle Eastern Country Over 18 Years

Presenting Author(s) and Co-Author(s):

A. Abdulelah. University of Jordan, Jordan

Z. Abdulelah. St Bartholomew's Hospital, London, England, United Kingdom

A. Alhajajeh. King Hussein Cancer Center, United States

A. Ghazzawi. King Hussein Medical City, United States

L. El-Amayreh. University of Jordan/ School of Medicine, United States

H. Abdel-Razeq. King Hussein Cancer Center, Amman, Jordan

Background: Breast cancer is the most common type of cancer among female adolescents and young adults (AYAs) aged 15-39 years at diagnosis. AYAs with breast cancer have worse prognosis and are more likely to present with unfavorable tumor biology. However, breast cancer in AYAs is still poorly reported in middle eastern populations.

Methodology: This is a retrospective cohort study which examined female AYAs patients aged 15 to 39 years at the time of diagnosis who were diagnosed with breast cancer between 2000 and 2018, using data from the Jordan Cancer Registry. Kaplan-Meier analysis was performed to assess the 5-year overall survival of the patients over time.

Results: A total of 3831 Female AYAs were diagnosed with breast cancer in Jordan between 2000 and 2018 with a median age of 34.2 (IQR 30.9-38.3) years. 43.2% of female AYAs breast cancer cases were right breast cancer, whereas left breast cancer occurred in 47.4% of cases, and only 2.15% of cases were bilateral breast cancer. Meanwhile, 7.31% of cases did not have a reported laterality in the registry records.

Most female AYAs patients had high grade breast cancer with grade III breast cancer being the most common (N=1349, 35.2%) followed by grade II breast cancer (N=1093, 28.5%).

Among this female AYA cohort, 2208 (59.3%) were treated with surgical intervention, 1621 (43.5%) patients were given chemotherapy, 1220 (32.7%) patients had radiotherapy, 265 (7.15%) patients had hormonal therapy and only 47 (1.27%) were treated with immunotherapy.

Among the entire studied cohort, 229 (5.98%) patients died during follow up period. The 5-year overall survival was 94% (95% CI 93.3% to 94.8%)

Conclusion: Female AYAs breast cancer tends to have a predilection towards the left breast, but presents at a more advanced grade compared with other age groups in females.

PO4-17-11

Normalized Breast Cancer Survival Outcomes in U.S. Tumor Registries

Presenting Author(s) and Co-Author(s):

T. Chanenchuk. Duke University Medical Center, United States

K. Crowell. Duke Cancer Institute, United States

S. Thomas. Duke University School of Medicine, Durham, North Carolina, United States

R. Greenup. Yale School of Medicine, New Haven, Connecticut, United States

J. Plichta. Duke University School of Medicine, Durham, North Carolina, United States

Background

The largest U.S. tumor registries, NCDB (National Cancer Database) and SEER (Surveillance, Epidemiology, and End Results Program), are vital sources of epidemiological data and are frequently utilized in research. Although the NCDB includes the majority of patients diagnosed with breast cancer, it is a hospital-based registry. In contrast, SEER is a population-based registry, but includes less than half of all breast cancer patients diagnosed each year. While the US Cancer Statistics Public Use Database (USCS) captures nearly all breast cancers, treatment and survival data are not included. As such, we sought to normalize the NCDB and SEER populations to mirror the USCS population and examine survival outcomes after normalization.

Methods

All patients diagnosed with stage I-IV breast cancer (2010-2018) were selected from the NCDB and SEER. Frequencies of patients by select characteristics were exported from the USCS. Rates from the USCS were then used to normalize the NCDB and SEER cohorts, using patient weighted frequencies for age, sex, race/ethnicity, tumor biomarkers [estrogen receptor (ER), HER2], and extent of disease (local, regional, distant; anatomic staging data not available in USCS). Of note, the USCS does not have individual patient-level data (only summary data for select variables), and thus, weighted frequencies were used for normalization. The weighted frequencies were calculated based on the total number of patients in the USCS database divided by the total number of patients in the NCDB or SEER separately for each variable (age, sex, race/ethnicity, etc). Weighted and unweighted data were summarized with N (%). Unweighted patient and disease characteristics (crude data) were compared using Chi-square tests. Overall survival (OS) was estimated using the Kaplan-Meier method before and after normalization.

Results

The USCS cohort included 2,473,739 patients; the NCDB included 1,441,556 and SEER 504,938. The median followup was 54.9 months for NCDB and 57 months for SEER. There were minimal differences between the cohorts based on age (age < 50y: USCS 18.1%, NCDB 19.3%, SEER 18.9%) or sex (female: USCS 99.1%, NCDB 99.1%, SEER 99.3%). However, there were notable differences in the racial/ethnic composition; non-Hispanic White: USCS 75%, NCDB 78.2%, SEER 68.2%; non-Hispanic Black: USCS 11.4%, NCDB 11.4%, SEER 9.9%; Hispanic: USCS 8.3%, NCDB 5.9%, SEER 11.7%; $p < 0.001$ for USCS vs NCDB and USCS vs SEER). There were minimal differences in tumor biomarkers (ER+: USCS 82.9%, NCDB 83%, SEER 84.9%; HER2+: USCS 14.5%, NCDB 14.1%, SEER 13.8%), but significant differences in extent of disease (local: USCS 66.1%, NCDB 80.2%, SEER 68.4%; distant: USCS 6%, NCDB 3.9%, SEER 3.9%; $p < 0.001$ for USCS vs NCDB and USCS vs SEER). For the variables that were similar without weighting (age, sex, tumor biomarkers), OS was also

similar after weighting (Table). After normalizing the NCDB based on race, 8-year OS remained comparable (crude 77.2% vs weighted 77.3%); similar findings were noted after normalizing SEER (crude 75.8% vs weighted 75.3%). After normalizing the NCDB based on extent of disease, 8-year OS was notably worse (crude 77.2% vs weighted 74.2%); similar findings were noted for SEER (crude 75.8% vs weighted 74.4%).

Conclusions

While national tumor registries afford researchers the opportunity to study large breast cancer cohorts, they do not always fully represent the entire breast cancer population. This limitation should be considered when working with these data sets.

Table: Summary of crude (unweighted) and weighted 8-year OS rates based on select variables.

Variable	NCDB, 8-year OS	SEER, 8-year OS
Crude (unweighted)	77.2%	75.8%
Weighted by age	77.0%	75.7%
Weighted by sex	77.2%	75.8%
Weighted by race	77.3%	75.3%
Weighted by ER	77.2%	75.6%
Weighted by PR	77.1%	75.7%
Weighted by HER2	77.2%	75.8%
Weighted by extent of disease	74.2%	74.4%

PO4-17-12

Early adherence to adjuvant abemaciclib: Data from the Belgian Medical Need Program

Presenting Author(s) and Co-Author(s):

M. Van Houdt. UZ Leuven, United States

M. Michaux. Lilly Belgium, United States

S. Altintas. Antwerp University Hospital, Edegem, Belgium, United States

A. Awada. Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, United States

J. Canon. Grand Hôpital de Charleroi, United States

H. Denys. Department of Internal Medicine and Pediatrics, Ghent University Hospital, Ghent, Belgium, United States

F. Duhoux. Cliniques universitaires Saint-Luc-institut Roi Albert II, United States

G. Jerusalem. Department of Medical Oncology, University Hospital of Liege, CHU Sart Tilman, Liege, Belgium, United States

J. Mebis. Jessa Hospital Hasselt, United States

R. Janssens. KU Leuven, United States

I. Huys. KU Leuven, United States

B. Liese. KU Leuven, United States

C. Verbeke. KU Leuven, United States

S. Han. University Hospitals Leuven, Leuven, Vlaams-Brabant, Belgium

H. Wildiers. University Hospitals Leuven, United States

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

Patient adherence profiles for adjuvant hormonal therapy combined with abemaciclib in HR+/HER2- High Risk EBC based on real world evidence (RWE) from a Medical Need Program in Belgium

Background

Following results of MonarchE, demonstrating clinically meaningful improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS), a 2-year treatment with abemaciclib has been reimbursed in Belgium since May 1st, 2023 for the adjuvant treatment of HR+, HER2-, lymph node-positive (>3 or 1-3 if pT3 or grade 3) early breast cancer (EBC). In this trial, adverse event related treatment discontinuation was reported in 18,5% (8.9% after dose reduction) of which 10.1% in the first 5 months after starting this CDK 4/6 inhibitor.

Prior to reimbursement, an early access program was initiated in Belgium on June 28 2022. We studied the proportion of patients estimated to be eligible for the program nationwide who effectively started adjuvant abemaciclib, as well as early treatment discontinuation and dose reductions.

Methods

The number of eligible patients for the adjuvant abemaciclib Medical Need Program (MNP) was estimated by the Belgian Cancer Registry based on the above mentioned reimbursement criteria for patients registered during the incidence year 2018. The MNP was active in Belgium from June 28 2022 until May 1 2023.

Discontinuation rate and proportion with dose reductions were calculated using a nationwide prospective managed monthly updated register of participating patients including information on age at diagnosis, time since therapy start, delivered doses and patient reported adverse events (AE). They all signed an informed consent and agreed to share their registered data after anonymization. Data analysis was retrospective . Descriptive statistics were used.

Results

In this 10-month period, 840 patients were estimated to be eligible to receive adjuvant abemaciclib in Belgium. A total of 311 patients (309 women, 2 men) were included in the program, 37% of the estimated number of patients.

Median age at initiation was 57 y. Median time on treatment was 4.5 months (156 patients >4.5 months on treatment). 21/311 (6.7%) patients discontinued (all causes). 2 patients never started. 10 patients (3.2%) discontinued their therapy without dose reduction. 12/311 (3.8%) had a starting dose of 2x100 mg/d. 128/311 (41.1%) had a dose reduction, 96/128 (75%) before 3 months of therapy.

In the subgroup of 156 patients starting treatment >4.5 months ago, 16/156 (10.2%) discontinued treatment, 13 patients have not yet been reported. 79/156 (50.6%) required a dose reduction, of which 7 (4.5%) discontinued after dose reduction.

The reasons for discontinuation reported: 8/21 (38%) gastro-intestinal intolerance, 3/21 (14.2%) real deterioration in renal function, 8/21 quality of life issues (not specified), 1/21 anal burning sensation and anal fistula, 3/21 asthenia and fatigue.

Conclusion

Of the estimated eligible patients in Belgium 37 % started with adjuvant abemaciclib. These results illustrate that there is a need to further improve implementation of adjuvant abemaciclib. Early results show that 89.8% of patients receiving adjuvant abemaciclib therapy in Belgium continued their treatment after 4.5 months and 50% of patients needed a dose reduction. Longer follow-up will be needed. Understanding the reasons of discontinuation and early dose adjustments can enable better patient support on adherence. This is a critical capability to ensure optimal patient compliance.

PO4-18-01

International Validation of a Staging Model for de novo Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Plichta. Duke University School of Medicine, Durham, North Carolina, United States
S. Thomas. Duke University School of Medicine, Durham, North Carolina, United States
S. Siesling. Netherlands Comprehensive Cancer Organization (IKNL) | University of Twente, Department of Health Technology and Services Research, Utrecht & Enschede, Netherlands
L. de Munck. Netherlands Comprehensive Cancer Organisation (IKNL), Netherlands
A. Lusque. Biostatistics & Health Data Science Unit, Institut Claudius Regaud, IUCT-oncopole, Toulouse, France, United States
T. Grinda. Department of Cancer Medicine, Gustave Roussy, 114 Rue Edouard Vaillant, 94800 Villejuif, France, United States
L. Gondara. BC Cancer, United States
S. Chia. British Columbia Cancer Agency, Vancouver, British Columbia, Canada
P. Cabrera-Galeana. Instituto Nacional de Cancerología, CDMX, Distrito Federal, Mexico
N. Reynoso-Noverón. Instituto Nacional de Cancerología, CDMX, México, United States
S. López-Tarruella. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain
I. Álvarez López. Medical Oncology Unit of Donostia University Hospital (Donostialdea IHO); GEICAM, Madrid, Spain, United States
S. Edge. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States
G. Hortobagyi. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background

Given the heterogeneity in outcomes for de novo metastatic breast cancer (dnMBC), a staging system was recently developed that refines prognostic estimates for patients presenting with distant metastases (JCO 2023;10:2546). This staging model was developed using the National Cancer Database and stratified patients into 4 subgroups, termed IVA, IVB, IVC, and IVD based on 3-year overall survival (OS): IVA >70%, IVB 50-70%, IVC 25-< 50%, and IVD < 25%; the primary factors affecting higher stage grouping were negative for ER, PR, and HER2 expression and a higher number of involved organ sites. Here, we aim to validate this model using an international data set.

Methods

Data for dnMBC patients were obtained from the Netherlands Cancer Registry (NCR, hosted by IKNL), Epidemiological Strategy and Medical Economics (ESME) by Unicancer, British Columbia Cancer (BCCan), Instituto Nacional de Cancerología, México (INCan), and Grupo Español de Investigación en Cáncer de Mama (GEICAM); the diagnosis years included varied by organization (range 2002-2021). Stage groups were assigned based on previously published criteria, defined by T-category, grade, ER, PR, HER2, histology, organ system site of metastases (bone-only, brain-only, visceral), and number of organ systems involved. For each cohort, followup time and OS were estimated using the reverse Kapan-Meier and Kaplan-Meier method, respectively. Median rates were estimated across all cohorts by weighting on cohort sample size or number at risk. Cox proportional hazards models were used to estimate the

PO4-18-02

Real-world (RW) utilization and patient outcomes across three CDK4/6 inhibitors in metastatic breast cancer (mBC)

Presenting Author(s) and Co-Author(s):

C. Weipert. Guardant Health, United States

S. Wander. Massachusetts General Hospital, Boston, Massachusetts, United States

A. Davis. Washington University in St Louis School of Medicine, United States

L. Bucheit. Guardant Health, United States

J. Saha. Guardant Health, United States

J. Liao. Guardant Health, United States

N. Zhang. Guardant Health, United States

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

M. Cristofanilli. Weill Cornell Medicine, United States

Background: While CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (ET) is standard-of-care first-line (1L) therapy for hormone-positive (HR+), HER2-negative mBC, there is ongoing debate regarding optimal use of the three FDA-approved CDK4/6i drugs. All three drugs have demonstrated significantly improved progression-free survival (PFS), but only two have significantly improved overall survival (OS). These trial data have prompted debate regarding optimal selection and sequencing of these drugs. To further evaluate this, we analyzed a RW clinical-genomic database to explore the use and outcomes associated with each of these CDK4/6i drugs.

Methods: RW data were queried using GuardantINFORM, a database combining de-identified genomic results from patients (pts) with cell-free circulating tumor (ctDNA) testing done via Guardant360, with administrative claims data. Pts with BC who had record of metastatic diagnosis, >2 medical or pharmacy claims, and CDK4/6i treatment in the mBC setting between March 2018 and March 2023 were included. In the subset of pts treated with CDK4/6i in the 1L or 2nd line (2L) with at least 12 months of follow-up (f/u) post-CDK4/6i initiation, RW time to next treatment (rwTTNT) and RW time to treatment discontinuation (rwTTD) were used as proxies for PFS. RW overall survival (rwOS), rwTTNT and rwTTD were reported in months (mos) and were measured based on time from first CDK4/6i treatment claim. Multivariate Cox regressions adjusted for pt age, gender, weighted comorbidity score (Elixhauser Comorbidity Index [ECI]), and year of CDK4/6i start were used to compare outcomes across CDK4/6i drugs. Chi-squared tests were used for comparison of categorical variables, while one-way ANOVA was used for continuous variables.

Results: 4556 pts with mBC were included, of whom 65% received palbociclib (palbo), 24% abemaciclib (abema) and 11% ribociclib (ribo). Ribo use increased post-2020, while palbo use decreased and abema remained similar (2020: ribo: 9%, palbo: 63%, abema: 28%; 2022: ribo: 18%, palbo: 54%, abema: 28%). Pts who received ribo were younger and had fewer comorbidities than those receiving palbo and abema [median age: 57, 61, 60 years, respectively ($p < 0.001$); ECI score: 19.8, 20.1, 21.3, respectively ($p < 0.001$)]. Median f/u for

pts included in outcomes assessment was 24.1 mos for abema, 30.1 mos for palbo, and 28.5 mos for ribo. Adjusted hazard ratios (HR) for rwTTD, rwTTNT, and rwOS for pts treated in the 1L or 2L showed no significant difference between the drugs (Table 1). 1120 pts had ctDNA analysis within +/- 90 days of CDK4/6i treatment end and these data will be shown at the time of presentation.

Conclusions: RW analysis shows increased use of ribo and decreased use of palbo in recent years, with potential preferential use of ribo in pts who are younger and have fewer comorbidities. Multivariate Cox regressions adjusted for pt age, gender, co-morbidities, and year of CDK4/6i start found no significant differences in rwTTD and rwTTNT for pts treated in the 1L or 2L between the drugs. While we only included pts with at least 12 months of f/u in the outcomes analysis, it is difficult to make conclusions regarding rwOS data as the median f/u still differs between the drugs at this time. These findings confirm anecdotal evidence suggesting shifting physician preferences in the use of the CDK4/6i drugs in mBC. Further investigation is needed to refine CDK4/6i drug selection in the rapidly changing mBC landscape.

Table 1. Comparison of patient outcomes across CDK4/6i agent.

Outcome	Treatment	1L Treatment				2L Treatment			
		N	Median Time to Outcome in Mos (95% CI)	Adjusted HR (95% CI)	P-value	N	Median Time to Outcome in Mos (95% CI)	Adjusted HR (95% CI)	p-value
rwTTD	Palbo	608	10.3 (9.2, 11.3)	Reference		755	9.6 (8.7, 11.1)	Reference	
	Abema	133	6.5 (5.3, 8.4)	1.18 (0.96, 1.44)	0.113	219	7.3 (5.8, 9.3)	1.17 (0.99, 1.38)	0.068
	Ribo	91	7.8 (4.6, 11.2)	1.16 (0.91, 1.47)	0.224	92	8.1 (5.4, 11.4)	1.24 (0.99, 1.57)	0.063
rwTTNT	Palbo	608	16.4 (15.0, 17.6)	Reference		755	15.6 (13.4, 17.2)	Reference	
	Abema	133	14.0 (9.9, 19.0)	1.06 (0.82, 1.37)	0.665	219	11.8 (9.0, 14.9)	1.14 (0.94, 1.39)	0.177
	Ribo	91	13.8 (11.1, 17.3)	1.14 (0.85, 1.51)	0.380	92	14.2 (10.8, 17.4)	1.12 (0.85, 1.49)	0.411
rwOS	Palbo	608	58 (58, NR)	Reference		755	NR (NR, NR)	Reference	
	Abema	133	NR (56, NR)	1.29 (0.85, 1.96)	0.229	219	NR (55, NR)	1.12 (0.8, 1.58)	0.506
	Ribo	91	NR (NR, NR)	1.04 (0.61, 1.77)	0.899	92	NR (NR, NR)	1.15 (0.71, 1.86)	0.570

PO4-18-03

Combined Treatment with Pyrotinib and Chrysin Synergistically Improve the Autophagy Level in HER2-Positive Breast Cancer by Regulating the miR-16-5p/ZBTB16/G6PD Axis

Presenting Author(s) and Co-Author(s):

T. Luo. 1. Department of Medical Oncology · Cancer Center, West China Hospital, Sichuan University; 2. Breast Center, West China Hospital, Sichuan University; 3. Multi-omics Laboratory of Breast Diseases, West China Hospital, Sichuan University, Chengdu, China, United States

X. Zhong. West China Hospital, Sichuan University, United States

P. he. Breast Disease Center, Cancer Center, West China Hospital, Sichuan University, Chengdu, United States

D. Zheng. Breast Disease Center, Cancer Center, West China Hospital, Sichuan University, United States

Y. Cheng. Breast Disease Center, Cancer Center, West China Hospital, Sichuan University, Chengdu, United States

K. Zhu. 1. Department of Medical Oncology · Cancer Center, West China Hospital, Sichuan University; 2. Breast Center, West China Hospital, Sichuan University; 3. Multi-omics Laboratory of Breast Diseases, West China Hospital, Sichuan University, Chengdu, China, United States

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) has been the most challenging subtype of BC, which consists of 20% of BC with an apparent correlation with poor prognosis. Despite that pyrotinib, a new HER2 inhibitor, has led to dramatic improvements in prognosis outcome, the efficacy of pyrotinib as monotherapy remain largely restricted due to its acquired resistance. Therefore, we aim at identifying a potent antitumor drug incorporated with pyrotinib for amplifying therapeutic efficacy for treating HER2-positive BC. Here, we reported a novel incorporation of pyrotinib in combination with chrysin, and explored its antitumor efficacy and the underlying mechanisms on HER2+ breast cancer. We determined that pyrotinib combined with chrysin yielded a potent synergistic effect to induce apoptosis and inhibit BT-474 and SK-BR-3 tumor cells, and suppressed *in vivo* tumor growth in tumor-bearing mice models. This may be mechanistically attributed to the induction of enhanced endoplasmic reticulum stress to increase the autophagy level. Furthermore, it was demonstrated that the combined treatment with pyrotinib and chrysin induced ubiquitination and G6PD degradation by regulating zinc finger and BTB/POZ domain-containing family protein 16 (ZBTB16) in tumorigenesis of BC. Besides, we identified that miR-16-5p is a potential upstream regulatory target of ZBTB16. Blocking miR-16-5p overexpression could inhibit HER2-positive tumorigenesis and significantly potentiate the efficacy of pyrotinib in combination with chrysin. Together, these findings demonstrate the utility of combined treatment with pyrotinib and chrysin as a potential option in the target treatment of HER2-positive BC through an unrecognized miR-16-5p/ZBTB16/G6PD axis.

The miR-16-5p/ZBTB16/G6PD axis plays a crucial role in the pyrotinib plus chrysin-enabled anti HER2-positive BC

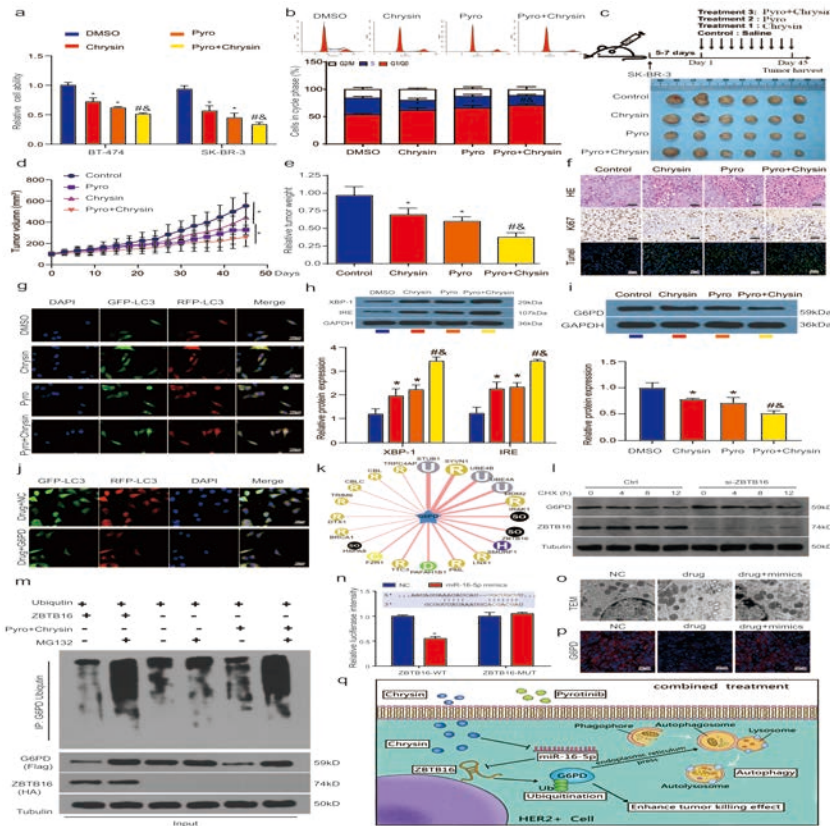


Fig.1 a Cell viability of SK-BR-3 cells received various treatments. b Detection of cell cycle arrest of SK-BR-3 cells after various treatments. c Schematic diagram of the established protocol of the animal models. Photograph of resected tumor tissues, tumor volume (d), and tumor weight (e) of mice in different treatment groups during the whole testing period. f H&E, Ki67, and TUNEL immunohistochemical staining of tumor sections of mice in various treatment groups. g Autophagy flux of SK-BR-3 cells labeled with mRFP-GFP-LC3 in the different treatment groups. h Expression level of ER stress markers in SK-BR-3 cells after various treatments via RT-qPCR and western blot. * $P < 0.05$, compared with control group (DMSO), # $P < 0.05$, compared with chrysin group, & $P < 0.05$, compared with pyrotinib group. i Western blot analysis of the expression of G6PD in different treatment groups. j Fluorescence images of SK-BR-3 cells subjected to G6PD overexpression for the detection of autophagy level. k Ubiquitin browser database predicting the E3 ubiquitin ligases that may be involved in the regulation of G6PD ubiquitination. l Western blot analysis of G6PD protein half-life in SK-BR-3 cells with ZBTB16 silence. Cells were co-incubated with cycloheximide (CHX, 50 μ g/ml) for the indicated time. m Determination of the ubiquitination of G6PD in cells pretreated with 10 μ M MG-132 for 3 h. Cells were transfected with ubiquitin after different treatments. The ubiquitinated G6PD was subjected to immunoprecipitation before western blot with ubiquitin antibody. n Dual-luciferase report verifying the targeting of ZBTB16 and miR-16-5p. o Transmission electron microscopy images of autophagosomes of tumors in various treatment groups ($\times 20000$). p Immunohistochemical staining images of tumor slices for the determination of G6PD. q Schematic diagram for the underlying mechanism of pyrotinib combined chrysin against HER2-positive BC.

PO4-18-04

An exploratory study of Trastuzumab Deruxtecan neoadjuvant therapy in HER2-positive or HER2-low early or locally advanced breast cancer after a poor response to neoadjuvant chemotherapy.

Presenting Author(s) and Co-Author(s):

J. Zhang. The 3rd Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin 300060, China, Tianjin, China (People's Republic)

Z. Shi. The 3rd Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin 300060, China, United States

J. Liu. The 3rd Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin 300060, China, United States

Background

The current standard of care for neoadjuvant treatment of HER2-positive early-stage breast cancer consists of dual HER2-blockade with trastuzumab (H) plus pertuzumab (P) and polychemotherapy with a pathological complete response (pCR) rate of 31%~50%. Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. T-DXd significantly prolonged progression-free and overall survival vs trastuzumab emtansine in HER2-positive unresectable and/or metastatic breast cancer (mBC) previously treated with H and taxane in DESTINY-Breast03 study. HER2-low breast cancer is currently treated as HER2-negative (HER2-low and HER2-zero) breast cancer, with patients stratified according to hormone-receptor (HR) status. In DESTINY-Breast04 study, T-DXd resulted in significantly longer progression-free and overall survival than the physician's choice of chemotherapy in HER2-low mBC. Given the efficacy of T-DXd monotherapy in HER2-positive or HER2-low mBC, we conduct an exploratory study to evaluate the efficacy and safety of T-DXd in HER2-positive or HER2-low early or locally advanced breast cancer after a poor response to neoadjuvant chemotherapy, and to identify sensitive biomarkers for T-DXd neoadjuvant therapy.

Methods

Eligible patients were women aged 18 years to 75 years with clinical stage cT2–cT4/cN0–cN3/cM0 (stage II–III) invasive breast cancer (>2 cm in size) confirmed as HER2-positive (immunohistochemistry [IHC] 3+) or HER2-low (IHC2+ or IHC1+/ situ hybridization-negative). Patients are required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, and baseline left ventricular ejection fraction of at least 55% (as measured by echocardiogram). Patients are also required to have adequate organ function and bone marrow function. Patients with HER2-positive breast cancer should receive taxane (paclitaxel or nab-paclitaxel) or docetaxel, carboplatin, and H plus P for 2 cycles. Patients with HER2-low and HR-

positive breast cancer should receive taxane (paclitaxel or nab-paclitaxel) or docetaxel, and cisplatin or carboplatin for 2 cycles. Patients with HER2-low and HR-negative breast cancer should receive taxane (paclitaxel or nab-paclitaxel) or docetaxel, and anthracycline (epirubicin, pirarubicin or liposomal doxorubicin) for 2 cycles. For patients who have responses of stable disease assessed by magnetic resonance imaging will receive T-DXd neoadjuvant therapy. T-DXd will be administered intravenously every 3 weeks at a dose of 5.4 mg per kilogram of body weight for 4 cycles. Peripheral blood and biopsy tissue will be collected before neoadjuvant chemotherapy and T-DXd neoadjuvant therapy, and peripheral blood and surgical tissue will be collected after the surgery. Lipid metabolites in peripheral blood and mass spectrometry-based protein quantification in tissue will be detected to find sensitive biomarkers for T-DXd neoadjuvant therapy. The primary endpoint is pCR rate (ypT0/Tis ypN0) and identify sensitive biomarkers for T-DXd neoadjuvant therapy. Secondary endpoints include objective response rate, breast-conserving rate and invasive disease-free survival.

PO4-18-05

Safety and Feasibility of Administration of an Oral Cannabis Preparation in The Preoperative Period in Breast and Oral Cavity Cancer

Presenting Author(s) and Co-Author(s):

R. Badwe. Tata Memorial Centre, Mumbai, India
S. Joshi. Tata Memorial Hospital, United States
S. Thiagarajan. Tata Memorial Centre, Mumbai, India
V. Gota. Advanced Centre for Treatment, Research and Education in Cancer, United States
V. Vanmali. Tata Memorial Hospital, United States
P. Daphale. Tata Memorial Centre, United States
J. Deodhar. Tata Memorial Centre, United States
R. Chaubal. Tata Memorial Center, United States
R. Hawaldar. Tata Memorial Centre, United States
J. Aadhi. Tata Memorial Centre, United States
S. Gupta. Tata Memorial Centre, Mumbai, India
D. Deolaliwala. The Bombay Hem Company Pvt Ltd, Mumbai, India
A. Bhansali. Sai Phytoceuticals Pvt Ltd, New Delhi, India
S. Mistry. The Bombay Hem Company Pvt Ltd, Mumbai, India
S. Singh. Sai Phytoceuticals Pvt Ltd, New Delhi, India
N. Nair. Tata Memorial Centre, United States
V. Parmar. Tata Memorial Centre, United States
S. Gupta. Tata Memorial Center, United States

Introduction-

Cannabis is world's oldest cultivated medicinal plant. It has potential applications in oncology, in reducing chronic pain, stimulating appetite, alleviating nausea/vomiting, improving overall well-being as well as its anti-cancer properties. We conducted a phase-1 dose escalation study to determine safety of pre-operative oral cannabis in breast and oral cavity squamous cell carcinoma (OC-SCC) with an intent to explore its anticancer potential in the "pre-operative" window. The primary objective was to determine maximum tolerated dose (MTD) and establish dose limiting toxicity (DLT). Secondary objectives were pharmacokinetic profiling and transcriptomic analysis of tumour tissue.

Methodology-

Primary objective was to determine maximum tolerated dose (MTD) and establish dose limiting toxicity (DLT). Secondary objectives were pharmacokinetic profiling and transcriptomic analysis of tumour tissue.

Non-metastatic breast and OC-SCC patients planned for curative surgery were consented after thorough medical and mini-psychiatric evaluation with Brief Psychiatry Rating Scale (BPRS). The investigational product (IP) comprised of a capsule containing 2.5mg of tetrahydrocannabinol (THC) and 2.5mg cannabidiol (CBD) in 100 mg monocrotolyn oil extract of dried leaves of *C. sativa*. The capsules were manufactured in an Ayurvedic GMP facility. The classical 3+3, phase-1 design used modified Fibonacci sequence for dose escalation, starting

with 5mg THC+5mg CBD. Patients received IP once a day for 5 days after breakfast with hemodynamic and psychiatric monitoring and underwent the planned surgery on day-6. Pharmacokinetic samples were collected at predefined time-points and plasma levels of THC, 11-OH-THC, 11-COOH-THC and CBD were determined using a validated LC-MS/MS method. Tumour tissue was collected before 1st dose of cannabis and during surgery for biomarker analysis.

Results-

A total of 12 patients were enrolled (6-breast, 3-buccal mucosa, and 3-tongue cancers). First 3 patients completed the study without DLT at 5+5mg dose. A DLT was observed at dose level-2 (10+10mg) and therefore additional 3 patients were enrolled at the same dose. Two patients out of six at this dose had DLT (anxiety- grade-3 and somnolence- grade-2) necessitating dose de-escalation in the next cohort. At 7.5+7.5mg dose, all 3 patients tolerated the IP(MTD). Ten patients completed the study protocol. Common adverse effects were headache (2/12, grade-1), heavy head (8/12, grade-1), hypotension (2/12, grade-1 and 3), epigastric discomfort (1/12, grade-1), diarrhoea (1/12, grade-1), hyponatremia (1/12, grade-1), hypertension (1/12, grade-2), anxiety (1/12, grade-2). Pharmacokinetics of both CBD and THC was less than dose proportional. At the MTD (7.5+7.5), day-1 and day-5 AUC₀₋₂₄ [median (range)] for CBD were 21.75 (12.44–41.44) ng/ml⁻¹*h and 24.85 (13.72–35.93) ng/ml⁻¹*h respectively. Similarly, for THC, day 1 and day 5 AUC₀₋₂₄ were 11.79 (8.06–70.58) ng/ml⁻¹*h and 68.98 (1.78 – 136.17) ng/ml⁻¹*h, respectively. Significant accumulation of both CBD and THC was observed across all doses from day 1 to 5. A high variability in pharmacokinetics was observed for both constituents (CV C_{max} = 101.26% and 117.48%; CV AUC₀₋₂₄ = 102.50% and 112.37% for CBD and THC respectively. The median half-life of CBD and THC was 2.2 (1.6–10.7) and 1.9 (1.6–2.4) h respectively. There was no correlation observed between drug exposure and toxicity. There was no significant change in BPRS score before and after IP.

Conclusion-

We report the first phase-1 study of cannabis in breast and OC-SCC cancer in pre-operative setting for its anti-cancer potential. Biomarker analysis is awaited. MTD identified will be further explored in phase 2/3 clinical trials in breast, oral cavity, lung and pancreatic cancer with survival endpoints.

PO4-18-07

A dose escalation and cohort expansion study of the CDK9 inhibitor KB-0742 in triple negative breast cancer and transcriptionally addicted relapsed or refractory solid tumors

Presenting Author(s) and Co-Author(s):

M. Mita. Cedars-Sinai, United States

A. Mita. Cedars-Sinai, Samuel Oschin Cancer Center, United States

M. Villalona-Calero. City of Hope National Medical Center, United States

N. Federman. UCLA Health, United States

D. Rasco. START San Antonio, United States

D. Spigel. Sarah Cannon Research Institute at Tennessee Oncology, United States

J. Luo. Dana-Farber Cancer Institute, United States

G. Cote. Massachusetts General Cancer Center, United States

R. Cutler. Kronos Bio, United States

P. Kumar. Kronos Bio, United States

C. MacKenzie. Kronos Bio, United States

C. Lin. Kronos Bio, United States

J. DiMartino. Kronos Bio, United States

E. Olek. Kronos Bio, United States

B. Van Tine. Washington University School of Medicine, United States

Background: MYC deregulation is a hallmark of triple negative breast cancer (TNBC) and is associated with aggressive tumors and poor clinical outcomes. Although MYC remains undrugged, targeting of its cofactors has emerged as an attractive strategy to inhibit MYC oncogenic activity. Cyclin-dependent kinase 9 (CDK9) is a critical regulator of oncogenic MYC expression and an important MYC cofactor. KB-0742 is an oral CDK9 inhibitor that demonstrates promising preclinical activity against TNBC.

In a real-world cohort, TNBCs have higher MYC expression and higher rates of MYC genomic amplification than other breast cancer subtypes. In primary patient-derived cell lines, KB-0742 treatment results in stronger cytotoxic effects in TNBC as compared to other subtypes. In patient-derived organoids and patient-derived xenografts, CDK9 inhibition by KB-0742 drives antiproliferative and anti-tumor growth effects, including in models that are resistant to standard of care. KB-0742 strongly downregulates MYC protein levels at doses that only partially inhibit CDK9 activity, suggesting a therapeutic window for tumor-specific activity (Saffran, D.C. et al, 2021). KB-0742 is currently being evaluated in a phase 1 / 2 dose escalation and cohort expansion study in patients with TNBC and other transcriptionally addicted tumors (NCT04718675).

Trial design: This phase 1 / 2 study includes two parts: dose escalation (part 1) and cohort expansion (part 2). Part 2 includes cohort A (solid tumors with high prevalence of MYC overexpression including TNBC, non-small cell lung cancer and ovarian) and cohort B (other transcriptionally addicted tumor types including sarcomas, adenoid cystic carcinoma, nut midline carcinoma and small cell lung cancer). KB-0742 is dosed orally once daily for 3 consecutive days, followed by 4 days, off on a weekly basis in 28-day cycles until unacceptable toxicity or disease progression.

Eligibility criteria: Part 1 dose escalation is open to patients with relapsed or refractory solid

tumors. Part 2 is defined by tumor indications in cohorts A and B. Eligibility criteria include age > 18 years (≥ 12 years old and with a body weight ≥ 40 kg part 2 for cohort B), acceptable organ function, and ECOG PS < 2.

Specific aims: Primary objectives include evaluation of pharmacokinetics (PK), pharmacodynamics (PD), safety, tolerability, preliminary anti-tumor activity, and identifying a maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). PK measurements include C_{max} , t_{max} , AUC_{0-last} , accumulation ratio (R_{acc}) and $t_{1/2}$. Safety data will be evaluated per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. The Modified Continuous Reassessment Method (mCRM) (Goodman et al., Stat Med 1995) will guide dose escalation and MTD.

RP2D nomination is informed by PD in peripheral blood mononuclear cells using assays to evaluate phosphorylation of the CDK9 substrate serine 2 on the RNA Polymerase II C-terminal domain (pSER2) and CDK9-responsive gene expression.

Radiographic tumor response to KB-0742 in patients is assessed every other cycle starting from cycle two after treatment using RECIST 1.1 criteria.

Target accrual: Targeted total enrollment is 170 patients. For additional information, contact clinicaltrials@kronosbio.com

PO4-18-09

SMALL: Open Surgery versus Minimally invasive vacuum-Assisted excision for small screen-detected breast cancer – a UK phase III randomised multi-centre trial

Presenting Author(s) and Co-Author(s):

S. McIntosh. Queen's University Belfast, United States

C. Coles. University of Cambridge, United Kingdom

D. Dodwell. University of Oxford, Oxford, England, United Kingdom

K. Elder. NHS Lothian, United States

J. Foster. university of Birmingham, United States

C. Gaunt. University of Birmingham, United States

A. Kirkham. University of Birmingham, United States

I. Lyburn. Gloucestershire University Hospitals NHS Trust, United States

S. Paramasivan. University of Bristol, United States

J. Morgan. University of Sheffield, United States

S. Pinder. School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom

S. Potter. Bristol Medical School, United States

T. Roberts. University of Birmingham, United States

N. Sharma. Leeds Teaching Hospitals NHS Trust, United States

H. Stobart. Independent Cancer Patients' Voice, United States

E. Southgate. University of Birmingham, United States

S. Taylor-Phillips. University of Warwick, United States

M. Wallis. Cambridge University Hospitals NHS Trust, United States

D. Rea. University of Birmingham, Cancer Research UK Clinical Trials Unit (CRCTU), England, United Kingdom

Background:

Mammographic screening programmes reduce breast cancer mortality but detect many small good-prognosis tumours which may not progress. Screen-detected cancers are currently treated with standard surgery and adjuvant therapies, with associated morbidities. There is a need to reduce overtreatment of good prognosis tumours and numerous studies are evaluating omission of radiotherapy in low-risk disease. However, there is little evidence to support surgical de-escalation, although percutaneous minimally invasive treatment approaches have been described. Vacuum-assisted excision (VAE) is in widespread use for management of lesions of uncertain malignant potential and benign lesions. SMALL (ISRCTN 12240119) is designed to determine the feasibility of using this approach to treat small invasive tumours detected within the UK NHS Breast Screening Programme.

Methods:

SMALL is a phase III multicentre randomised trial comparing standard surgery with VAE for screen-detected cancers. Main eligibility criteria are age ≥ 47 years, unifocal grade 1 tumours with maximum diameter 15mm, strongly ER/PR+ve and HER2-ve, with negative axillary staging. Patients are randomised 2:1 to VAE or surgery, with no axillary surgery in the VAE

arm. Completeness of excision is assessed radiologically, and if excision is incomplete, patients undergo surgery. Adjuvant radiotherapy and endocrine therapy are mandated in the VAE arm but may be omitted following surgery.

Co-primary end-points are:

1. Non-inferiority comparison of the requirement for a second procedure following excision
2. Single arm analysis of local recurrence (LR) at 5 years following VAE

Recruitment of 800 patients will permit demonstration of 10% non-inferiority of VAE for requirement of a second procedure. This ensures sufficient patients for single arm analysis of LR rates, where expected LR free survival is 99% at 5 years, with an undesirable survival probability after VAE of 97%. To ensure that the trial as a whole only has 5% alpha, the significance level for each co-primary outcome is set at 2.5% with 90% power. The Data Monitoring Committee will monitor LR events to ensure these do not exceed 3% per year. Secondary outcome measures include time to ipsilateral recurrence, overall survival, complications, quality of life and health economic analysis.

A novel feature of SMALL is the integration of a QuinteT Recruitment Intervention (QRI), which aims to optimise recruitment to the study. Recruitment challenges are identified by analysing recruiter/patient interviews and audio-recordings of trial discussions, and by review of trial screening logs, eligibility and recruitment data and study documentation. Solutions to address these are developed collaboratively, including individual/group recruiter feedback and recruitment tips documents.

Results:

SMALL opened in December 2019, but recruitment halted in 2020 for 5 months due to COVID-19. At 6th July 2023, 39 centres are open, with 300 patients randomised from 32 of these, with a randomisation rate of approximately 45%, and a per site recruitment rate of 0.4-0.5 patients/month. Despite the pandemic, SMALL achieved the internal pilot feasibility targets and continues to recruit to the main study, with estimated completion of recruitment in June 2025.

Drawing from preliminary QRI findings and insights from patient representatives, a recruitment tips document has been circulated (on providing balanced information about treatments, encouraging recruiters to engage with patient preferences, and explaining randomisation). Individual recruiter feedback has commenced and wider feedback is being delivered across sites via recruitment training workshops.

Conclusion:

Despite pandemic-related challenges, SMALL has excellent recruitment to date and is expected to have a global impact on treatment of breast cancer within mammographic screening programmes.

SMALL is funded by the UK NIHR HTA programme award 17/42/32

PO4-18-10

Randomized controlled trial of Young, Empowered & Strong (YES), a web-based patient-reported symptom monitoring and self-management portal for adolescent and young adult (AYA) breast cancer (BC) survivors

Presenting Author(s) and Co-Author(s):

S. Rosenberg. Weill Cornell Medicine, New York, New York, United States

Y. Zheng. Dana-Farber Cancer Institute, United States

D. Hershman. Columbia University, New York, New York, United States

C. Snow. Dana-Farber Cancer Institute, United States

K. Dibble. Dana-Farber Cancer Institute, United States

M. Contreras. Dana-Farber Cancer Institute, United States

N. Roma. Dana-Farber Cancer Institute, United States

N. Tayob. Dana-Farber Cancer Institute, United States

M. Naughton. The Ohio State University, United States

A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: BC is the most common malignancy diagnosed in AYAs. AYAs develop more biologically aggressive BC and present at more advanced stages, necessitating more intensive therapy with curative intent. While acute physical sequelae often resolve following initial treatment, the long-term physical and psychosocial impact of BC on a survivor's life may worsen or emerge in survivorship. This impact includes symptoms (e.g., sexual problems, anxiety, fatigue, stress, sleep issues, hot flashes) as well as concerns unique to, or accentuated by, being young (e.g., fertility, genetics, childrearing, educational/work attainment). With provider attention to these issues often sub-optimal, strategies that empower patients have the potential to improve their well-being. To engage and activate AYA BC survivors, we developed YES, a web-based portal that leverages electronic patient-reported outcomes (ePROs) to facilitate self-monitoring and management of symptoms/AYA concerns. In contrast to ePRO models dependent on clinician interaction, our approach emphasizes self-management of chronic survivorship concerns outside of the clinic environment. This model is grounded in the reality that most clinicians have limited bandwidth to address these needs and considers that AYAs can have competing demands (e.g., missing work, child-care) that may make accessing in-person support challenging.

Methods: The YES study is a randomized controlled trial of the YES intervention vs. usual care. YES supports participants to 1) self-monitor needs/symptoms; and 2) provides a repository for information and resources on self-management of symptoms/AYA concerns. Eligibility criteria include: female, age 15-39 years at diagnosis, stage 0-III BC, within 3 years of diagnosis, no recurrent/second primary BC, no other malignancy since BC diagnosis, and English speaking. Participants randomized to the YES arm are prompted through a monthly text or email to complete an ePRO assessment regarding current symptoms/AYA concerns. For each symptom/concern endorsed, information/resources to address the symptom/concern is automatically provided via the YES portal. The portal is monitored, and providers are contacted if participants report severe distress or suicidality. YES also provides peer support via a chat room and self-support through a journaling platform in the portal. Participants in the usual care group are offered access to YES for up to 3 months at the end of their 9-month study participation. All participants complete a REDCap survey with validated measures of quality of

life (QOL), symptoms, and other PROs at baseline, 3, 6, and 9 months after randomization and provide a dried blood spot specimen via a self-administration kit at baseline and 6 months. The primary study aim is to determine the efficacy of YES vs. usual care in improving life quality measured by the QOL in Adult Cancer Survivors [QLACS] scale at 6 months post-randomization. With a planned sample size of 360 participants, the study will have $\geq 90\%$ power to detect a 6-point mean change (6 months vs. baseline) in the cancer-specific QLACS score between arms. Secondary outcomes include efficacy of YES in reducing symptoms/AYA concerns at 6 months and sustainability of the effects of YES at 9 months. Repeated measures regression will be used with link functions selected based on the type of outcome data analyzed. Exploratory aims will evaluate moderators and mediators of intervention efficacy and the effects of YES on inflammatory biomarkers. At study completion, a subset of 30 participants diverse in age, race, ethnicity, and gender identity are invited to participate in an interview to understand their survivorship preferences/concerns and to understand how the portal supported their self-management. The YES trial opened to enrollment in 9/2021. As of 6/2023, 245 participants are enrolled. Clinical Trials Information: NCT04906200

PO4-18-11

Phase 1 study of the tissue factor-targeting antibody-drug conjugate XB002 in patients with advanced solid tumors (JEWEL-101): Design of the triple-negative and hormone receptor-positive breast cancer expansion cohorts

Presenting Author(s) and Co-Author(s):

S. Ulahannan. University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, United States

M. Johnson. Sarah Cannon Research Institute, Nashville, TN, USA, United States

M. Weiss. Washington University School of Medicine in St. Louis, St. Louis, MO, USA, United States

A. Vandross. NEXT Oncology, San Antonio, TX, USA, United States

S. Vidal-Cardenas. Exelixis, Inc., Alameda, CA, USA, United States

M. Syed. Exelixis, Inc., Alameda, CA, USA, United States

A. Tolcher. NEXT Oncology, San Antonio, TX, USA, United States

Background: Tissue factor (TF) is a transmembrane protein that functions as a factor VIIa receptor, initiating the extrinsic coagulation cascade. TF is aberrantly expressed in multiple solid tumors, including breast cancer (BC), and its expression is associated with disease progression and poor prognosis (van den Berg et al. Blood 2012). Microtubule-targeting agents are a cornerstone of treatment for metastatic BC. XB002 is a novel antibody-drug conjugate (ADC) composed of a high-affinity TF-directed human monoclonal antibody conjugated to the zovodotin linker-payload. Zovodotin consists of an auristatin-based payload and a protease-cleavable linker and is designed to lower off-target deconjugation and improve tolerability compared with other microtubule inhibitor linker-payloads. In preclinical studies, XB002 did not interfere with coagulation and demonstrated antitumor activity with an encouraging safety profile. XB002 is being evaluated in JEWEL-101, an ongoing trial in patients (pts) with advanced solid tumors, including BC. Preliminary results from the dose-escalation stage of JEWEL-101 showed XB002 was well tolerated at multiple dose levels with no bleeding events or treatment-related peripheral neuropathy (PN) and low-grade ocular toxicity (Ulahannan et al. ENA 2022). Presented here is the study design of the tumor-specific expansion stage, including triple-negative BC (TNBC) and hormone receptor-positive BC (HR+ BC) cohorts.

Trial design and statistical methods: JEWEL-101 (NCT04925284) is a multicenter, open-label, phase 1 trial evaluating the safety, tolerability, pharmacokinetics (PK), and antitumor activity of XB002 in advanced solid tumors. Single-agent XB002 at the recommended dose will be assessed in the BC expansion cohorts utilizing Simon's Two-Stage design.

Eligibility criteria: The trial will enroll adult pts with TNBC (ER-/PR-/HER-2-negative or low) and HR+ BC (ER+ and/or PR+ and HER-2-negative or low) into 2 separate cohorts. HER-2 negativity is defined as either HER-2 negative or low by local ISH or IHC assessment. For both cohorts, pts must have received 1–3 lines of prior systemic anticancer therapies for locally advanced or metastatic disease. Pts in the HR+ BC cohort must have received prior endocrine therapy and CDK4/6 inhibitor. All pts must have cytologically or histologically and radiologically confirmed BC that is inoperable, locally advanced, metastatic, or recurrent. Documented radiographic progression during or following their last systemic anticancer therapy is required. All pts must also have measurable disease per RECIST 1.1 by investigator assessment, archival (< 2 years) or fresh tumor tissue, ECOG PS 0 or 1, and adequate organ and marrow

function. Pts with grade 1 PN are allowed. Concomitant anticoagulation therapy while receiving XB002 is permitted if clinically indicated. Key exclusions are prior use of TF-targeting or auristatin derivate-based ADC; uncontrolled, significant intercurrent or recent illness, including acute or chronic significant ocular disorders; major surgery within 4 weeks; and corrected QT interval calculated by the Fridericia formula >480 ms per ECG.

Specific aims: The primary objective of the expansion stage is to evaluate the preliminary efficacy of XB002 by estimating the objective response rate per RECIST 1.1 as assessed by the investigator. Secondary objectives include safety and tolerability, PK, immunogenicity, progression-free survival, duration of response, and overall survival.

Accrual: Up to 28 pts will be enrolled into each BC cohort. Enrollment is planned across sites in the US, Europe, and Asia-Pacific.

Contact information: Exelixis Clinical Trials, druginfo@exelixis.com, 1-888-393-5494

PO4-18-12

MELODY: A prospective non-interventional multicenter cohort study to evaluate different imaging-guided methods for localization of malignant breast lesions (EUBREAST-4 / iBRA-NET, NCT 05559411)

Presenting Author(s) and Co-Author(s):

M. Banyś-Paluchowski. Department of Obstetrics and Gynecology, Asklepios Hospital Barmbek, Hamburg, Germany

T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany

Y. Masannat. Aberdeen Breast Unit, Aberdeen Royal Infirmary, Aberdeen, United Kingdom, United States

N. Ditsch. Department of Gynaecology and Obstetrics, University Hospital Augsburg, Augsburg, Germany

A. Esgueva. Breast Surgical Unit, Clinica Universidad de Navarra, Madrid, Spain, United States

N. Cabioğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Bakırköy, Istanbul, Turkey

D. Murawa. Department of General Surgery and Surgical Oncology, Collegium Medicum, University of Zielona Góra, Poland, Poland

N. Canturk. Kocaeli University School of Medicine, Department of General Surgery, Kocaeli, Turkey, United States

I. Rubio. Clínica Universidad de Navarra, Madrid, Spain, United States

J. de Boniface. Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, and Department of Surgery, Capio St. Göran's Hospital, Stockholm, Stockholms Lan, Sweden

A. Karakatsanis. Department for Surgical Sciences, Uppsala University, Uppsala, Sweden

R. Dave. Manchester University NHS Foundation Trust, Manchester, UK, United States

S. Potter. Bristol Medical School, United States

A. Kothari. Guy's & St Thomas NHS Foundation Trust, Kings College, London, United Kingdom, United States

O. Gentilini. Breast Surgery Unit, San Raffaele University Hospital, Milan, Italy

W. Weber. Breast Center, University Hospital of Basel, Basel-Stadt, Switzerland

N. Krawczyk. Department of Gynecology and Obstetrics, Heinrich Heine University Düsseldorf, Düsseldorf, Germany, Germany

S. Hartmann. Department of Gynecology and Obstetrics, University Hospital Rostock, Germany

G. Karadeniz Cakmak. Zonguldak Bulent Ecevit University, Department of Surgery, Turkey

M. Hahn. Universitätsklinikum Tübingen, United States

M. Lux. St. Vincenz-Kliniken Paderborn, Germany

T. Tvedskov. Herlev-Gentofte Hospital, Hovedstaden, Denmark

L. Pankratjevaite. Faculty of Health and Medical Sciences, University of Copenhagen, Dept of Breast Surgery, Herlev & Gentofte University Hospital, Copenhagen, Denmark, United States

M. Kontos. 1st Department of Surgery, Laiko Hospital, National and Kapodistrian University of Athens, Greece

F. Peintinger. Univ.Prof. Priv.Doiz. Dr. Florentia Peintinger, Austria
A. Lowery. Discipline of Surgery, University of Galway, Ireland, United States
M. Smidt. Department of Surgical Oncology, Maastricht University Medical Center, Maastricht, The Netherlands, United States
L. Rebaza. Clinica Oncosalud Auna, Lima, Peru, United States
M. Vasconcelos. Breast Unit, Champalimaud Clinical Centre, Champalimaud Foundation, Lisbon, Portugal, United States
B. Gulluoglu. Marmara University School of Medicine, Department of Surgery, Istanbul, Turkey
B. Aktas Sezen. European Breast Cancer Research Association of Surgical Trialists (EUBREAST), United States
R. Di Micco. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), Italy
S. Nietz. University of the Witwatersrand, United States
F. Malherbe. Breast and Endocrine Surgery Unit, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa, United States
M. Gasparri. Department of Gynecology and Obstetrics, Ente Ospedaliero Cantonale, Ospedale Regionale di Lugano, Lugano, Switzerland, Ticino, Switzerland
S. Alran. Hôpital Paris Saint Joseph, United States
S. Deo. All India Institute of Medical Science, New Delhi, New Delhi, Delhi, India
M. Khan. Breast Care Service, Department of Surgery, Khyber Medical College & Khyber Teaching Hospital, Peshawar Pakistan, United States
J. Harvey. Manchester Foundation Trust, United States

Background:

In the last decades, the proportion of breast cancer patients receiving breast-conserving surgery has increased, reaching 70-80% in developed countries. In case of non-palpable lesions, surgical excision requires some form of breast localization. While wire-guided localization has long been considered gold standard, it carries several limitations, including logistical difficulties, the potential for displacement and patient discomfort, and re-excision rates reaching 21%. Other techniques (radioactive seed or radio-occult lesion localization, intraoperative ultrasound, magnetic, radiofrequency and radar localization) have been developed with the aim of overcoming these disadvantages. However, comparative data on the rates of successful lesion removal, negative margins and re-operations are limited. In the majority of studies, the patient's perspective with regard to discomfort and pain level has not been evaluated. The aim of MELODY (MEthods for LOcalization of Different types of breast lesions) is to evaluate different imaging-guided localization methods with regard to oncological safety, patient-reported outcomes, and surgeon and radiologist satisfaction.

Methods:

The EUBREAST and the iBRA-NET have initiated the MELODY study to assess breast localization techniques and devices from several perspectives (NCT05559411, <http://melody.eubreast.com>). MELODY is a prospective intergroup cohort study which enrolls female and male pts. requiring breast-conserving surgery and imaging-guided localization for invasive breast cancer or DCIS. Multiple or bilateral lesions and neoadjuvant chemotherapy are allowed. Primary outcomes are: 1) Intended target lesion and/or marker removal, independent of margin status on final histopathology, and 2) Negative resection margin rates at first surgery. Secondary outcomes are, among others: rates of second surgery and secondary mastectomy, Resection Ratio (defined as actual resection volume divided by the calculated optimum

specimen volume), duration of surgery, marker dislocation rates, rates of marker placement or localization failure, comparison of patient-reported outcomes, rates of “lost markers” and diagnostician/radiologist’s and surgeon’s satisfaction as well as the health economic evaluation of the different techniques. Target accrual: 7,416 patients. Enrollment started in January 2023. The study will be conducted in 30 countries and is supported by the Oncoplastic Breast Consortium (OPBC), AWOgyn, AGO-B and SENATURK. Financial support will be provided by Endomag, Merit Medical, Sirius Medical and Hologic.

PO4-19-01

The SURVIVE-HERoes trial – a secondary adjuvant treatment intervention study with trastuzumab-deruxtecan in patients with HER2 positive/HER2 low early breast cancer and a molecular relapse, based on a positive ctDNA result

Presenting Author(s) and Co-Author(s):

S. Huesmann. University hospital Ulm, Department for obstetrics and gynecology, United States

F. Mergel. University hospital Ulm, Department for obstetrics and gynecology, Ulm, Baden-Wurttemberg, Germany

K. Pfister. University hospital Ulm, Department for obstetrics and gynecology, United States

A. Fink. University hospital Ulm, Department for obstetrics and gynecology, United States

F. Mehmeti. University hospital Ulm, Department for obstetrics and gynecology, United States

P. Möller. University hospital Ulm, Institute of pathology, United States

T. Fehm. University Hospital Düsseldorf, Düsseldorf, Germany

V. Müller. Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

K. Pantel. Department of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

T. Friedl. Department of Obstetrics and Gynecology, University Hospital Ulm, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

B. Rack. Department of Obstetrics and Gynecology, University Hospital Ulm, Germany

W. Janni. Department Gynecology and Obstetrics, University of Ulm, Ulm, Baden-Wurttemberg, Germany

Background: Despite current adjuvant treatment strategies, $\geq 20\%$ of patients with early breast cancer (EBC) experience a metastatic relapse. In the new era of highly effective antibody drug conjugates (ADCs), secondary adjuvant treatment options for EBC patients at a high risk of relapse arise. The ADC trastuzumab-deruxtecan (T-DXd) has so far shown promising efficacy in patients with HER2-positive and HER2-low metastatic breast cancer (DESTINY Breast 03 and -04 trial) and is currently tested in the post-neoadjuvant setting in patients with non-pCR (DESTINY Breast 05 (TRUDY) trial). However, to successfully apply ADCs as a secondary adjuvant treatment, identification of patients who would benefit the most is required. The detection of minimal residual disease (MRD) using liquid biopsy, e.g. ctDNA, may offer a promising approach for patient selection. The efficacy of such a secondary adjuvant treatment in terms of delaying or even preventing distant metastases has yet to be evaluated in a randomized clinical trial.

Trial design: The SURVIVE-HERoes trial is a prospective, randomized, open label comparative Phase III superiority trial in patients with intermediate to high-risk HER2-positive or HER2-low EBC, who participate in the large breast cancer surveillance trial SURVIVE (NCT05658172) and experience a molecular relapse as determined by a positive ctDNA result, but show no evidence of relapse or metastatic disease based on imaging by CT-scan and SPECT. In total, 180 patients will be enrolled and randomized with 2:1 allocation to treatment with T-DXd + (only endocrine therapy, if HR positive) versus standard of care (including endocrine treatment +/- CDK4/6-inhibitors or Neratinib). The treatment period lasts 12 months during which ctDNA levels will be repeatedly measured every 3 months (additional ctDNA testing will be performed

at month 24 and 36). Stratification factors are HER2-, hormonal- and nodal status. Recruitment start is planned for Q1 2024.

Eligibility criteria: Eligible patients are adult females/males, with HER2-positive or HER2-low EBC, as defined in the ASCO-CAP guidelines, and a positive ctDNA result (obtained in the SURVIVE study) that has to be confirmed ≤ 8 weeks before randomization. Primary anti-tumor therapy (surgery, adjuvant chemo- or radiotherapy) has to be completed ≥ 14 months, (postneo)-adjuvant treatment with anti-HER2-antibodies, T-DM1, Capecitabine, Pembrolizumab and Olaparib ≥ 4 weeks before randomization. Adequate bone marrow and cardiac function and no signs of ILD are mandatory.

Statistics: The primary objective of SURVIVE-HERoes is the comparison of ctDNA clearance rates 6 months after randomization between the two study arms, which will be analysed using the chi square test for two independent proportions. Secondary objectives include the comparison of overall survival (OS), invasive disease-free survival (IDFS), distant disease-free survival (DDFS), distant recurrence-free survival (DRFS), breast cancer specific survival (BCSS), invasive breast cancer free survival (IBCFS) and quality of life (QoL) between the study arms as well as the safety and tolerability of T-DXd. Secondary survival endpoints will be estimated by the Kaplan Meier method and compared between the randomization arms using log-rank tests and cox regression models.

Special aims: This trial is a proof of principle study with the aim to establish the efficacy of secondary adjuvant treatment with the ADC T-DXd in patients with HER2-positive/HER2-low early breast cancer, who are at high risk of relapse, as evidenced by detection of ctDNA in the blood.

Conclusion: If SURVIVE-HERoes is successful, it could lead to a treatment shift towards early intervention with secondary adjuvant targeted therapies following liquid-biopsy based MRD detection.

Contact: University Hospital Ulm, Dpt. Obstetrics & Gynecology, Germany, mail: studienzentrale.ufk@uniklinik-ulm.de

PO4-19-02

Genetic risk estimation in breast cancer and assessing health disparities

Presenting Author(s) and Co-Author(s):

L. Cornell. Mayo Clinic Florida, Jacksonville, Florida, United States

S. Pruthi. Mayo Clinic, Rochester, Minnesota, United States

L. Hasadsri. Mayo Clinic, United States

S. McLaughlin. Mayo Clinic, Jacksonville, United States

Background: Breast Cancer (BC) incidence and the distribution of BC risk factors vary between racial and ethnic groups within the United States. It has been demonstrated that providing education on individualized breast cancer risk will improve patient uptake to recommended BC screening and prevention strategies. Most clinical risk assessment tools, including the validated IBIS model were derived from data using non-Hispanic white women. Consortia have also now identified over 300 common genetic susceptibility loci for BC, summarized by the polygenic risk score (PRS). When combined with clinical risk assessment tools, such as the IBIS or BCRAT models, the PRS can further refine risk estimation for patients. To date, most studies on the use of PRS have been done in non-Hispanic white women. While these PRS still perform well in racial minorities, there has been a recognized need to improve racial and ethnic diversity in genomic research cohorts. Herein, we aim to combine clinical risk assessment models that are already used in routine clinical practice with information derived from PRS testing in women of racial minorities to determine if this can improve risk estimation, patient understanding, and uptake to recommended breast cancer screening and prevention strategies. Design: This is a minimal risk prospective study with a single arm incorporating the PRS into a standard breast cancer risk reduction consultation, followed by annual surveys over 10 years to determine if and how the information provided by the PRS influenced patient decisions regarding recommended BC screening and prevention. Patients will have IBIS and BCRAT risks calculated at baseline visit. A survey of patient perceptions/understanding of risk, intention to undergo screening, and use of preventive medicine is completed after baseline visit prior to receiving the PRS results. Blood sample is obtained at baseline and DNA samples are analyzed for approximately 300 SNPs on a custom-designed, targeted SNP panel from ThermoFisher Scientific by the Mayo Clinic Genomics Laboratory. This PRS result is then combined with the clinical risk assessments (IBIS and BCRAT scores) using the R package Individualized Coherent Absolute Risk Estimators (iCare) tool to provide a new estimate of breast cancer risk for 5year, 10year, and lifetime risk. Patients are seen for follow-up to review results and then complete a second survey to assess their understanding of the results, BC risk, and how the PRS impacted their decision to undergo screening/prevention strategies. Eligibility Criteria: Women who self-identify as African American/Black or Hispanic/Latinx between 30-75 years old with any of the following: 1.) IBIS score of $\geq 5\%$ for the 10 year risk OR BCRAT score of $\geq 3\%$ for the 5 year risk. 2.) History of biopsy proven atypical hyperplasia 3.) History of biopsy proven lobular carcinoma in situ. Specific Aims: Aim 1: The primary aim of this study is to explore if the addition of PRS to the BCRAT and IBIS score will improve intentions to undergo recommended breast cancer screening strategies such as mammography, MRI, or molecular breast imaging in women of underserved racial minorities Aim 2: To explore if the addition of the PRS to the BCRAT and IBIS risk score will aid women of racial minorities in deciding whether to take preventative endocrine therapy. Aim 3: To understand how individualized risk assessment and information on PRS may alter perceived risk of breast cancer. Statistical Methods Analysis will be mostly descriptive. Continuous variables will be summarized as mean (standard deviation) or median (range) and categorical variables will be reported as frequency (percentage). Kaplan-Meier

method will be used to estimate the long-term cumulative risk of cancer. Current Accrual: 3.
Target Accrual: 50

PO4-19-03

FES-PET/MRI for Tailored treatment of luminal A and lobular breast cancer: a prospective cohort study

Presenting Author(s) and Co-Author(s):

R. Di Micco. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), Italy

C. Canevari. Nuclear Medicine Department, San Raffaele University and Research Hospital, Milan, Italy, Milan, United States

F. Gallivanone. IBFM-CNR Institute of Bioimaging and Molecular Physiology of the Italian National Research Council, Milan, Italy, United States

N. Rotmensz. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), United States

V. Zuber. Breast Surgery Unit, San Raffaele University and Research Hospital, Milan, Italy, United States

S. Baleri. Breast Surgery Unit, San Raffaele University and Research Hospital, Milan, Italy, United States

G. Cisternino. Breast Surgery Unit, San Raffaele University and Research Hospital, Milan, Italy, United States

M. Rampa. Breast Surgery Unit, San Raffaele University and Research Hospital, Milan, Italy, United States

S. Zambelli. Medical Oncology Department, San Raffaele University and Research Hospital, Milan, Italy, United States

G. Viale. Medical Oncology Department, San Raffaele University and Research Hospital, Milan, Italy, United States

P. Zucchinelli. Medical Oncology Department, San Raffaele University and Research Hospital, Milan, Italy, United States

M. Morgante. Breast Surgery Unit, San Raffaele University and Research Hospital, Milan, Italy, United States

P. Scifo. Nuclear Medicine Department, San Raffaele University and Research Hospital, United States

E. Venturini. Breast Radiology Unit, San Raffaele University and Research Hospital, Milan, Italy, United States

P. Magnani. Nuclear Medicine Department, San Raffaele University and Research Hospital, United States

I. Sassi. Pathology Department, San Raffaele University and Research Hospital, Milan, Italy, United States

V. Bagnardi. Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy, United States

P. Panizza. Breast Radiology Unit, San Raffaele University and Research Hospital, Milan, Italy, United States

G. Bianchini. IRCCS Ospedale San Raffaele, Milan, Lombardia, Italy

A. Chiti. Nuclear Medicine Department, San Raffaele University and Research Hospital, United States

O. Gentilini. Breast Surgery Unit, San Raffaele University Hospital, Milan, Italy

Background: Breast cancer (BC) staging is essential to planning the most appropriate treatment pathway. Currently, BC management has become more tailored to the tumor's and patient's characteristics. However, BC imaging shows varying performance according to tumor subtypes. In particular, routine imaging may pose some challenges when evaluating luminal A BC (LumA) and lobular BC (Lob). LumA, due to low grade and proliferation index (< 20%) shows lower sensitivity on axillary US, reduced MRI enhancement, and low FDG-avidity on PET. Similarly, Lob, due to its peculiar single-cell growth pattern, exhibits inferior sensitivity on axillary MRI and FDG-avidity. LumA and Lob account for >50% of all BCs. Despite their favourable prognosis, metastases and recurrences still occur; this translates into a higher absolute number of events than in other subtypes. As a result, a concrete risk of disease underestimation and under-treatment exists. Two ongoing studies on FDG-PET/MRI imaging in our institution have already demonstrated that its sensitivity also decreases in LumA and Lob. Based on these premises, our hypothesis states that by combining the advantages of hybrid PET/MRI with the high accuracy of $^{16}\alpha$ - ^{18}F -fluoro- $^{17}\beta$ -estradiol(FES), a radiolabeled form of estrogen binding to functionally active ER, we could obtain a reliable, non-invasive, operator-independent, one-stage imaging method for staging LumA and ER-positive Lob.

Trial design: This is a prospective cohort study where patients with LumA and ER-positive Lob will be enrolled in four cohorts undergoing: A) primary surgery; B) induction endocrine therapy; C) neoadjuvant chemotherapy, and D) systemic therapy for metastatic disease. FES PET/MRI examinations will be performed at baseline for local and systemic staging in all cohorts and a second exam after systemic therapy in cohorts C-D. Correlations between the FES PET/MRI parameters and pathology, gene expression, and FDG PET parameters, when available, will be investigated.

Study aims will evaluate: 1) the performance of the FES PET/MRI in axillary staging compared with axillary surgery; 2) potential correlations between changes in FES uptake and changes in proliferation index after three weeks of endocrine therapy (ET); 3) the performance of the FES PET/MRI in systemic staging of patients undergoing systemic therapy in comparison with standard imaging; 4) biological determinants of tumor heterogeneity on pathological, imaging, and genomic levels.

Statistics: The primary analysis in cohort A will test the sensitivity of the FES PET/MRI in detecting macrometastatic axillary nodes. Assuming that the probability that a patient has positive nodes is 33%, 119 patients (10% drop-out included) will provide 80% power to reject the null hypothesis about sensitivity at a 5% significance level if the true sensitivity is at least 50%. Results from the FES PET/MRI will be also compared with standard imaging in terms of sensitivity and number of lesions detected using the Mc-Nemar test for paired proportions and the Wilcoxon signed-rank test for paired data. The primary analysis in Cohort B will test the association between the FES-SUV change from pre-ET to post-ET and the Ki-67 change from core biopsy to post-ET in ER positive BC patients with a Ki-67 >10%. The association between these changes will be measured by the Pearson correlation index ρ . A total of 52 patients (10% drop-out included) from Cohort B will provide 80% power to reject the null hypothesis about ρ at a 5% significance level if the true ρ is at least 0.4. No formal sample size was calculated for cohort C and D: results will be considered descriptive in nature, informing sample size considerations for future trials. We intent to recruit 20 and 30 patients, respectively. Accrual has not started yet.

Project funded by AIRC (Associazione Italiana Ricerca sul Cancro) Next Gen Clinician Scientist ID 28378

Contact: Dr. Rosa Di Micco, dimicco.rosa@hsr.it

PO4-19-04

AXSANA – EUBREAST-3: An international prospective multicenter cohort study to evaluate different surgical methods of axillary staging in clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany

S. Hartmann. Department of Gynecology and Obstetrics, University Hospital Rostock, Germany

E. Stickeler. Klinik für Gynäkologie und Geburtsmedizin, Uniklinik RWTH Aachen, Germany, United States

J. de Boniface. Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, and Department of Surgery, Capio St. Göran's Hospital, Stockholm, Stockholms Lan, Sweden

O. Gentilini. Breast Surgery Unit, San Raffaele University Hospital, Milan, Italy

S. Fröhlich. Department of Gynecology and Obstetrics, University Hospital Rostock, Rostock, Germany, United States

F. Ruf. University Hospital Schleswig-Holstein Campus Lübeck, Germany, United States

M. Thill. Agaplesion Markus Krankenhaus, 60431 Frankfurt a.M., Hessen, Germany

M. Hauptmann. Brandenburg Medical School Theodor Fontane, Neuruppin, Germany, United States

G. Karadeniz Cakmak. Zonguldak Bulent Ecevit University, Department of Surgery, Turkey

I. Rubio. Clínica Universidad de Navarra, Madrid, Spain, United States

M. Gasparri. Department of Gynecology and Obstetrics, Ente Ospedaliero Cantonale, Ospedale Regionale di Lugano, Lugano, Switzerland, Ticino, Switzerland

M. Kontos. 1st Department of Surgery, Laiko Hospital, National and Kapodistrian University of Athens, Greece

E. Bonci. Department of Surgical Oncology, "Prof. Dr. Ion Chiricuță" Institute of Oncology, Cluj-Napoca, Romania 16)Department of Oncological Surgery and Gynecological Oncology, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania, United States

L. Niinikoski. Breast Surgery Unit, Comprehensive Cancer Center, Helsinki University Hospital, University of Helsinki, Finland, United States

B. Aktas Sezen. European Breast Cancer Research Association of Surgical Trialists (EUBREAST), United States

R. Di Micco. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), Italy

D. Murawa. Department of General Surgery and Surgical Oncology, Collegium Medicum, University of Zielona Góra, Poland, Poland

G. Kadayaprath. Max Hospital, Patparganj, New Delhi, India, Germany

D. Pinto. Breast Unit, Champalimaud Clinical Center, Champalimaud Foundation, Lisboa, Portugal, United States

F. Peintinger. Institute of Pathology, Medical University of Graz, Graz, Austria / Universitätsklinik für Frauenheilkunde und Geburtshilfe, Graz, Austria, United States

M. Appelgren. Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, United States

J. Simons. GROW – School for Oncology and Developmental Biology, Maastricht University, Maastricht, Netherlands /Department of Radiation Oncology, Erasmus Medical Center, Rotterdam, Netherlands, United States

M. Smidt. Department of Surgical Oncology, Maastricht University Medical Center, Maastricht, The Netherlands, United States

E. Schlichting. Oslo University Hospital, Oslo, Norway

L. Dostalek. Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University, General University Hospital, Prague, Czech Republic, United States

E. Thiemann. Brustzentrum Osnabrück / Niels-Stensen-Kliniken, Osnabrück/Georgsmarienhütte, Germany, United States

M. Hahn. Universitätsklinikum Tübingen, United States

M. Schrauder. Department of Gynecology and Obstetrics, Klinikum Aschaffenburg-Alzenau, Germany, United States

S. Gunay. Ministry of Health Istanbul Provincial, Health Directorate Prof. Dr. Cemil Taşcioğlu City Hospital, Istanbul, Turkey, United States

G. Gurleyik. Ministry of Health Istanbul Provincial Health Directorate Istanbul Haydarpaşa Numune Research and Training Hospital, Istanbul, Turkey, United States

N. Helidon. Department of Surgery, Oncology Hospital, Tirana, Albania, United States

H. Valiyeva. Oncologic Clinic of Azerbaijan Medical University, Baku, Azerbaijan, United States

A. Kothari. Guy's & St Thomas NHS Foundation Trust, Kings College, London, United Kingdom, United States

M. Vanhoeij. Universitair Ziekenhuis Brussel, Brussel, Belgium, United States

A. Perhavec. Department of Surgical Oncology, Institute of Oncology Ljubljana, Slovenia, United States

T. Ivanov. Heart and Brain Hoospital, Pleven, Bulgaria, United States

D. Zippel. Surgical Oncology C, Sheba Medical Centre, Ramat Gan, Israel, United States

L. Rebaza. Clinica Oncosalud Auna, Lima, Peru, United States

S. Thongvitokomarn. Queen Sirikit Centre for Breast Cancer, Bangkok, Thailand, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

M. Banys-Paluchowski. Department of Obstetrics and Gynecology, Asklepios Hospital Barmbek, Hamburg, Germany

Background

The optimal surgical staging procedure of the axilla in patients who convert from a clinically positive (cN+) to a clinically negative node status (ycN0) through neoadjuvant chemotherapy is still controversial. Widely diverse techniques such as full Axillary Lymph Node Dissection (ALND), Targeted Axillary Dissection (TAD), Targeted Lymph Node Biopsy (TLNB) and Sentinel Lymph Node Biopsy (SLNB) alone are given preference in different international guidelines. So far, no comparative data on the oncological outcome or the morbidity of the different procedures are available. Further research is needed to safely de-escalate the extent of axillary surgery in this patient group.

Trial design

The AXSANA study is an international prospective cohort study including cN+ patients converting to ycN0 status and treated with different axillary staging techniques according to the standard at their treating institution. The study was initiated by the EUBREAST network. The trial includes patients with cT1-4c tumors, who present initially with axillary lymph node metastasis scheduled for neoadjuvant chemotherapy. According to an amendment in 2020 the inclusion of patients with highly suspicious nodes without confirmation using a minimally invasive biopsy is allowed. All patients converting to ycN0 status undergo follow-up for 5 years irrespectively of the ypN status.

Primary endpoints: Invasive disease-free survival, axillary recurrence rate and health-related quality of life (HRQoL). HRQoL are evaluated using four standardized questionnaires (EORTC QLQ-C 30, EORTC QLQ-BR 23, Lymph ICF and SOC-13) at baseline and after 1, 3 and 5 years after surgery.

Secondary endpoints are the feasibility and performance of different axillary staging techniques (detection rate, number of removed lymph nodes and association with complications, arm morbidity and quality of life, operating time and use of clinical and economic resources); impact of learning curve, and the detailed mapping of surgical and oncological treatment standards in different countries. The impact on different regional treatment strategies (radiotherapy, ALND) in patients with ypN0(i+), ypN1(mi) and ypN1 is assessed.

Current status of the study: 4336 patients from 284 study sites and 26 countries were enrolled in the study between June 2020 and June 2023. Among 3722 patients with a defined surgical concept 1631 women were scheduled for TAD, 1483 for ALND, 469 for SLNB, 25 for TLNB and 109 for other procedures. A target lymph node was marked in 2309 patients, most frequently using clips/coils (1850, 80.1%), followed by magnetic seeds (219, 9.5%), carbon ink (171, 7.4%), radar marker (80, 3.5%), radioactive seeds (4, 0.2%) and other techniques (24, 1.0%).

Funding: AGO-B, GBG, Claudia-von Schilling Foundation, Ehmann Foundation, Eugen und Irmgard Hahn Foundation, AWOgyn, Merit Medical, Endomagnetics, Mammotome

Contact information:

Prof. Dr. Thorsten Kühn
Department of Gynecology and Obstetrics
University of Ulm, Germany
Baumreute 37
D-73730 Esslingen
Germany
E-Mail: kuehn.thorsten@t-online.de

PO4-19-05

OptimICE-pCR: De-escalation of therapy in early-stage TNBC patients who achieve pCR after neoadjuvant chemotherapy with checkpoint inhibitor therapy (Alliance A012103)

Presenting Author(s) and Co-Author(s):

- S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
- K. Ballman. Weill Cornell Medicine, New York, New York, United States
- C. Perou. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA, United States
- D. Cescon. Princess Margaret Cancer Centre/UHN, Toronto, Ontario, Canada
- M. Gatti-Mays. The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States
- V. Blinder. Memorial Sloan Kettering Cancer Center, United States
- S. Rosenberg. Weill Cornell Medicine, New York, New York, United States
- E. Mittendorf. Dana Farber Cancer Institute, Boston, Massachusetts, United States
- A. Weiss. Division of Surgical Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States
- H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States
- A. Ho. Duke Cancer Center, United States
- D. Casey. University of North Carolina at Chapel Hill, United States
- B. Singh. White Plains Hospital, United States
- F. Smiellauskas. Wayne State University/Karmanos Cancer Institute, United States
- Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States
- V. Damarla. Illinois CancerCare, United States
- J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States
- L. Carey. UNC-Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States
- A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: For patients with stage II-III triple-negative breast cancer (TNBC), standard of care systemic therapy consists of neoadjuvant pembrolizumab with chemotherapy, followed by 27 weeks of adjuvant pembrolizumab based on the results of the phase III KEYNOTE-522 trial. This trial demonstrated that pathologic complete response (pCR) rates and event-free survival (EFS) were significantly better among patients who received neoadjuvant followed by adjuvant pembrolizumab in addition to chemotherapy compared to chemotherapy alone. An exploratory analysis from this study demonstrated better EFS among patients who experienced a pathologic complete response (pCR) to neoadjuvant therapy compared to those with residual disease. Additionally, other studies, including GeparNuevo, which did not include adjuvant checkpoint inhibition, demonstrated EFS benefit from the addition of preoperative checkpoint inhibitor therapy to chemotherapy. It is therefore unclear if adjuvant pembrolizumab improves outcomes for patients with early-stage TNBC who achieve a pCR after neoadjuvant pembrolizumab plus chemotherapy. OptimICE-pCR trial utilizes response to preoperative therapy to tailor adjuvant therapy, and the goal is to determine whether patients who achieve

pCR to pembrolizumab plus chemotherapy can achieve a similar recurrence-free survival (RFS) with observation compared to adjuvant pembrolizumab monotherapy

Methods: OptimICE-pCR is an open-label, multicenter, randomized phase III trial that is enrolling patients with stage T1cN1-2 or T2-4N0-2 TNBC. To be eligible, patients must have experienced a pCR after the completion of neoadjuvant therapy containing a minimum of six cycles of chemotherapy in combination with pembrolizumab. Participants are randomized 1:1 to receive either 27 weeks of adjuvant pembrolizumab or to observation. Participants on the pembrolizumab arm receive pembrolizumab 200 mg IV on day 1 of each 21-day cycle for 9 cycles, or 400 mg IV on day 1 of each 42-day cycle for 4 cycles, followed by one dose of 200 mg IV every 21 days. The primary objective is to evaluate whether observation results in non-inferior RFS compared to adjuvant pembrolizumab. Non-inferiority is defined as an estimated 3-year RFS of 91% or higher in the observation arm compared to 94% in the pembrolizumab arm. The total sample size will be 1,295 patients, which will provide 80% power at one-sided significance level of 0.05 to detect this difference, which corresponds to a non-inferiority hazard ratio of 1.52. Key secondary endpoints include overall survival, locoregional recurrence, quality of life, financial toxicity, work productivity impairment, cost-effectiveness, and safety and tolerability. Key correlative objectives include detection of ctDNA at baseline and association with RFS and association of key biomarkers (TILs, PDL1, immune gene expression) from the primary tumor with RFS. The trial is currently open and enrolling patients.

Support: U10CA180821, U10CA180882; U24 CA196171; U10CA180820 (ECOG-ACRIN); U10CA180863 (CCTG); <https://acknowledgments.alliancefound.org>.
ClinicalTrials.gov Identifier: NCT05812807

PO4-19-06

Phase II study of a PARP inhibitor, talazoparib, in HER2- metastatic breast cancer with a somatic BRCA1/2 mutation present in cell-free DNA or tumor tissue genotyping

Presenting Author(s) and Co-Author(s):

N. Vidula. Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, United States

S. Damodaran. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Bhave. Emory University School of Medicine, Atlanta, Georgia, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

A. Shah. Northwestern University, United States

E. Blouch. Massachusetts General Hospital, United States

N. Royce Ruffle-Deignan. Massachusetts General Hospital, United States

O. Ogbenna. Massachusetts General Hospital, United States

L. E. Flaum. Northwestern University, Chicago, IL, United States

M. Cristofanilli. Weill Cornell Medicine, United States

J. Sparano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

H. Ostrer. Albert Einstein College of Medicine, United States

V. Abramson. Vanderbilt University Medical Center, United States

N. Horick. Massachusetts General Hospital, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background: PARP inhibitors improve both progression free survival (PFS) and patient quality of life in germline BRCA1/2 mutant metastatic breast cancer (MBC), which accounts for 5-10% of breast cancer, leading to their approval in this setting. We have previously shown that a subset of patients with MBC who are not germline BRCA1/2 carriers may harbor pathogenic somatic BRCA1/2 mutations that are identified by cell-free DNA and/or tumor tissue genotyping. In our prior work, we developed a circulating tumor cell culture from a patient with MBC harboring a pathogenic somatic BRCA1 mutation, and demonstrated that a PARP inhibitor induced cell growth inhibition similar to germline BRCA1/2 mutant cultures. Thus, we hypothesize that a PARP inhibitor may be effective in treating somatic BRCA1/2 mutant MBC. In this clinical trial, we are studying the efficacy of a PARP inhibitor in somatic BRCA1/2 mutant MBC. Our work may help expand the clinical application of PARP inhibitors in MBC.

Trial Design: This phase II investigator-initiated clinical trial is enrolling 30 patients with MBC who have a pathogenic somatic BRCA1/2 mutation identified by a CLIA certified cell-free DNA and/or tumor tissue genotyping assay. Patients are treated with the PARP inhibitor talazoparib 1 mg/day until progression of disease. Imaging (CT chest, abdomen and pelvis, and bone scan) occurs for disease assessment at baseline and every 3 months. Cell-free DNA is collected at baseline and then monthly to evaluate changes in the genomic environment. Patients also undergo the Cancer Risk B (CR-B) assay, a novel flow variant assay to identify double-strand break repair mutations in circulating blood cells, at baseline.

Eligibility Criteria: Patients must have MBC with a pathogenic somatic BRCA1/2 mutation identified in a cell-free DNA and/or tumor tissue genotyping assay, with pathogenicity confirmed by a genetics counselor using validated genomic databases such as ClinVar. Patients may have triple-negative (receipt of at least 1 prior chemotherapy) or hormone receptor positive/HER2- MBC (receipt of at least 1 prior hormone therapy). Patients must not be known germline BRCA1/2 carriers. Any number of prior therapies including a prior platinum (in absence of progressive disease on a platinum) are allowed, but patients should not have received a prior PARP inhibitor. Patients must have adequate organ function and performance status.

Specific Aims: The primary aim is to determine PFS (RECIST 1.1). Secondary aims include determining the objective response rate and toxicity (NCI CTCAE v 5.0). Exploratory aims include evaluating serial changes in BRCA1/2 mutant allelic frequency in cell-free DNA, understanding the impact of BRCA1/2 reversion mutations in cell-free DNA, comparing pre- and post-treatment cell-free DNA results to understand changes in the genomic environment, studying the CR-B assay positivity rate, and correlating these biomarker analyses with treatment response.

Statistical Methods: This study has 81% power to demonstrate that the 12-week PFS is 53% or higher. In contrast, there is a 4% (alpha) probability of concluding that the 12-week PFS is \geq 53% if the true 12-week PFS is 30% or lower. If 14 or more of 30 total patients achieve PFS > 12 weeks, the null hypothesis (12-week PFS \leq 30%) will be rejected.

Present accrual and target accrual: This study (NCT03990896) is open at Massachusetts General Hospital, MD Anderson, University of California San Francisco, Emory, Northwestern, and Vanderbilt. As of 7/2023, 14/30 patients are enrolled.

Funding: This study is funded by a Pfizer ASPIRE award and Conquer Cancer Foundation of ASCO–Breast Cancer Research Foundation- Career Development Award.

Contact information: Neelima Vidula, MD, Massachusetts General Hospital, nvidula@mgh.harvard.edu.

PO4-19-07

Tailored Axillary Surgery (TAS) in Patients with Clinically Node-Positive Breast Cancer in the Upfront Surgery Setting: A Prospective, Single-Arm, Multicenter Trial

Presenting Author(s) and Co-Author(s):

K. Terata. Akita University Hospital, Department of Breast and Endocrine Surgery, United States

Y. Sagara. Hakuai Sagara Hospital, Kagoshima, Kagoshima, Japan

T. Shien. Okayama University Hospital, Okayama-city, Okayama, United States

T. Sakai. Breast Surgical Oncology, Cancer Institute Hospital of JFCR, United States

S. Takayama. Department of Breast Surgery, National Cancer Center Hospital, Tokyo, Japan

D. Kitagawa. National Center for Global Health and Medicine, United States

T. Iwatani. Department of Breast and Endocrine Surgery, Okayama University, United States

T. Tsukioki. Okayama University Hospital, United States

M. Ogita. The University of Tokyo Hospital, United States

N. Sanuki. Yokkaichi Municipal Hospital, United States

M. Yoshida. Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo, Japan, United States

H. Tsuda. National Defense Medical College, United States

S. Yamamoto. Shizuoka Graduate University of Public Health, United States

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

A brief background discussion:

Axillary lymph node dissection (ALND), which can induce lymphedema, has been omitted in clinically node-negative (cN0) patients with positive sentinel lymph nodes (SLNs) if they meet the eligibility criteria of ACOSOG Z0011. Furthermore, the omission of ALND has been attempted through targeted axillary dissection (TAD) in patients whose clinically node-positive (cN+) status converts to ycN0 after neoadjuvant chemotherapy. However, ALND remains the standard of care in patients with cN+ who undergo upfront surgery.

Trial design:

This is a prospective, single-arm, multicenter phase II feasibility trial with the participation of 41 hospitals belonging to the breast cancer study group of Japan Clinical Oncology Group (JCOG). Tailored axillary surgery (TAS) removes labeled lymph node (LN) with clip, wire, or tattoo, palpable LNs, and SLNs. ALND is performed after TAS. These LNs removed by ALND other than TAS are defined as non-TAS LNs.

Eligibility criteria:

The eligibility criteria are as follows: 1) histologically-proven invasive breast cancer, 2) upfront surgery is planned, 3) pathologically diagnosed metastatic LN (cytology or core needle biopsy), 4) 1-3 LN metastases in level I by imaging, 5) cT1-3, and 6) females aged ≥ 18 and ≤ 74 years on the enrollment date.

Specific aims:

This trial aims to establish a surgical method of tailored axillary surgery (TAS) among patients with cN+ who undergo upfront surgery and to determine the appropriate criteria for the next

phase III TAS trial, which omits ALND by TAS safely. The primary endpoint is the non-TAS LNs positive rate. Clinicopathological factors (the number of suspected metastases by imaging, the number of metastases in LNs resected by TAS, tumor size, and invasive ductal/lobular carcinoma) are analyzed to predict the non-TAS LN metastasis rate (e.g., < 10%). The secondary endpoints are the TAS LNs identification rate, marked LN resection rate, arm edema incidence rate, and QOL (FACT-B, QuickDASH).

Statistical methods:

In this trial, among the combinations of factors involved in treatment selection, the objective is to narrow down the combinations that will result in a non-TAS metastasis-positive rate of less than 10% when TAS is performed. For a single combination, 167 cases need to be considered to reject a non-TAS metastasis-positive rate of 10% or more (5% one-sided alpha error, 70% power, and 5% expected value). However, performing these studies for all combinations lacks feasibility. Therefore, we decided to improve the estimation accuracy by using a regression model with the non-TAS metastasis-positive rate as the outcome variable and the factors involved in treatment selection as explanatory variables and to search for combinations of factors with a non-TAS metastasis-positive rate less than 10%. Based on the rule of thumb that a sample size of at least ten times the number of factors is required when using regression methods, a regression model is used when 60 cases are accumulated. The combinations with a 90% confidence upper limit of less than 10% of non-TAS metastasis positivity as the predictive value of the regression model will be selected as candidate combinations that fulfill the conditions. If the accuracy of the predictive value is considered insufficient, 60 cases will be added sequentially up to a maximum of 300 cases.

Present accrual and target accrual:

The patient recruitment was started in April 2023. Up to 300 patients will be enrolled over a 2-year recruitment period. Twenty-one patients were already enrolled until July 2023.

PO4-19-08

Randomized phase II study of talazoparib vs talazoparib plus atezolizumab for patients with premenopausal HR+/HER2- metastatic breast cancer harboring homologous recombination deficiency scar (Young-PALETTA, KCSG BR21-09)

Presenting Author(s) and Co-Author(s):

H. Ahn. Gachon University Gil Medical Center, United States

J. Lee. Division of Medical Oncology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Republic of Korea

J. Kim. Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

K. Lee. Seoul National University Hospital, United States

J. Kim. Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea

M. Kim. Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, United States

M. Kwon. Ajou University School of Medicine, United States

H. Kim. Division of Hematology and Oncology, Department of Internal Medicine, Soonchunhyang University Hospital, Republic of Korea

K. Jung. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Not Applicable, Republic of Korea

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

Background

Cyclin D kinase-4/6(CDK4/6) inhibitor combined with endocrine treatment have significantly increased progression free survival(PFS) and overall survival(OS) of patients with hormone receptor(HR)-positive/HER2-negative metastatic breast cancer, and currently is a standard 1st line endocrine treatment option. Homologous recombination deficiency(HRD) including germline(g) BRCA1/2 pathogenic mutation is known to be prevalent among young premenopausal patients. Recently several retrospective data suggested that patients with germline BRCA1/2 pathogenic mutation or HRD have poorer outcome with CDK4/6 inhibitor treatment, however there is no prospective evidence. Poly ADP-ribose polymerase(PARP) inhibitors have shown significant benefit over standard chemotherapy in patients with HER2-neg metastatic breast cancer and gBRCA1/2 pathogenic mutation in two Phase 3 trials. Since preclinical data suggested that PARP inhibitors play a role in anti-tumor immune modulation, immunotherapy combined with PARP inhibitors were explored and showed promising antitumor efficacy in several single arm trials. In this trial, we investigate talazoparib and atezolizumab combination compared with talazoparib monotherapy in premenopausal women with HR+/HER2- metastatic breast cancer with HRD-scar after failure with 1st line palbociclib and endocrine treatment combination.

Methods

This study is a multicenter, randomized, open-label phase II trial comparing talazoparib versus talazoparib with atezolizumab in premenopausal women with HR+/HER2- metastatic breast cancer harboring HRD scar whose disease have progressed with endocrine and palbociclib combination as the 1st-line endocrine treatment. Prior one line of cytotoxic chemotherapy other

than platinum for metastatic setting is allowed, but prior palliative endocrine treatment is not allowed. Eligible patients will be pre-screened with tumor tissue biopsy and peripheral blood sampling before endocrine and palbociclib treatment commencement. HRD status is determined through targeted sequencing(SOLIDaccuTest™ by NGeneBio) of tumor tissue and germline HRD genes including BRCA1/2 variant test. Whole genome sequencing and RNA sequencing are performed for biomarker analyses. Patients harboring HRD scar will receive first line endocrine treatment with palbociclib plus aromatase inhibitor with ovarian suppression. After progression with 1L endocrine treatment, patients will be randomized to either talazoparib alone or talazoparib plus atezolizumab combination. Germline BRCA1/2 pathogenic mutation is a stratification factor. Primary endpoint is a progression free survival after randomization(PFS2). Secondary objectives are a composite of PFS1 and PFS2, PFS1, overall survival, patient reported outcome, and biomarkers for treatment response. A total of 178 subjects are required to detect hazard ratio of 0.62 (median PFS2 of at least 10.5 months with talazoparib and atezolizumab combination vs 6.5 months with talazoparib alone), to achieve 80% power at a two-sided a significance level at 10%, considering drop-out rate of 5%. The study period is expected to be 72 months overall(36 months for accrual and randomization and 24 months of follow-up for primary endpoint PFS2).

PO4-19-09

Comparison of clinical efficacy between letrozole + ribociclib vs. Fulvestrant + letrozole + ribociclib in Hormone receptor positive, HER2 negative metastatic breast cancer – a randomized, phase 2 study (KCSG BR22-20)

Presenting Author(s) and Co-Author(s):

J. Lee. Division of Medical Oncology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Republic of Korea

S. Koh. Department of Hematology and Oncology, Ulsan University Hospital, Ulsan University College of Medicine, United States

J. Kwon. Division of Hemato-Oncology, Department of Internal Medicine, Chungnam National University Sejong Hospital, Sejong-Si, United States

G. Kim. Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, United States

J. Kim. Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

H. Kim. Division of Hematology-Oncology, Hallym University Sacred Heart Hospital, United States

H. Kim. Department of Internal Medicine, Chung-Ang University College of Medicine, Republic of Korea

K. Park. Division of Hematology-Oncology, Department of Internal Medicine, Keimyung University Dongsan Hospital, Daegu, United States

K. Park. Korea University Anam Hospital, Republic of Korea

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

M. Ahn. Department of Hematology-Oncology, Ajou University School of Medicine, United States

H. Ahn. Gachon University Gil Medical Center, United States

G. Lee. Department of Internal Medicine Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, United States

K. Lee. Division of Hematology Oncology, Department of Internal Medicine, School of Medicine, Ewha Womans University, Republic of Korea

K. Lee. Seoul National University Hospital, United States

M. Lee. Department of Internal Medicine, Inha University School of Medicine, United States

S. Lee. Department of Hematology-Oncology, Inje University Haeundae Paik Hospital, United States

J. Lee. Division of Hematology and Medical Oncology, Department of Internal Medicine, Daegu Fatima Hospital, Republic of Korea

K. Jung. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Not Applicable, Republic of Korea

J. Jung. Department of Internal Medicine, Hallym University Medical Center, Dongtan Sacred Heart Hospital, Republic of Korea

I. Park. Department of Hemato-Oncology, Division of Internal Medicine, Korea University College of Medicine, Guro Hospital, Republic of Korea

Background

The current standard first-line treatment in advanced or metastatic hormone receptor (HR) positive breast cancer is combination of aromatase inhibitor (AI) and cyclin D kinase-4/6 (CDK4/6) inhibitor. Emergence of ESR1 mutation is a key mechanism of resistance during first-line AI + CDK4/6 inhibitor treatment. Selective estrogen receptor downregulator (SERD) such as elacestrant or fulvestrant is suggested as second-line treatment, but the progression-free survival (PFS) outcome of second-line treatment is reported up to 3.78 months in patients who harbour ESR1 mutation. Recently, early switch of AI + CDK4/6 inhibitor to fulvestrant + CDK4/6 inhibitor at the point of rising ESR1 mutation showed prolongation of PFS up to 6 months, suggesting there may be a new strategy to overcome ESR1 mutation by modifying endocrine treatment. SWOG S0226 suggested that upfront fulvestrant + AI is feasible and associated with prolongation of PFS compared to AI alone. After CDK4/6 inhibitor has been introduced to standard treatment, there were no trials evaluating the role of AI + fulvestrant with CDK4/6 inhibitor. In this trial, we investigated triplet combination of AI + fulvestrant + CDK4/6 inhibitor as a treatment to overcome resistant mechanism such as development of ESR1 mutation when compared to current standard treatment of AI + CDK4/6 inhibitor as the first line treatment in HR positive advanced or metastatic breast cancer.

Methods

This study is a randomized, multicenter, open-label phase II trial comparing AI plus ribociclib versus AI, fulvestrant plus ribociclib in HR-positive advanced or metastatic breast cancer. De novo patients or patients with treatment-free interval (TFI) over 12 months after completion of adjuvant AI can be enrolled. If patients received adjuvant tamoxifen, patients with TFI less than 12 months can be also enrolled for the study. Prior endocrine treatment or cytotoxic chemotherapy at metastatic setting was not allowed. In cases of premenopausal women, gonadotropin releasing hormone agonist (GnRHa) is administered every 4 weeks with treatment. A total of 202 patients will be enrolled for 30 months, and 30 months of follow-up is planned after last-patient enrolment. Patients are randomized to 1:1, stratified based on the presence of visceral metastasis and previous administration of adjuvant AI. Study treatment of the control arm consists of letrozole 2.5mg daily with ribociclib 600mg (Day 1-Day 21 daily by month, 1 week off) until progression. In the experimental arm fulvestrant 500mg intramuscular injection is added (Day 1, Day 15, Day 29 and every 4 weeks thereafter) until progression. For exploratory analysis of ESR1 mutations, circulating tumor DNA (ctDNA) is collected at baseline, and then every 3 months thereafter. Primary endpoint is to evaluate the difference of 24-months PFS rate. Secondary endpoint included PFS, overall survival (OS), emergence and frequency of ESR1 mutation, overall response rate (ORR) and clinical benefit rate (CBR). The analysis is planned after completion of 30 months of follow-up, which provides approximately 90% power to detect superiority 24 months-PFS rate assumed by Kaplan-Meier curve of letrozole + fulvestrant + ribociclib versus letrozole + ribociclib using a log-rank test, assuming a hazard ratio of 0.64 at a two-sided alpha of 0.2.

PO4-19-10

Selective Avoidance of Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy In HER-2 Positive/Triple Negative Breast Cancer Patients With Excellent Radiologic Response to the Breast and Axilla.

Presenting Author(s) and Co-Author(s):

J. Ryu. Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam, Ulsan-gwangyoksi, Republic of Korea

W. Han. Seoul National University Hospital, Seoul, Republic of Korea

H. Lee. Seoul National University Hospital, United States

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

H. Kim. Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

H. Park. Department of Surgery, Yonsei University College of Medicine, United States

J. Choi. Samsung medical center, United States

H. LEE. Division of Breast Surgery, Department of Surgery, Samsung Medical Center, United States

H. Kim. Samsung medical center, United States

J. Lee. Samsung Medical Center, Seoul, Republic of Korea

Background

Neoadjuvant chemotherapy (NACT) for breast cancer (BC) is downstaging inoperable tumors into operable tumors and de-escalating breast/axillary surgery. According to advanced NACT, dual human epidermal growth factor-2 (HER2) blockage in HER2-positive BC, carboplatin, and immunotherapy in triple-negative breast cancer (TNBC) revealed pathologic complete response (ypCR) rates of up to 68% and 80%, the indications for NACT have expanded to early BC and the expected ypCR rate has increased. Therefore, it may be reasonable to consider omitting surgery in cases with excellent responses to NACT.

Although sentinel lymph node biopsy (SLNB) is minimally invasive, some patients still experience complications such as lymphedema, pain, sensory loss, and axillary web syndrome. Several recent retrospective studies and pilot prospective studies have reported axillary pathologic complete response (ApCR) is highly correlated with breast pathologic complete response (BpCR). In cN0 with HER2+ BC and TNBC, the ApCR rate in BpCR after NACT was reported up to 100%, and in cN1 with HER2+ BC and TNBC, the ApCR rate in BpCR after NACT was reported about 85%.

There are many studies predicting BpCR using radiologic imaging such as breast mammography (MMG), ultrasonography (USG), and magnetic resonance imaging (MRI). However, the combination of tri-modality (MMG, USG, MRI) could not confirm BpCR. The current study is screened in cT1-3N0-1M0, HER2+ or TNBC, and planned breast-conserving surgery (BCS) patients after NACT with excellent response at the combination of tri-modality imaging (breast MMG, breast USG, breast MRI) and with expected BpCR at physical examination.

Methods

Trial design

The ASLAN trial is a prospective, multicenter, single-arm, clinical study. The five tertiary care

hospitals in South Korea are participating which are members of the Korean Breast Cancer Study Group (KBCSG).

Eligibility

Inclusion criteria: women aged 20-69; cT1-3N0-1M0; HER2+ or TNBC (defined by ER-negative (< 10% positive cells in IHC) and PR-negative (< 10% positive cells in IHC)); expected complete remission at physical examination and radiological expected Tumor size \leq 2cm or non-mass enhancement \leq 4cm at breast MRI after standard NACT; planned breast-conserving surgery (BCS) with whole-breast irradiation; ECOG performance status 0-1.

Exclusion criteria: SLNB before NACT; previous axillary surgery; bilateral BC; pregnancy.

Intervention

In eligible patients, BCS was performed. After BCS, patients who showed BpCR are enrolled with the omission of SLNB. Patients with no BpCR proceed with routine axillary surgery.

Sample size calculation

The assumption for an acceptable 5-year RFS \geq 84% is based on previous study findings. The calculated total case number for per-protocol analysis is N=178. By Jun 2023, 153 patients had been enrolled and the target accrual of 178 patients is expected to be complete by Dec 2023.

Study outcomes

Primary endpoint: 5-year recurrence-free survival.

Secondary endpoint: local recurrence-free survival, breast cancer-specific survival, overall survival, ipsilateral axillary recurrence interval, distant metastasis-free survival, contralateral breast-free survival, re-operation rate according to breast biopsy after NACT, adverse event, and quality of life.

Accrual Plans

The first patient was enrolled on Sep 2021. Among 223 patients who were screened, 153 patients have been enrolled in Jun 2023. We plan to complete the target accrual by Dec 2023.

Conclusion

The primary aim of the ASLAN trial is to demonstrate the oncologic safety of omitting axillary surgery for the excellent response after NACT in HER2+ or TNBC, early breast cancer patients undergoing BCS and adjuvant RT

ASLAN trial, altogether with the EUBREAST-01 and ASCIS trials, will answer the very important question that may alter the axillary surgery in highly selected patients after NACT

PO4-19-11

A Multicenter, Phase Ib/II Study of Abemaciclib in Combination with Bicalutamide for Androgen Receptor-positive, HER2-negative Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

N. Casasanta. Icahn School of Medicine at Mount Sinai/Icahn School of Medicine at Mount Sinai, United States

C. Landry. Memorial Sloan Kettering Cancer Center, United States

T. Shao. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

P. Klein. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

J. Fasano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

A. Bhardwaj. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

N. Berger. New York-Presbyterian Westchester, United States

E. Moshier. Icahn School of Medicine at Mount Sinai, United States

G. Joshi. University of Vermont Cancer Center, United States

R. Vaccaro. Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, United States

J. Sparano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

A. Tiersten. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New, New York, United States

Background The androgen receptor (AR) is expressed in approximately 30% of breast cancers. Phase I and II trials of bicalutamide in HR-negative and enzalutamide in both triple negative breast cancer (TNBC) and hormone receptor (HR) positive populations have shown safety and favorable clinical benefit rates (CBR). Additionally, cell cycle (CC) inhibitors, such as abemaciclib, have demonstrated improved progression free survival (PFS) for patients with HR-positive metastatic breast cancer (MBC) in combination with ET in the first line and subsequent lines of therapy. A preclinical study showed that anti-androgen therapies enhanced CDK4/6 induced cytostatic effect in AR-positive TNBC cell lines. We performed a retrospective, institutional study evaluating metastatic HR+ tumor samples with immunohistochemistry (IHC) from patients treated with CDK4/6 inhibitor, palbociclib. We found a statistically significant increase in event free survival (EFS) for those that had any expression of AR (>0%, median EFS 19 months vs 5 months, HR 0.26, p=0.01). Additionally, AR expression was associated with intact phosphorylated retinoblastoma (Rb) expression (100%, P=0.02), which may represent a mechanism by which CC inhibition is effective in AR+ MBC.

Trial Design NCT 05095207 is an ongoing, Phase Ib/II, open label, multi-center study. The primary objective for the phase I portion is to determine the recommended phase II dose (RP2D) of abemaciclib in combination with bicalutamide. The primary objective for the phase II portion is to determine the disease control rate (DCR) at 6-month treatment with abemaciclib and bicalutamide. Patients with HER2-negative MBC who are AR+ (IHC >1%) are eligible. HR-positive participants must have had one prior line of ET in the metastatic setting and no more than 2 prior lines of cytotoxic chemotherapy. HR-negative participants may have had up to 4 prior lines of cytotoxic chemotherapy.

In the Phase I portion, up to 12 patients are given abemaciclib 100 mg oral, twice daily on days

1 to 28 and bicalutamide 150 mg oral, daily on days 1 to 28. If there is no toxicity after cycle 1 for the first 3 patients, the dose of abemaciclib will increase to 150 mg twice daily. However, if there is a dose limiting toxicity (DLT) within the first cycle (28 days) of therapy, the dose will decrease to 50 mg twice daily. In the Phase II portion, 51 patients will receive abemaciclib at the RP2D twice daily in addition to bicalutamide 150 mg daily on days 1 to 28. The estimated study duration is 36 months. The drugs will be administered until disease progression or unacceptable toxicity.

The primary end points include the DLT and the RP2D for abemaciclib administered with bicalutamide and the DCR at 6 months. The secondary end points include the frequency of adverse effects, the DCR stratified by HR status, and PFS. Exploratory endpoints are to determine whether Ki67, cyclin D1, p16, and phosphorylated Rb expression at baseline are predictors of response to abemaciclib and to determine potential mechanisms for resistance to treatment.

For Phase Ib, we will utilize the Bayesian optimal interval (BOIN) design, the RP2D will be selected as the dose closest to the target toxicity rate of 0.3. The observed DLT rate at the current dose is ≤ 0.236 , the next cohort will be treated at the next higher dose level, if it is ≥ 0.359 the next cohort will be treated with the next lower dose level. For Phase II, we will assess the DCR using a Simon 2 stage optimal design. If among the 46 evaluable patients, 12 or fewer achieve disease control, the treatment will be rejected, however if 13 or more have disease control, the treatment will be considered worthy for further study. We define inactivity as DCR of 0.20 and activity as DCR of 0.35. To date, the study has recruited 21 participants, the goal accrual is 60 patients.

PO4-19-12

Trial in progress: An Observational Study to Examine Changes in Metabolic Syndrome Components in Patients With Breast Cancer Receiving (Neo)Adjuvant Aromatase Inhibitors

Presenting Author(s) and Co-Author(s):

A. LeVee. City of Hope Comprehensive Cancer Center, United States

N. Ruel. City of Hope Comprehensive Cancer Center, United States

V. Seewaldt. City of Hope Comprehensive Cancer Center, United States

J. Mortimer. City of Hope, Duarte, California, United States

Background: (Neo) adjuvant systemic therapy has been shown to adversely impact metabolic health manifested as weight gain, dyslipidemia, and insulin resistance, which ultimately lead to the development of metabolic syndrome (MetS). MetS increases the risk of development for type 2 diabetes mellitus and cardiovascular disease and is associated with an increased risk of breast cancer recurrence, death due to breast cancer, and all-cause mortality. We have previously reported that 76% of metabolically healthy women receiving (neo) adjuvant chemotherapy will develop MetS at a median of 15 weeks. The impact of aromatase inhibitors (AIs) on metabolic health has not been systematically assessed in a longitudinal study. We hypothesize that AIs in the (neo) adjuvant setting will alter metabolic parameters and have embarked on a clinical trial to study this.

Methods: This is a prospective observational study that will include: postmenopausal patients with newly diagnosed, early-stage hormone receptor (HR)-positive breast cancer with planned (neo)adjuvant treatment with an AI. Participants will be excluded if they have received or have planned treatment with (neo)adjuvant chemotherapy or are currently receiving antidiabetic medications or cholesterol-lowering agents. All patients will undergo a baseline assessment that includes: BMI, physical exam inclusive of blood pressure, waist circumference, assessment of body fat, lipid profile, insulin, metabolic biomarkers, and completion of the Functional Assessment of Cancer Therapy – Endocrine Symptoms (FACT-ES). Following institution of an AI, reassessment of the aforementioned tests will be repeated after 4 months and 12 months of therapy. The primary endpoint is the change in insulin resistance (as measured by HOMA-IR, homeostatic model assessment for insulin resistance) at 4 months. Secondary endpoints include the change in HOMA-IR at 12 months and the change in individual MetS components, metabolic biomarkers, anthropometric measurements, as well as FACT-ES scores from baseline to 4- and 12-months of AI treatment. The mean paired differences will be calculated for HOMA-IR measurements as well as for the secondary endpoints, and the 1-sided paired t-test will be used to test for statistical significance. One-way analysis of covariance will be used to compare means while adjusting for age, race/ethnicity, and BMI. Using a 1-sided paired t-test for the mean difference in HOMA-IR measurements from baseline to 4 months, we will have 80% power to detect an effect size of 0.405 with 40 patients ($\alpha = 0.05$). Enrollment began in April 2023 and is ongoing. Contact alevee@coh.org for more information. Given the increased recognition of the importance of metabolic health in breast cancer outcomes, this data will inform future trials that focus on maintaining metabolic health in breast cancer survivors.

PO4-20-01

A PROSPECTIVE PILOT STUDY OF MAMMOGRAPHIC PREDICTION OF WOMEN'S RISK (M-POWER) IN NIGERIA

Presenting Author(s) and Co-Author(s):

O. Shonukan. Yemanja Cancer Care Initiative, Inc, TIVERTON, Rhode Island, United States

H. Ibrahim. Medicaid Radiodiagnostics, Nigeria, Nigeria

e. Udoh. Omnis Health Partners Limited, Nigeria, Nigeria

W. Egbeolu. Yemanja (Nig) Cancer Care Initiative, Nigeria

K. Oyeyinka. Omnis Health Partners Limited, Nigeria, Nigeria

J. Haggstrom. Cytel.com, United States

Background There have been no sustained efforts at stemming the rising incidence and mortality from breast cancer in sub-Saharan African countries like Nigeria. Mammography is the gold standard for breast cancer screening and is associated with improved survival particularly among women 50 to 69. Reports from various parts of Nigeria show very low mammography screening uptake. Causes include lack of geographical access, financial issues (less than 5% of the population is covered by the National Health Insurance Scheme), lack of awareness and the increasing expertise gap from the continued brain drain, despite the already low number of radiologists in the country. Given these obstacles, our long-term goal is to devise a rational basis for identifying mammographic risk categories so that this resource can be deployed cost-effectively. We propose to carry out a 5-year prospective mammographic study in Nigerian women and to use machine learning to develop a risk prediction algorithm, so that following a single screening mammogram, the appropriate frequency of subsequent mammograms can be determined. Our immediate goal is to examine the feasibility of performing such a study. To this end, we have initiated a cross-sectional pilot study that will recruit up to 2000 women in multiple urban centers in Nigeria. Objective: To explore feasibility of creating a digital mammography image database representative of the radiological features of the breast of Nigerian women. Objective: To explore feasibility of creating a database that can be used to inform a predictive mammographic risk model for breast cancer and identify the appropriate population that will benefit from breast cancer screening in Nigeria. Design This is a prospective, open-label, cross-sectional pilot study in 2000 eligible women in Nigeria and will include a single screening mammography examination. The mammography images will be read by the study radiologist. The Pilot phase will determine the feasibility and aid in the design of the of the Extension phase in which up to 20,000 participants will undergo yearly mammography examination for 5 years. Incident cases of breast cancer during the study period will permit the development of deep learning algorithms for predicting the risk of breast cancer in this population. Main Eligibility Criteria: Inclusion Criteria

1. All consecutive women aged ≥ 40 years and < 65 years presenting for screening mammography at the participating institutions will be eligible.
2. Signed study-specific written informed consent.

Exclusion Criteria

1. Complaint of a focal dominant lump or a bloody or clear nipple discharge.
2. History of breast implants.
3. Any woman who is pregnant or has reason to believe that she might be pregnant.

Statistical Methods Analyses of continuous data will be summarized using descriptive statistics where the following parameters will be reported: Number of observations, Number of missing observations, Mean, Median, Standard deviation (SD), Minimum (Min), Maximum (Max) Categorical data will be presented with absolute and relative frequency (n and %). Present Accrual and Target accrual Two hundred ninety-six women have been enrolled and screening digital mammographic images using GE Digital mammography equipment have been obtained on all participants at 2 study sites in 2 cities in Southern Nigeria. The target accrual is 2000 participants over 12 months. Conclusion Our preliminary experience to date suggests the feasibility of proceeding with a larger prospective study to define mammographic risk groups in Nigerian women which will permit the rational allocation of resources for breast cancer prevention activities in this underserved population. Contact Information: Dr Toyin Shonukan at tshonukan@yemanjacancercare.org

PO4-20-02

A prospective, randomized, controlled clinical trial comparing different PEG-rhG-CSF administration times to treat chemotherapy-induced neutropenia and febrile neutropenia in early breast cancer

Presenting Author(s) and Co-Author(s):

X. Zha. the First Affiliated Hospital of Nanjing Medical University, United States

J. Wang. the First Affiliated Hospital of Nanjing Medical University, United States

Y. Xu. Jiangsu province of hospital, United States

J. He. Jiangsu province hospital, United States

Y. Wang. Jiangsu province hospital, United States

W. Zhang. Jiangsu province hospital, United States

X. Wan. Jiangsu province hospital, United States

W. Shi. Jiangsu province hospital, United States

Background: Pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) injection time is still referred as recombinant human granulocyte CSF (rhG-CSF) as a treatment for preventing febrile neutropenia (FN) in patients with early breast cancer. The trial examined whether PEG-rhG-CSF injection on day 7 following chemotherapy was superior to injection on day 3.

Patients and methods: Patients with early breast cancer were randomly assigned to receive a preventive injection on days 7 or 3 following chemotherapy. The experimental group (n = 80) received PEG-rhG-CSF treatment on day 7 after chemotherapy, whereas the control group (n=80) received it on day 3. The occurrence of grades 3–4 neutropenia and FN was the primary endpoint. The secondary endpoint was the frequency of PEG-rhG-CSF dose reduction.

Results: Compared with the control group, the white blood count (WBC) or absolute neutrophil count (ANC) in the experimental group was higher on days 9 and 13 ($P < 0.05$) after chemotherapy, and the incidence of grade 3–4 neutropenia was lower ($P = 0.038$). The experimental group met the standard for lowering the PEG-rhG-CSF dose were more than that in the control group (69.74% vs. 35.06%, $P < 0.001$). Patients receiving a lower PEG-rhG-CSF dose had higher WBC count and ANC after chemotherapy, but were more likely to suffer from mild arthralgia. ($P < 0.05$).

Conclusion: In comparison with PEG-rhG-CSF injection on day 3 after chemotherapy, the incidence of grade 3–4 myelosuppression is lower, and the safety is more manageable after the injection on day 7. Thus, more patients will receive dose reduction and lower patient medical costs.

PO4-20-03

HIPEX: Adjuvant palbociclib plus endocrine therapy in ER-positive HER2-negative early breast cancer with high recurrence score according to GenesWell™ BCT; a multi-center single arm phase II clinical trial (KCSG BR 19-13)

Presenting Author(s) and Co-Author(s):

J. Kim. Samsung Medical Center, United States

S. Sim. National Cancer Center, United States

J. Lee. Division of Medical Oncology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Republic of Korea

I. Park. Department of Hemato-Oncology, Division of Internal Medicine, Korea University College of Medicine, Guro Hospital, Republic of Korea

K. Park. Korea University Anam Hospital, Republic of Korea

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

J. Kim. Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

K. Lee. Division of Hematology Oncology, Department of Internal Medicine, School of Medicine, Ewha Womans University, Republic of Korea

J. Lee. Samsung Medical Center, Seoul, Republic of Korea

J. Ryu. Samsung Medical Center, Sungkyunkwan University School of Medicine, United States

Y. Shin. Seoul National University, United States

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

Background: In estrogen receptor (ER)-positive human epidermal growth factor receptor2 (HER2)-negative early breast cancer (EBC) patients, NCCN treatment guideline recommend 21-gene tests for decision of adjuvant chemotherapy if tumor size is over 0.5cm or node positive disease. In addition, GenesWell™ BCT is a prognostic assay that predict the risk of recurrence in patients with ER-positive HER2-negative and nodal stage 0-1 EBC.

According to gene tests, EBC patients with high recurrence risk would have help from adjuvant chemotherapy to increase the rate of disease free survival but toxicities of chemotherapy are not negligible. Therefore, the effort for escaping adjuvant chemotherapy has been performed and currently CDK4/6 inhibitor would be considered as the substitute for cytotoxic chemotherapy in ER-positive HER2-negative EBC patients.

Methods: HIPEX trial is a multi-center, phase II clinical trial to determine the efficacy of adjuvant palbociclib plus endocrine therapy in ER-positive HER2-negative EBC with high recurrence score according to GenesWell™ BCT (NCT04247633). Eligible patients are women who received curative surgery and diagnosed as ER-positive, HER2-negative and pathologic stage T1b-T2 and/or N0-1. Clinical recurrence risk is high according to the modified Adjuvant! Online guideline and GenesWell™ BCT score is 4 or more which being genomic high risk. Other criteria include ECOG performance status ≤1, adequate organ functions and availability of an archival surgical specimens.

Patients receive palbociclib 125mg once daily for 21 days of 28-day cycle plus tamoxifen or

aromatase inhibitor (anastrozole, letrozole or exemestane) once daily for every day. Palbociclib would be taken for two years and endocrine therapy for five years or more. If adjuvant radiotherapy is required, palbociclib should be taken two weeks after the end date of radiotherapy. If patients are premenopausal status, GnRH agonist is allowed.

Primary endpoint is 3-year event free survival (EFS) rate of high clinical and genetic risk ER-positive EBC. Secondary endpoints include 3-year overall survival, quality of life, safety and tolerability of palbociclib with endocrine therapy as an adjuvant setting, exploratory analysis of predictive and prognostic biomarkers and the performance of GenesWell™ BCT for 3-year EFS rate.

In total, 578 patients would be enrolled in this trial. Based on the previous results of GenesWell™ BCT in Korea, the 3-year EFS rate for the past control group (chemotherapy followed by endocrine therapy) is 87.0% and the treatment group in this clinical trial is assumed to be 90.5%. (hazard ratio for EFS = 0.717). Null hypothesis is the 3year-EFS rate in patients received adjuvant palbociclib and endocrine therapy is not less than that of the past control group. Alternative hypothesis is the 3year-EFS rate of this trial is less than that of the past control group (one-sided). Significance level is 0.025, power is 0.80. Considering 10% drop out rate, 4-years of accrual patient enrollment and 3-years of follow up period, 578 patients were required in this clinical trial.

PO4-20-04

A Randomized Window of Opportunity Study of Preoperative Letrozole and Simvastatin Versus Letrozole Alone in Stage I-III Hormone Receptor Positive, HER2 Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

- R. Sacks. Emory University / Winship Cancer Institute, Atlanta, Georgia, United States
- E. Haas. Emory University / Winship Cancer Institute, United States
- J. Jones. Emory University / Winship Cancer Institute, United States
- M. Bhave. Emory University School of Medicine, Atlanta, Georgia, United States
- K. Gogineni. Emory University Hospital, Atlanta, GA, United States
- J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States
- D. Smith-Graziani. Dept of Hematology and Medical Oncology, Emory University School of Medicine, United States
- S. Pakkala. Emory University / Winship Cancer Institute, United States
- S. Friend. Winship Cancer Institute of Emory University, United States
- C. Arciero. Emory University / Winship Cancer Institute, United States
- L. Postlewait. Emory University School of Medicine, Atlanta, Georgia, United States
- C. Farley. Emory University / Winship Cancer Institute, United States
- C. Graham. Emory University, United States
- T. Styblo. Emory University / Winship Cancer Institute, United States
- M. Rizzo. Emory University / Winship Cancer Institute, United States
- R. Pickett. Emory University / Winship Cancer Institute, United States
- N. Crasta. Emory University / Winship Cancer Institute, United States
- L. Brown. Emory University / Winship Cancer Institute, United States
- X. Li. Emory University, United States
- S. Badve. Emory University School of Medicine, United States
- M. Dhodapkar. Emory University, United States
- K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

Hormone receptor positive (HR+), HER2 negative (HER2-) breast cancers are poor responders to immunotherapy. There is a need for innovative approaches to improve immune responses in these tumors. The combination of statins and aromatase inhibitors have demonstrated antiproliferative and immunomodulatory properties. However, this combination has never been studied in the preoperative setting; thus, our ongoing study represents an opportunity to investigate this approach.

We designed a randomized two-arm presurgical “window of opportunity” trial to evaluate the effects of letrozole and simvastatin versus letrozole alone 14 days prior to surgery. Tissue and blood will be obtained at baseline and 14 days after completion of therapy at the time of surgery. Inflammatory markers in the blood and multiplex immunohistochemistry (IHC) in tissue will be assessed. To be eligible for the trial, participants must be postmenopausal women with histologically confirmed stage I-III HR+, HER2- invasive breast cancer with baseline ki-67 $\geq 10\%$

that have not received prior chemotherapy, endocrine therapy, and/or immunotherapy within 3 months prior to trial enrollment. They should also not have received any cholesterol lowering medication within 3 months prior to trial enrollment.

The primary objective is to determine if the addition of simvastatin to letrozole compared to letrozole alone will result in a decrease in geometric mean % change in ki-67 from pre-surgical baseline to 14 days following preoperative therapy. Ki-67 is a validated surrogate marker for disease-free survival in HR+, HER2- breast cancer. The main secondary objective is to determine if the addition of simvastatin to letrozole compared to letrozole alone will result in increased immune activation from pre- to post-treatment based on the evaluation of the immune subtype composition in tissue via multiplex immunofluorescence.

We aim to enroll 16 patients in each arm to achieve 90% power and detect a minimum difference of 7.5% in ki-67 using a two-sided Mann-Whitney U or Wilcoxon Rank-Sum test. After accounting for a possible drop off rate of 20%, the study's target accrual will be 40 participants. Statistical analyses will be performed using SAS 9.4. the significance level will be set at $\alpha = 0.1$. Descriptive statistics will be applied to tissue and blood biomarkers of interest at 2 designated time points, prior to preoperative therapy and following completion of preoperative therapy. The absolute change or percentage change of those biomarkers will also be calculated and compared between the 2 arms using the nonparametric Mann-Whitney U test. The correlation among biomarkers will be described by Pearson correlation coefficient with 95% confidence interval. The p-value will be adjusted by Benjamini-Hochberg procedure to control the false discovery rate. All adverse events experienced data will be described by summary statistics and will be assessed according to CTCAE version 5.0.

Currently, the study has accrued 2 participants. After completing accrual, we will assess whether the tumor-immune milieu has undergone modulation, resulting in a more immunogenic environment. If an immunogenic effect is demonstrated, this will provide rationale for a future multi-center trial assessing the combination of letrozole, simvastatin, and immunotherapy.

PO4-20-05

An open label phase III randomized trial to evaluate the efficacy of Post-chemotherapy Axillary Conservation Surgery in breast cancer (PACS)

Presenting Author(s) and Co-Author(s):

S. Joshi. Tata Memorial Hospital, United States
J. Shah. Tata Memorial Centre, Mumbai, Maharashtra, India
P. Daphale. Tata Memorial Centre, United States
R. Hawaldar. Tata Memorial Centre, Maharashtra, India
A. Daptardar. Tata Memorial Centre, Mumbai, India
A. Sahay. Tata Memorial Centre, United States
T. Shet. Tata Memorial Centre, United States
P. Popat. Tata Memorial Centre, India
T. Wadasadawala. Tata Memorial Centre, United States
N. Nair. Tata Memorial Hospital, United States
V. Parmar. Tata Memorial Centre, United States
B. Bandre. Tata Memorial Centre, United States
S. Siddique. Tata Memorial Hospital, United States
V. Vanmali. Tata Memorial Hospital, United States
S. Gupta. Tata Memorial Centre, Homi Bhabha National Institute (HBNI), United States
R. Badwe. Tata Memorial Centre, Mumbai, India

Background-

Axillary lymph nodes (ALN) status is the most important prognostic factor in breast cancer. Traditionally, a complete axillary lymph node dissection (ALND) has been standard of care for those patients who have a positive node pre-chemotherapy. However, lately axillary conservation is paving its way in the post-chemotherapy setting as well to avoid significant morbidity of ALND. Most sentinel node biopsy studies have failed to achieve the desired false negative rate(FNR). (Boughey JC et al, JAMA. 2013 Oct; Kuehn T et al, Lancet Oncol. 2013; Boileau JF et al, J Clin Oncol. 2015 Jan). We previously reported a low FNR of low axillary sampling (LAS) in the post-chemotherapy setting. (Parmar et al, JCO-GO, 2021) We are conducting a phase III, randomised controlled trial of LAS versus complete ALND in post-chemotherapy negative (ypN0) axilla.

Aims and objectives-

The primary objective is to assess the non-inferiority of LAS in patients who are rendered ypN0 by pre-operative chemotherapy with disease-free survival as primary end point. The secondary objectives are comparing the morbidity of ALND (lymphedema, paraesthesia, and shoulder dysfunction) in the LAS and ALND arms, and to evaluate the impact on overall survival, local, regional, and distant recurrence free survival and quality of life.

Trial design-

This is a prospective, open label, randomised, phase III trial where histologically proven, non-metastatic, cT1-4, N0-2 breast cancer patients who are rendered ycN0 after pre-operative systemic chemotherapy are being accrued. Patients with prechemo N3 disease, inflammatory

breast cancer, recurrent disease, pregnancy associated breast cancer are being excluded from the study. The chemotherapy regimens and surgical assessment is as per standard institutional protocols. After obtaining informed consent, patients undergo LAS during surgery and lymph nodes(LN) are sent for frozen section analysis. If any LN is found to be involved, a complete ALND is carried out. If the staging procedure is negative, then patients are randomised into 2 groups- observation v/s complete ALND. Stratification factors are T stage, N stage, Hormone receptor status, Her2 receptor status and number of chemotherapy cycles taken. Morbidity assessment is done with- Constans shoulder score, arm volumetry, paraesthesia assessment, and a QOL questionnaire- Self-reported Breast cancer Lymphedema Symptom Experience Index (BCLSEI). A baseline assessment pre-surgery is followed by 6 monthly morbidity assessments and regular oncologically relevant follow-up up to 5 years. A two-sided log-rank test with an overall sample size of 2316 with a 10% dropout rate (1158 in ALND and 1158 in LAS group) achieves 80% power at a 0.05 significance level to detect a hazard ratio of 1.16 (upper limit of non-inferiority) when the proportion surviving in the control group is 0.71. An interim analysis will be carried out at 25% events and conditional power will be calculated. If the conditional power is below 20%, then the study will be discontinued for futility.

The study has been approved by Institutional Ethics Committee (CTRI/2022/07/044461)

Expected Study and Results-

We started accrual in February 2023 and have screened 63 and randomized 45 patients until now. Ours is a first large randomised prospective study in the post-chemotherapy axillary management setting which will help us understand the efficacy of axillary conservation surgery in patients who are node negative post neoadjuvant chemotherapy. In future, lesser morbid procedures than LAS like targeted axillary dissection can be tested in the same trial. However, LAS as a technique of axillary conservation suits resource constraints and high volume setting such as ours.

PO4-20-06

Impact of iatrogenic menopause on vaginal health and sexuality

Presenting Author(s) and Co-Author(s):

N. Willers. UZ Leuven / KU Leuven / AZ Sint Blasius Dendermonde, Belgium

S. Han. University Hospitals Leuven, Leuven, Vlaams-Brabant, Belgium

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

P. Enzlin. KU Leuven / Institute for Family and Sexual Sciences (IFSW), United States

S. Lebeer. University Antwerp, United States

S. Ahannach. University Antwerp, United States

Background

Due to the lowering of circulating estrogens symptoms of genitourinary syndrome of menopause (GSM) may arise with premenopausal breast cancer patients who become menopausal due to breast cancer treatment. Clinical signs of GSM are i.a. vaginal dryness, dyspareunia, loss of libido, dysfunction of arousal and/or orgasm: this may negatively impact vaginal health, sexual activity and quality of life. The composition and function of the vaginal microbiome may also change due to changes of gonadal hormones during the menopausal transition. This change may contribute to vaginal discomfort and problems during sexual activity.

With this prospective research we aim to uncover the relationship between vaginal health and sexuality, it gives an unique opportunity to investigate the vaginal changes and possible shift of vaginal microbiome when menopause occurs. This is a first in time study where longitudinal samples of the vaginal microbiome in one patient are investigated before and after menopause. The vaginal microbiome might be a future target to treat vaginal discomfort after treatment for breast cancer.

Trial design

This is a prospective minimal invasive study where participants are asked to undergo a baseline gynecologic examination, again 3 and 6 months after menopause. During this examination we measure vaginal pH, describe vaginal hydration and anatomy (using vaginal-, and vulvar assessment scale (VAS, VuAS)) and sample the vaginal microbiome (analyzed with 16S rRNA gene sequencing and quantitative real-time polymerase chain reaction (qPCR)). At the same time, a blood test is performed (Estradiol, FSH) and participants complete a survey (demographic information, medical history, current well-being using World Health Organisation-Five Well-Being Index (WHO-5), sexual functioning using the Female Sexual Functioning index (FSFI), Female Sexual Dysfunction Scale – revised (FSDS-R) and Short Sexual Functioning scale (SSFS)).

Eligibility criteria

- Patients (>18 years) with Stage I, IIA, IIB, IIIA, IIIB, IIIC breast cancer
- Reproductive age or menopausal transition according to STRAW+10 criteria
- Iatrogenic menopause caused by ovarian function suppression (OFS), bilateral salpingo-ovariectomy (BSO) or by starting chemotherapy
- Any partner status
- Latest cervical cytology is normal
- No prior history of hysterectomy

- Patients who take oral contraceptives or have a Levonorgestrel- containing IUD can participate. Oral contraceptives should be stopped or the Levonorgestrel-containing IUD should be removed before systemic breast cancer therapy

Specific aims

To accurately describe what vaginal changes occur during breast cancer treatment

To evaluate if the onset of menopause is related to changes in vaginal microbiome

To evaluate if there is a relation between the objective vaginal changes and the subjective complaints related to GSM

To evaluate if there is a relation between the objective vaginal changes and a possible alteration in sexuality

Statistical methods

Using multiple comparison procedures in ANOVA (analysis of Variance) model, the clinical findings (VAS, VuAS, pH, composition of microbiome) and validated questionnaires (WHO-5, FSFI, FSDR-r, SSFS) are linked to analyze if vaginal changes are related to changes in sexual wellbeing.

The interpretation of the results of this investigation should be interpreted with caution due to the explorative nature of the study.

Present accrual / Target accrual

23 /60 participants are included (JULY 2023)

PO4-20-07

Dense Breast Tissue in a High-Risk African-American Woman with DCIS and Nodal Metastasis of Intra-ductal Carcinoma: A Case Report and Discussion on the Current USPSTF Draft Recommendation

Presenting Author(s) and Co-Author(s):

V. Akula. UT Health Houston, McGovern Medical School, United States

J. Jones. UT Health Houston, Houston, Texas, United States

Introduction and objectives:

The incidence of breast cancer (BC) in younger women has increased in recent years, raising the discussion on adjustments to screening recommendations. This past May, a new draft recommendation to the USPSTF guidelines for BC screening adjusted the age of screening from 50 to 40. However, there is still insufficient evidence to recommend adjusted screening guidelines for patients at increased risk including ethnic minorities with higher mortality and women with dense breasts. The paucity of trials and reviews for many of these at-risk groups may be leading to later diagnosis and poorer outcomes. This case highlights the importance of clinical judgment when screening patients whose presentation lies outside the guidelines.

Clinical Case:

A 29-year-old AAW with past medical history of bipolar disorder presents to her primary care physician in April 2023 with concern for left breast mass. Patient was previously on risperidone and Depakote for her bipolar disorder one year prior which resulted in drug-induced amenorrhea and breast tenderness with evidence of elevated prolactin. She was taken off her medication with return of her menses, but breast tenderness persisted for three months. During this time, she noticed a palpable breast mass. Family history is not significant for breast cancer. Breast ultrasound and mammography revealed “extremely dense” breast tissue bilaterally. Imaging significant for 7.6 x 6.2 x 6.3 cm irregular mass in the lower inner quadrant of the left breast with pleomorphic calcifications. Biopsy subsequently performed with breast pathology significant for ER+/PR- ductal carcinoma in situ. However, lymph node pathology showed evidence of invasive ductal carcinoma raising question of diagnosis of possible occult breast cancer versus breast cancer with axillary metastasis. PET CT did not show evidence of metastatic disease. She was started on neoadjuvant chemotherapy.

Discussion and Conclusion:

It is well known that African American women (AAW) are at increased risk for mortality due to BC, aggressive secondary BC, and for high-risk tumor biology. Additionally, AAW generally have more dense breast tissue, another risk factor for BC. Dense breast tissue can make it more difficult to characterize high-risk lesions on screening modalities. In regard to this patient, her dense breast tissue may obfuscate characterization of areas of possible primary cancer being the cause of her nodal metastasis. Current guidelines do not take these well-known associations and risk factors into account. A separate treatment algorithm may be required to work up a patient from high-risk groups such as this patient case. It is crucial that future guidelines on screening should incorporate specific risk factors which would help detect BC earlier in vulnerable populations.

PO4-20-09

Successful outcome of locally advanced HR+HER2+ breast cancer treatment in a young female after pancreas-kidney transplantation. 3-year follow-up

Presenting Author(s) and Co-Author(s):

L. Zhukova. MCSC named after A.S.Loginov, United States

N. Polshina. Moscow Clinical Scientific Center Named after A.S.Loginov, United States

Background

Solid organs recipients with subsequent cancer comprise a group of patients with unmet medical needs: they lack any clinical trials or guidelines for treatment. There are only individual case reports in literature. Meanwhile their number is growing due to achievements in transplantology and improved cancer diagnosis.

Case presentation

A young 34-year-old female attended our center in September 2019 with a palpable mass and peau d'orange of the left breast. A core-needle biopsy of the left breast mass revealed invasive ductal carcinoma G3, estrogen receptor 7 (Allred), progesterone receptor 6 (Allred), HER-2 (3+), Ki-67 49%. Left axillary lymph node biopsy revealed metastatic breast cancer. After a complete examination the clinical stage was cT4bN1fM0, IIIB stage.

The patient had a history of Type 1 diabetes mellitus since 2003 leading to multiple complications including terminal diabetic nephropathy, which required renal replacement therapy with the use of long-term hemodialysis since July 2014. The other complications consisted of severe retinopathy with corneal transplantation on the left eye in April 2013, an episode of right eye hemophthalmia in March 2016 with consequent loss of vision in the right eye, polyneuropathy, gastropathy and enteropathy. The patient underwent a simultaneous pancreas-kidney transplantation in April, 2016 and was on permanent immunosuppressive therapy with tacrolimus 8 mg daily and methylprednisolone 8 mg daily. The function of both transplants was satisfactory. This unique case was published by Pinchuk A. et al. in *Transplant Proceedings*, 2017 [doi: 10.1016/j.transproceed.2017.10.005].

A multidisciplinary approach was applied to tailoring treatment plan for this patient. Initially immunosuppressive therapy was modified: the patient discontinued methylprednisolone and started everolimus with simultaneous tacrolimus dose reduction (their doses adjusted according to blood concentrations). The tumor board decision was to start neoadjuvant therapy with regimen with the mildest and the most manageable toxicity profile and to avoid anthracyclines. From October to December 2019 the patient received 12 cycles of paclitaxel 80 mg/m² day 1 weekly and 4 cycles of anti-HER2 dual blockade: trastuzumab 8 mg/kg day 1 followed by 6 mg/kg day 1 every 21 days + pertuzumab 840 mg day 1 followed by 420 mg day 1 every 21 days. Adverse events were: stomatitis grade 1, palmar-plantar erythrodysesthesia grade 1, diarrhea grade 2. Partial response was evaluated in the end of December 2019, but due to persistent skin edema, she was not a candidate for surgical treatment. The tumor board decision was to proceed with T-DM1 + pertuzumab based on the results of the KRISTINE trial [doi:10.1016/s1470-2045(17)30716-7]. From January to March 2020 the patient received 4 cycles of trastuzumab-emtansine 3,6 mg/kg day 1 every 21 days + pertuzumab 420 mg day 1 every 21 days. The patient tolerated this treatment with mild toxicity: ALT & AST increase grade 2 and diarrhea grade 2. Considering that the edema was significantly reduced, surgical treatment was planned. The patient underwent a modified radical mastectomy for left breast cancer on 14 of April 2020. The pathological stage was ypT1aN0 R0, RCB I. The patient

continued trastuzumab emtansine until November 2020 (up to 1 year of anti-HER2 targeted therapy) in the adjuvant setting. In June 2020 she underwent locoregional radiation therapy. Tamoxifen with ovarian function suppression (LHRH agonists) for 5 years was started in June 2020. Fortunately, after 3 years of follow-up after surgery there is no evidence of disease and no delayed cancer treatment complications.

Conclusion:

Personalized multidisciplinary team decisions for cancer patients after organ transplantation are crucial to further improve the long-term outcome of these patients.

PO4-20-10

Value of 16 α -18F-fluoro-17 β -fluoroestradiol PET imaging in ER-positive breast cancer: a case report

Presenting Author(s) and Co-Author(s):

M. Wong. City of Hope Comprehensive Cancer Center, California, United States

V. Jones. City of Hope, California, United States

D. Yamauchi. City of Hope National Medical Center, United States

J. Mortimer. City of Hope, Duarte, California, United States

Introduction: An appropriate use criteria workgroup recently recommended the use of PET imaging utilizing the 16 α -18F-fluoro-17 β -fluoroestradiol (FES) radiotracer as a measure of disease progression and endocrine treatment response for ER-positive breast cancers. Past studies report limitations of decreased FDG uptake, the most common PET radiotracer, when measuring low Ki-67 scoring tumors; FES-PET may noninvasively address this shortcoming in FDG activity detection. Its benefit of detecting low-grade, ER-positive tumor activity was demonstrated in a patient with breast cancer who exhibited tumor growth only on FES-PET while FDG-PET showed no measurable disease.

Clinical Case: A 57-year-old postmenopausal woman presented in December 2017 with de novo metastatic invasive ductal carcinoma that was ER+ (100%), PR+ (100%), and HER2-involving the right breast, bone, lungs, and internal mammary, subcarinal, and right hilar lymph nodes. She received nab-paclitaxel and radiation to the right breast, regional lymph nodes, and T11 bone. In March 2019, she underwent a right mastectomy with pathology that noted residual disease in the breast measuring <5 mm and was placed on exemestane in April 2019.

She transferred her care to City of Hope and follow-up FDG-PET restaging showed no evidence of new metabolically active metastatic disease. Her cancer antigen 27.29 levels were also within normal limits. In the absence of measurable disease growth, she continued to be treated with single agent exemestane.

Due to persistent back discomfort that she attributed to breast asymmetry, she requested the left breast to be removed. One week prior to surgery, both FDG-PET/CT and bloodwork inclusive of tumor markers were normal. She underwent a left mastectomy in March 2023. Pathology identified an incidental 1.4 cm lymph node in the 2000 g specimen that was ER+ (>95%), PR-, and HER2- with a Ki-67 of 1-3%. Somatic gene testing of the tumor revealed an ESR1 D538G mutation. As her progressive disease was not evident on previous FDG-PET imaging, an FES-PET/CT was performed and demonstrated uptake in the ilium, T10, and T12 bones that was not identified on FDG-PET/CT. With objective evidence of evaluable disease, exemestane was discontinued and fulvestrant and ribociclib were initiated. Clinically, she has evidence of early response to therapy with improvement in back pain.

Discussion: This case demonstrates the value of FES-PET/CT in identifying disease that was not appreciated on FDG-PET/CT or by cancer antigen 27.29 monitoring. Additionally, ESR1 status has not been consistently reported in studies of patients undergoing FES-PET imaging that investigate the radiotracer's value in predicting response to subsequent endocrine therapy. Our patient has a documented ESR1 mutation, her disease was clearly identified only on FES-PET/CT, and FES uptake predicted for response to subsequent endocrine therapy. Incorporating FES-PET in routine staging should be considered in patients with metastatic

breast cancer that is low-grade and ER-positive. Further evidence of response prediction in patients with ESR1 mutations will enhance the utility of FES-PET in the clinical management of these patients.

PO4-20-11

Excellent Response to Trastuzumab Deruxtecan in “HER-2 Low” Leptomeningeal Breast Cancer and Diagnostic and Monitoring Utility of CNSide Assay

Presenting Author(s) and Co-Author(s):

S. Stanford. University of Rochester Medical Center, Rochester, NY, USA, United States

Z. Kharel. Rochester Regional Health, Rochester, NY, USA, United States

L. Hemminger. Department of Neurology, University of Rochester Medical Center, NY, USA, United States

T. Schmidt. Department of Neurosurgery, University of Rochester Medical Center, NY, USA, United States

S. Hardy. University of Rochester Medical Center, Rochester, NY, USA, United States

J. Zittel. Department of Medicine, University of Rochester Medical Center, Rochester, NY, USA, United States

N. Mohile. University of Rochester Medical Center, United States

A. Dhakal. University of Rochester Medical Center, Rochester, New York, United States

A 72-year-old female presented to the emergency department with sudden onset of imbalance and cognitive decline. Two years ago, she was diagnosed with stage III estrogen receptor (ER) positive, progesterone receptor (PR) negative and human epidermal growth factor receptor 2 (HER2) negative (immunohistochemistry score: 0) invasive breast cancer. She subsequently underwent lumpectomy, adjuvant radiation and chemotherapy. She had been taking adjuvant letrozole at the time of presentation. Magnetic resonance imaging (MRI) of the brain showed obstructive hydrocephalus without any parenchymal lesion or leptomeningeal enhancement. MRI of spine, computerized tomography of chest/abdomen/pelvis and bone scan were unrevealing except a left adrenal mass which was equivocal for metastasis. Cerebrospinal fluid (CSF) analysis showed rare malignant cells. Based on the morphology of malignant cells and the patient's prior history of breast cancer, the diagnosis of leptomeningeal disease with breast primary was made. There were insufficient cells for additional studies. CNSide, a microfluidic platform that uses antibody capture method to detect CSF tumor cells, showed 4678 tumor cells per milliliter (ml) of CSF. Immunocytochemistry of these cells showed that the cells were ER negative (criterion: < 2.6% ER positive cells) and programmed cell death ligand 1 (PD-L1) negative (criterion: < 3.4% PD-L1 positive cells). Fluorescence in situ hybridization (FISH) testing showed 22% of tumor cells with HER2 amplification (either HER2 to CEP17 ratio ≥ 2.0 or HER2 copy number ≥ 6). She underwent ventriculoperitoneal (VP) shunt placement with complete recovery of her neurological symptoms. Five weeks later, she was started on trastuzumab deruxtecan (T-DXd) mainly because of the HER2 FISH results from CNSide. She did not receive central nervous system (CNS) irradiation due to complete resolution of neurological symptoms with VP shunt placement. After two cycles of T-DXd, MRI brain showed mild leptomeningeal enhancement along bilateral superior cerebellar sulci. Positron emission tomography/computed tomography (PET/CT) scan showed a new sclerotic rib focus, thought to represent treatment response. It also showed decrease in size of the adrenal mass. The adrenal mass was hypermetabolic on PET, consistent with malignancy. CSF cytology was negative, while CSF tumor cell count significantly reduced to 6.72 cells/ml using CNSide. There were no new neurological symptoms. Despite MRI brain findings, she was continued on T-DXd given overall favorable clinical, radiological and CSF data. After 7th cycle of T-DXd, repeat CSF cytology continued to remain negative, CNSide CSF tumor cell count decreased further to 6.27 cells/ml, MRI brain showed interval resolution of prior leptomeningeal enhancement, CT scan

showed further decrease in size of the adrenal mass (baseline 5.4cm to 3cm), stable rib sclerotic lesion and no additional metastatic lesion. To date, she has undergone eight cycles of T-DXd which has effectively controlled her disease for a period of seven months. She has not needed VP shunt revision and continues to do well. To our knowledge, this is the first case demonstrating the activity of T-DXd against CSF tumor cells where a small subset exhibited HER2 amplification. This case also highlights the benefits of using advanced and highly sensitive CSF assays to diagnose and surveil leptomeningeal disease and to assess HER2 signaling. This case is well-timed especially in the era of next-generation, CNS penetrating, potent HER2-directed antibody-drug conjugate like T-DXd which can mount antitumor activity even with minimal HER2 expression in tumors.

PO4-20-12

Case Report: Should core needle biopsy showing primary leiomyosarcoma of the breast warrant a second look for accurate diagnosis and management?

Presenting Author(s) and Co-Author(s):

A. Ritter. Burrell College of Osteopathic Medicine, Las Cruces, New Mexico, United States

S. Shimunov. Burrell College of Osteopathic Medicine, United States

A 68-year-old female with unknown medical history presented to the emergency department with an exceptionally large necrotic mass of the right breast. Initial core needle biopsy showed morphology consistent with the exceedingly rare leiomyosarcoma of the breast. This patient's necrotic, fungating tumor with abscess warranted urgent surgical excision. The pathology report that followed revealed malignant phyllodes tumor as her final diagnosis. The patient did well after surgery with no sign of metastasis and continued to follow-up with oncology. Lack of clinical guidance for breast leiomyosarcoma begs the question as to when further workup is indicated since it is known to imitate the histological and radiological features of other breast lesions. We discuss the need for updated guidance from prospective future studies to change national guidelines.

PO4-21-01

Recurrent Desmoid Tumor and Ductal Carcinoma In Situ in an African-American Woman: A Case Report and Discussion on Disparities for These Two Cancer Subtypes

Presenting Author(s) and Co-Author(s):

V. Akula. UT Health Houston, McGovern Medical School, United States

J. Jones. UT Health Houston, Houston, Texas, United States

Introduction: Disparities in cancer care in patients from different races and ethnicities unfortunately do exist and are well described in literature. Hormonal-driven cancers, such as some soft-tissue tumors and DCIS, have been demonstrated to impact African-American women (AAW) disproportionately. These patients are at increased risk for not only development of these cancers, but also experience disparities in survival, treatment outcomes, and modalities of treatment.

Clinical Case: A 47-year-old premenopausal AAW with past medical history of recurrent desmoid sarcoma of the abdomen and ductal carcinoma in-situ (DCIS) of the left breast presented to oncology clinic with recurrent abdominal mass. The patient was originally diagnosed with DCIS in the left breast in 2018 and subsequently underwent left breast mastectomy with TRAM reconstruction and fat graft later that year. In 2020, the patient noticed a left lower abdominal growth that quickly enlarged and became painful. She underwent imaging without biopsy and was taken to surgery in April 2021 with tumor removal and mesh placement. Pathology showed desmoid fibromatosis infiltrating skeletal muscle and involving the inked resection margin of the specimen. Conservative re-excision and additional therapy was recommended but not done at the time. In 2022, the patient had resection of the area again with pathology of the incisional scar showing skin and deep soft tissue foci suspicious for recurrent desmoid fibromatosis extending to the inked deep margin. No mesh was placed, and the wound closed almost completely. The patient was not aware of positive margins at the time. In January 2023, patient again notice a new bump that was bothersome. Initial CT and MRI without finding of defined mass, but with right rectus thickening and enlarged right external iliac lymph node. Core biopsy in June 2023 confirmed recurrent desmoid fibromatosis. In April 2023, annual screening with mammogram was performed with a finding of 2.9 cm cluster of heterogenous calcification in the right breast. Diagnostic mammogram and ultrasound performed. Core needle biopsy was subsequently performed in May with pathology consistent with high grade DCIS with low ER and PR positivity. Lymph node biopsy was negative, but clinically positive. She is currently undergoing further genetic testing with surgical workup for mastectomy.

Discussion and Conclusion: AAW diagnosed with DCIS have higher all-cause and disease specific mortality in comparison to white women (WW) diagnosed with DCIS. AAW are also at increased risk of aggressive secondary breast cancers in both the ipsilateral and contralateral breast in comparison to other races. In regards to tumor biology, WW have been shown to have higher ER and PR positivity in both primary and primary breast cancers than AAW. In many of these large-scale studies higher mortality, recurrence, and metastasis in AAW have been identified regardless of treatment modality. Research into differences in treatment between AAW and WW has shown that AAW, in contrast to our patient case, are more likely to undergo endocrine and radiation therapy rather than mastectomy. Although there does not seem to be an increased risk of desmoid fibromatosis in AAW when compared to WW, other soft-tissue tumors and malignancies do show a predilection for AAW. Incidence of sarcoma in black patients is higher than white patients, and black patients also have poorer survival outcomes.

This case provides an example of the intersectionality of two cancer subtypes that impact black patients disproportionately. More evidence is required to unearth the reasons why these two cancer subtypes which are driven by similar processes impact AAW to a greater degree.

PO4-22-02

pSmad2 as a marker of radiotherapy benefit in breast cancer- results from the randomized SweBCG91RT trial

Presenting Author(s) and Co-Author(s):

P. Karlsson. Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, United States

V. Thurfjell. Department of Immunology, Genetics and Pathology, Uppsala University,, Sweden

A. Kovács. Department of Clinical Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden, Vastra Gotaland, Sweden

F. Killander. Lund University, Skane Lan, Sweden

E. Niméus. Lund University, Skane Lan, Sweden

E. Holmberg. Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, United States

C. Strell. Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

A. Stenmark Tullberg. Department of Oncology, Institute of Clinical Sciences, University of Gothenburg, Sweden, Sweden

Background: The TGF-beta pathway can have both pro- and antitumoral effects in breast cancer. Experimental studies further suggest that TGF-beta can mediate radioresistance, either through direct effects on tumor cells or indirectly by its immunomodulatory properties. However, the effect of TGF-beta signaling is highly depending on tumor stage, mutational status and microenvironmental cell composition. In order to explore TGF-beta signaling as a potential biomarker or therapeutical target it is therefore important to perform analyses in well-defined study populations. The purpose of this study was to study the effect of active TGF beta signaling in tumor cells, on the risk of ipsilateral breast tumor recurrence (IBTR) and benefit from radiotherapy (RT) in specifically early-stage breast cancer using nuclear, phosphorylated Smad2 (pSmad2) as a marker.

Methods: The SweBCG91RT cohort included 1179 patients with stage I-IIA tumors randomized to breast-conserving surgery (BCS) with or without postoperative RT. Nuclear pSmad2 expression was assessed as for 987 available tumors on TMAs as the mean proportion of tumor cells with positive nuclear staining. Based on the distributions, tumors were categorized as having high ($\geq 80\%$, $n=344$), medium (21-79%, $n=428$) or low ($\leq 20\%$, $n=161$) pSmad2 staining. The primary endpoint was time to ipsilateral breast tumor recurrence as the first event within 10 years.

Results: pSmad2^{Low} tumors were more likely to be of grade III ($p < 0.001$) and tended to be larger than pSmad2^{Medium} ($p=0.002$, median 15 vs 12 mm) and pSmad2^{High} ($p < 0.001$, median 15 vs 12 mm) tumors. No associations between pSmad2 and subtype or age were found. Numerically, tumors with pSmad2^{low} (HR 1.55, CI 95% 0.80-3.02, $p=0.19$) or pSmad2^{Medium} (HR 2.53, CI 95% 1.52-4.22, $p < 0.001$) had a higher risk of IBTR than pSmad2^{high} tumors (reference). These findings remained significant after adjustment for age, histological grade, and RT. The benefit from RT was similar for pSmad2^{High} (HR 0.41, CI 95% 0.15-1.07, $p=0.068$), pSmad2^{Medium} (HR 0.36, CI 95% 0.21-0.63, $p < 0.001$), and pSmad2^{Low} (HR 0.51, CI 95%

0.18-1.46, $p=0.21$) tumors ($p_{\text{interaction}}=0.86$).

Conclusions: Early-stage breast tumors with high nuclear pSmad2 staining may be at a reduced risk of an IBTR. However, the relative benefit from RT does not seem to differ from tumors with medium or low pSmad2 staining. These results need to be confirmed in additional studies, but they provide initial evidence that tumoral TGF-beta signaling has rather tumor restraining functions in early-stage breast cancer. Next analytical steps should include the tumor mutation status (particularly for TGF-beta signaling components TGFBR2, SMAD4 and TP53), as well as the TGF-beta signaling status within the tumor microenvironment.

PO4-22-03

Intensity Modulated Proton Therapy (IMPT) for the Definitive Adjuvant Management of Women with Breast Cancer: A Single Institutional Experience of 5-Year Oncologic Outcomes

Presenting Author(s) and Co-Author(s):

E. Nichols. University of Maryland School of Medicine, Baltimore, Maryland, United States

G. Singh. University of Maryland School of Medicine, Baltimore, Maryland, United States

D. Lejano. University of Maryland School of Medicine, Baltimore, Maryland, United States

S. McAvoy. University of Maryland School of Medicine, Baltimore, Maryland, United States

M. Mishra. University of Maryland School of Medicine, Baltimore, Maryland, United States

M. Vyfhuis. University of Maryland School of Medicine, Baltimore, Maryland, United States

Purpose: There is limited data reporting the oncologic outcomes of breast cancer patients treated definitively with adjuvant proton beam therapy. Here we report a single institutional experience of oncologic outcomes, treating a predominantly vulnerable breast cancer patient population and compare these to historical standards primarily utilizing photon therapy.

Materials and Methods: Unver IRB approval, we retrospectively reviewed 453 definitively treated breast cancer patients from 2016 – 2023 using adjuvant IMPT as part of their cancer care. Patients with recurrent disease, receiving re-irradiation, and those with less than 1-year of follow up were excluded from this analysis. Patients were treated with surgery and systemic therapies as per standards of care. Radiation therapy was administered using pencil beam scanning IMPT with daily image guidance. χ^2 and Mann-Whitney U tests were performed to determine differences between select variables. Kaplan-Meier analysis and Cox proportional hazard models were used to analyze overall survival (OS).

Results: With a median follow up of 22 months for the entire cohort, 453 patients were treated at XXXX as part of definitive adjuvant management for their breast cancer. Nearly 30% of patients self-identified as black (n=135), average patient age was 54 and 56% (n=255) self-identified as being married with approximately 25% (n=109) of patients having Medicare/Medicaid insurance. 198 patients (43.8%) had an intact breast and the remainder mastectomy of which 37.4% had reconstruction at the time of their radiation. 229 patients (50.7%) received neoadjuvant chemotherapy while 55 patients (12%) received concurrent chemotherapy which was either her2+ directed or Xeloda. The number of patients (%) corresponding to the AJCC 8th edition anatomical staging is as follows: Stage 0: 12 (2.7%); Stage I: 91 (20.1%); Stage 2: 197 (43.6%); Stage 3: 152 (33.6%). Median RT dose delivered for patients receiving comprehensive treatment was 50.4 Gy with 81% of patients receiving a boost to either scar, lumpectomy cavity and/or LN regions. Median RT dose delivered for patients receiving whole breast radiation was 42.56 Gy with a 10 Gy lumpectomy cavity boost. 5-yr OS by stage was 0: 100%; stage I: 98.8%; stage 2: 93.5%; stage 3: 90.8%. Five-year OS for black, white and other race patients were 85.3%, 95.8% and 96%, respectively (White as Ref: HR 3.176, 95% CI: 1.313-7.681, p=0.010 for black patients). For the entire cohort, patients with triple negative disease had a 5-yr OS of 80.4% (HR: 4.33, 95% CI 1.87-10.04, p< 0.001) and there was no difference in OS when insurance status was considered (p=0.378).

Conclusions: To the best of our knowledge this represents the largest series of definitively treated breast cancer patients utilizing adjuvant proton therapy and the 5-year OS rates in our

analysis coincide with published standards¹. Results from the on-going randomized RADCOMP study will provide further guidance as to which patients benefit the most from proton therapy and will further support equivalent oncological outcomes when compared to photon therapy.

1. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al. Validation study of the American Joint Committee on Cancer eighth edition prognostic stage compared with the anatomic stage in breast cancer. *JAMA Oncol.* 4(2):203-209, 2018.

PO4-22-04

Evaluation of acute toxicity in breast cancer patients receiving concurrent capecitabine and radiation

Presenting Author(s) and Co-Author(s):

A. Shalaby. RWJ/CINJ, New Brunswick, New Jersey, United States

Z. Sherwani. RWJ/CINJ, New Jersey, United States

L. Hathout. RWJ/CINJ, New Jersey, United States

I. Jan. CINJ, New Jersey, United States

B. Haffty. Rutgers Cancer Institute of New Jersey, United States

M. George. Rutgers Cancer Institute of New Jersey, United States

S. Kumar. Rutgers Cancer Institute of New Jersey, United States

C. Omene. Rutgers Cancer Institute of New Jersey, United States

D. Toppmeyer. Rutgers Cancer Institute of New Jersey, United States

N. Ohri. Rutgers Cancer Institute of New Jersey, United States

Purpose: Adjuvant capecitabine has been shown to improve disease-free survival and overall survival in breast cancer patients who have residual disease after neoadjuvant chemotherapy, particularly in those with triple negative breast cancer (TNBC). While adjuvant chemotherapy is often completed prior to adjuvant radiotherapy (RT), capecitabine may be administered concurrent with RT to reduce the time from surgery to RT. The purpose of this study was to evaluate the feasibility of concurrent therapy and the associated rates of acute loco-regional toxicity.

Materials and Methods: A retrospective chart review was performed to identify all breast cancer patients who received adjuvant capecitabine and RT. Patients with a history of prior RT, patients who were treated with capecitabine and RT sequentially, and patients who were treated with palliative intent were excluded. Capecitabine was given Monday-Friday during RT. Patient and disease characteristics, capecitabine and RT treatment details, acute toxicity, and treatment breaks were recorded. Toxicity was scored by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Results: A total of 27 patients with non-metastatic breast cancer who received concurrent capecitabine and RT with definitive intent treated from 2013 to 2023 were identified. Median age at diagnosis was 52 years [Interquartile Range (IQR) 40-60]. Adjuvant capecitabine dose ranged from 500-1500 mg twice daily. Adjuvant RT dose ranged from 42.56 Gray (Gy) to 50.4Gy. The majority of patients (92.6%) received a sequential 10-14 Gy boost to the lumpectomy site or mastectomy scar, and 70.3% of patients received elective regional nodal RT. During treatment, all patients developed Grade 1 or 2 radiation dermatitis, while Grade 3 radiation dermatitis was noted in 4 (14.8%) patients. Two patients required a treatment break from RT, and both patients were able to subsequently complete their planned RT course. Seven patients (25.9%) required a capecitabine dose reduction or capecitabine treatment break during RT. No Grade 4 or 5 toxicities were reported. Median follow-up from RT completion was 7 months [IQR 0.98-12.2]. At last follow-up, radiation dermatitis had improved to Grade 0-1 for all patients.

Conclusion: Concurrent adjuvant capecitabine and RT is a feasible treatment approach that is well tolerated with acceptable acute toxicities.

PO4-22-05

Changes in Treatment Recommendation for Patients with Ductal Carcinoma In Situ Using a 7-Gene Predictive Biosignature: Analysis of the PREDICT Australia Study

Presenting Author(s) and Co-Author(s):

Y. Zissiadis. GenesisCare, United States

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

D. Speakman. Peter MacCallum Cancer Centre, United States

C. Saunders. University of Melbourne, Australia

M. Dreosti. GenesisCare, United States

C. Pyke. University of Queensland, United States

D. De Viana. Pindara Private Hospital Gold Coast, United States

M. Bochner. Royal Adelaide Hospital, United States

J. French. Westmead Breast Cancer Institute, Westmead, New South Wales, Australia

S. Baron-Hay. GenesisCare, United States

K. Mittal. PreludeDx, United States

S. Shivers. PreludeDx, St Johns, Florida, United States

T. Bremer. PreludeDx, United States

Background: The role of adjuvant radiotherapy (RT) following breast-conserving surgery (BCS) for women with ductal carcinoma in situ (DCIS) remains controversial. Although there is Level 1 evidence supporting the use of RT to reduce the risk of local recurrence, prognostic and predictive tools are needed to better stratify the individual risks and benefits of RT. The 7-gene predictive DCIS biosignature provides a validated score (DS) for women receiving BCS that assesses 10-year risk of DCIS recurrence and development of invasive breast cancer with and without adjuvant RT. We established a registry to evaluate the decision impact of the 7-gene predictive biosignature on DCIS treatment recommendations in an Australian setting.

Methods: The PREDICT study is a prospective, multi-institutional registry for patients who received DCISionRT testing as part of their routine care. The registry includes females 26 and older who are diagnosed with DCIS and are candidates for BCS and eligible for RT. Treating physicians completed treatment recommendation forms before and after receiving test reports to capture surgical, radiation and hormonal treatment (HT) recommendations and patient preferences.

Results: This planned interim analysis was performed in 483 patients with complete data treated at 43 clinical sites in Australia. The median age of patients was 61 years, 19% were 50 or younger, nuclear grade was high in 51%, and tumor size was 2.5 cm or greater in 15%. Overall, RT recommendation (yes/no) was changed for 41% of women and HT recommendation was changed for 9% after testing with a net reduction in recommended RT of 14% (66% pre-assay to 52% post-assay $p < 0.001$). Of patients recommended to receive RT pre-test, 42% were recommended to not receive RT post-test and of the patients recommended to not receive RT pre-test, 40% were recommended to receive RT post-test. The post-test RT recommendation rate increased with increasing DS score (< 2, 2-4, >4), with 9% of patients recommended RT for DS < 2, 62% for DS 2-4, and 100% for DS 4-10. The use of the test resulted in different RT recommendations than with clinicopathology alone, where RT

recommendations were changed for 49%, 37%, and 34% for women of age < 50 yrs, with Grade 3 DCIS, or with DCIS > 2.5 cm, respectively. Collectively, this suggests that physicians had a high confidence in the test results when making their final treatment recommendations with the test results.

Conclusions: This analysis demonstrates that the use of the 7-gene predictive biosignature resulted in significant changes in recommendations to add or omit RT in this study of 483 women. The integration of DCISionRT into the clinical decision-making processes has a substantial impact on recommendations to personalize care and prevent over- or under-treatment.

Table 1: Impact of DCISionRT on Adjuvant Radiation Recommendations by Clinicopathologic Features

Clinical Factor	n	RT Recommended			Pre- to Post-Test Change in RT Recommended		Total Change in RT Recommended		
		Pre-Test (%)	Post-Test (%)	Net Change (%)	Yes to No (%)	No to Yes (%)	Overall Change (%)	95% CI	p-Value
All Cases	483	66%	52%	-14%	42%	40%	41%	37-46%	<0.0001
Age									
Under 50	69	65%	42%	-23%	56%	38%	49%	38-61%	0.0061
50 - 69	308	67%	46%	-20%	46%	30%	41%	35-46%	<0.0001
70 and over	106	66%	75%	8%	23%	69%	39%	30-48%	0.1599
Nuclear Grade									
Grade 1	52	27%	54%	27%	36%	50%	46%	33-59%	0.0043
Grade 2	186	51%	40%	-11%	56%	36%	46%	39-53%	0.0310
Grade 3	245	86%	60%	-26%	36%	38%	37%	31-43%	<0.0001
Tumor size									
≤1 cm	212	43%	38%	-5%	59%	36%	46%	39-53%	0.3232
1 - 2.5 cm	228	79%	59%	-20%	38%	46%	40%	33-47%	<0.0001
>2.5 cm	105	93%	68%	-26%	32%	60%	34%	24-45%	0.0001
Tumor Necrosis									
Present	380	80%	55%	-25%	42%	43%	42%	34-48%	<0.0001
Absent	204	45%	49%	4%	48%	46%	47%	37-56%	0.5637
RTOG-9804-like									
Good Risk	185	40%	40%	0%	57%	38%	46%	38-53%	1.0000
Not Good Risk	308	83%	59%	-24%	38%	43%	39%	33-44%	<0.0001
DS Risk Groups									
Low Risk	274	64%	19%	-45%	75%	7%	50%	44-56%	<0.0001
Elevated Risk	209	69%	95%	26%	3%	91%	30%	24-36%	<0.0001

PO4-22-06

Outcomes following Stereotactic Radiotherapy in Oligometastatic Breast Cancer: a single centre retrospective review

Presenting Author(s) and Co-Author(s):

S. Lynch. Guy's and St. Thomas' NHS Foundation Trust, London, United States

S. Sukumar. Guy's and St. Thomas' NHS Foundation Trust, United States

E. Sawyer. Guy's and St. Thomas' NHS Foundation Trust/King's College London, United States

D. Smith. Guy's and St. Thomas' NHS Foundation Trust, London, United States

C. Goldsmith. Guy's and St. Thomas' NHS Foundation Trust, London, United States

Introduction:

Stereotactic radiotherapy (SABR) is an increasingly used treatment for oligometastatic disease with evidence of survival benefit shown in the SABR-COMET trial. However, the benefit in oligometastatic breast cancer has been brought into question following initial results from the NRG-BR002 trial.

Methods:

A retrospective review of all patients with primary breast cancer treated with stereotactic radiotherapy for oligometastases at our institution was carried out. A total of 31 patients received treatment to 36 lesions between August 2015 and December 2022.

Results:

Neither median overall survival nor progression free survival were reached after median follow up time of 21.5 months. Hormone receptor status as follows: ER+, HER2- (n=25), ER+, HER2+ (n=4), TNBC (n=2). The majority of lesions treated were bony metastases (92%, of which 17 vertebral and 11 pelvic lesions). The majority had oligometastatic disease at time of SABR (67%), with 33% treated for oligoprogression. Most patients were on systemic anti-cancer therapy (SACT) at the time of SABR, or had a planned start of SACT shortly following treatment. Breakdown of systemic therapy as follows: Endocrine therapy (ET) alone 9 patients (29%), CDK4/6 inhibitor plus ET 13 patients (42%), chemotherapy 3 patients (10%), antibody drug conjugate 2 (6%), anti-HER2 therapy + ET 2 patients (6%), none 2 patients (6%). All patients also received bone-targeted agents (zoledronic acid or denosumab). Local control was achieved in 33 lesions (92%), all of which were bony lesions. Local control was maintained in both patients who were not on SACT: one patient with ER+ HER2- disease developed distant progression after 27 months, the other with TNBC remains disease free after 13 months. Loss of local control was observed in all non-bony sites (lung, IMC node, peri-ureteric soft tissue mass) at a median interval of 10 months (range 7-43 months). 14 patients subsequently developed distant disease progression at median interval of 15 months (range 0-43 months). 12 month progression free survival was 77%. 13 patients received further SACT at median interval of 16 months.

Conclusions:

SABR for bony metastases from breast cancer has excellent local control rates in combination with systemic treatment but may also give patients significant time off treatment. Questions remain regarding the ideal sequencing and combination of SABR and SACT, particularly in hormone receptor positive patients where there are a number of lines of effective SACT.

PO4-22-08

Ten-Year Oncologic Outcomes in T1-3N1 Breast Cancer After Targeted Axillary Sampling: A Retrospective Study

Presenting Author(s) and Co-Author(s):

B. Kang. Kyungpook National University Chilgok Hospital, Taegu-jikhalsi, Republic of Korea

J. Lee. Department of Breast & Thyroid Surgery, Kyungpook National University Chilgok Hospital, United States

Y. Chae. Department of Oncology/Hematology, Kyungbook National University, Chilgok Hospital, Daegu, Republic of Korea, Republic of Korea

H. PARK. Department of Breast & Thyroid Surgery, Kyungpook National University Chilgok Hospital, United States

J. JUNG. Department of Breast & Thyroid Surgery, Kyungpook National University Chilgok Hospital, United States

Background

Targeted axillary sampling (TAS) is a new surgical concept for the assessment of axillary lymph node status in breast cancer that is hypothesized to be more effective at minimizing postoperative morbidities than axillary lymph node dissection (ALND), provided the metastatic axillary lymph node can be accurately detected without missing data; however, the oncologic outcomes over long-term follow-up have not been sufficiently investigated. This was a retrospective analysis to evaluate the 10-year oncologic outcomes in T1-3N1 breast cancer after TAS.

Methods

Clinically, we defined TAS as removal of a bunch of ALNs located around SLNs and targeted LNs, but without full exposure of the axillary vein, long thoracic nerve and thoracodorsal nerve. Between 2008 and 2013, 230 female patients with cT1-3N1 breast cancer underwent breast and axillary surgery (ALND, n = 171; TAS, n = 59) at our institute. After TAS was applied, additional axillary radiotherapy was performed. Various postoperative complications, including postoperative seroma, lymphedema, and 10-year oncological outcomes, were evaluated and compared between the ALND and TAS groups.

Results

Although overall survival during the 10-year follow-up period was better in the TAS group, there was no statistically significant difference in oncologic outcomes, including locoregional recurrence, distant metastasis, and overall survival (p = 0.395, 0.818, and 0.555, respectively). Furthermore, the incidence of lymphedema on the ipsilateral arm was significantly higher in the ALND group (p < 0.001).

Conclusions

The 10-year oncological outcomes of TAS were not inferior to those of conventional ALND in T1-3N1 breast cancers; however, the incidence of lymphedema was significantly higher in the ALND group.

PO4-22-09

Impact of time to surgery after neoadjuvant chemotherapy on pCR rate in locally-advanced breast cancer

Presenting Author(s) and Co-Author(s):

A. Petrovskiy. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

V. Amosova. N.N. Blokhin National Cancer Research Center, United States

O. Trofimova. N.N. Blokhin National Cancer Research Center, United States

M. Frolova. N.N. Blokhin National Cancer Research Center, United States

A. Soloshenko. N.N. Blokhin National Cancer Research Center, United States

A. Rumyantsev. N.N. Blokhin National Cancer Research Center, United States

Objective: Neoadjuvant chemotherapy along with surgical treatment are the important parts of treatment for locally advanced breast cancer. Extending the interval between the end of neoadjuvant chemotherapy and surgery may decrease tumor response in patients with locally advanced breast cancer. However, data if timing of surgery after neoadjuvant therapy affect the Pathologic complete response (pCR) rate is controversial.

Materials and methods: We performed a retrospective analysis of 874 consecutive patients with IIIA-IIIC breast cancer that received neoadjuvant chemotherapy and surgery between 2000 and 2020 in N.N. Blokhin National Cancer Research Center. The median interval between the last injection of chemotherapy and surgery was 30 days (range 10 to 95 days). The variables were compared using log-rank statistics and Cox regression model.

Results. Pathologic complete response (pCR) was registered in 250 (31,4%) patients. Univariate analysis showed that extending the interval between the end of neoadjuvant chemotherapy and surgery for each day were associated with decrease of probability of pCR (OR 0,982; $p = 0,009$). Patients with triple-negative and ER-/HER2+ achieved higher rates of pCR compared to luminal A subtype ($p < 0,0001$). Tumor grade, tumor size, Ki67 were independent predictive factors for tumor pCR ($p < 0,001$). Multivariate analysis also showed an independent negative effect of the time interval before surgery on the achieving pCR. Then the patients were stratified into three cohorts according to the time of surgery after neoadjuvant chemotherapy: < 22 days, 22-42 days, or > 42 days. The odds ratio (OR) for pCR was 1 for < 22 days (reference), 0,833 for 22-42 days ($p=0,332$) and 0,576 for ≥ 43 days ($p=0,033$). Cox regression model demonstrated that the interval between the end of neoadjuvant chemotherapy and surgery (more than 42 days), tumor size, triple-negative and ER-/HER2+ were the significant predictive factors for pCR. Tumor grade, tumor size and age of patients were not independent predictive factors for in-breast pCR.

Conclusion: Our study showed improved pCR if surgery was performed within 6 weeks after the end of neoadjuvant chemotherapy in locally advanced breast cancer.

Results of multivariate logistic regression analysis to assess the probability of achieving complete pathomorphological regression

Factor	OR	95% CI	p
β_0 (intercept)	0,178	0,067-0,430	<0,001
Tumor size	0,990	0,981-0,999	0,032
Grade*	1,090	0,851-1,398	0,493
Time			
<42 days	1 (reference)	-	-
\geq 43 days	1,490	1,001-2,378	0,049
Subtype			
Lum A	1 (reference)	-	-
Lum B	1,684	0,984-2,986	0,064
HER2+	4,354	2,482-7,905	<0,001
TNBC	5,477	3,182-9,802	<0,001

Results of multivariate logistic regression analysis to assess the probability of achieving complete pathomorphological regression

PO4-22-10

Prognostic impact of preoperative lymph node diagnostic tools for patients with suspicious node positive breast cancer

Presenting Author(s) and Co-Author(s):

R. NAKAMURA. Chiba Cancer Center, division of breast Surgery, United States

S. Hayama. Chiba Cancer Center, division of breast Surgery, United States

R. Nakamura. Division of Breast Surgery, Chiba Cancer Center, Chiba, Chiba, Japan

N. Yamamoto. Division of Breast Surgery, Chiba Cancer Center, United States

(Abstract)

Recently, the SOUND trial demonstrated the feasibility for omission of sentinel lymph node biopsy (SNB) in cases with negative ultrasound (US)-guided fine-needle aspiration cytology (FNA) of suspicious lymph nodes (LNs). An important consideration for omission of SNB depends on a highly accurate assessment of preoperative staging for axillary LNs.

(Purpose)

The purpose of this study was to investigate the impact of preoperative diagnostic tools for axillary lymph nodes (LNs) staging of early breast cancer.

(Materials and Methods)

A total of 3088 consecutive patients with operable breast cancer were retrospectively identified at our institution between April 2013 and March 2020. Patients with suspicious axillary LN of breast cancer were assessed using preoperative US and computed tomography (CT), underwent FNA or core needle biopsy (CNB). The inclusion criteria for both FNA and CNB were a cortical thickness ≥ 3 mm or abnormal morphological characteristics. Patients with biopsy-proven metastasis underwent axillary lymph node dissection (ALND), and those with a negative FNA or CNB underwent SNB. If the SNB was positive, ALND was performed.

Diagnostic accuracy for SNB was calculated for both FNA and CNB. In addition, the patients in this study were divided into two groups as follows: the cN0-FNA negative group (suspicious LN but negative FNA) and the cN0-CNB group (suspicious LN but negative CNB). Overall survival (OS) and invasive disease survival (iDFS) was estimated by using the Kaplan-Meier method and compared by using the log-rank test.

(Results)

A number of patients with negative or suspicious metastasis US/CT findings of LNs were 3187, with 963 undergoing FNA and 395 undergoing CNB for suspicious LNs. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 63, 99, 99, 73, and 81% in FNA, and 87, 100, 100, 91 and 95% in CNB, respectively.

SNB was performed in 207 (cN0-CNB group) of 395 CNB and 581 (cN0-FNA group) of 963 FNA patients. Two hundred and seven patients from the cN0-CNB group (T1ab; 42, T1c; 72, T2; 84, T3; 9 patients) treated with SNB were compared to 581 from the cN0-FNA group (T1ab; 86, T1c; 193, T2; 278, T3; 24 patients) in terms of number of LN metastasis. A number of patients with micrometastases, 1, 2, 3 or more than 4 positive LNs were 5(2%), 7(3%), 3(1%), 9(3(1%)) and 0 (0%) in cN0-CNB group, and 23(4%), 67(12%), 26(4%), 12(2%) and 29 (5%) in cN0-FNA group, respectively. The significant

difference in 5ys iDFS and OS was observed between CNB group and FNA group (94.2% vs.91.4%, p =0.04 and 99% vs. 95%, p=0.004, respectively).

Conclusions The preoperative diagnosis of axillary LNs was influenced by the diagnostic tool used. CNB is a reliable method for the preoperative diagnosis of LN metastasis.

The prognosis of early breast cancer with clinically metastasis-negative lymph nodes diagnosed by CNB is better than that by FNA.

Number of positive lymph nodes cN0-FNA (%) cN0-CNB (%)

Total	207	100	581	100
0	189	91	424	73
micrometastasis	5	2	23	4
1	7	3	67	12
2	3	1	26	4
3	3	1	12	2
4 more than	0	0	29	5

PO4-22-11

Study to Compare the Safety of Immediate One-stage IBBR With Expander-Implant Two-stage IBBR Augmented With TiLoop® Bra(COSTA)

Presenting Author(s) and Co-Author(s):

B. Yang. Fudan University Shanghai Cancer Center, Shanghai, China, Shanghai, China (People's Republic)

J. Liu. Hangzhou first people's hospital, United States

H. Wang. Breast Center, Qingdao University Affiliated Hospital, China (People's Republic)

Y. Chen. The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

C. Geng. Breast Center, the Fourth Hospital of Hebei Medical University, China (People's Republic)

N. Rao. Breast tumor center, Sun Yat-sen Memorial Hospital, United States

S. Han. The first hospital of China medical university, United States

A. Zhang. Maternal and Child Health Care Hospital of Guangdong Province, United States

J. Shi. JANG SU PROVINCE HOSPITAL, United States

Q. Zhang. Cancer Hospital of China Medical University, United States

W. Zhao. SIR RUN RUN SHAW HOSPITAL. ZHETIANG UNIVERSITY SCHOOL OF MEDICINE, United States

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Background: The use of TiLOOP@ Bra in implant-based breast reconstruction (IBBR) becomes standard of care in mainland China. But evidence is limited about complication of one-stage and two-stage IBBR using TiLOOP@ Bra. A prospective randomized trial was conducted to compare the safety of immediate IBBR with that of immediate-delayed IBBR, both with TiLOOP@ Bra.

Methods: We did an open label, randomized, controlled trial in eleven hospitals in the mainland China. Inclusion criteria: Women aged above 18 with cT0-T2N0M0 breast carcinoma which requires to undergo nipple or skin-sparing mastectomy (NSM or SSM) and immediate IBBR. Randomization was done electronically, stratified per center and in blocks of four or six to achieve approximately balanced groups of patients assigned to undergo one-stage or two-stage IBBR. Both procedures were undergone pectoralis major and TiLOOP@ Bra to build pockets. The primary endpoint of the present study was the incidence of postoperative complications (within 90 days after surgery), while the secondary endpoints were the quality of life at 18 months after surgery, satisfaction with breast appearance, aesthetic scores of reconstructed breasts, type of reoperation and TiLOOP@ Bra angiopathological assessment. This study is registered at clinicaltrials.gov, number NCT03589924.

Findings: Between June 2018 and May 2022, a total of 418 eligible patients were randomly assigned to either two-stage implant reconstruction (n=194) group or immediate one-stage implant reconstruction (n=224) group. In terms of surgical procedures, NSM was more commonly (72.7%) chosen, with the two-stage implant reconstruction group having a lower

proportion compared to the immediate one-stage implant reconstruction (66.3% vs. 78.3%; $p=0.010$). At 3 months after breast reconstruction surgery, the incidence of complications was lower in the two-stage implant reconstruction group than that in the immediate one-stage implant reconstruction group, with significant difference of 14.5% vs 23%; $p=0.038$. The incidence of nipple or areola necrosis was lower in the two-stage implant reconstruction group compared to the immediate one-stage implant reconstruction group, with statistically significant difference of 9.8% vs 17.1%; $p=0.048$. The implant loss rate was only 0.7%. It was discovered that the incidence of severe complications was lower in the two-stage implant reconstruction group than in the immediate one-stage implant reconstruction group (2.6% vs. 3.7%), and the difference was not statistically significant. Patients who experienced complications had a higher proportion of chemotherapy (69.2% vs. 38.9%; $p < 0.001$), endocrine therapy (74.4% vs. 53.9%; $p=0.002$), and targeted therapy (24.4% vs. 9.6%; $p=0.001$), and the differences were statistically significant. In terms of surgical procedures, 67 (85.9%) patients who experienced complications underwent NSM, while the proportion of NSM in patients who did not experience complications was lower at 69.6%, which were 231 patients, and the difference was statistically significant ($p=0.011$). In addition, the complication incidence of patients who received implants sizes of 300-400ml was higher than that of the group that did not (32.1% vs. 17.8%; $p=0.012$).

Conclusion: Both one-stage and two-stage TiLOOP@-assisted IBBR demonstrated perioperative safety. The complication rate within three month of two-stage is lower than one-stage. The implant loss rate was only 0.7% perioperatively. Our results suggest that use of TiLOOP@ Bra be considered carefully for one-stage NSM with IBBR but can be considered for SSM patients.

PO4-22-12

Robot-assisted nipple-sparing mastectomy using da Vinci SP single-port system: primary results from the pilot trial RASPIM-01

Presenting Author(s) and Co-Author(s):

W. Kuo. Chang Gung Memorial Hospital, United States

C. Chu. Chang Gung Memorial Hospital, United States

J. Huang. Chang Gung Memorial Hospital, United States

Background

Robot-assisted breast surgery was developed in 2014 for nipple-sparing mastectomy through a concealable lateral chest wall incision smaller. Although successful experiences have been reported using a multi-arm surgical robotic system, collisions between robotic arms and instruments often result in the discontinuation of console workflow and limit the performance of the surgical robot. Compared to multi-armed robot systems, the SP system is single-armed, equipped with flexible instruments containing multiple joints that may avoid instrument collision, a controllable camera reducing visual dead spots, and a designated non-third-party port that allows single-port entry and full deployment of the instrument. The RASPIM-01 trial (NCT05448963) is a single-armed pilot study assessing the feasibility of robot-assisted nipple-sparing mastectomy (NSM) using a new SP system.

Method

This study is a pilot trial conducted in a single-arm, non-randomized design with a recruitment of 30 participants. The SP surgical robot is used in NSM through the lateral chest wall incisions. The major inclusion criteria are 1) Breast cancer with preoperative clinical tumor sizes less than 5 cm, with an adequate tumor-skin distance of at least 3mm, and without nipple-areolar involvement in at least 1cm around the nipple by image, 2) Breast cancer up to clinical stage IIIA (T3, N1-2) showing adequate response to neoadjuvant therapy and meeting criteria 1), 3) Germline pathogenic/likely pathogenic BRCA1 or 2 variant carriers with or without a breast cancer diagnosis, requiring unilateral or bilateral therapeutic mastectomy or prophylactic mastectomy. Exclusion criteria include extensive breast skin or nipple involvement such as inflammatory breast cancer, Paget's disease, nipple discharge associated with malignancy, image suggestive of cancer involvement of the nipple and subareolar tissue, and stage III breast cancer without response to neoadjuvant therapy, and previous radiotherapy of the surgical side breast. The endpoint measurements include Primary endpoint: The ability to complete nipple-sparing mastectomy with an SP system in the per-protocol population without additional assistant port or conversion to open surgery. Statistical analysis includes point estimation with a 95% confidence interval to analyze the mean or proportion of key performance parameters. No interim analysis will be performed due to the limited number intended to recruit.

Results

The study recruited 30 breast cancer patients and conducted 30 NSMs, while no prophylactic mastectomy case was recruited. The median age was 44 years old, BMI was 22.4 (18.9-30.0) kg/m². Median tumor size was 3.0 (1.0-14.6) cm, and axillary lymph node metastases were present in 7 cases (23.3%). T2 (13 cases, 43.3%) tumors were the majority, followed by Tis (10 cases, 33.3%), T1 (5 cases, 16.7%), and T3 (2 cases, 6.7%). The anatomical stages of invasive cancer were Ia (16.7%), IIa (26.7%), IIb (16.7%), and IIIa (6.7%), among them 9 (30.3%) received neoadjuvant chemotherapy before surgery. All NSMs met the primary

endpoint of successful completion using the SP robot system without conversion to open mastectomy or the addition of an assistant port. Median console time was 108.5 (73-285) min and docking time was 2.5 (1-9) min. Specimen weight was 311.6 (107-838) gm, while 2 (6.7%) cases had their nipple excised due to cancer-involved margin reported from the frozen section. Twenty-six (86.6%) cases received autologous free flap reconstruction, among which 25 (83.3%) cases received DIEP, and 1 (3.3%) received PAP reconstruction. Four cases received implant (2 cases, 6.7%) or tissue expander (3 cases, 6.7%).

Conclusion

This is the first NSM clinical trial operated with SP surgical robot system and met its primary endpoint showing the feasibility to conduct NSM. Secondary and exploratory endpoints data will be reported after the completion of clinical follow-ups.

PO4-23-01

Imaging tailored axillary approach combined with radiotherapy eliminates axillary lymph node dissection in low-volume axillary disease after neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

M. Muslumanoğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey

B. Mollaveliöglu. Istanbul University, Istanbul Faculty of Medicine, Department of General Surgery, Istanbul, Turkey, Istanbul, Turkey

S. Emiroglu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey

H. Karanlık. Istanbul University Institute of Oncology, Department of Surgical Oncology, Istanbul, Turkey

M. Tukenmez. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey

K. İbis. Istanbul University, Istanbul Faculty of Medicine, Department of Radiation Oncology, Istanbul, Turkey

A. Bayram. Istanbul University, Istanbul Faculty of Medicine, Department of Pathology, Istanbul, Turkey, Istanbul, Turkey

R. Yılmaz. Istanbul University, Istanbul Faculty of Medicine, Department of Radiology, Istanbul, Turkey, Istanbul, Turkey

N. Cabiođlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Bakırköy, Istanbul, Turkey

A. İgci. American Hospital, Department of Surgery, Istanbul, Turkey

ABSTRACT

Background

Individualized treatment strategies are highlighted for breast cancer patients in the last decades. Therefore aggressive surgical approaches have begun to evolve towards minimally invasive tailored interventions. SLNB is widely used in patients who received neoadjuvant treatment (NAC) and axillary lymph node dissection (ALND) is recommended for patients with axillary residual disease after NAC. In our study, we investigated regional recurrence rates in patients with limited axillary residual disease after NAC who underwent imaging-guided (MR+USG) axillary surgery plus radiotherapy (RT) instead of ALND.

Materials and Methods

139 patients whose clinical stages were T1-3 and N1 at the time of diagnosis, who had a clinically good or complete axillary response after neoadjuvant therapy, and who had axillary residue (≤ 3 pathological lymph nodes) with favorable response to NAC ($>50\%$ fibrotic changes) in the final pathological examination were included in the study. The tumor stage and the number of pathological lymph nodes were assessed by USG, MMG, MR, and PET-CT examination (The minimum number of lymph nodes to be removed was determined according to imaging findings). All patients underwent imaging-guided SLNB (blue dye) and imaging-guided palpable lymph node excision. The patients were re-evaluated with their final pathology results in the multidisciplinary councils for suitable further treatments, ALND or RT. Peripheral lymphatic radiotherapy was applied to patients whose radiology and pathology results were compatible and no further surgery was done. The patients whose radiologically detected number of positive nodes was inconsistent with the number of metastases in pathology

examination and who were presumed to have the gross residual disease underwent ALND. These patients were excluded from the study.

Results

The median age was 47 years. The median number of lymph nodes excised was 4. The total number of excised lymph nodes was between 1-3 in 64 (46%) patients and between 4-6 in 62 (45%) patients. 13 (9%) patients had ≥ 7 lymph nodes. 1 metastatic lymph node was found in all patients with 1 positive lymph node according to imaging findings. Of 41 patients with 2 radiologically positive lymph nodes, 1 metastatic lymph node was found in 17 (41%) patients, 2 metastatic lymph nodes in 22 (53%), and 3 metastatic lymph nodes in 2 (5%) patients respectively. Radiology reported 3 positive lymph nodes in 22 patients, of which 1 metastatic lymph node was found in 8 (36%), 2 metastatic lymph nodes in 10 (45%), and 3 metastatic lymph nodes in 4 (18%).

The median follow-up period was 44 months. One patient had breast recurrence at the 31st month and one patient had lymphatic recurrence in the supraclavicular area at the 39th month. Systemic recurrence was noted in 6 (4.3%) patients. No axillary recurrence occurred during the follow-up period.

Conclusions

Patients with pathological-suspicious ≤ 3 lymph nodes shown by imaging (USG, MR, and PET-CT) who responded to NAC but still have residual disease in the axilla can be safely treated with SLNB(blue dye)+imaging-guided axillary approach and adjuvant RT. This approach eliminates the need for ALND in patients with low-volume residual axillary disease.

Patient characteristics

Table 1. Patient characteristics

Characteristics(N=139)	Category	n(%)
Median follow-up for patients (months), median(IQR)	All	44(29-56)
Median age(minimum-maximum)	All	47(21-73)
Age	≤ 50	89(64)
	> 50	50(36)
Clinical T stage	cT1/2	128(92.1)
	cT3	11(7.9)
Type of Breast Surgery	BCT	83(59.7)
	Mastectomy	56(40.3)
Histopathology of core biopsy and surgical specimen	Invasive ductal carcinoma	123(88.5)
	Invasive Lobular carcinoma	2(1.4)
	Invasive ductal&lobular carcinoma	11(7.9)
	Other	3(2.2)
pCR (breast)	Complete	28(20.1)
	Near complete($>90\%$)	30(21.6)
	80-90%	24(17.3)
	50-80%	34(24.5)
HER2- neu	$<50\%$	23(16.5)
	Negative	108(77.4)
	Positive	31(22.3)
	Luminal A	13(9.4)
Tumor Subtype (IHC)	Luminal B/HER2(-)	76(55.1)
	Luminal B/HER2(+)	19(13.8)
	Non luminal B/HER2(+)	12(8.7)
	Triple negative	18(13)
Tumor Subtype (IHC)	Luminal	109(78.4)
	Non-luminal	30(21.6)
Sentinel Lymph Node Methodology	Blue Dye	115(82.7)
	Combined (Blue dye and radioisotope)	24(17.3)
Radiologic lymph node involvement	1ln	77(55.4)
	2ln	40(28.8)
	3ln	22(15.8)
TAD	Yes	10(7.2)
	No	129(92.8)
Number of sentinel lymph nodes	1-3	92(66.2)
	≥ 4	47(33.8)
Number of metastatic sentinel lymph nodes	1	112(80.6)
	≥ 2	27(19.4)
Number of total LN	1-3	64(46)
	≥ 4	75(54)
Number of total metastatic LN	1	101(72.7)
	≥ 2	38(27.3)
Characteristics of metastatic lymph nodes (LNs) removed	Macrometastasis	80(57.6)
	Micrometastasis	43(30.9)
	Isolated tumor cells	16(11.5)
Presence of extracapsular extension	Yes	23(16.5)
	No	116(83.5)
Non sentinel lymph node positivity(n=52)	Yes	12(23.1)
	No	40(76.9)

IQR: Inter-Quantile Range(P_{25} - P_{75}), BCT: Breastbreast conserving treatment

PO4-23-02

Blue Dye-Only for Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy in Patients with Initially Node-positive Breast Cancer

Presenting Author(s) and Co-Author(s):

F. Pimentel Cavalcante. Hospital Geral Fortaleza (HGF), United States

F. Zerwes. PUC-RS, United States

A. Souza. PUC-RS, Rio Grande do Sul, Brazil

P. Ziegelmann. UFRGS, Rio Grande do Sul, Brazil

R. Alcantara. Hospital Geral de Fortaleza, Ceara, Brazil

A. Cardoso. Hospital Geral de Fortaleza, Ceara, Brazil

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

E. Millen. Oncoclinicas, United States

A. Frasson. PUC-RS, Rio Grande do Sul, Brazil

Importance: Randomized trials evaluated the false negative rate (FNR) of sentinel lymph node biopsy (SLNB) in initially node-positive (cN1/2) breast cancer (BC) patients who downstaged after neoadjuvant chemotherapy (NAC): the studies were negative, as they found FNR above 10%. However, the FNR was adequate when the lymph node was marked with a clip before NAC or at least 3 lymph nodes were removed. SLNB using a combination of blue dye and a radiotracer (Technetium-99) was encouraged to facilitate identification and maximize SLNB results in this scenario. However, radiotracer is unavailable in many services around the world, particularly in low- and middle-income countries (LMIC), but the feasibility and the recurrence rates of SNLB with the use of blue dye-only, in previous cN1/2 patients, are unknown.

Objective: The aim of this study was to evaluate the feasibility, proportion of patients undergoing SLNB without axillary dissection (AD) and mean number of resected sentinel nodes (SN), and recurrence rates (axillary recurrence [AR], ipsilateral breast recurrence [IBR], new contralateral primary, disease-free survival [DFS] and overall survival [OS]) of SNLB with the use of blue dye-only in initially node-positive BC (cN1/2).

Design, Setting, and Participants: From 2013 to 2023, a cohort of patients undergoing NAC was evaluated at a public institution in Brazil (Hospital Geral de Fortaleza - HGF). Radiotracer and clips were not available. Patients with prior cN1/2 were identified and evaluated. AD was not recommended in cases of negative histopathological results for lymph node metastases after SLNB using blue dye-only. Inflammatory, cN0 and cN3 BC patients were excluded.

Results: Among 119 cN1/2 BC patients treated with NAC, 100 (84%) cases underwent SLNB with blue dye-only and 70 (59%) had SLNB alone. The median of SN were 3.1 and 55 (78%) cases had 3 or more SN. No events related to blue dye occurred. The median age of these 70 patients was 49 (25-84) years, and most cases were T2 (n=40/57.1%), followed by T3 (n=18/25.7%), T4 (n=6/8.6%) and T1 (n=6/8.6%), while N1 predominated in axillary status (n=64/91.4%). Regarding breast cancer subtype, there were 19 (27.1%) hormone receptor-positive/HER2-negative, 16 (22.9%) hormone receptor-negative/HER2-positive, 21 (30%) hormone receptor-positive/HER2-positive and 14 (20%) triple-negative cases. 55 (79%) patients received regimens containing anthracyclines and taxanes. Anti-HER2 therapy was used in all cases, but pertuzumab associated with trastuzumab were available in only 8 patients

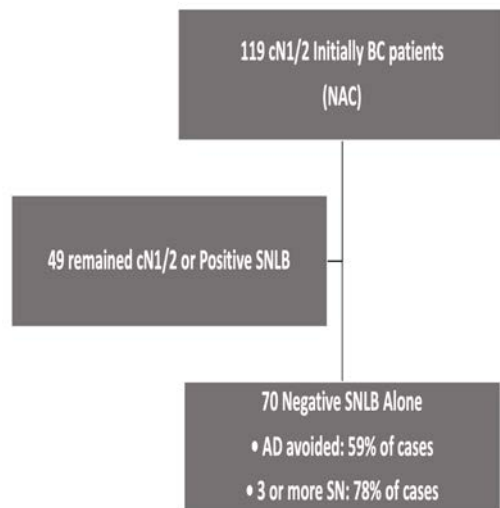
(8/37). Breast-conserving surgery was performed in 40 (57%) cases while total mastectomy in 30 (43%). Patients with hormone-positive BC received endocrine therapy. Adjuvant radiotherapy was made in all cases, except one who underwent mastectomy. After 36 months of median follow-up, no axillary recurrences were observed. One patient had a new primary in the contralateral breast. Three patients had distant disease and two died.

Conclusions: This cohort found that the use of SLNB with blue dye-only in Initially cN1/2 BC patients who achieved complete response after NAC is feasible, with very low axillary recurrence rates, like previous reports in the literature that used a combination of tracers. These data reinforce the need for further studies in this scenario, as it maintains the possibility of avoiding AD in places with difficult access to oncological treatment, especially in LMIC.

Table 1- Demographic Characteristics

Demographic characteristics	Overall (n=70)
Median of age (y)	49 (25-84)
Tumor	
T1	n=6 (8.6%)
T2	n=40 (57.1%)
T3	n=18 (25.7%)
T4	n=6 (8.6%)
Node Stage	
N1	n=64 (91.4%)
N2	n=6 (8.6%)
Immunohistochemistry Subtype	
Hormone receptor-positive/HER2-negative	n=19 (27.1%)
Hormone receptor-positive/HER2-positive	n=21 (30%)
Hormone receptor-negative/HER2-positive	n=16 (22.9%)
Triple-negative	n=14 (20%)
Breast Surgery	
Breast-conserving surgery	n=40 (57%)
Mastectomy	n=30 (43%)

Figure 1 - Flowchart



cN: Clinical node stage; BC: Breast cancer; NAC: Neoadjuvant chemotherapy;
SNLB: Sentinel lymph node biopsy; AD: Axillary dissection; SN: Sentinel node

PO4-23-03

The Influence of Reconstruction Type on Outcomes in Women Undergoing Mastectomy with Immediate Reconstruction: A Nationwide Study

Presenting Author(s) and Co-Author(s):

L. Castro Hernandez. Memorial Healthcare System, United States

J. Parreco. Memorial Healthcare System, United States

INTRODUCTION:

Outcomes after mastectomy with immediate reconstruction may vary depending on the type of reconstruction, but the evidence is limited and inconsistent. The purpose of this study was to compare the most common reconstruction techniques in a large national cohort of women undergoing these procedures.

METHODS:

The Nationwide Readmissions Database for 2016-2020 was queried for all women aged 18 years or older undergoing mastectomy for breast cancer with immediate reconstruction. The primary outcome was prolonged length of stay (LOS) greater than 7 days. The secondary outcomes were readmission within 30 days and readmission to a different hospital. The types of reconstruction were compared along with all other relevant variables from the database. Univariable comparison was performed using chi-squared tests for each outcome. Multivariable logistic regression was performed using all significant confounders.

RESULTS:

During the study period, 35,430 patients were identified undergoing mastectomy for breast cancer with immediate reconstruction. The rate of prolonged (LOS) was 2.4% (n= 840) and the readmission rate was 5.4% (n=1,919). From the readmitted patients, the rate of readmission to a different hospital was 14.2% (n=273). Controlling for confounders with multivariable logistic regression revealed the strongest risk factors for prolonged LOS were latissimus dorsi flap (OR 5.4 [4.0-7.4] p< 0.001) and an investor-owned hospital (OR 4.3 [3.5-5.2] p< 0.001). The highest risk of readmission was a transverse rectus abdominis flap (OR 1.3 [1.1-1.6] p< 0.001) and the highest risk of readmission to a different hospital was a small hospital (OR 2.2 [1.6-3.1] p< 0.001).

CONCLUSION:

Reconstruction type influences outcomes in women undergoing mastectomy. These outcomes have significant implications for surgical decision-making and fragmentation of care. Further research to identify ways to reduce adverse outcomes and improve patient satisfaction is warranted.

PO4-23-04

Is breast-conserving surgery an optional local therapy for non-inflammatory skin involvement (T4b) breast cancer? A Propensity Score Matching and Inverse Probability Weighting Analysis of SEER Database Results

Presenting Author(s) and Co-Author(s):

J. Lin. Fujian Medical University Union Hospital, China (People's Republic)

S. Luo. Fujian Provincial Cancer Hospital, United States

J. Zhang. Fujian Medical University Union Hospital, United States

C. Song. Fujian Provincial Cancer Hospital, United States

Introduction: Although breast-conserving surgery (BCS) usage has been widespread in breast cancer treatment, it is still controversial about its application in non-inflammatory skin involvement (T4b) breast cancer. We designed this study to compare the prognosis for BCS versus mastectomy in this population.

Methods: This retrospective cohort study included patients from the SEER database diagnosed with tumor stage T4b breast cancer from 1998 to 2019. To create prognostic factors, balance between BCS+RT and Mastectomy+RT groups, we calculated propensity scores for each patient. The calculation was based on the advance assessment for factors affecting prognosis, with the use of univariable and multivariable Cox proportional hazards models. Based on it, two propensity score-based matchings were conducted, including propensity score matching (PSM) and inverse probability weighting (IPTW). After adjustment, we performed Kaplan-Meier curves and multivariable Cox proportional hazards models to estimate BCSS and OS.

Results: Of 4,680 patients who met the criterion, 588 received BCS+RT, and 4092 received Mastectomy+RT. In the propensity score matching (PSM) cohort, BCS+RT was found to improve breast cancer cause-specific survival (HR, 0.67; 95% CI, 0.53 to 0.85; $p=0.001$) and overall survival (HR, 0.72; 95% CI, 0.59 to 0.88; $p=0.001$). Similar results in the analysis of the IPTW-matched cohort confirm this result (BCSS: HR, 0.672; OS: HR, 0.722). Subgroup analysis revealed that those less than 70 years old, grade I+II, 3cm or smaller tumor size, hormone receptor-positive, or received chemotherapy treatment were more likely to benefit from BCS+RT (all $p < 0.05$).

Conclusions: Locally treatment with BCS usage presented a significantly better survival than with mastectomy for non-inflammatory skin involvement (T4b) breast cancer patients. This finding provided evidence of selection in the local treatment of these patients.

PO4-23-05

Magnetic lymphatic tracing for omission of sentinel lymph node biopsies in mastectomy patients: a community cancer center experience

Presenting Author(s) and Co-Author(s):

M. Samaha. Trihealth, United States

B. Wexelman. Trihealth, United States

A. Kurtizky. Trihealth, United States

K. Raque. Trihealth, United States

A. Fellner. Trihealth, United States

Background

Patients with ductal carcinoma in situ (DCIS) and patients undergoing risk reduction mastectomy traditionally undergo sentinel lymph node biopsy (SLNB) at the time of mastectomy to complete axillary staging were invasive malignancy to be identified on final pathology. About 10% of patients with DCIS undergoing mastectomy will have invasive disease on final pathology; thus, about 90% would be able to avoid SLNB. Standard lymphatic mapping for SLNB includes a combination of radioisotope and blue dye, which have a short half-life. Superparamagnetic tracers, such as Magtrace®, are non-inferior to this standard and remain active for several weeks, allowing many patients to avoid SLNB in the setting of mastectomy. Reducing SLNB may also reduce associated risks with SLNB such as hematoma, seroma, and subsequent lymphedema.

Objective

We hypothesized using Magtrace® would reduce the number of SLNB in patients undergoing mastectomy for DCIS or risk reduction. Consequently, this would reduce the number of SLNB-associated complications. We report a community cancer center experience with Magtrace® for omission of SLNB in select mastectomy patients.

Methods

This was a retrospective review of 52 female patients with DCIS or known genetic predisposition undergoing mastectomy. Magtrace® was injected ipsilateral to DCIS or bilateral for prophylactic mastectomy patients. Our primary outcome was rate of return to the OR for delayed SLNB. Secondary outcomes included post operative complications within 30 days of surgery and OR time. We compared outcomes to a control group of 28 women undergoing mastectomy for DCIS or risk reduction who underwent SLNB at their index operation. Continuous variables were reported using median and interquartile range (IQR) and were compared using the Mann-Whitney U-test. Categorical data were reported using frequency and percent; they were compared using Pearson's Chi-Square or Fisher's Exact test, as appropriate. Alpha was set to 0.05 to determine statistical significance.

Results

There were a total of 80 patients (52 Magtrace®, 28 control). Median age of Magtrace patients was 49.5 (IQR 40-60.75) vs. 54.5 (IQR 48-65) years for the controls. 57.7% of Magtrace® patients underwent mastectomy for DCIS vs. 89.3% in the control group. 8 Magtrace® patients (15.4%) had invasive ductal carcinoma on final pathology and 7 of those patients underwent SLNB and none were positive for metastatic disease. Of these, 6 patients underwent mastectomy for DCIS. Average number of sentinel lymph nodes was 1.57 in Magtrace® patients and 1.60 in the control patients. Rates of post operative complications were similar

between the groups, including hematoma, seroma, surgical site infection, skin necrosis. OR times were also similar with median OR time 202 minutes (min) for the Magtrace® group vs. 195 min for the control group.

Conclusion

Use of Magtrace® avoided SLNB in 84.6% of our patients. We found no difference in rates of postoperative complications or operative times in patients using Magtrace® for omission of SLNB at time of mastectomy compared to the control group. Our findings suggest SLNB can be avoided in a majority of patients undergoing mastectomy for DCIS or risk reduction in the setting of genetic predisposition.

Demographic	Magtrace® (total = 52 patients)	Control (total = 28 patients)	P-value
Race			
African American	10 (19.2%)	1 (3.6%)	
White	40 (76.9%)	25 (89.3%)	
Asian	0 (0.0%)	1 (3.6%)	
Other	2 (3.8%)	1 (3.6%)	0.142
Age			
	49.5 (IQR 40.0 – 60.8)	54.50 (48.0 – 65.0)	
Indication			
DCIS	30 (57.7%)	25 (89.3%)	
Genetic	22 (42.3%)	8 (10.7%)	0.03
Reconstruction			
Yes	42 (80.8%)	23 (82.1%)	
No	10 (19.2%)	5 (17.9%)	0.567

Outcome	Magtrace® (total = 52 patients)	Control (total = 28 patients)	P-value
OR Time			
	202.0 (144.3 – 254.8)	190.5 (123.5 – 259.3)	
IDC On Final Pathology			
Yes	8 (15.4%)	1 (3.6%)	
No	44 (84.6%)	28 (96.4%)	

Outcome	Magtrace® (total = 52 patients)	Control (total = 28 patients)	P-value
SLNB Biopsy			
Yes	7 (13.5%)	25 (89.3%)	
Yes + DCIS	6 (85.7%)		
No	45 (86.5%)	3 (10.7%)	0.00
Post-op Complication			
Yes	10 (19.2%)	6 (21.4%)	
No	42 (80.8%)	22 (78.6%)	0.516

PO4-23-06

Outcomes and experiences of women denied immediate breast REconstruction after maSTectOmy for bREast cancer during the COVID-19 pandemic - The RESTORE C19 Study

Presenting Author(s) and Co-Author(s):

K. Fairhurst. Bristol Medical School, United States

R. Dave. Manchester University NHS Foundation Trust, Manchester, UK, United States

B. Kim. Leeds Teaching Hospitals NHS Trust, Leeds, UK, United States

R. O'Connell. The Royal Marsden Hospital, London, UK, United States

R. Vidya. The Royal Wolverhampton NHS Trust , Wolverhampton, UK, United States

P. Roy. University of Oxford, Oxford, UK, United States

S. McIntosh. Queen's University Belfast, United States

P. Fairbrother. Independent Cancer Patients' Voice (ICPV), United States

J. Skillman. University Hospitals Coventry and Warwickshire , Coventry, UK, United States

L. Rooshenas. University of Bristol, Bristol, UK, United States

S. Potter. Bristol Medical School, United States

Introduction

40% of women diagnosed with breast cancer in the UK each year undergo mastectomy and immediate breast reconstruction (IBR) is routinely offered to improve quality of life. During COVID19, this offer was withdrawn to prioritise frontline and emergency services. The RESTORE C19 study aimed to use mixed methods to explore the outcomes, lived experiences and views of women denied IBR during the pandemic.

Methods

Women not offered IBR between March & October 2020, were identified via B-Map-C, a UK prospective multicentre cohort study documenting changes in breast cancer treatment decisions during the pandemic. All patients were followed up between December 2021 & July 2022 (21-28 months following mastectomy) to explore their ongoing management including whether they had undergone, were awaiting, or had decided against delayed breast reconstruction (DBR) and the procedures performed. Descriptive statistics were used to summarise results.

Semi-structured qualitative interviews were undertaken to explore the experiences of this group in more depth. Women were purposively sampled based on treatment centre, age, decision regarding DBR, and procedure performed. A topic guide was developed to explore experiences of breast cancer care; feelings about not having been offered IBR and factors influencing subsequent surgical decision-making. Interviews were transcribed in full and analysed thematically, with data collection and analysis undertaken concurrently and iteratively until saturation was achieved. Full ethical approval was obtained: IRAS 302580, Wales REC 4 21/WA/0347.

Results

Some 366 women were identified as not having been offered IBR in the B-MaP-C study for whom follow up data was available for 311 (85.0%) from 55 centres. The median age was 50 (range 27-83 years). Most women presented with symptomatic breast cancer (n=239, 76.8%),

were fit with no significant comorbidities, had T1 or 2 tumours (n=215, 69.1%) and were node negative (n=186, 59.6%).

Almost a fifth (n=58, 18.6%) of women had decided against breast reconstruction completely. Of the remainder, just under 60% (n=149/253), had attended a surgical consultation to discuss DBR and only a third (n=91/253, 36%) had been referred to plastic surgical services to discuss autologous procedures. Only 21 women (6.8%) had received DBR; (16 free flaps, 4 implants, 1 pedicled flap+/-implant).

Interviews were performed with 18 women from 5 centres with a median age of 49 years (range 34-67): n=5 women had either received/were awaiting DBR; n=4 had undergone/were awaiting contralateral symmetrising mastectomy and n=9 had decided against/were undecided about further surgery. Whilst all women reported feeling 'grateful' for their breast cancer treatment, some felt 'abandoned' by healthcare professionals, others that they needed to chase breast surgical teams for care, advice, and support. Partners were also impacted by their experiences with some women describing lasting effects on their relationships. Many women described how their desire for symmetry, either by breast reconstruction or symmetrising mastectomy, had "paled into insignificance" in the months and years following treatment.

Conclusions

The impact of COVID19 continues to be felt by women treated for breast cancer in the UK. Most women not offered IBR are either still awaiting DBR almost three years after their initial mastectomy or have decided against further surgery.

The interviews highlight the trauma many women experienced receiving breast cancer treatment during the pandemic and ongoing issues that, for some, are yet to be fully addressed.

There is a need for individualised support to provide women with equitable and timely access to DBR and/or symmetrising mastectomy depending on patient preference to help them move on with their lives.

PO4-23-07

Impact of distance between tumor and nipple on locoregional recurrence in breast cancer

Presenting Author(s) and Co-Author(s):

J. Cheun. Seoul Metropolitan Government Seoul National University Boramae Medical Center, United States

E. Kang. Seoul National Univ. Hospital, Surgery, Republic of Korea

H. Kim. Seoul National Univ. Hospital, Surgery, Korea, United States

H. Lee. Seoul National University Hospital, United States

H. Moon. Seoul National University, Republic of Korea

W. Han. Seoul National University Hospital, Seoul, Republic of Korea

K. Hwang. SMG-SNU Broamae Medical Center, United States

Introduction: Mastectomy is usually recommended for centrally located tumors due to the risk of nipple invasion. While it is well known that there is no significant difference in survival outcomes according to tumor location, central tumors have a higher likelihood of main lactiferous duct invasion, which can result in the migration of tumor cells to the periphery. Therefore, we conducted an investigation specifically focusing on locoregional recurrence (LRR) rates based on the tumor-to-nipple distance (TND).

Method: We retrospectively collected the data of patients who underwent breast cancer surgery between 2004-2018 from two institutions. Patients who underwent neoadjuvant chemotherapy were excluded. TND information was obtained from preoperative MRI records.

Results: A total of 9,014 patients were included in the study, and the median tumor-to-nipple distance (TND) was 3.4 (0.0-15.0) cm. For all patients, the restricted cubic spline curve analysis showed that the hazard risk of LRR increased with shorter TND. The pattern was more pronounced in the breast-conserving surgery (BCS) group, whereas the mastectomy group showed a relatively constant risk regardless of TND. Thus, we conducted survival analysis for 5,455 patients who underwent BCS. We set the cutoff for TND as 2.5cm as it showed the lowest p-value for LRR rate. Compared to those with TND >2.5cm, patients with TND ≤2.5cm showed significantly lower LRR (HR, 1.83; 95%CI, [1.37-2.46], p< 0.001) and distant metastasis (DM) (HR, 1.53; 95%CI, [1.16-2.02], p=0.002) rates. Overall survival was not different between two groups (p=0.405). Cox-regression analysis revealed that TND still impacts LRR (HR, 1.52; 95%CI, [1.11-2.09], p=0.010) but not DM. Importantly, TND still remained significant factor affecting LRR when analyzed as continuous variable (HR, 1.04; 95%CI, [1.02-1.06], p< 0.001). The prognostic impact of TND was particularly evident in patients with high mammographic density.

Discussion: BCS can be performed for centrally located tumors, as it offers considerable oncologic safety compared to mastectomy. However, for patients who have a fear of recurrence and are reluctant to undergo re-operation, mastectomy would be a good choice.

PO4-23-08

Estrogen therapy induces receptor-dependent DNA damage enhanced by PARP inhibition in ER+ breast cancer

Presenting Author(s) and Co-Author(s):

N. Traphagen. Dana Farber Cancer Inst, United States

G. Schwartz. Dartmouth College, United States

S. Tau. Dartmouth College, United States

A. Roberts. Dartmouth College, United States

A. Jiang. Dartmouth College, United States

S. Hosford. Dartmouth College, United States

J. Marotti. Dartmouth Hitchcock Medical Center / Dartmouth Cancer Center, United States

A. Goen. Dartmouth College, United States

B. Romo. Dartmouth College, United States

A. Johnson. Dartmouth College, United States

E. Duffy. Dartmouth College, United States

E. Demidenko. Dartmouth College, United States

P. Heverly. Champions Oncology, United States

Y. Mosesson. Champions Oncology, United States

S. Soucy. Dartmouth College, United States

F. Kolling. Dartmouth College, United States

T. Miller. Dartmouth College, Lebanon, New Hampshire, United States

Although clinical evidence indicates that treatment with estrogens elicits anti-cancer effects in ~30% of patients with advanced endocrine-resistant ER+ breast cancer, the underlying mechanism of action is unclear and this treatment remains under-utilized. ER+ breast cancer cells with acquired resistance to long-term estrogen deprivation (LTED) were used to model resistance to aromatase inhibitors (AIs) seen clinically. Genome-wide CRISPR/Cas9 knockout screening and transcriptomic profiling of LTED cells highlighted DNA Damage Response as a required pathway for therapeutic response to the estrogen 17 β -estradiol. Tumor specimens from 2 patients with advanced ER+ breast cancer showed increased DNA damage response upon treatment with 17 β -estradiol therapy compared to baseline. LTED cells treated with 17 β -estradiol exhibited replication-dependent markers of DNA damage and the DNA damage response prior to apoptosis, while parental cells did not. Such DNA damage was partially driven by the formation of DNA:RNA hybrids (R-loops), and RNase H1-mediated prevention of R-loop formation abrogated 17 β -estradiol-induced DNA damage. Pharmacological suppression of the DNA damage response via poly(ADP-ribose) polymerase (PARP) inhibition with olaparib enhanced 17 β -estradiol-induced DNA damage. PARP inhibition synergized with 17 β -estradiol to suppress growth and prevent tumor recurrence in both BRCA1/2-mutant and BRCA1/2-wild-type cell line and patient-derived xenograft models. We therefore conclude that 17 β -estradiol-induced ER activity drives DNA damage and growth inhibition in endocrine-resistant breast cancer cells, and inhibition of the DNA damage response using drugs such as PARP inhibitors can exacerbate transcriptional stress and enhance therapeutic response to 17 β -estradiol. This concept is being explored clinically in the PHOEBE trial testing the combination of 17 β -estradiol and olaparib (NCT05900895). These findings also warrant further study of other DNA damage

response inhibitors in advanced ER+ breast cancer. Moreover, these data indicate that PARP inhibitors may have applications beyond homologous recombination-deficient tumors.

PO4-23-09

Dual inhibition of FGFR4 and HER2/EGFR with Lapatinib improves targeting of Erk and Akt signaling in HER2+ breast cancer cells

Presenting Author(s) and Co-Author(s):

J. Beardsley. Burnett School of Biomedical Sciences at University of Central Florida, United States

J. Goode. Burnett School of Biomedical Sciences at University of Central Florida, United States

D. Altomare. Burnett School of Biomedical Sciences at University of Central Florida, United States

In HER2-enriched (HER2E) breast cancer (BC), the dual HER2/EGFR inhibitor Lapatinib is a standard of care for advanced staged disease. Anti-HER2 therapies disrupt tumor progression through inhibition of the PI3K/AKT pathway. Some treated tumors will override inhibition by shifting to MAPK/ERK signaling to fuel cell growth, thus fostering resistance to anti-HER2 therapy. The tyrosine receptor kinase FGFR4 is included in the profile for a HER2E subtype. FGFR4 is overexpressed in ~30% of BC and can signal through PI3K/AKT and MAPK/ERK. Inhibitors for FGFR4 such as BLU554 are being investigated in phase I/II clinical trials for hepatocellular carcinoma, showing success in tumors that are positive for FGFR4's preferred ligand FGF19. According to cBioPortal patient data, FGF19 is amplified in ~20% of BC, and has been shown to trigger an autocrine loop in triple negative BC through FGFR4. We examined BLU554 as a dual therapeutic with Lapatinib and dissected intracellular signaling stemming from the combination in HER2E BC. MDA-MB-453 BC cells (HER2+FGFR4+) were used for a dual strategy with BLU554 and Lapatinib. Cell viability assays were performed at matched doses, then as a dose response matrix, ranging from 0.1-20 μ M. Findings were used for synergy analysis using synergyfinder.fimm.fi. Western blots determined protein activity in response to treatments. Ridaforolimus (mTOR inhibitor) was used in combination with either BLU554 or Lapatinib to assess MAPK/ERK and PI3K/AKT pathway crosstalk in MB-453 cells. Additionally, FGF19 was added to cells after a 2-hour pre-treatment to challenge BLU554 + Lapatinib and compare changes in signaling with FGF19 present. MB-453 cells treated with BLU554 decreased cell viability similarly to Lapatinib at 10 μ M (65% [SD \pm 3.3] and 63% [SD \pm 2.1], respectively). Dual treatment decreased viability compared to single agents at all concentrations but the greatest difference was observed at 20 μ M (38.5% in dual compared to Lapatinib [p-value = 0.00006]; 45.1% in dual compared to BLU554 [p-value = 0.00016]). Dose-response matrix of dual treatment yielded a ZIP synergy score of 16.852 ± 2.97 (>10 is synergistic), with the greatest synergy and inhibition at 10 μ M and 20 μ M of both drugs. BLU554 caused a therapeutic potency shift of Lapatinib, such that lower doses of Lapatinib (0.1 μ M, 1 μ M) are effective at higher doses of BLU554 (10 μ M, 20 μ M). Westerns of MB-453 with one dose of BLU554 increased phospho-ERK1/2 (pERK1/2) at 16- or 48-hr time points versus control, but when BLU554 was re-dosed then pERK1/2 was successfully inhibited. Both pAKT and pS6RP were increased by re-dosing BLU554. Cells treated for 2 hrs with Lapatinib decreased pAKT and pS6RP and did not change pERK, whereas a 2-hr treatment of BLU554 increased pAKT and decreased pERK. Dual treatment exhibited inhibition of ERK, AKT, 4EBP1, and S6RP phosphorylation all to a greater extent than single agents in combination with Ridaforolimus. Challenge by ectopic FGF19 of BLU554 + Lapatinib was unable to restore downstream signaling of AKT and ERK. BLU554 synergistically interacts with Lapatinib to decrease cell viability while increasing its therapeutic potency. Lapatinib primarily inhibits AKT signaling, whereas BLU554 targets ERK. Dual treatment simultaneously blocks MAPK/ERK and PI3K/AKT signaling and yields decreases of mTOR downstream effectors pS6RP and

p4EBP1. These effects are maintained even when challenged with FGF19, suggesting that dual inhibition of FGFR4 and HER2 could prevent pathway activation from external stimuli.

PO4-23-10

Restoring the efficacy of standard of care in treatment-refractory ER+ breast cancer by re-activation of cAMP-ROS-DNA damage axis

Presenting Author(s) and Co-Author(s):

O. Saatci. Medical University of South Carolina, United States

M. Cetin. Medical University of South Carolina, United States

M. Uner. Hacettepe University, United States

U. Tokat. Bilkent University, United States

I. Chatzistamou. University of South Carolina, United States

P. Ersan. Bilkent University, United States

E. Montaudon. Institut Curie, United States

A. Akyol. Hacettepe University, United States

S. Aksoy. Hacettepe University Medical School, Ankara, Turkey, Turkey

A. Uner. Hacettepe University, United States

E. Marangoni. Institute Curie, United States

S. Mathew. University of South Carolina, United States

O. Sahin. Medical University of South Carolina, United States

Estrogen receptor (ER)-positive (ER+) breast cancer has the highest incidence rate and accounts for around 75% of all cases. Endocrine therapy has been the mainstay therapy for the treatment of both early and late-stage ER+ breast cancer for decades. Although most ER+ breast cancer patients initially respond well to endocrine therapy, resistance is common. The addition of CDK4/6 inhibitors to endocrine therapy led to significant improvements in clinical outcome, and they are now considered one of the standard of care (SOC) therapies. However, a significant proportion of patients still suffer from disease relapse upon prolonged use of endocrine therapy in combination with CDK4/6 inhibitors, representing a major clinical challenge that reduces the long-term benefit and patient survival. Therefore, elucidating the mechanisms of sensitivity and resistance to SOC therapy and identifying novel actionable targets are urgently needed. Here, we show that endocrine therapies and CDK4/6 inhibitors cause toxic PARP1 trapping and generation of a functional BRCAness phenotype by downregulating key DNA repair proteins that ultimately result in increased histone parylation and reduced H3K9 acetylation, leading to transcriptional blockage and cell death.

Mechanistically, we found that SOC therapy downregulates phosphodiesterase 4D (PDE4D), resulting in increased cAMP levels, PKA-dependent phosphorylation of mitochondrial COXIV-I, generation of mitochondrial reactive oxygen species (ROS), and DNA damage. Importantly, we identified PDE4D as a novel ER target gene that in turn stimulates ER activity in a feedforward loop in endocrine-responsive models and regulates BRCA1 expression. However, during SOC resistance, an ER-to-EGFR switch induces PDE4D overexpression via c-Jun. Inhibition of PDE4D using BPN14770, the first-in-class PDE4D allosteric inhibitor that has successfully completed Phase II trials in Fragile X syndrome, or its upstream EGFR in combination with SOC therapies in drug-resistant settings, including multiple acquired SOC resistant cell line models, primary cultures and organoids of endocrine resistant ER+ PDXs reinstates PARP1 trapping and BRCAness, leading to drug sensitization in vitro and in vivo. Notably, we demonstrated that high PDE4D mRNA and protein expression is associated with dramatically worse disease-free survival and overall survival in endocrine therapy-treated ER+ breast

cancer. Considering the availability of potent and non-toxic PDE4D inhibitors, clinically approved EGFR and PARP1 inhibitors, our findings have great translational potential.

PO4-23-11

Resistance Mechanisms to CDK4/6 Inhibitors and/or Tamoxifen Using Comprehensive Thermostable Group II Intron Reverse Transcriptase Sequencing

Presenting Author(s) and Co-Author(s):

T. Iwase. Translational Cancer Research, University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

H. Xu. Institute of Cellular and Molecular Biology Department of Molecular Biosciences, The University of Texas at Austin, United States

N. Oh. Translational Cancer Research, University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

J. Lee. Translational Cancer Research, University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

A. Lambowitz. Institute of Cellular and Molecular Biology Department of Molecular Biosciences, The University of Texas at Austin, United States

N. Ueno. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

Background Understanding the mechanisms of resistance to CDK4/6 inhibitors (CDK4/6i) and endocrine therapy (ET) is pivotal in exploring new therapeutic strategies for hormone receptor-positive (HR+), HER2-negative metastatic breast cancer. To decipher these resistance mechanisms, we analyzed the alterations in comprehensive RNA-seq (coding and non-coding RNAs) of HR+ HER2-negative BC cell lines via thermostable group II intron reverse transcriptase sequencing (TGIRT-seq). **Methods** We established Tamoxifen-resistant (TMR), Abemaciclib-resistant (ACR), Palbociclib-resistant (PCR), Tamoxifen/Abemaciclib double-resistant (TMR-ACR), and Tamoxifen/Palbociclib double-resistant (TMR-PCR) BC cell lines from MCF7 and T47D HR+/HER2- BC cell lines through stepwise dose-escalation continuous drug exposure. We performed a TGIRT-seq transcriptomic analysis using a protocol that allows the sequencing of both long and short non-coding and protein-coding RNAs in a single library. All libraries were sequenced using paired-end 150 bp on the Novaseq platform, resulting in an average of 50 million reads per library. For analysis, raw reads underwent adapter trimming, small RNA mapping, whole genome mapping, and the generation of annotated genes' read count. We used raw counts to detect differentially expressed genes (DEGs) with DESeq2 in R using the cut-off (\log_2 [fold change] > 1, FDR < 1e-3). We then used the selected DEGs for Gene Set Enrichment Analysis (GSEA) and Kaplan-Meier survival analysis from the TCGA database. **Results** The TGIRT-seq analysis identified 1171 to 3472 DEGs in different drug resistance and cell line combinations. Most DEGs in resistant cells were consistently downregulated compared to parent cells. Seventy-five percent of DEGs were protein-coding genes, with the rest being non-coding RNAs, such as small nucleolar RNAs, microRNAs, long non-coding RNAs, and transposable element RNAs, which conventional RNA-seq poorly detects. In principal component analysis (PCA) plots, replicates per drug resistance clustered clearly in both cell line backgrounds. PCA also indicated distinctive pathways for acquiring drug resistance in MCF7 and T47D cells. The estrogen receptor (ER) expression decreased, while HER2 increased in resistant cell lines. DEGs identified were enriched in ESR1-related pathways in all MCF7 and T47D cell lines resistant models. Several ER-regulating genes like IL-1R1 and RET were upregulated, while ADCY1 was consistently downregulated across different resistance types. A significant overlap with single-resistance DEGs was observed among the DEGs in double-resistance cell lines, but 20-50% of up/down-regulated DEGs in double-resistance cell lines were uniquely altered. Several previously identified DEGs (e.g.,

SALL4, TOP2A) and 21 novel candidate genes correlated with poor survival outcomes.

Conclusion The analysis identified unique DEGs in double resistance cell lines, suggesting that double resistance mechanisms may not merely be a cumulative effect of single resistance mechanisms, necessitating further investigation and validation. CDK4/6i and/or ET-resistant BC cell lines displayed significant transcriptome reprogramming during the development of drug resistance. In previously published research, ESR1-related pathway alterations were proposed in tamoxifen resistance cell lines. Here we find that CDK4/6i-resistant cells also modify these ESR1-related pathways. Additionally, we identified several targetable genes, such as IL-1R1 and RET, involved in ESR1-related pathways that could pave the way for developing new treatment strategies.

PO4-24-01

Comprehensive Molecular and Immunological Characterization of Invasive Ductal Triple-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

P. Advani. Mayo Clinic, United States

S. Deshmukh. Caris Life Sciences, United States

S. Wu. Caris Life Sciences, United States

J. Andring. Caris Life Sciences, United States

J. Xiu. Caris Life Sciences, United States

A. Farrell. Caris Life Sciences, United States

J. Leone. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

P. Jayachandran. University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, United States

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

M. Oberley. Caris Life Sciences, United States

G. Sledge Jr. Caris Life Sciences, United States

A. Chanan-Khan. Mayo Clinic, United States

Background: Triple-negative breast cancer (TNBC) is a heterogeneous disease and characterized by poor outcomes with a lack of targeted therapies. A comprehensive analysis of the molecular and immune landscape of invasive ductal TNBC can help improve our understanding of TNBC biology and identify novel targets and/or pathways for better management of this disease. Here, we characterized the molecular and immune signature of invasive ductal (ID) TNBC.

Methods: 13,036 BC samples (ID TNBC, n=392; ID non-TNBC, n=927) were analyzed by NGS (592, NextSeq; WES, NovaSeq), WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ). A total of 10 pro-apoptotic (BAX, BAK1, BID, BAD, BIK, BCL2L11, BMF, HRK, PMAIP1, BBC3) and 6 anti-apoptotic (BCL2, BCL2L1, BCL2L2, MCL1, BCL2A1, BCL2L10) BCL2 family genes were analyzed. Immune cell fractions were calculated by deconvolution of WTS: Quantiseq. Real world overall survival (OS) and treatment-associated survival was extracted from insurance claims and calculated from tissue collection or treatment start to last contact using Kaplan-Meier estimates. Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q < 0.05$).

Results: ID TNBC had a higher frequency of TP53, RB1, NF1, PIK3R1, NOTCH1, CREBBP, BRCA1, FANCI, and HRAS mutations (Table 1), NOTCH2 (4.3% vs 0.47%), EGFR (3.4% vs 0%), NFIB (4% vs 0.6%), MYB (3.5% vs 0.5%), CCNE1 (4.4% vs 1.1%) and AKT2 (2.4% vs 0.3%) copy number alterations, and NOTCH2 (1.6% vs 0.2%) fusion (all $p < 0.05$) compared to invasive ductal non-TNBC. Analysis of inferred immune cell infiltrates showed that ID TNBC had increased infiltration of Tregs (2% vs 1.7%), DC (3.2% vs 2.4%), CD8 T cells (0.5% vs 0.1%), and M1 macrophages (M) (3.4% vs 2.9%), but decreased infiltration of B cells (4.5% vs 6%) and M2M (2.9% vs 4.5%) (all $p < 0.05$). ID TNBC had increased T cell inflamed score (23 vs -9, $p < 0.05$), IFNy score (-0.24 vs -0.34, $p < 0.05$), MHC class I genes (HLA-A, HLA-B, TAP1, TAP2, FC: 1.1-1.5, all $p < 0.05$), immune checkpoint genes (CD274, PDCD1, CTLA4,

PD-L2, FOXP3, IDO, FC: 1.1-2, all $p < 0.05$) and PD-L1 protein expression (SP142: 49.8% vs. 28.4%; 22c3: 41.7% vs. 16.8%, all $p < 0.05$). ID TNBC had differential expression of BCL2 family genes (upregulation: BAK1, BID, MCL1, BCL2A1, BCL2L10, FC: 1.1-2.0; downregulation: BAD, BIK, BBC3, BCL2, BCL2L1, BCL2L2, FC: 1.2-2.8, all $p < 0.05$) compared to invasive ductal non-TNBC. ID TNBC was associated with worse OS compared to ID non-TNBC (mOS: 24.5 vs 54.6 months; HR: 0.5, 95% CI 0.47-0.57; $p < 0.00001$) but trend towards better survival with pembrolizumab (mOS: 29.4 vs 8.8 month; HR: 0.67, 95% CI 0.28-1.5; $p=0.3$) treatment. No significant OS difference was noted for by high vs. low pro and anti-apoptotic BCL2 genes except for anti-apoptotic BCL2A1 (higher expression associated with better OS (mOS: 5.7 months, HR: 0.78, 95% CI 0.6-0.99; $p=0.047$).

Conclusion: These data indicate that ID TNBC is associated with distinct mutational profile compared to non-TNBC, has increased T cell inflamed score, IFN γ score, MHC class I and immune checkpoint gene expression, and differential immune cell infiltration. Interestingly, TNBC was associated with increased M1 and decreased M2M. There is evidence to suggest that transcriptomically defined M1 high tumors are clinically aggressive and have worse OS in TNBC. BCL2 family genes are not prognostic for TNBC outcomes except BCL2A1, which needs further prospective validation.

Table 1: Mutation frequency in invasive ductal TNBC and invasive ductal non-TNBC

Features	Invasive ductal non-TNBC (%)	Invasive ductal TNBC (%)	Change %	p-value	q-value
PIK3CA	38.7	14.0	-24.7	2e-18	2e-16
TP53	41.4	90.0	48.6	4e-56	5e-54
GATA3	14.9	0.7	-14.2	4.8e-14	3e-12
MAP3K1	8.3	1.5	-6.8	1e-05	0.0004
KMT2C	7.3	3.3	-4.0	0.009	0.08
ESR1	5.4	0.0	-5.4	2e-06	8e-05
ARID1A	5.3	1.5	-3.8	0.002	0.03
ERBB2	3.3	0.7	-2.5	0.008	0.08
CDH1	3.0	0.7	-2.2	0.01	0.1
RB1	3.8	8.7	4.8	0.002	0.03
NF1	4.4	8.4	3.9	0.03	0.1
CBFB	2.2	0.5	-1.7	0.03	0.2
PIK3R1	2.0	4.9	2.9	0.004	0.05
CDKN1B	1.7	0.2	-1.5	0.03	0.1
SF3B1	1.5	0.2	-1.3	0.04	0.2
RUNX1	2.4	0.0	-2.4	0.008	0.08
BRCA1	1.6	4.9	3.3	0.0006	0.01
MEN1	1.1	0.0	-1.1	0.04	0.2
NOTCH1	0.8	3.2	2.4	0.01	0.08
CREBBP	0.3	3.4	3.0	3e-05	0.0007
FANCI	0.0	1.6	1.6	0.02	0.1
HRAS	0.0	1.0	1.0	0.008	0.08

Table 1: Mutation frequency in invasive ductal TNBC and invasive ductal non-TNBC

PO4-24-02

Comprehensive Characterization of BCL2 Family Genes in Metaplastic Triple Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

P. Advani. Mayo Clinic, United States

S. Deshmukh. Caris Life Sciences, United States

S. Wu. Caris Life Sciences, United States

J. Andring. Caris Life Sciences, United States

J. Xiu. Caris Life Sciences, United States

A. Farrell. Caris Life Sciences, United States

M. Radovich. Caris Life Sciences, Inc., Irving, Texas, United States

G. Sledge Jr. Caris Life Sciences, United States

D. Trapani. Dana Farber Cancer Institute, United States

E. Roussos Torres. University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, United States

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

A. Chanan-Khan. Mayo Clinic, United States

Background: Metaplastic Breast Cancer (MBC) is rare (0.2-5%), aggressive form of BC characterized by chemotherapy resistance and has worse outcomes in comparison to other BC subtypes. Resistance to chemotherapeutic agents is related to defects in intact intrinsic apoptosis pathway and the BCL2 family of proteins are the central regulators of this pathway. Majority of MBC have triple-negative receptor status and have no standard therapeutic approach and validated prognostic markers. Here, we examine the association of BCL2 family pro-apoptotic and anti-apoptotic genes expression with metaplastic TNBC (MTNBC) patient survival. Methods: 13,036 BC samples (MTNBC, n=102; metaplastic non-TNBC, n=20) were analyzed by next-generation sequencing (592, NextSeq; WES, NovaSeq), Whole Transcriptome Sequencing (WTS; NovaSeq) (Caris Life Sciences, Phoenix, AZ). A total of 10 pro-apoptotic (BAX, BAK1, BID, BAD, BIK, BCL2L11, BMF, HRK, PMAIP1, BBC3) and 6 anti-apoptotic (BCL2, BCL2L1, BCL2L2, MCL1, BCL2A1, BCL2L10) BCL2 family genes were analyzed. MTNBC with PMAIP1-high(H) and -low(L) expression was classified by top and bottom quartile, respectively. Pathway enrichment was determined by GSEA (Broad Inst). Real world overall survival (OS) was extracted from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier estimates. Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q < 0.05$). Results: MTNBC had enrichment of apoptosis (NES: 1.4, FDR: 0.05), glycolysis (NES: 1.48, FDR: 0.03), PI3K/AKT/mTOR signaling (NES: 1.43, FDR: 0.05), P53 (NES: 1.51, FDR: 0.06), NOTCH signaling (NES: 1.39, FDR: 0.05), TGF β signaling (NES: 1.41, FDR: 0.05), WNT β catenin signaling (NES: 1.41, FDR: 0.05) and IL2/STAT5 signaling (NES: 1.33, FDR: 0.09) pathways compared to metaplastic non-TNBC. MTNBC had higher expression of BCL2 pro-apoptotic genes BAX (Fold Change (FC): 1.6), BAK1 (FC: 1.3), BID (FC: 2), BAD (FC: 1.6), BCL2L11 (FC: 2.5) and BBC3 (FC: 1.5), and anti-apoptotic genes BCL2L1 (FC: 1.6) and BCL2L2 (FC: 1.3) (all $p < 0.05$) compared to metaplastic non-TNBC. Higher PMAIP1 gene expression was associated with worse MTNBC patient survival (mOS: 14.3 month; HR: 0.37;

95% CI 0.19-1.41; p=0.002) (Table 1), but not in metaplastic non-TNBC (mOS: Inf; HR: 1.96; 95% CI 0.64-6.02; p=0.23). PMAIP1-H MTNBC had higher expression of immune checkpoint genes CD274 (FC: 2.8), PDCD1 (FC: 2.2), TIM3 (FC: 1.8), LAG3 (FC: 2.1) and IDO1 (FC: 5.7) (all p < 0.05), compared to PMAIP1-L MTNBC. PMAIP1-H MTNBC had higher frequency of IHC-PD-L1 positivity (68.4% vs 14.3%, p < 0.05). PMAIP1-H MTNBC had higher expression of stem cell related genes CD44 (FC: 1.7), ALDH1A2 (FC: 2.2), ALDH1A3 (FC: 2.6), SOX2 (FC: 5.21) and NANOG (FC: 2.13) (all p < 0.05) compared to PMAIP1-L MTNBC. Conclusion: This is the first comprehensive analysis of expression and prognostic role of BCL2 family proteins in MBC. Our data suggest a strong association of higher expression of PMAIP1 with worse MTNBC patient survival, potentially attributed to higher immune checkpoint, stem cell-related genes expression, and higher frequency of PD-L1 positivity in PMAIP1-H tumors. These findings indicate PMAIP1 as a potential prognostic biomarker candidate in MTNBC but needs further validation in large prospective studies

Table 1. Overall survival of metaplastic TNBC patient based on BCL2 family gene expression.

	Gene	HR	95% CI	> Median	< Median	Δ(month)	p-value
Pro-apoptotic genes	<i>BAX</i>	0.79	(0.43-0.68)	20.05	25.38	5.33	0.44
	<i>BAK1</i>	1.12	(0.6-2.0)	25.58	22.55	3.02	0.72
	<i>BID</i>	0.59	(0.31-0.9)	20.05	25.58	5.52	0.09
	<i>BAD</i>	0.76	(0.41-0.71)	18.94	25.58	6.64	0.37
	<i>BIK</i>	0.57	(0.31-1.1)	25.91	20.05	5.85	0.09
	<i>BCL2L11</i>	0.76	(0.4-0.7)	22.55	25.58	3.02	0.37
	<i>BMF</i>	1.11	(0.63-2)	22.55	24.99	2.43	0.74
	<i>HRK</i>	0.74	(0.39-1.37)	25.38	20.05	5.33	0.33
	<i>PMAIP1</i>	0.37	(0.19-1.41)	12.23	26.60	14.37	0.002
	<i>BBC3</i>	1.00	(0.54-1.85)	24.99	21.93	3.06	0.99
Anti-apoptotic genes	<i>BCL2</i>	1.10	(0.59-2)	22.55	25.58	3.02	0.78
	<i>BCL2L1</i>	0.81	(0.43-1.52)	20.05	25.38	5.33	0.49
	<i>BCL2L2</i>	0.71	(0.38-0.74)	22.19	26.60	4.41	0.28
	<i>MCL1</i>	0.77	(0.41-1.45)	22.55	25.38	2.83	0.41
	<i>BCL2A1</i>	1.16	(0.62-2.17)	24.99	22.55	2.43	0.63
	<i>BCL2L10</i>	0.68	(0.36-1.32)	22.19	25.91	3.72	0.24

Table 1. Overall survival of metaplastic TNBC patient based on BCL2 family gene expression.

PO4-24-03

Adiponectin modulates cell polarity according to ER α expression in breast cancer cells

Presenting Author(s) and Co-Author(s):

G. Naimo. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

M. Forestiero. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

A. Paoli. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

L. Gelsomino. University of Calabria, Italy

R. Malivindi. University of Calabria, Italy

A. Leonetti. University of Calabria, Italy

F. Giordano. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

M. Panno. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

L. Mauro. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

S. Andò. Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cosenza, ITALY, Italy

INTRODUCTION: Tumor microenvironment (TME) is a complex and heterogeneous network, consisting of stromal and immune cells, embedded with cytokines, growth factors, soluble receptors, and exosomes. Mutual and dynamic crosstalk among cancer, stromal and immune cells predispose cancer cells to metastasis. Particularly, the main component of breast TME is represented by adipocytes, which secretory activity is compromised in obesity. Indeed, hypertrophic, and hyperplastic adipocytes undergo to a modified cytokines secretory pattern, characterized by a reduced secretion of Adiponectin, now recognized as a crucial factor in the pathogenesis of breast cancer. LKB1 is one the most important effector of Adiponectin transduction pathways, and recently it has been demonstrated its role as ER α coactivator in promoting breast cancer cell growth. Moreover, LKB1 is a key regulator in controlling cell polarity along with E-cadherin and Cdc42. Cell polarity has been considered essential for mammary epithelial integrity, and disruption of individual polarity proteins is sufficient to induce tumor progression. The aim of the present study was to investigate the effects of adiponectin on the regulation and alteration of cell polarity, essential for breast cancer cell growth and invasiveness.

METHODS: Immunofluorescence analyses were done to detect protein localization in breast cancer cells. Protein expression was performed by immunoblotting in the presence or absence of ER α and LKB1 siRNA. LKB1/Cdc42 and LKB1/E-cadherin interaction was detected by Proximity ligation and immunoprecipitation assay respectively. Wound healing assay was carried out to evaluate GM130 orientation. Growth and metastatic potential of breast cancer cells were assessed in vivo by orthotopic model and metastatic study respectively.

RESULTS: In Adiponectin-treated MCF-7 cells LKB1 is mostly present in the nucleus, recruited as ER α -coactivator, while in BT20 cells LKB1 is localized with E-cadherin in the cytosolic

compartment, suggesting its role in polarity. Our results showed that in MCF-7 cells Adiponectin increases Cdc42 level depending on LKB1 expression. Moreover, Cdc42 and LKB1 interact and colocalized in the nucleus of Adiponectin-treated MCF-7 cells. On the contrary, LKB1 and Cdc42 are located with E-cadherin in the cytosol of BT20 cells, addressing their cytosolic cooperation in maintaining cell polarity, as confirmed by an increased Cdc42 activity. Immunofluorescence analyses demonstrated a lack of Golgi realignment toward the front of the leading edge in MCF-7 cells treated with Adiponectin, not observed in BT20 cells. All this suggest a loss of cell polarity organization that predispose to cancer growth and progression, as confirmed by an increased tumor volume mass and a major number of lung metastatic events upon tail vein injection of adiponectin-treated ER α -positive cells with respect to untreated cells.

CONCLUSION: In ER α -positive breast cancer cells Adiponectin modulates the expression of the main proteins involved in cell polarity, leading to increased growth, progression, and distant metastasis.

PO4-24-04

Identifying the interactome of TACC3, a major driver in aggressive cancer cells with centrosome amplification

Presenting Author(s) and Co-Author(s):

O. Saatci. Medical University of South Carolina, United States

O. Akbulut. University of South Carolina, United States

M. Cetin. Medical University of South Carolina, United States

V. Sikirzhyski. University of South Carolina, United States

M. Uner. Hacettepe University, United States

D. Lengerli. Gazi University, United States

E. O'Quinn. Medical University of South Carolina, United States

M. Romeo. Medical University of South Carolina, United States

B. Caliskan. Gazi University, United States

E. Banoglu. Gazi University, United States

S. Aksoy. Hacettepe University Medical School, Ankara, Turkey, Turkey

A. Uner. Hacettepe University, United States

O. Sahin. Medical University of South Carolina, United States

Transforming Acidic Coiled-Coil Containing Protein 3 (TACC3) is a centrosome- and spindle-associated protein that drives the growth of highly aggressive tumors, such as those with centrosome amplification (CA). In recent years, it has become apparent that TACC3 not only functions at the centrosomes and spindles but may also have many other non-canonical functions facilitating the growth of tumors. Given the multifaceted roles of TACC3 in driving tumor aggressiveness, the identification of novel interactors of TACC3 that are responsible for mediating key TACC3-driven processes is crucial. This will not only uncover novel drug targets but will also expand the patient subpopulations that can benefit from TACC3 inhibition. Here, we characterized the cancer cells with CA in terms of their dependency on TACC3 for executing distinct cellular processes depending on the cell cycle phase. We demonstrated that TACC3 is strongly upregulated in cancers with CA at mRNA and protein levels and associated with worse clinical outcome in highly aggressive patient subpopulations, especially in TNBC. We further demonstrated that in mitotic cancer cells with CA, TACC3 is localized at the centrosomes in a complex with KIFC1, thus mediating the clustering of extra centrosomes to enable bipolar spindle formation and faithful mitosis. We showed that inhibiting TACC3 blocks the interaction between TACC3 and KIFC1, thus leading to mitotic cell death in the highly TACC3-dependent cancer cells with CA. While TACC3-KIFC1 complex is needed for mitotic cancer cells with CA, we found that in CA-bearing interphase cells, TACC3 interacts with HDAC2 and MBD2, the two major components of the chromatin remodeling NuRD complex within the nucleus. Inhibiting TACC3 prevented its nuclear localization, thus unloading the NuRD complex from the chromatin, leading to transcription of key tumor suppressors driving G1 arrest and apoptosis. To obtain the proteome-wide interaction network of TACC3 in these highly TACC3-dependent mitotic and interphase cancer cells with CA, we mapped the TACC3 interactome using the state-of-the-art APEX2 method. This uncovered potentially novel partners of TACC3 that could be critical for the survival of mitotic and interphase cancer cells with CA. We performed an extensive bioinformatic analysis to identify the most clinically relevant interactors in the context of cancers with CA. We generated correlation matrices of the mitotic

and interphase-specific interactors and coupled them with pathway enrichment analysis to identify the key processes that the interactors are potentially involved in. Altogether, our results map, for the first time, the novel cell cycle-dependent TACC3 interactome in cancer cells with CA. Our results support targeting this multi-functional protein and hold great promise to improve clinical outcome in these highly aggressive cancers given the availability of the first-in-class IND-approved TACC3 inhibitor.

PO4-24-05

Fluid forces and hormone levels during mammary gland development drive changes in breast epithelium that are relevant to the progression of postpartum breast cancer.

Presenting Author(s) and Co-Author(s):

M. Stibbards-Lyle. University of Calgary, Canada

K. Rinker. University of Calgary, United States

L. Hall. University of Calgary, United States

S. Badawy. University of Calgary, United States

K. Zhan. University of Calgary, United States

Postpartum breast cancer (PPBC), diagnosed in the 5-10 years after childbirth, has an elevated risk of metastasis and death. Poor outcomes are thought to be due to factors involved in mammary gland involution, an important stage of mammary gland development. Involution functions to return the mammary gland to the normal post-lactation state and involves activation of multiple processes such as inflammation, wound healing, and lymphangiogenesis.

Previously, these processes have been linked to mechanical forces induced by fluid flowing past cells, known as fluid shear stress (FSS). We and others have shown FSS impacts processes associated with lactation and breast cancer metastasis. Herein, we describe the results of a cell model for mimicking lactation and the cessation of lactation as an investigative tool for probing the mechanisms involved in PPBC development and progression. We identified changing levels of FSS as a potential physiologic biomarker through which pathways associated with the progression of PPBC could be identified.

The role of fluid shear stress in the progression of cancer remains relatively unexplored, mostly due to practical research barriers. Since FSS cannot be accurately measured *in vivo*, most research to date has relied on *in vitro* modelling. In contrast, the role of the involuting mammary gland on the progression of breast cancer has often been studied using rodent models. As a result, studying the interactions between fluid shear stress and involution poses a novel engineering challenge.

To address this problem, we developed a bioreactor cell model to enable cell exposure to fluid flow, mimicking forces experienced during lactation, in presence of lactogenic hormones (dexamethasone, insulin, prolactin). Previous work has induced FSS using parallel plate flow chambers, and induced lactation in mammary epithelial cells grown *in vitro* using lactogenic hormone treatment. To our knowledge, this is the first time these experimental conditions have been studied in combination. We established three distinct stages of treatment, consistent with the fluid shear stress and hormonal levels expected in (1) lactation, (2) cessation of lactation, and (3) involution. To determine whether the model mimicked expected *in vivo* conditions in the postpartum mammary gland, we used morphological markers and measured the protein expression of β -casein (CSN2), a milk protein that is an established marker of lactation. Each stage was validated and analyzed using proteomic and genomic sequencing. Generated datasets were further analyzed using unsupervised clustering, combining publicly available datasets with our data.

We determined that β -casein levels were highest when protein was collected after the lactation stage, followed by an initial drop-off in β -casein expression when fluid shear stress were lowered during the cessation period. The β -casein levels continued at a constant, low level during the involution period, despite a reintroduction of fluid shear stress. This suggests that

breast cancer cells are initially responsive to shear stress stimulation, consistent with what would be expected in the postpartum mammary gland in vivo. Proteomic and genomic datasets generated from cells exposed to FSS demonstrated that multiple pathways associated with metastasis are upregulated, as compared to static controls. When combined with publicly available involution datasets, pathways involved in extracellular matrix remodeling, inflammation, and lymphangiogenesis emerged. Multiple targets identified through this analysis have been previously linked to metastatic activities during breast cancer, suggesting that FSS and involution are relevant physiologic biomarkers in the context of PPBC. Work to validate hormonal and fluid shear stress conditions in combination is ongoing. Future work will use the validated model to test relevant targets identified from analysis of generated datasets.

PO4-24-06

The function of GATA3-PARP1 complex in breast cancer during GATA3-mediated cellular reprogramming

Presenting Author(s) and Co-Author(s):

M. Cooper. University of North Dakota, United States

M. Takaku. Chiba University, United States

In eukaryotic cells, genomic DNA is packaged into chromatin, a complex of DNA, histones, and other proteins. Chromatin acts as a physical barrier for many transcription factors, preventing them from efficiently binding to their recognition sequences within the nucleosome. Pioneer factors are a class of transcription factors that bind to nucleosomes and activate silent chromatin. Pioneer factors are frequently involved in various immune cell pathways, tissue development, and homeostasis, thereby, underscoring their important roles in development and disease. Previous research found that pioneer factors have at least three fundamental properties:

1. They can interact with their cognate recognition sequences before transcription activation
2. They can increase local chromatin accessibility
3. They have integral roles in lineage establishment.

However, the molecular mechanisms of pioneer factor-mediated cellular reprogramming (mesenchymal-to-epithelial transition (MET)) are largely unknown. For this study, I will use GATA3-mediated MET to study the pioneer factor-mediated cellular reprogramming.

GATA3 is a transcription factor that plays a pivotal role in mammary gland development, luminal epithelial differentiation, and cellular reprogramming. Additionally, it has been implicated in various cellular processes such as proliferation, migration, and invasion and is a critical regulator in breast cancer, including triple-negative breast cancer (TNBC). In TNBC, GATA3 expression is often downregulated, correlating with poor prognosis. Our lab and others have shown that GATA3 functions as a pioneer factor that actively changes the chromatin state from closed to open. In luminal breast cancer cells, ER-alpha and FOXA1 are well-known GATA3 co-factors. In mesenchymal breast cancer cells, GATA3 can suppress tumor metastasis by inducing MET in the absence of well-known GATA3 co-factors FOXA1 and ER-alpha1. These findings suggest that GATA3 works with additional, unknown co-factors during MET. We have been studying how GATA3 activates silent chromatin. More than 7 million GATA3 motifs exist in the human genome, yet the experimental data from GATA3 ChIP-seq analysis indicates less than 1% of the motifs are occupied by the pioneer factor, GATA3. In addition to binding selectivity, we have shown that the pioneer factor action is site-specific (context-dependent) and only induces chromatin opening and enhancer formation at a subset of binding sites. To identify a novel co-factor that is involved in GATA3-mediated MET, we performed a rapid immunoprecipitation mass spectrometry

of endogenous proteins (RIME) assay, which identified the chromatin-modification enzyme, Poly ADP-ribose polymerase 1 (PARP1), as a potential GATA3 co-factor. PARP1 is essential for gene expression regulation and initiating DNA repair. Previous studies have shown PARP1 as a co-factor to the pioneer factor, SOX2. Our genomics data strongly suggest that PARP1 is involved in such context-dependent action of GATA3.

Our overall goal is to investigate GATA3-PARP1 interaction during MET to understand the role of pioneer factors in cellular reprogramming. To do so, we are dissecting the GATA2-PARP1 function in two distinct steps:

1. Determine the function PARP1 has in the selective nucleosome binding of GATA3
2. Determine the role(s) of PARP1-GATA3 interaction in gene activation

PO4-24-07

The Impact of GPER Modulation on Cancer Associated Fibroblasts on Extracellular Matrix Formation in Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Fertal. UW-Madison, United States

B. Burkel. UW-Madison, United States

F. Murdoch. UW-Madison, United States

K. O'Leary. UW-Madison, United States

L. Schuler. UW-Madison, United States

S. Ponik. UW-Madison, United States

Background: The G-protein coupled estrogen receptor (GPER) is a noncanonical estrogen receptor (ER) that is estimated to be present in roughly 50-60% of all breast cancer (BC) subtypes. Previous studies have suggested that the presence of GPER during primary disease aids in disease progression, metastasis, as well as chemotherapy resistance due to the agonistic activity of traditional chemotherapies for ER+ BC, tamoxifen and fulvestrant. It is also well established that the extracellular matrix (ECM), specifically collagen, contributes to the overall risk and progression of BC in patients. Importantly, fibroblasts are one of the primary cell types responsible for ECM deposition in the tumor microenvironment. We hypothesize that the modulation of cancer-associated fibroblasts (CAFs) via estrogen signaling through GPER regulates the deposition and structure of key ECM proteins, such as collagen, to aid in disease progression.

Methods: CAFs, isolated from human BC surgical resections, were plated at 100% confluency, and incubated with either 10nM β -estradiol (E2), 50nM G1 (a GPER specific agonist) or a vehicle control and 50ug/mL ascorbic acid daily for 14 days to induce matrix deposition. Phenol-free, high glucose DMEM with 10% charcoal stripped FBS was used as media to reduce FBS sourced estrogen. Following the 14-day incubation, cell proliferation was quantified prior to extracting the cells to isolate the CAF-derived matrix (CDM). The organization and composition of ECM was analyzed in CDMs through immunofluorescence (IF) or western blot, respectively. An unpaired t-test was conducted on biological triplicates and between vehicle control and either G1 or E2. Significance was determined as $p < 0.05$.

Results: Culturing CAFs with E2 resulted in a 10% increase in cell proliferation ($n=3$, $p < 0.05$) and a 1.6-fold ($n=3$, $p < 0.05$) increase in total ECM deposition by western blot. Key ECM proteins such as collagen, fibronectin, and periostin had a 1.8, 1.3, and 1.3-fold increase, respectively ($n=3$, $p < 0.05$), in protein deposition with E2 treatment when normalized to cell number. Collagen fiber analysis of IF stained CDM for collagen resulted in a coefficient of alignment with E2 of 0.76 compared to 0.51 without ($n=3$ for E2 and $n=6$ for vehicle, $p < 0.05$). To confirm E2 was acting through GPER, CDMs were subsequently generated with exposure to 50nM G1, a specific GPER agonist. Collagen fiber analysis of the G1 exposed CDMs resulted in a coefficient of alignment with G1 of 0.71 compared to 0.51 without ($n=3$ for G1 and $n=6$ for vehicle, $p < 0.05$).

Conclusions: This study demonstrates that estrogen signaling through GPER modulates the deposition of fibronectin, periostin, and collagen as well as the organization of collagen

architecture. These results highlight the need to further investigate how the interplay between the ECM, GPER activity, and fibroblasts impacts breast cancer progression.

PO4-24-08

Genomic Landscape of Malignant Phyllodes Tumors Identifies Subsets for Targeted Therapy

Presenting Author(s) and Co-Author(s):

R. Bansal. Duke University, Raleigh, North Carolina, United States

T. Adeyelu. Caris Life Sciences, United States

A. Elliott. Caris Life Sciences, United States

A. Tan. Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, United States

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

M. Oberley. Caris Life Sciences, United States

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States

G. Sledge Jr. Caris Life Sciences, United States

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

L. Rosenberger. Department of Surgery, Duke University Medical Center, Durham, NC, USA, Durham, North Carolina, United States

Introduction:

Phyllodes tumors (PT) are rare fibroepithelial tumors of the breast, comprising ~1% of all breast cancers, a subset of which have considerable malignant potential. Malignant phyllodes tumors (MPTs) have aggressive biological behavior and high local and distant recurrence rates. Distant metastases of MPTs have a poor prognosis given the limited treatment options available.

Surgery remains the primary treatment modality for these patients; however, initial investigations suggest a potential for targeted therapies in managing this disease. The identification of targetable opportunities and a comprehensive understanding of the mutational profiles of MPTs could greatly enhance treatment options. Therefore, we aimed to assess the molecular landscape of these tumors.

Methods:

Phyllodes tumor samples underwent molecular profiling at Caris Life Sciences through DNA (592-gene panel or whole exome) and RNA sequencing (whole transcriptome). The MPTs were classified into primary and metastatic based on the specimen biopsy site. PD-L1+ expression was tested by IHC (SP142; $\geq 2+$, $\geq 5\%$). Tumor mutational burden (TMB)-High was defined as ≥ 10 mutation/Mb. Immune cell fractions in the tumor microenvironment (TME) were estimated using quanTIseq (Finotello, 2019). Mann-Whitney U, Chi-square, and Fisher-Exact tests were applied where appropriate.

Results:

We identified 57 analyzed MPTs, all from female patients, with a median age of 53 years (range: 19-88). Approximately half of samples (53%, n=30) were labeled as from primary breast sites, and the remaining sites were metastatic (47%, n= 27). Of metastatic sites, lung was the most common location (74.1%, n=20/27), followed by bone, sacrum, pancreas and small bowel. Alterations in MPT include TERT promoter (56.8%, n=21/37), MED12 (51.6%, n=16/31), TP53 (40.0%, n=22/55), and NF1 (31.8%, n=14/44) mutations, with less frequent mutations of EGFR (10.5%, n=6/57), PIK3CA (7.0%, n=4/57), and BRAF (3.5%, n=2/57). As compared to primary

MPT, metastatic MPT had roughly 2-fold higher prevalence of NF1 (45.5%: n=10/22 vs 18.2% n=4/22, p=0.05), KMT2D (25.9%: n=7/27 vs 10.7%: n=3/28, p=0.18), and RB1 (25.0%: n=6/24 vs 9.5%: n=2/21, p=0.25) though not significant. Multiple gene mutations were observed exclusively in lung metastases, as compared to non-lung sites including: TERT promoter (64.3%: n=9/14 vs 0.0%, p=0.08), MED12 (60.0%: n=6/10 vs 0.0%, p =0.044), and RB1 (35.3%: n=6/17 vs 0.0%, p=0.01). Conversely, NF1 (43.8%: n=7/16 vs 50.0%: n=3/6, p=1.0) and KMT2D (20.0%: n=4/20 vs 42.9%: n=3/7, p=0.32) mutation prevalence was higher in other metastatic sites. PD-L1+ expression was observed in 13.3% (n=7) of MPT overall, with similar prevalence among local and metastatic sites. No dMMR/MSI-H was observed, while low LOH (those with genomic LOH in < 16% of segment analyzed) was seen across MPT. Compared to a large cohort of breast adenocarcinoma samples (n=9,926) representing both HER2+ and HER2- tumors, MPT had low ERBB2 expression comparable to HER2- samples. B cells, M2 macrophages and neutrophils had the highest median cell fractions in the TME of MPT. Additionally, one MPT sample harbored a pathogenic NTRK1 fusion (TPM4:NTRK1), and treatment with larotrectinib for over 16 months suggests a clinical response to therapy.

Conclusions:

Our study demonstrates the importance of employing next generation sequencing (NGS) in MPTs to detect actionable genomic alterations. To effectively analyze fusions, an NGS panel that include RNA sequencing is recommended, considering the occurrence of NTRK1 fusion reported herein. Although HER2 transcriptional expression was low, further investigations examining HER2 IHC in PTs are still necessary. These finding therefore highlight the importance of NGS in phyllodes tumors research, as it may uncover potential targeted treatment options for patients.

PO4-24-09

Grape seed extract inhibits EGFR signaling pathway as a main factor of tamoxifen resistant in hormone receptor positive breast cancer

Presenting Author(s) and Co-Author(s):

S. Jung. Korea University Anam Hospital, United States

E. Lee. Korea university Anam hospital, United States

J. you. Korea university Anam hospital, United States

J. Chun. Korea university Anam hospital, United States

H. Kim. Korea university Anam hospital, United States

Purpose Because more than 60% of breast cancers are hormone-receptor (HR) positive, endocrine therapy plays an important role. Tamoxifen is an antagonist of estrogen receptor- α and main treatment drug for HR-positive breast cancers. However, efficacy is not satisfactory because of the development of resistance. EGFR expression was associated with poor prognosis in HR-positive breast cancers. Loss of ER by EGFR activation induced tamoxifen resistance. And extracellular signal-regulated kinase (ERK) is another important factor for tamoxifen resistance. Activation of ERK signaling in breast cancer is not only associated with augmented tumor growth and metastasis but also with tamoxifen resistance. Therefore, the inhibition of ERK/EGFR signaling associated with tamoxifen resistance could improve the survival rate. Grape seed extract (GSE) is which contains a high content of flavonoid polyphenolic compounds. GSE is known to have various pharmacological effects, including antioxidant, anti-inflammatory, antitumor activity. In this study, we explored the activity of GSE in tamoxifen resistant breast cancer cells by inhibiting EGFR signaling pathway. **Method** We examined the suppressive effect of GSE on various signaling pathways. To confirm the pharmacological activity of GSE, we treated EGFR positive breast cancer cells with GSE. Levels of mRNA and protein expression were analyzed by real-time PCR and western blot. And cell proliferation and invasiveness were analyzed by the colony-forming assay and the Boyden chamber assay. **Results** 1. GSE down regulates EGFR and ERK in EGFR positive breast cancer cell line. The cells were treated with the indicated concentrations GSE for 48 hrs. The levels of p- and t-ERK and t-EGFR were measured through Western blotting. The levels of phosphorylated EGFR and ERK were decreased by GSE at the indicated doses for 48hrs. 2. EGF, a ligand of EGFR, upregulates the MMP-9 and GSE suppresses MMP-9. Matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) are upregulated in most cancers and play crucial roles in modulating invasion and metastasis. EGFR with its ligand epidermal growth factor (EGF) regulates Matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9). After treating EGFR positive breast cancer cells with EGF and TGF, MMP-9 levels were increased. However, MMP-9 level was decreased with GSE as indicated doses for 48hrs. **Conclusion** Taken together, GSE inhibited the ERK/EGFR and EGF/MMP-9 signaling pathway in EGFR positive breast cancer cells. Therefore, we propose the possibility of GSE as an effective adjuvant for tamoxifen resistant breast cancer.

PO4-24-10

Prognostic role of SOX2 and STAT3 expression on circulating T lymphocytes and CD44⁺/CD24^{neg} cells in the locally advanced and metastatic breast cancer

Presenting Author(s) and Co-Author(s):

D. Viana. Hospital de Cancer de Pernambuco - HCP, Recife, Brazil, Pernambuco, Brazil

V. Andrade. A.C.Camargo Cancer Center, São Paulo, Brazil, São Paulo, Pernambuco, Brazil

M. Salgado. Hospital de Câncer de Pernambuco - HCP, Recife, Brazil, Pernambuco, Brazil

C. Vasconcelos. Hospital de Cancer de Pernambuco - HCP, Recife, Brazil, Recife, Pernambuco, Brazil

L. Torres. Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, Brazil; Hospital de Cancer de Pernambuco (HCP), Recife, Brazil; Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil, Recife, Pernambuco, Brazil

Introduction: Breast cancer (BC) is associated with a continuous increase in incidence, with high mortality rates in several countries. There are four immunophenotypes of BC, luminal A, luminal B, triple negative (TN), and HER2+. Some proteins in tumor cells and the tumor microenvironment are part of tumorigenesis and metastases. The CD44 molecule is considered an important marker of the inflammatory response. CD44 is present in all leukocytes and on the surface of tumor stem cells, involving tumor invasion and metastasis. Some authors have demonstrated that the signal transducer and activator of transcription 3 (STAT3) and sex-determining region Y-related group box 2 (SOX2) are related to the regulation of somatic cell division and tumorigenesis and metastasis in BC. Aim: To evaluate SOX2 and STAT3 expression on circulating T lymphocytes and CD44⁺/CD24^{neg} cells in locally advanced and metastatic breast cancer. Methods: A cross-sectional study was conducted at the Hospital de Cancer de Pernambuco (HCP) and the Translational Research Laboratory of the Instituto de Medicina Integral Prof. Fernando Figueira (IMIP) from March 2017 to April 2018. Sixty-five women diagnosed with breast cancer participated in this study, aged between 28 and 64. Of these, 51 women had stage III (locally advanced) breast tumors, and 14 with metastatic disease (stage IV). There were 24 healthy women aged 18 to 65 as a control group. The analysis of CD44, SOX2, and STAT3 expression was performed by flow cytometry. Results: elevated levels of CD44⁺/CD24^{neg} cells and CD44⁺/CD24^{neg}/SOX2⁺ cells were observed in the blood of BC patients with luminal B, HER2+, and TN compared to the control group (p < 0.0001). Low CD44⁺/CD24^{neg}/STAT3⁺ levels in the patient's blood compared to the control group. Elevated CD44⁺/CD24^{neg} and CD44⁺/CD24^{neg}/STAT3⁺ cells were observed in locally advanced BC compared to metastatic group (p < 0.05). Patients with TNBC had elevated SOX2⁺T lymphocyte levels compared to luminal B and HER2+ subtypes groups (p < 0.05). HER2+ patients had low levels of T lymphocytes and SOX2⁺T cells compared to controls and luminal A groups (p < 0.05). High levels of total T cells (p=0.0007) and low SOX2⁺T lymphocytes (p=0.02) in locally advanced compared to metastatic disease (stage IV). Elevated levels of SOX2⁺T lymphocytes in patients with negative lymph nodes (N0) compared to N1 and N2 groups (p=0.004 and p < 0.0001, respectively). High levels of CD44⁺/CD24^{neg}STAT3⁺ cells and T lymphocytes and low levels of STAT3⁺T lymphocytes in locally advanced TN subtype (stage III) compared to metastatic (stage IV). Conclusion: SOX2 and STAT3 expression on circulating T lymphocytes and CD44⁺/CD24^{neg} cells in peripheral blood are prognostic roles in breast cancer. SOX2 and STAT3 expression are potential predictive biomarkers of disease

progression in breast cancer regardless of tumor subtype. Investigating these biomarkers in peripheral blood has some advantages because peripheral blood collection is less invasive, easy to access, and allows evaluation at diagnosis, during treatment, and in cases of recurrence.

PO4-24-12

Premenopausal breast cancers show higher proportion of immunologically cold tumors and are associated with distinct immune cell infiltrate

Presenting Author(s) and Co-Author(s):

V. Nimbalkar. St.John's Research Institute,Bangalore, United States

S. VP. St.John's Research Institute,Bangalore, United States

S. Rajarajan. St.John's Research Institute,Bangalore, C.V.Raman Nagar, Bangalore, Karnataka, India

A. Alexander. St John's Research Institute, Karnataka, India

R. Ramesh. St. John's Medical college and hospital, Karnataka, India

B. Srinath. Sri Shankara Cancer Hospital and Research Center, United States

J. Prabhu. St.John's Research Institute,Bangalore, United States

Background

Breast cancers (BC) in the young women tend to have poor outcomes and higher proportion of aggressive subtypes. Immunotherapy has shown promising results lately, especially for aggressive categories like triple negative breast cancers (TNBC). Success of the immunotherapy is shown to be dependent on the tumor immune microenvironment (TIME) which plays important role in disease progression and response to therapy. Though numerous studies have demonstrated immune hot tumors are associated with better prognosis, mechanism of immunologically hot TIME is not yet deciphered.

Material and methods

Gene expression data derived from RNA sequencing (n=40) of primary BC was used to divide them into immune hot and cold tumors by using 15 gene signature (Wang et al., Sci. Adv. 2021). Average expression of the hot and cold (hot=12 and cold=3) genes was derived for each tumor and median value of their ratio was used to categorize them into immunologically hot and cold tumors. Association of the hot and cold tumors with clinical characteristics was examined. CIBERSORT algorithm was used to identify immune cell subtypes and Kaplan Meier survival analysis was performed to assess the prognostic significance. Similar analysis was replicated in TCGA (n=1083) dataset.

Results

Equal proportion of immune hot and cold tumor was observed in the cohort. Higher proportion of cold tumors were observed in younger and premenopausal (p=0.002) patients. Subtype analysis showed higher proportion of cold tumors in TNBC compared to hormone receptor positive tumors (p< 0.0001). No significant difference was observed in other clinicopathological characteristics between the groups. Further analysis of cold tumors for immune cell subtypes, categorized by the menopausal status showed higher proportion of plasma cells and CD4 memory resting cells and lower proportion of M2 macrophages and B memory cell in premenopausal (n=129, TCGA) compared postmenopausal (n=322, TCGA) tumors. In addition, premenopausal cold tumors were associated with better overall survival compared to postmenopausal group (p=0.001).

Conclusion

Younger premenopausal women with BC are likely to have more immunologically cold tumors. Though circulating levels of sex steroid hormones is the predominant difference between the

pre and postmenopausal women, its influence on TIME and therapeutic significance must be explored.

PO4-25-01

Selective elimination of CD169+ macrophages in lymph nodes invaded by breast cancers

Presenting Author(s) and Co-Author(s):

Y. Maeshima. Department of Breast Surgery, Kyoto University Hospital, Graduate School of Medicine, United States

T. Kataoka. Department of Pathology, Iwate Medical University, United States

A. Vandenberg. Institute for Life and Medical Sciences, Kyoto University, United States

M. Hirata. Kyoto University Hospital, Japan

Y. Takeuchi. Kyoto University, Japan

Y. Suzuki. Graduate School of Frontier Science, The University of Tokyo, United States

Y. Fukui. Department of Breast Surgery, Kyoto University Hospital, Graduate School of Medicine, Kyoto, Japan

Y. Ibi. Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, United States

H. Haga. Kyoto University Graduate School of Medicine, Kyoto, Kyoto, Japan

S. Morita. Kyoto University Graduate School of Medicine, Kyoto, Kyoto, Japan

M. Toi. Graduate School of Medicine, Kyoto University, Kyoto, Japan

S. Kawaoka. Inter-Organ Communication Research Team, Institute for Frontier Life and Medical Sciences, Kyoto University, United States

K. Kawaguchi. Department of Breast surgery, Kyoto University Hospital, United States

Lymph node metastasis is a prognostically significant factor in breast cancer, though the colonization mechanism of cancer cells in this immune cell-rich organ remains elusive. This study aimed to elucidate the impact of breast cancer on the lymph node immune cell landscape. Multiscale transcriptomic analyses were performed on both metastatic and non-metastatic lymph node samples from breast cancer patients with lymph node metastasis. Twenty laser-micro-dissected sections were obtained from 17 lymph nodes across six breast cancer patients at stages II–III, with each patient contributing both types of lymph nodes for direct comparison.

Comparing the transcriptomes of paired lymph nodes with and without metastasis from the same patients revealed selective downregulation of CD169+ macrophage-related genes in metastatic lymph nodes. The spatial transcriptome indicated a potential depletion of CD169+ macrophages, initiators of anticancer immunity, from their residence (sinuses) in metastatic lymph nodes, while other principal immune cell types were unaltered. Mass spectrometry imaging revealed that the numbers of CD169+ macrophages were smaller in the metastatic lymph nodes than in the non-metastatic lymph nodes, suggesting that cancer cells uprooted CD169+ macrophages from the lymph nodes. Conversely, the count of B, T, Treg, and CD11c+ cells remained comparable in both lymph node types, albeit an enrichment of Treg cells around metastasized cancer tissues was observed. Additional immunohistochemistry analysis of 315 non-metastatic lymph nodes and 159 metastatic lymph nodes from 58 patients with breast cancer showed that a reduced CD169+ macrophage population was prevalent in various breast cancer subtypes. A subset of metastatic lymph nodes (37 out of 159) displayed a complete absence of detectable CD169+ macrophages. The data also depicted a gradual decline in CD169+ macrophages correlating with the pN classification, while no correlation was identified with pathological tumor size classification (pT) or metastasized cancer volume. The data

suggest precedence of CD169+ macrophage elimination over other reported immune cell abnormalities, such as cell number and metabolic irregularities. CD169+ macrophages are a unique type of resident macrophages in the lymphoid organs that present cancer-derived antigens to CD8+ cells. The antigen-presenting role of CD169+ macrophages to T cells, a pivotal step in adaptive immunity, signifies the catastrophic implications of their suppression. This study underscores CD169+ macrophage suppression as a pronounced pathological phenotype in lymph nodes with breast cancer metastasis, thereby establishing it as a critical future therapeutic target.

PO4-25-02

Long-range Deployment of Tumor-antigen Specific Cytotoxic T Lymphocytes Inhibits Lung Metastasis of Breast Cancer

Presenting Author(s) and Co-Author(s):

Y. Xing. Sun Yat-Sen Memorial Hospital, United States

S. Su. Sun Yat-Sen Memorial Hospital, United States

E. Song. Breast Tumour Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, United States

Effector Immune Cell Deployment (EICD) refers to systemic deployment of anti-tumor effector immune cells in cancer patients, including the priming, circulation, trafficking, activity and fate of the immunocytes, and is a panorama to reflect the generation, distribution and development of anti-tumor immunity. Tumor antigen-specific T cells are the main component of effector immune cells in anti-tumor immune responses, but their systemic deployment in breast cancer patients and the underlying mechanisms remain largely unknown. Here, we identified a cluster of CD8⁺ T cell exhibiting tissue-resident memory (T_{RM}) phenotype in the tumor-draining lymph nodes (TDLNs) of 487 breast cancer patients, whose abundance specifically predicts improved lung, but not other target organ metastasis-free survival. Also, high lung CD8⁺ T_{RM} infiltration is associated with lower metastatic burden in breast cancer patients. Using single-cell RNA sequencing, we observed that in multiple mouse cancer models, CD8⁺T_{RM} accumulate at early tumor stages when lung metastasis was not identified. Functionally, the CD8⁺T_{RM} isolated from pre-metastatic lungs of the animals were tumor antigen specific and cytotoxic to the tumor cells. Nevertheless, the abundance of CD8⁺T_{RM} in the lungs were dramatically decreased in the lungs upon metastasis establishment. Moreover, in Cd8^{cre/+} Itgae^{loxp/+}-diphtheria toxin receptor conditional knockout mice, we unambiguously demonstrated that specific depletion of the CD8⁺ T_{RM} subset facilitates lung metastasis in vivo, while adoptive transfer of CD8⁺ T_{RM} successfully inhibited lung metastasis and prolonged survival of the mice. Mechanistically, using cell-tracing techniques in the photo-convertible Kaede-Tg mice, we found that tumor-specific CD8⁺ T_{RM} were generated in the TDLNs of the mice and were recruited to the lungs via CCL25/ CCR9 signaling axis. However, the circulating exosomes secreted by primary tumor cells were taken up by alveolar macrophages and polarized them to release IDO1 and impaired anti-tumor T cell immunity, facilitating lung metastasis. More importantly, inhibition of IDO1 effectively retrieves T_{RM}-mediated protection against lung metastasis. Collectively, we have revealed a cross-talk between tumor cells and the inflammatory environment of distant organs, which could drive lung metastasis by impairing EICD. Our findings also highlight the therapeutic potential of orchestrating EICD in turning “cold” metastatic tumor foci to “hot” ones.

PO4-25-03

Comprehensive immune profiling reveals factors associated with neoadjuvant chemotherapy response in triple negative breast cancer

Presenting Author(s) and Co-Author(s):

R. Seager. Omniseg, United States
H. Ko. Labcorp Oncology, United States
S. Pabla. Omniseg, United States
M. Senosain. Omniseg (Labcorp Oncology), United States
P. Kalinski. Roswell Park Comprehensive Cancer Center, United States
E. Van Roey. Omniseg (Labcorp Oncology), United States
S. Gao. Labcorp, Buffalo, New York, United States
K. Strickland. Labcorp Oncology, United States
R. Previs. Labcorp Oncology, United States
M. Nesline. Labcorp Oncology, United States
S. Hastings. Labcorp Oncology, United States
S. Zhang. Labcorp Oncology, United States
J. Conroy. OmniSeq, Inc., Buffalo, New York, United States
T. Jensen. Labcorp Oncology, United States
M. Eisenberg. Labcorp, United States
B. Caveney. Labcorp, United States
E. Severson. Labcorp Oncology, United States
S. Ramkissoon. Labcorp Oncology, United States
S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

Background: KEYNOTE-522 has resulted in FDA approval of the immune checkpoint blocker pembrolizumab with neoadjuvant chemotherapy for patients with high-risk triple negative breast cancer (TNBC), given the remarkable improvement in pCR rate to 65% along with improvement in event free survival, while with chemotherapy alone, the pCR rate is 40-50%. Unfortunately, use of pembrolizumab is associated with several immune related adverse events (irAE), some of which can be life-threatening and debilitating, including cardiomyositis, encephalitis, and adrenal insufficiency, among others. Hence, there is an unmet need to identify biomarkers in the tumor microenvironment which could predict patients who may attain pCR with chemotherapy alone and be spared the side effects from the added PD-1 inhibition. Methods: Comprehensive immune profiling, including PD-L1 IHC and the expression of 395 immune genes by RNA-seq, was performed on 1:2 matched FFPE tumor samples from 23 stage 1-3 TNBC patients (2 stage 1, 6 stage 2, 15 stage 3). All patients were female with an average age of 48 years (range: 25-79 years). 14 patients were treated with neoadjuvant chemotherapy alone (NAC) and 9 were treated with neoadjuvant chemotherapy combined with the checkpoint inhibitor pembrolizumab (NAC+I). mRNA expression signatures of tumor inflammation (TIGS, weak/moderate/strong), cell proliferation (CP, poor/moderate/high), and cancer testis antigen expression burden (CTAB) were determined by RNA-sequencing. Statistical comparisons of quantitative biomarkers between groups were calculated using the Wilcoxon Rank-Sum test, overrepresentation analysis of categorical variables between groups was calculated by

proportions test, and survival differences were quantified by Cox proportional hazards analysis. Pathological responses were documented as pathological complete response (pCR) vs. non-pCR. Results: Across the entire cohort, patients with a BMI < 30 had significantly higher PD-L1 expression (assessed by RNA) than those with a BMI \geq 30 [$p=0.047$]. While not a statistically significant association, the NAC+I group tended to have a higher pCR rate compared to the NAC group [44.4% vs. 28.6%, $p=0.66$]. Across the entire cohort, tumors with high CTA expression, designated as CTAB high, had a higher pCR rate than CTAB low tumors [54.5% vs 16.7%, $p=0.089$]. No significant difference in pCR rate between TIGS or CP groups was detected for the NAC group, but in the NAC+I group, highly proliferative tumors had a lower pCR rate than moderately proliferative tumors [0% vs. 80%, $p=0.048$]. The pCR and non-pCR groups for each treatment type also exhibited distinct gene expression profiles. Among the NAC group, underexpression of FOXP3 and overexpression of MAPK14 and CD44 were associated with pCR [$p\leq 0.031$], while underexpression of IFNB1, MAPK14, and CD44 was associated with non-pCR [$p\leq 0.029$]. Among the NAC+I group, overexpression of CXCR4, TNFR and CCL20 was associated with non-pCR [$p\leq 0.046$]. Interestingly, SDHA was significantly overexpressed in the non-pCR subset of patients in the NAC group and significantly underexpressed in the non-pCR subset of patients in the NAC+I group [$p\leq 0.031$]. Conclusions: The development of biomarkers of treatment response is essential to the integration of immunotherapy with chemotherapy as a combined cancer treatment. Our study profiled the immune context of both NAC and NAC+I and identified several key microenvironmental differences underlying divergent treatment response in both groups. A comprehensive understanding of these factors could potentially predict pCR to chemotherapy alone, enabling the avoidance of the unnecessary treatment of these tumors with immunotherapy.

PO4-25-04

MHC Class I and II Expression, Functional Tertiary Lymphoid Structure (TLS), and Outcomes in Early-Stage HER2-Positive (HER2+) Breast Cancer in NCCTG N9831 (Alliance)

Presenting Author(s) and Co-Author(s):

S. Chumsri. Mayo Clinic, Jacksonville, Jacksonville, Florida, United States

T. Shachner. Mayo Clinic, United States

Z. Li. Mayo Clinic, Jacksonville, United States

N. Norton. Mayo Clinic, United States

A. Moreno-Aspitia. Mayo Clinic, Jacksonville, Florida, United States

G. Colon-Otero. Mayo Clinic, United States

E. Perez. Mayo, United States

A. Nassar. Mayo Clinic, United States

E. Thompson. Mayo Clinic, United States

K. Knutson. Mayo Clinic, United States

Background: Tertiary lymphoid structure (TLS) is an organized form of ectopic lymphoid aggregates (LA) with secondary lymphoid organ structure. Several studies showed that the presence of TLS associates with improved outcomes in multiple cancers when treated with immune checkpoint inhibitors. However, data is currently limited regarding TLS and outcomes in HER2+ breast cancer patients (pts) treated with adjuvant trastuzumab. Furthermore, distinguishing TLS and simple LA is challenging in standard hematoxylin and eosin (H&E) staining, particularly when the germinal center is absent. Emerging studies also showed the prognostic value of MHC expression in breast cancer but mainly in triple-negative breast cancer. In this study, we evaluated integrated pathological quantification and genomic data to assess functional TLS in association with MHC expression and outcomes in the N9831 trial.

Methods: Pathological evaluation of LA in H&E slides from pts treated in Arm A (chemotherapy alone) and Arm C (chemotherapy with concurrent trastuzumab) in N9831 was performed. NanoString was used to quantify mRNA of MHC class I and II expression as well as TLS-related immune genes, including IFNG, ICOSLG, CXCL13, CXCR3, BCL6, IL21R, ICOS, PDCD1, CXCR5, CXCL9, TBX21, CD38, CXCL10, CLXCL11, IL21, CD200, CD19, MS4S1. Wilcoxon rank sum test, Chi-squared test, Kaplan-Meier method, and Cox regression model were used to evaluate the association between LA and baseline characteristics, MHC expression, and outcomes.

Results: LA was evaluated in 526 pts in Arm A and 485 in Arm C. Greater number of LA was significantly associated with stromal tumor-infiltrating lymphocytes (sTILs), hormone receptor negative, and higher tumor grade, but not stage and age. Using multivariable Cox regression analysis, increasing numbers of LA were associated with improved recurrence-free survival in both arms combined (RFS, p 0.028). However, when evaluating each arm separately, LA was associated with improved RFS only in Arm A (HR 0.6, 95%CI 0.43-0.84, p 0.003) but not in Arm C (HR 0.72, 95%CI 0.47-1.1, p 0.134). We further evaluated TLS-related immune genes in 252 pts in Arm C with LA ≥ 1 . As a continuous variable, higher expression of BCL6 (HR 0.61, 95%CI 0.41-0.92, p 0.019) and IL21R (HR 0.78, 95%CI 0.62-0.98, p 0.03) were associated with improved RFS in Arm C pts with LA ≥ 1 . However, these genes were not significantly

associated with outcomes in Arm C pts without LA with BCL6 (HR1.07, 95%CI 0.67-1.71, p 0.776) and IL21R (HR 0.96, 95%CI 0.71-1.29, p 0.775). Moreover, we evaluated differential gene expression between tumors with LA \geq 1 with high BCL6 vs. LA 0. All MHC class I and II (HLA A, B, C, E, DQ, DM, DO, DP, and DQ) were significantly higher in tumors with LA \geq 1 with high BCL6 (p < 0.001).

Conclusion: A greater number of LA was associated with improved outcomes in pts with early-stage HER2+ breast cancer, particularly when treated with chemotherapy alone. Using histologic and genomic integration with the combination of pathological LA and TLS-related immune genes, we identified that pts with functional TLS with LA \geq 1 and higher expression of BCL6 or IL21R had significantly improved outcomes when treated with trastuzumab. High MHC class I and II expressions are associated with the presence of functional TLS, underscoring the crucial role of antigen presentation in the generation of an effective adaptive immune response.

Support: U10 CA180821, U10 CA180882, U24 CA196171,
<https://acknowledgments.alliancefound.org>; Genentech; Clinicaltrials.gov Id: NCT00005970

PO4-25-05

LYVE-1 expressing macrophages modulate the extracellular matrix and contribute to mammary tumor growth

Presenting Author(s) and Co-Author(s):

A. Elfstrum. University of Minnesota, United States

A. Rumahorbo. University of Minnesota, United States

B. McCluskey. Minnesota Supercomputing Institute, University of Minnesota, United States

E. Nelson. University of Minnesota, United States

K. Schwertfeger. University of Minnesota, United States

Macrophages represent a heterogeneous myeloid population with varied functions in normal tissue and tumors. We identify a tissue resident macrophage subpopulation marked by the protein LYVE-1 in both the female mammary gland and mammary tumor. In a genetic LYVE-1⁺ macrophage deletion model, loss of LYVE-1⁺ macrophage leads to accumulation of the extracellular matrix glycosaminoglycan hyaluronan. Further, qRT-PCR of tissue lacking LYVE-1⁺ macrophages yields a gene signature associated with extracellular matrix disorganization. Supporting a tissue remodeling functionality, inducing a LYVE-1 macrophages phenotype in vitro prompts HA internalization and increases hyaluronidase expression. In a murine tumor model, deletion of LYVE-1⁺ macrophages slows tumor progression and increases HA accumulation, suggesting an anti-tumorigenic, tissue remodeling phenotype. LYVE-1⁺ macrophages preferentially localize to HA dense regions of tumors, specifically in the tumor stroma, while scRNA-seq of murine tumors demonstrates a LYVE-1⁺ macrophage phenotype associated with tissue remodeling and immunosuppression. Our data illustrate a LYVE-1⁺ macrophage population critical for HA homeostasis and tumor progression.

PO4-25-06

SerMa (Seroma of the Mammary gland) pilot - Is there a possible link between macrophage-based immune response and age?

Presenting Author(s) and Co-Author(s):

M. Koepke. University Hospital Augsburg, United States

F. Schneider. University Hospital Augsburg, Germany, United States

C. Kuhn. Department of Gynaecology and Obstetrics, University Hospital Augsburg, Germany, United States

M. Wild. Department of Gynaecology and Obstetrics, Data Management and Clinical Decision Support, University Hospital Augsburg, Germany, United States

M. Schneider. Department of Gynaecology and Obstetrics, University Hospital Augsburg, Germany, United States

N. Pochert. Department of Gynaecology and Obstetrics, Department of Environmental Medicine, University of Augsburg, Germany, United States

C. Traidl-Hoffmann. Department of Environmental Medicine, University of Augsburg, Germany, United States

J. Sagasser. Department of Obstetrics and Gynecology, University Hospital of Augsburg, Augsburg, Germany, Germany

C. Dannecker. Department of Gynaecology and Obstetrics, University Hospital Augsburg, Germany, United States

C. Hinske. Data Management and Clinical Decision Support, University Hospital Augsburg, Germany, United States

M. Banys-Paluchowski. Department of Obstetrics and Gynecology, Asklepios Hospital Barmbek, Hamburg, Germany

M. Untch. AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany, Berlin, United States

T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany

U. Jeschke. University Hospital Augsburg, United States

N. Ditsch. Department of Gynaecology and Obstetrics, University Hospital Augsburg, Augsburg, Germany

Background

The primary objective of the SerMa pilot study was to identify possible immunological or inflammatory factors related to seroma formation after mastectomy in cases with primary breast cancer.

Preliminary data suggest a distinct association between age and seroma formation. The work presented here investigates therefore a possible link between age and differences in the microenvironment represented by tumor-associated macrophages. The latter have been characterized by the expression of CD68 and CD163 receptors, that are markers of cells from the monocyte/macrophage lineage with known clinical implications.

Methods

Tumor tissue of 80 primary breast cancer cases of the SerMa pilot study was available for further analyses. Immunohistochemistry based on antibody staining against CD68 and CD163 was used and due to the mean age of 63 years two groups were formed and compared:

patients aged under 63 and patients aged 63 and older. The number of macrophages (standardized manually quantified) was compared in these two groups regarding seroma formation.

Results

Seroma formation occurred significantly more frequently with older age of the patient ($p < 0.001$). For the overall cohort, the number of CD68-positive macrophages was significantly increased ($p=0.036$) in patients with seroma formation, as well as for CD163 ($p=0.027$). The macrophage polarization was shown to be independent of tumor biological characteristics ($p > 0.130$). However, closer examination revealed an age-dependent effect of the macrophage polarization. In the group 63 years and older, there was no significant difference in the number of CD68- or CD163-positive macrophages ($p = 0.610$ and $p = 0.425$, respectively) in relation to seroma formation. A significant effect was seen in this analysis only in patients younger than 63 regarding CD163 ($p < 0.001$) and a non-significant trend for CD68 ($p = 0.065$).

Conclusions

These data demonstrate an age-dependent significant correlation of CD163 positive macrophages measured in the tumor environment with seroma formation in the breast after mastectomy. For CD68 positive macrophages a trend was seen, but didn't reach statistical significance due to the small number of cases. These data show a different immunological response in tumor tissue depending on age and therefore support the thesis that seroma formation is primarily related to immunological/inflammatory processes. In the future, detection of CD163-positive macrophages in the tumor microenvironment could therefore be considered a marker for patients under 63 years at increased risk of seroma.

The planned international SerMa study (EUBREAST 5) will have to show whether these results can be transferred to a prospective design with higher case number.

PO4-25-08

Secretory breast carcinoma (SBC) in an 8-year-old male: Report of an exceptionally rare case with review of clinicoradiologic and pathomolecular findings of SBC in the male pediatric population

Presenting Author(s) and Co-Author(s):

R. Brassington. University of Alberta, Edmonton, Alberta, Canada

S. Silverman. Misericordia Community Hospital & University of Alberta, Edmonton, Alberta, Canada

I. Bratu. Stollery Children's Hospital & University of Alberta, Edmonton, Alberta, Canada

Secretory breast carcinoma (SBC) is a rare and distinct disease, comprising approximately 0.01% of all breast carcinomas. This is a case of an 8-year-old boy who presented with a 1.5-year history of a non-tender, slowly enlarging left subareolar mass, not associated with nipple discharge. Serologic workup revealed minimally elevated prolactin with normal-range FSH, LH, estradiol and testosterone, as well as normal-range beta-hCG, LDH and AFP. Ultrasound showed a circumscribed solid hypoechoic lesion with internal arterial vascularity, favoured to represent a sebaceous cyst. Excisional biopsy was performed, and histologic examination revealed the classic intra- and extracellular secretory material typically seen in SBC. Immunohistochemical (IHC) stains for mammaglobin, S-100 and high molecular weight keratin (CK5) were positive. ER was positive, though not strong staining, and PR and HER2 were negative. A screen for NTRK fusions with pan-TRK IHC was positive. No skin, perineural or lymphovascular invasion was identified. RNA-based NGS demonstrated ETV6-NTRK3 fusion and confirmed the diagnosis of SBC. The patient underwent mastectomy and SLNB, which showed no residual tumor and no positive lymph nodes. A full metastatic work-up was not performed and the patient did not receive neoadjuvant therapy.

First described as "juvenile breast carcinoma," SBC has since been recognized to occur across a wide age range, with most cases occurring in adults. SBC in male pediatric patients is exceptionally rare, with fewer than 20 cases reported in the literature. In this demographic, SBC is usually detected clinically as a subareolar mass not associated with nipple discharge, and appears as a well-circumscribed mass on imaging, mimicking benign entities. SBC is usually detected at a low stage, treated surgically, and follows a clinically indolent course with excellent outcomes. Positive axillary nodes have been identified in a few male children, who subsequently underwent chemo- and/or radiotherapy, with no recorded recurrences in these cases. Distant metastases are an extremely uncommon feature of SBC and have not been reported in the pediatric male population; however, due to the rarity of this diagnosis, particularly in this demographic, robust long-term follow-up data are still lacking.

The name "secretory" derives from the histologic appearance of the dense eosinophilic secretory material seen in tumor lumina and bubbly material in the cytoplasm of tumor cells. Similar to the cytologic characteristics of other translocation-driven neoplasms, SBC shows minimal pleomorphism. Mitoses are absent or rare. IHC stains are typically positive for S-100 and high molecular weight keratins and negative for ER, PR, and HER2. Despite the immunophenotypic similarities to triple negative / basal-like carcinomas (TNBC/BLC) the molecular relationship between SBC and TNBC/BLC is unclear. Though initially defined by its distinctive secretions on histology, SBC is now chiefly characterized by a balanced translocation, t(12;15)(p13;q25), resulting in oncogenic ETV6-NTRK3 fusion. Recent cases have demonstrated this using a variety of molecular techniques, including FISH, RT-PCR, and

in our case, RNA-based NGS. This translocation also characterizes non-breast secretory carcinomas and has been identified in several other neoplasms, including pediatric mesenchymal tumours and adult acute myeloid leukemia.

The rarity of SBC, particularly in the male pediatric population, underlines the necessity of this case report. Additionally, this case highlights the importance of considering SBC as a potential diagnosis in male children presenting with a breast mass, even in the presence of benign imaging characteristics.

Table 1: Clinicoradiologic and pathomolecular characteristics of SBC in pediatric males

Author	Year	Age (y)	Symptom Duration	Laterality / Site	Nipple Discharge	Size (cm)	Node Status	Surgical Treatment	CT / RT	Distant Metastases / Recurrences	ER / PR status	NRXN / Fusion	Follow-up
Simpson	1969	5	nd	nd	-	nd	nd	LE	-/-	-/-	nd	nd	NED 4y
Tavassoli	1980	9	nd	nd	nd	nd	nd	LE	-/-	-/-	nd	nd	NED 1.75y
Karl	1985	3.5	1mo	L/SA	-	1.5	+(1/4)	SM AND	-/-	-/-	nd	nd	nd
Serour	1982	17	4y	L/PA	-	2	-	WLE AND	+/-	-/-	+/-	nd	NED 5y
Chevallier	1999	9	14mo	L/RA	nd	2.0	-	LE AND	-/-	nd	-/-	nd	NED 46mo
Yildirim	1999	11	1y	R/PA	-	1.5	+(1/18)	MRM	+/-	-/-	-/nd	nd	NED 12mo
Bhagwanram & Titas	1996-2000	9	1mo	R/PA	nd	1.2	-	MRM	-/-	-/-	-/-	nd	NED 20mo
de Bree	2001	17	2y	R/SA	-	3.0	-	MRM	-/-	-/-	-/-	nd	NED 6mo
Kavakuz	2004	17	6mo	R/SA	nd	6.0	+(10/12)	MRM	+/-	+/- (B m)	-/nd	nd	NED 13mo
Scatini	2004	7.5	6mo	R/SA	-	1.7	-	RM SLNB	-/-	-/-	-/-	nd	NED 7mo
Cabello	2011	13	4y	R/SA	-	1.5	+(1/28)	SM AND	+/-	-/-	-/-	nd	NED 10y
Li	2012	10	0.5mo	R/SA	nd	2.0	-	MRM	-/-	-/-	-/-	nd	NED 1y
Dong	2013	15	8y	L/nd	-	1.5	-	SM AND	nd	nd	-/-	nd	nd
Mera	2016	8	10mo	R/RA	-	1.8	-	LE, SM, SLNB	-/-	nd	+/-	+ FISH	NED 3y
Chill	2018	6	nd	L/RA	-	1.0	-	WLE, SLNB	-/-	-/-	-/-	+ PCR	NED 46mo
Klippel	2020	14	5y	L/RA	+	3.5	-	LE, SM, SLNB	-/-	-/-	+/-	nd	NED 16mo
Chen	2022	7	nd	R/nd	nd	2.1	-	SM AND	-/-	-/+	-/-	+ FISH	LN met 5y
This case	2023	8	1.5 y	L/PA	-	0.9	-	LE, SM, SLNB	-/-	-/nd	+/-	+ NGS	NED 2mo

AND, axillary node dissection; CT, chemotherapy; ER, estrogen receptor; FISH, fluorescence in situ hybridization; LE, local excision; MRM, modified radical mastectomy; nd, no data; NED, no evidence of disease; NGS, next-generation sequencing; NS, nodal sampling; PA, periareolar; PR, progesterone receptor; RA, retroareolar; RM, radical mastectomy; PCR, polymerase chain reaction; RT, radiotherapy; SA, subareolar; SLNB, sentinel lymph node biopsy; SM, simple mastectomy; WLE, wide local excision

*Not reported as strong staining

Table 2: Immunohistochemical phenotype of secretory breast carcinoma

Markers	ER	PR	HER2	Mammaglobin	GATA-3	EMA	S-100	Sox-10	CK5	PanTRK
Typical	.	.	.	+	+	+	+	+	+	+
Our Case	+	.	.	+	+	+	+	+	+	+

EMA, epithelial membrane antigen; ER, estrogen receptor; PR, progesterone receptor

*Not reported as strong staining

Table 3: Laboratory investigations

Laboratory Test	Value	Range
Prolactin	16.9	4.0-15.0 (ug/L)
FSH	0.6	<3.0 (IU/L)
LH	<0.3	<7.0 (IU/L)
Estradiol	<30	<30 (pmol/L)
Testosterone	<0.2	<0.2 (nmol/L)
Beta-hCG	<1	<5 (IU/L)
AFP	<2	<9 (ug/L)
LDH	230	140-320 (U/L)

AFP, alpha fetoprotein; FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; LH, luteinizing hormone

PO4-25-09

HER2-Low and Ultra-Low expression in young women with luminal breast cancer in México

Presenting Author(s) and Co-Author(s):

J. Hernandez Hernandez. Instituto Tecnológico y de Estudios Superiores de Monterrey, Puebla, Puebla, Mexico

C. Lara Torres. Instituto Nacional de Cancerología, Distrito Federal, Mexico

B. Moreno Moran. Universidad Popular Autónoma del Estado de Puebla, Jiutepec, Morelos, Mexico

C. Villarreal Garza. Tecnológico de Monterrey, Monterrey, Mexico

F. Porrás Reyes. Instituto Nacional de Cancerología, Distrito Federal, Mexico

V. Pérez Sánchez. Instituto Nacional de Cancerología, United States

A. Mohar. Instituto Nacional de Cancerología, United States

Background and objective

HER2-Low in breast cancer is a biomarker with new approaches for prognosis and medical treatment decisions. However, HER2-Ultra-Low is an area of novel research. Our objective was to describe the clinicopathologic characteristics and HER2 expression status of a group of Mexican young patients with luminal breast cancer.

Methods

One hundred and fifty-seven young patients (< 40 years) with luminal breast cancer diagnosed from 2014 to 2020 were included. Clinicopathologic features, hormone receptors, HER2 expression, and tumor infiltrating lymphocytes (TILs) were assessed. We categorized patients in three groups: HER2 negative (n=95, 60.5%), HER2-Low (n=33, 21.0%), and HER2-Ultra-Low (n=29, 18.5%). Descriptive statistics were used to report demographic, clinical and histopathological characteristics. Kaplan-Meier curves and log-rank or Mantel-Cox tests were used to determine survival. Statistical significance was established using a P value < 0.05. This analysis was performed using R (version 4.0.4) through R Studio interface (version 1.4.1106).

Results

The median of age at diagnosis was 36.1 years [range 32.8-38.8], with a median of follow-up of 5.08 years [range 3.58-6.52]. The most frequent histologic type was ductal infiltrating carcinoma (81%), and 49.4% presented grade two of differentiation. T2, N0 and clinical stage II were the most common (45.2%, 44.5, and 48.1%, respectively), and fourteen patients (9.0%) presented clinical stage IV. We found statistically significant differences in Ki67 and total TILs quantification between HER2 negative and HER2-Low. Progesterone receptor levels were higher for HER2 negative and Ultra-Low in comparison to HER2-Low. The total population had a 5-year overall survival of 84.9%. We found statistically significant differences in the median of survival between HER2 groups, with a shorter survival for HER2-Low.

Conclusion

To date, there are no studies that describe the clinical profile and OS of HER2-Low and Ultra-Low in young patients with luminal breast cancer in México. These preliminary findings could indicate the need for further investigation in prognosis, outcomes, and specific treatment in these patients. This study contributes to better understand the clinicopathologic profile of the

HER2-Ultra-Low group and its differences with the HER2-Low group.

PO4-25-10

Towards personalized medicine for DCIS - the role of hormone receptors, HER2, and Ki67 status in high-grade DCIS

Presenting Author(s) and Co-Author(s):

H. Schandiz. Department of Pathology, Akershus University Hospital, Norway, United States

L. Farkas. Department of Pathology, Akershus University Hospital, Norway and Faculty of Medicine, University of Oslo, Campus Ahus, Norway, United States

D. Park. Department of Pathology, Oslo University Hospital, Norway, United States

S. Andersen. Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Campus Ahus, Norway, United States

J. Geisler. University of Oslo, Norway, Lorenskog, Norway

T. Sauer. Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Campus Ahus, Norway, United States

Objective: This study aimed to investigate the molecular details in breast ductal carcinoma in situ (DCIS). Expression status of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67 were investigated among luminal A (LumA), luminal B HER2-negative (LumB HER2-), luminal B HER2-positive (LumB HER2+), HER2-enriched, and triple-negative (TPN), subtypes of DCIS. **Materials & Methods:** The study comprised formalin-fixed paraffin-embedded (FFPE) specimens of 357 DCIS grade 3 cases diagnosed between 1996 – 2018. Routine diagnostic immunohistochemical (IHC) staining were performed. DCIS cases were classified as LumA, LumB HER2-, LumB HER2+, HER2-enriched or TPN, according to the 2013 St. Gallen guidelines, which is used for molecular subtyping of invasive breast carcinoma (IBC). Each subtype was sorted into three subcategories: “pure” meaning those without an invasive component; “w/invasive” meaning those with an invasive component; and “all” meaning the entire group of the given subtype. Furthermore, ER and PR-receptor expression was registered for LumA, LumB HER2- and LumB HER2+ cases as intervals. The distribution of Ki67 was analyzed within each subtype. For some analyses, we combined the LumA and LumB HER2- subtypes into one entire group. The inter-observer variability of Ki67 was calculated by setting a cut-off value of 20% (2013 St. Gallen). A cohort (n = 47) of DCIS cases with a median Ki67 value of 18% was selected. Ki67 was calculated by analyzing 200 DCIS cells in two separate hotspots. Cohen's Kappa coefficient was calculated based on these data. HER2 (IHC) was scored based on ASCO/CAP guidelines established for routine diagnostic work-up for IBC. 16 equivocal cases (2+) were further investigated using dual SISH. **Results:** 98% of “all” cases of the LumA subtype showed an ER \geq 50%. PR expression \geq 50% was found in 91% of cases in this subtype. The incidence of ER-receptor at a cut-off \geq 50% in the LumA subtype was significantly higher than that in the LumB HER2- and LumB HER2+ subtypes ($p < 0.0001$, Chi-square). In contrast, there was a statistically significant reduction in ER-receptor expression at a cut-off $< 10\%$ in LumA compared to the latter subtypes. The proportion of cases with PR-receptors with a cut-off of $< 20\%$ showed significant differences between LumA, LumB HER2- and LumB HER2+ subtypes (1.6%; 47% and 37%, respectively). There was also a significantly higher proportion of PR-receptor $\geq 50\%$ cases among the LumA subtype. We found a significant association between PR $< 20\%$ and HER2 (3+) in luminal subtypes ($p < 0.0004$, Fisher's exact). There was no significant difference in ER/PR expression in “pure” cases of luminal subtypes of DCIS versus those with an invasive component ($p = 0.1831$, Chi-square). The Ki67 in the entire population (n = 357) varied from $< 1\%$ to $> 80\%$. The mean and median were around 20% in those subtypes whose classifications

were not depended on Ki67. There was a significant difference in the distribution of Ki67 when cases of LumA “all” and those of LumB HER2- “all” were combined as one entire group and were compared to LumB HER2+ “all” and HER2-enriched “all” (p-adjusted < 0.0001, Kruskal Wallis). The assessment of Ki67 among different observers showed a Cohen's kappa coefficient of 0.29 – 0.31 (fair agreement). We compared the HER2 (IHC) 0, 1+ and 2+ score among LumA and LumB HER2- subtypes and did not find a statically significant difference, when the “pure” and “w/invasive” were compared (p = 0.603, Chi-square). Conclusions: Ki67 was highly variable in DCIS grade 3. Inter-observer agreement was (as expected) suboptimal, and the cut-off at 20% defined by the 2013 St Gallen guidelines for IBC is not reliable for the distinction of LumA and LumB HER2 subtypes of DCIS. The LumB subtype of DCIS is heterogeneous with considerable variability among the four IHC markers used in the present study. A low PR is strongly associated with HER2 (3+), in luminal subtypes (p < 0.0004, Fisher's exact).

PO4-25-11

Inconclusive Her2 by immunohistochemistry compared to in situ hybridization in breast cancer: a cross-sectional study

Presenting Author(s) and Co-Author(s):

F. Marcondes de Oliveira Coelho. Mater Dei Health Network, Brazil

R. Capanema Saliba Franco. Mater Dei Health Network, Brazil

E. Melo de Lima. Mater Dei Health Network, Brazil

M. Dias. Mater Dei Health Network, Brazil

A. Dias Salvador. Mater Dei Health Network, Brazil

W. José de Almeida Junior. Mater Dei Health Network, Brazil

J. Wanderley Rennó. Pontifical Catholic University of Minas Gerais, Brazil

J. Campos de Avelar. Mater Dei Health Network, Brazil

Introduction: Breast cancer stands as the most common malignancy diagnosed among women worldwide, with the Her2-positive subtype accounting for approximately 15% of the cases. The introduction of HER-targeted therapies has changed the natural history of this subtype, however, evaluating the Her2 status using immunohistochemistry (IHC), can yield inconclusive results in a significant percentage of cases, which requires the use of in situ hybridization techniques. The study of such cases has not been thoroughly explored, particularly in the Brazilian population, and increasing interest in this subgroup of patients arises as the "Her2 low" category gathers evidence of clinical applicability. The present study aimed to assess the final Her2 status of samples with indeterminate IHC results and compare these findings with current literature.

Methods: We conducted a cross-sectional study at the breast unit service of a private health network in the state of Minas Gerais, Brazil (Rede Mater Dei de Saúde). Breast tissue samples obtained over the past 5 years were analyzed, and specimens with inconclusive IHC results for Her2 were included in the study. Subsequently, the final Her2 status was determined through fluorescence in situ hybridization (FISH) test, or reanalysis in cases in which a new sample (surgical specimen) was obtained.

Results: Among the initially identified 73 samples with indeterminate IHC results for Her2, a total of 15 patients were excluded due to lack of follow-up within the breast unit service. The final cohort consisted of 58 women aged between 28 and 71 years. Notably, approximately 91% of the patients exhibited positive hormone receptor tumors, whereas 9% displayed negative hormone expression. After reviewing the medical records, approximately 36% of the patients were classified as having a positive final Her2 status, while 62% had a negative final status. One patient had an inconclusive FISH result.

Conclusion: The present study revealed that approximately 10% of the breast tissue samples included in the study yielded inconclusive results for Her2 by immunohistochemistry. Following FISH testing, the majority of these patients were reclassified into the negative final Her2 status category. The classification of most patients to what is known as the emerging "Her2 low" category, aligns with international publications, and highlights the clinical relevance of exploring this subset of breast cancer that gains relevance as advances provide prospects for targeted therapies.

Table 1. Summarized results for the final Her2 status

Patients with inconclusive Her2 by immunohistochemistry	
Final Her2 status	Number os patients
Positive	21 (36,2%)
Negative	36 (62,1%)
Inconclusive	1 (1,7%)
Total	58

Absolute and percentage values for the final HER2 status in the study cohort

PO4-25-12

Improving HER2 Low Scoring Consistency and Accuracy: Insights from the Australian HER2 Low Concordance Study for Invasive Breast Cancer

Presenting Author(s) and Co-Author(s):

G. Farshid. SA Pathology, Adelaide, South Australia, Australia

B. Kumar. Monash Health, United States

N. Pathmanathan. Douglass Hanley Moir Pathology, United States

H. Mahajan. Institute of Clinical Pathology and Medical Research, Westmead Hospital, Australia

B. Dessauvage. Clinipath Laboratories, Perth WA, Western Australia, Australia

J. Armes. Sullivan Nicolaides Pathology, Birtinya, Queensland, Australia

C. Snell. Peter McCallum Cancer Centre, Melbourne Vic, Victoria, Australia

A. Gilhota. SA Pathology, United States

Introduction: The Destiny Breast-04 Trial (DB-04) demonstrated the survival benefits of Trastuzumab Deruxtecan (T-DXd) for women with metastatic HER2 Low breast cancer, characterised by 1+ or 2+ IHC staining without amplification. While the DB-04 study applied the standard 2018 ASCO CAP IHC scoring criteria, in clinical practice, distinguishing HER2 0 from 1+ cancers is challenging as i) HER2 Low is not a biologically distinct subset of breast cancer, ii) there are no reference standards for HER2 Low cancers, iii) second-tier test, like ISH, are not applicable, and iv) there are no known controls for cases that have 0 or 1+ HER2 scores. For two decades this distinction was clinically immaterial, but now differentiating between HER2 0 and 1+ has now become crucial for determining patient eligibility for T-DXd therapy. Concerns regarding the subjectivity, imprecision and poor concordance between pathologists in scoring IHC in HER2 Low cancers raise the potential for misalignments in patient treatment. Ensuring pathologists have access to focused training for interpreting IHC scores at the low end of the HER2 expression spectrum, quality assurance procedures and reference sets are essential steps to help pathologists assess HER2 Low breast cancers more accurately and consistently.

Design: In this study, a group of 9 experienced breast pathologists compiled a deidentified set of 60 breast cancer core biopsies from 3 laboratories. The Ventana 4B5 HER2 assay had been used for evaluation and the local laboratories had scored the samples as HER2 0 or 1+. We teased out the ASCO CAP 2018 criteria and used our collective expertise of reporting HER2 IHC for many years to specify HER2 Low-focused scoring conventions, including some potential pitfalls. Subsequently, using these conventions, each pathologist reviewed digitized whole slide images of the IHC slides and scored HER2 expression for each case. At a consensus workshop, the cases were jointly reviewed to establish consensus scores and determine the percentage of HER2-expressing tumor cells in each case. We then evaluated the concordance between individual pathologists' HER2 scores and the consensus opinion and ascertained reasons for discordance.

Results: Among the cases discussed during the consensus conference, 43 out of 60 (71.7%) were classified as HER2 Low, with 40 cases designated as 1+ and three as 2+ (known to be not amplified). The consensus score matched the majority opinion of the pathologists' independent scores in 93.3% (56 out of 60) of the cases. Utilizing the HER2 Low-focused IHC scoring conventions, 7 out of 17 (41.2%) cases locally reported as HER2 0 were reclassified as HER2 Low. Conversely, among the 32 cases with local scores of 1+, 7 (21.8%) were

reclassified as ultralow or null. When compared to the consensus score, individual pathologists' scores demonstrated concordance levels ranging from 71.7% to 91.7%, with a mean concordance rate of 81.3%. Cases with less than 20% of tumor cells expressing HER2 had lower inter observer concordance.

This reference set of cases with expert consensus HER2 scores obtained through our study will be invaluable for peer training and the development of external quality assurance programs for HER2 Low cancers, including the quality assurance program of the Royal College of Pathologists of Australasia.

Conclusion: This study revealed that when breast pathologists were provided explicit instructions on scoring pitfalls and HER2 Low-focused scoring conventions, their HER2 scores were concordant with expert consensus scores in 71.7% to 91.7% of cases. Discordant cases primarily involved cases with less than 20% of tumor cells expressing HER2. Utilising such an approach, peer training and quality assurance procedures will improve the accuracy and consistency of HER2 IHC assessment for better patient care. Reassessing older cases using HER2 Low focused scoring conventions may result in revisions of HER2 scores from HER2 Low to zero, and vice versa.

Individual pathologists' concordance with the consensus HER2 IHC score

Pathologist ID	Number of cases concordant with consensus score	Concordance %
A	49	81.7
B	46	76.7
C	55	91.7
D	51	85.0
E	43	71.7
F	46	76.7
G	44	73.3
H	51	85.0
I	54	90.0
Set of 60 cases		Mean concordance: 81.3%

Applying our HER2 Low-focused IHC scoring conventions in a set of 60 core biopsies of invasive breast cancer with low or 0 HER2 protein expression.

PO4-26-01

Computational pathology: Revolutionizing diagnostics and clearing the way for precision medicine

Presenting Author(s) and Co-Author(s):

M. Gustavson. AstraZeneca Precision Medicine & Biosamples, Oncology R&D, Cambridge, United Kingdom, United States

M. Schick. AstraZeneca, United States

A. Kapil. AstraZeneca Computational Pathology GmbH, United States

A. Shumilov. AstraZeneca Computational Pathology GmbH, Early Oncology, Munich, Germany, München, Bayern, Germany

C. Barrett. AstraZeneca, United States

H. Sade. AstraZeneca, Munich, Bayern, Germany

While targeted cancer therapies often rely on subjective and semi-quantitative visual assessment of protein biomarkers by pathologists through immunohistochemically stained tissue, the transformative force of computational pathology is reshaping healthcare by unleashing unprecedented diagnostic accuracy and unlocking personalized treatments. In recent years, we have established a large integrated computational pathology unit to foster collaboration between interdisciplinary teams of computer scientists, pathologists, molecular biologists, and data scientists. This integration of cutting-edge technologies enabled us to develop a computational pathology approach called Quantitative Continuous Scoring (QCS). QCS deploys the power of Deep Learning (DL) to provide objective and continuous expression data of biomarkers in digitized IHC whole slide images (WSI), particularly of proteins expressed at low levels. While manual scoring of IHC WSIs is limited by subjectivity and semi-quantitative assessment of protein expression, QCS overcomes these limitations with an unprecedented accuracy.

QCS utilizes two DL-based algorithms, which we developed fully supervised by using pathologist input as the reference standard. These algorithms identify invasive tumour areas and segment each tumour cell across the WSI into cell nuclei, cytoplasm and membrane. Based on an accurate subcellular segmentation, we can compute biomarker expression, on a continuous scale, as mean Optical Density (OD) in each subcellular compartment based on the Hue-Saturation-Density (HSD) model. Therefore, this approach enables precise detection of the low biomarker expression range with single-cell resolution. Importantly, it also allows the computation of the spatial distribution of tumour cells across the WSI.

We have successfully used QCS to drive the selection of antibody clones for IHC assays and to delineate the mode of action and PK/PD mechanisms. Of note, the combination of assessing continuous target expression and capturing the spatial distribution of tumor cells has provided surrogate markers to predict potential bystander activity of antibody drug conjugates (ADCs). This approach outperformed traditional pathologist scoring in identifying patient populations having maximum treatment benefit through retrospective analysis of multiple clinical trials.

At present, all computational pathology approaches are developed based on conventional IHC assays that have been optimized for manual scoring. Importantly, we draw a vision in which the assay serves as a critical catalyst for unleashing the full potential of computational pathology by providing high-quality, standardized data inputs. We suggest an approach utilizing orthogonal methods as a reference standard to develop highly sensitive IHC assays, capable of detecting even subtle molecular and cellular changes with precision and exhibiting exceptional specificity for accurately identifying and distinguishing target biomarkers from background noise.

In summary, we here describe and discuss a computational pathology-based approach for precise biomarker quantification and superior patient selection with broad applicability and the potential to transform the very fabric of how we diagnose and treat cancer.

PO4-26-02

Evaluation of Tumor Infiltrating Lymphocytes as a predictive biomarker of recurrence in patients with Ductal Carcinoma In Situ of the breast.

Presenting Author(s) and Co-Author(s):

C. Pasetto. University of Sao Paulo, Curitiba, Parana, Brazil

F. Aguiar. University of Sao Paulo, Sao Paulo, Brazil

M. Peixoto. University of Sao Paulo, Sao Paulo, Brazil

M. Doria. Centro de Doenças da Mama- Breast Unit Nossa Senhora das Graças Hospital, United States

B. Mota. Instituto do Cancer do Estado de São Paulo, Sao Paulo, Brazil

J. Maesaka. University of Sao Paulo, Sao Paulo, Brazil

J. Filassi. ICESP, São Paulo, Brazil

E. Baracat. University of Sao Paulo, Santa Catarina, Brazil

R. Gonçalves. ICESP, São Paulo, Brazil

Introduction: Ductal carcinoma in situ (DCIS) represents around 20% of early breast cancer diagnoses globally. Some studies evaluated risk factors associated with DCIS recurrence. Among these, age, surgical margins, comedonecrosis (CN), high nuclear grade, negative hormone receptors and HER2 expression stand out. Recent approaches have been evaluating the role of the immune microenvironment and its association with recurrence and progression of DCIS.

Objective: To evaluate the association between Tumor Infiltrating Lymphocytes (TILs) in DCIS samples and disease recurrence. To characterize the immunological microenvironment of DCIS, analyzing the presence of TILs, “touching TILs” and desmoplastic reaction and their association with recurrence. Epidemiological, clinical, histological and immunohistochemical (IHC) characteristics were also evaluated.

Methods: This is a retrospective cohort study with patients diagnosed with DCIS and treated at Sao Paulo State Cancer Institute and Hospital das Clinicas of University of Sao Paulo. We included women over 18 years old with a diagnosis of DCIS who underwent treatment from Jan/2007 to Dec/2020. Male patients, patients with a diagnosis of invasive or microinvasive disease in the anatomopathological examination of the surgical specimen or patients with history of any neoplasm were excluded.

The main outcome was survival analysis according to the quantification of TILs, adjusted for potential confounders. For that, we collected data on age, presence of palpable mass, imaging findings, histological and IHC characteristics, such as expression of estrogen receptor (ER), progesterone receptor (PR) and hyperexpression of HER2, type of surgical approach, type of radiation therapy, use of endocrine therapy, length of follow-up, recurrence, and its type. Two pathologists evaluated TILs in the sample with the highest tumor representation and numerically quantified it as percentage. They also evaluated the presence of “touching tils” (lymphocytes in contact with the basement membrane) and desmoplastic reaction in the tumor stroma. Kaplan-Meier curves, log-rank tests and Cox regression models were used to evaluate survival. Chi-square tests were used to evaluate the association between categorical variables.

Results: 283 patients met the eligibility criteria. Mean age of patients was 55 years. 15% had a

palpable nodule at physical examination. Clustered amorphous microcalcifications were the most prevalent mammographic presentation, found in 41% of the patients. The most frequent histological and IHC features were cribriform presentation (73%) and ER positivity (86%), respectively. Desmoplastic reaction was absent in 10.5%, discreet in 51.9%, moderate in 24% and intense in 13.6% of the patients. Breast conserving surgery was performed in 189 patients, and 100 of them received adjuvant radiation therapy. Mean follow-up was 77.2 months, with a recurrence rate of 9.2%. We observed that tumors with focal necrosis (HR 6.4 [1.39-34.71] p 0.018) or CN (HR 4.53 [1.34 – 15.28] p 0.015) had higher risks of recurrence. Patients with a percentage value of TILs greater than or equal to 17% also had a higher risks of recurrence (HR 2.97 (1.17-7.51) p 0.02). These patients were mostly under 65 years of age (OR 0.45 [0.21 - 0.97] p 0.049). In a multivariate model, CN and TILs>17% remained significantly associated with recurrence (p=0.034 and p=0.035 respectively). There was a trend for invasive recurrence in 76.9% of the patients that relapsed when TILs were greater than or equal to 17% (p 0.062). “Touching TILs” were present in 12.9% of the patients but were not associated with recurrence (p=0.575).

Conclusion: In our cohort, high value of TILs ($\geq 17\%$) and presence of CN were independently associated with DCIS recurrence. Our findings suggest that TILs are a prognostic immunological biomarker in DCIS and warrant further investigation in prospective trials to determine the most adequate cut-point.

PO4-26-03

Collagen deposition in the breast cancer microenvironment correlates with ER-positive, Histological Grade I and low proliferation tumors.

Presenting Author(s) and Co-Author(s):

- A. Koutras. University of Patras, United States
- C. Sirinian. University of Patras, United States
- O. Bogri. University of West Attica, United States
- M. Nifora. University of West Attica, United States
- m. theakou. University of Patras, United States
- S. Degn. Aarhus University, United States
- i. mouratidis. Penn State University, United States
- D. Chaniotis. University of West Attica, United States
- S. Peroukidis. Panarkadikon General Hospital, United States
- I. Georgakopoulos-Soares. Penn State University, United States
- A. Papanastasiou. University of West Attica, United States

Breast cancer is a highly heterogeneous neoplasm both at the molecular and histological levels. Breast cancer cells present extremely high levels of genetic heterogeneity concerning mutational burden, copy number variations (CNVs) and epigenetic signatures. While this level of heterogeneity is well established, other layers of heterogeneity, such as tumor microenvironment (TME) heterogeneity, remains to be elucidated. TME in breast cancer is an intricate network encompassing tumor cells, "normal" stroma cells such as fibroblasts, lymphocytes, and a plethora of extracellular matrix (ECM) proteins produced either by cancer cells or stromal cells. These three interacting modules (cancer cells, stromal cells and the ECM) can affect each other in a reciprocal way with profound effects on patient prognosis and treatment outcome. Major protein components of the TME are ECM-related collagens, that are produced by breast cancer cells or/and cancer associated fibroblasts. The ECM collagen in breast cancer, that is mainly composed of collagen types I, III and V, has multiple roles modulating tumor growth, cancer cell invasiveness and metastasis. Here by Masson Trichrome and Immunohistochemistry/Aniline Blue co-stains for collagen fibers and proliferation index (Ki-67) in breast cancer FFPE tissue samples, we identified a statistically significant correlation between collagen deposition and Estrogen Receptor (ER) status ($p < 0.05$, proliferation index ($p < 0.01$) and histological Grade ($p = 0.01$). Further, in order to expand and support our findings, we analyzed the METABRIC study through the cBioPortal hub in relevance to collagen genes and multiple clinicopathological parameters. We were able to identify a coregulated subset of collagen genes that presented a positive correlation with ER-positive ($p < 10^{-10}$, $q < 10^{-10}$), low proliferating ($p < 10^{-10}$, $q < 10^{-10}$), Grade I ($p = 2.35e^{-9}$, $q < 1.07e^{-8}$) group of breast cancer cases, supporting our findings. In addition, analyses of collagen-high patients from the METABRIC study indicated that most cases presented with PIK3CA, CFBF and MAP3K1 mutations, while through the g.Profiler software we identified collagen-high relevant gene signatures that encompassed gene ontology terms related to tissue development, extracellular matrix organization and cell migration. Collectively, our preliminary results indicate that ECM collagen deposition in breast cancer is characteristic of low-grade tumors with a better differentiation and possibly with a favorable prognosis.

PO4-26-04

Immunolocalization of cytoplasmic ER in ER-negative breast carcinoma as a potent favorable prognostic predictor

Presenting Author(s) and Co-Author(s):

A. Ebata. Department of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

T. Suzuki. Departments of Anatomic Pathology, Graduate School of Medicine, Tohoku University, Japan

N. Shoji-Harada. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, Japan

Y. Hamanaka. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

M. Miyashita. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

E. Iwabuchi. Departments of Pathology and Histotechnology, Graduate School of Medicine, Tohoku University, United States

K. Takagi. Departments of Pathology and Histotechnology, Graduate School of Medicine, Tohoku University, United States

Y. Miki. Departments of Anatomic Pathology, Graduate School of Medicine, Tohoku University, United States

H. Tada. Departments of Breast and Endocrine Surgical Oncology, Graduate School of Medicine, Tohoku University, United States

T. Ishida. Division of Breast and Endocrine Surgical Oncology, Tohoku University Graduate School of Medicine, Miyagi, United States

Background: It is known that estrogen receptor (ER) has extranuclear signaling functions in addition to classical genomic pathway, and estrogenic actions have been reported in ER-negative breast carcinoma cells. However, significance of cytoplasmic-ER immunoreactivity has not been reported in ER-negative breast carcinoma tissues.

Methods: We immunolocalized cytoplasmic ER in 155 ER-negative breast carcinoma tissues and evaluated its clinicopathological significance including the prognosis. As a comparative cohort set, we also used 142 ER-positive breast carcinomas.

Results: Cytoplasmic-ER immunoreactivity was detected in the carcinoma cells, but not in the non-neoplastic mammary epithelium. Cytoplasmic-ER immunoreactivity was positive in the 35 out of 155 (23%) ER-negative breast carcinoma cases, whereas it was detected only in 2 out of 142 (1.4%) ER-positive cases. Cytoplasmic ER status was positively associated with cytoplasmic-PR status, but inversely associated with Ki67 labeling index or distant free-relapse survival rate. Moreover, cytoplasmic-ER status turned out to be an independent good prognostic factor for both distant relapse-free survival and breast cancer specific survival.

Conclusion: These findings suggested that cytoplasmic ER plays important roles in the ER-negative breast carcinoma, and cytoplasmic ER is a potent good prognostic factor. (accepted in *Acta Histochemica et Cytochemica*, 2023/Jun/27)

PO4-26-05

Dual HER2 Testing With Both Immunohistochemistry (IHC) and ISH (In Situ Hybridization): Long Term Analysis of Dual Testing in a Single Academic Institution.

Presenting Author(s) and Co-Author(s):

X. Xu. University of Vermont, United States

A. Ambaye. University of Vermont, United States

K. Landry. university, United States

P. Kaufman. University of Vermont Cancer Center, Burlington, Vermont, United States

Background:

HER-2 critically guides therapies and is prognostic in breast cancer (BC). Current ASCO/CAP guidelines for immunohistochemistry (IHC) define 3+ as positive, 0 and 1+ as negative, and 2+ as equivocal, with additional testing recommended. Current guidelines for in situ hybridization (ISH) define a HER-2/CEP17 ratio of ≥ 2.0 , with an average HER-2 copy number of ≥ 4.0 signals/cell as ISH positive. With < 4.0 copies HER-2/cell, and for various other ISH groups that are borderline, further specific additional testing is recommended. Data suggest that HER-2 copy number does have clinical relevance in HER-2+ BC, however most clinical trials evaluating HER-2 targeted therapeutics have defined HER-2+ as specifically a HER-2/CEP17 ratio ≥ 2.0 . Limited studies have explored HER-2 copy number and its clinical implication in the HER-2 1+, and 2+ ISH negative population, recently described as HER-2 low. Further, the guidelines for HER-2 testing have changed twice over the past decade, and little is known about the impact of these changes.

Design:

From 2001- March 2023, all new invasive BC cases tested at University of Vermont (UVM) for HER-2 with both IHC and ISH were analyzed. All testing was performed on formalin-fixed paraffin-embedded tissue, using the HercepTest kit (Dako Corp, Carpinteria, California) (2001-2012) 4B5 Rabbit Monoclonal Antibody (Ventana) (2013-2023) for IHC and the INFORM dual ISH DNA probe (Ventana) for CISH. Interpretation was performed using published criteria at the time of original testing, and all cases with both IHC and CISH testing were independently analyzed by two experienced reviewers.

Results:

2734 cases had dual testing with IHC and CISH. 2407 patients (88%) had a HER-2/CEP17 ratio < 2.0 , of these, 6.4% had a HER-2 copy number ≥ 4 and < 6 . Only 12% of cases overall had a ratio ≥ 2.0 . In IHC 0 and 1+ cases with HER-2/CEP17 ratio of < 2 , 0.4% and 4.3% have excess HER-2 copies/cell (defined as ≥ 4), respectively, compared to 13.8% for IHC 2+. For IHC 2+ cases, only 13.6% overall demonstrate amplification, with however, again, an additional 13.8% having excess copy number. Interestingly, 9.6% of the IHC 3+ cases had a ratio of < 2.0 , however 50% of those demonstrate HER-2 amplification. Overall, 6.4% of HER-2 non-amplified cases with a ratio < 2.0 have an excess HER-2 copy number. In our full institutional pathology database, 11.2% of cases are HER2+, by either IHC or ISH. Lastly, 43% of cases overall, at UVM, from 2018 – March 2023 would fall into the current classification as HER-2 low (IHC 1+, or IHC 2+ and ISH negative), as well.

Additionally, we have evaluated the change in IHC and ISH results that occurred with the changes in the ASCO/CAP guidelines in both 2013 and 2018, further data will be available for presentation.

Conclusion:

In this large single institutional analysis of dual HER-2 testing, only 12% of cases demonstrate HER-2 amplification, and overall in our institutional pathology database, from 2001 – March 2023, 11.2% of cases are HER-2+ by either IHC or ISH. In our dual tested cohort, only 13.6% of IHC 2+ cases demonstrate amplification, and 13.8% are non-amplified, but have excess HER-2 copy number. We demonstrate a numerical increase in the rate of amplification, and copy number in non-amplified cases, associated with IHC score. In all cases tested with IHC at UVM from 2018 – March 2023, we find 43% of cases meet the current criteria for HER-2 low. Finally, the ASCO/CAP guideline changes from 2013 to 2018 had modest impact on the overall percentage of HER-2+ cases in our series, further data on this impact will be available for presentation.

Simultaneously tested IHC and CISH data for new invasive breast cancer cases

IHC	n	HER-2 Signals/Cell					Non-amplified with excess HER-2 signals/cell
		ISH ratio ≥ 2.0 , n (%)	ISH ratio < 2.0 , n (%)	< 4 n	4-6 n	> 6 n	
0	502	0 (0)	502 (100)	500	2	0	0.4%
1+	1157	21 (1.8)	1136 (98.1)	1087	48	1	4.3%
2+	867	118 (13.6)	749 (86.3)	636	103	10	13.8%
3+	208	188 (90.3)	20 (9.6)	10	9	1	NA
Total	2734	327 (12)	2407 (88)	2233	162	12	6.4%

PO4-26-06

Identifying mutation-independent signaling pathway activation in molecular subtypes of triple negative breast cancers

Presenting Author(s) and Co-Author(s):

C. Schroff. Department of Pathology, New York University Langone Health and Grossman School of Medicine, New York, New York, United States

L. Lin. NYU Grossman School of Medicine, United States

D. van Strijp. InnoSIGN, Eindhoven, Netherlands

D. Roses. NYU Grossman School of Medicine, United States

S. Neerken. InnoSIGN, Eindhoven, Netherlands

F. Schnabel. NYU Grossman School of Medicine, New York, New York, United States

F. Darvishian. NYU Grossman School of Medicine, United States

M. Snuderl. NYU Grossman School of Medicine, United States

Introduction

Triple negative breast cancer (TNBC) is an aggressive cancer defined by the absence of estrogen receptors (ER), progesterone receptors (PR), and lack of human epidermal growth factor receptor 2 (HER-2). We previously identified molecular subgroups with distinct mutational, epigenetic, and clinicopathologic signatures. Here, we sought to identify signaling pathways using targeted RNA expression-based pathway analysis.

Methods

We analyzed 44 TNBC cases diagnosed at NYU Langone Health between March 2011 and April 2018. Samples were compared based on histology, immunohistochemistry, and epigenetics. We assessed mRNA expression levels of pathway-specific target genes with RT-qPCR using the OncoSIGNal pathway profiling assay. Signal transduction pathway analyses were used to measure activity of the estrogen receptor (ER), androgen receptor (AR), phosphoinositide-3-kinase (PI3K), mitogen-activated protein kinase (MAPK), Hedgehog (HH), Notch, and transforming growth factor beta (TGF- β) pathways.

Results

DNA methylation Cluster 1, which is enriched for apocrine histology and PI3K/Akt mutations, showed no increased activity in PI3K pathway by RNA expression, but showed increase of AR and MAPK signaling, with a single case of increased ER signaling in the absence of ESR1 activating mutations. In contrast, both DNA methylation Cluster 2 (no recurrent mutations) and Cluster 3 (DNA instability cluster) showed upregulation in PI3K pathway in 4/7 (57%) and 11/25 (44%) of cases, respectively. PI3K pathway activation was invariably associated with high Ki-67 >15%, however not all high Ki-67 cases showed high PI3K activity. Invasive ductal carcinoma (IDC) morphology was characterized by a nearly even split between MAPK (13/28, 46%) and PI3K (12/28, 44%), with single HH and TGF- β driven cases. In 5/28 (18%) of IDC we did not identify an upregulated pathway.

Discussion

We show that RNA expression-based pathway activity and mutational and epigenetic analyses provide complimentary information about the molecular landscape of TNBC. PI3K mutations are early drivers and lead to distinct epigenetic signatures, however they are not associated with increased PI3K pathway activity by RNA expression. In contrast, TNBC without PI3K

mutations may show activation of the PI3K pathway in the absence of PI3K/Akt mutations. Our observation suggests that distinct biomarkers may be differently suited to predict response to PI3K inhibitors in TNBC. This may include expanding the number of patients for which PI3K/Akt pathway inhibition might be a therapeutic option, as well as explaining the lack of response in PI3K mutated tumors.

PO4-26-07

HER2-low prevalence in early breast cancer (BC) across reference laboratories in Brazil: potential impact of immunohistochemistry (IHC) antibody assay sensitivity

Presenting Author(s) and Co-Author(s):

L. M da Silva. Oncoclinicas Precision Medicine, United States

F. Orpinelli Rego. Oncoclinicas Precision Medicine, United States

M. Costa e Silva. Grupo Oncoclinicas, Brazil

T. Reinert. Oncoclinicas Group, United States

F. Koyama. Oncoclinicas Precision Medicine, United States

D. Bueno da Cunha. Oncoclinicas Precision Medicine, United States

V. Duarte. Oncoclinicas Precision Medicine, United States

E. Pereira. Oncoclinicas Precision Medicine, United States

B. Ferrari. Grupo Oncoclinicas, United States

R. Dienstmann. Oncoclinicas Group, United States

Background: Current definition of HER2-positive and HER2-low BC follows ASCO/CAP guidelines using IHC and/or in situ hybridization (ISH)-based techniques. Although there is no recommendation for a specific antibody assay, the companion diagnostic test for trastuzumab deruxtecan in the USA is Ventana PATHWAY anti-HER2 monoclonal antibody (4B5) run on Benchmark Ultra instrument. In this study, we assessed the prevalence of HER2-low BC in samples stained with Dako anti-HER2 polyclonal antibody (A0485) and analyzed with Autostainer Link 48 Agilent/Dako, commonly used in different large-volume laboratories in Brazil.

Methods: Retrospective study of all early-stage BC samples without exposure to neoadjuvant therapy tested for HR plus HER2 status in Oncoclinicas Precision Medicine (Locus Lab) from 2021 to 2023 and analyzed following ASCO/CAP guidelines. Tumors with HER2 IHC score 0 were classified as HER2-zero, whereas tumors with HER2 score 1+ and those with HER2 score 2+ with ISH-negative were classified as HER2-low. To assess the impact of preanalytical factors on HER2-low positivity, we stratified samples as in-house (part of Oncoclinicas network) or external (other institutions' FFPE preparation conditions not controlled). Results were also validated in independent IRA Lab using the same Dako anti-HER2 polyclonal antibody (A0485) on Autostainer Link 48 Agilent/Dako.

Results: Out of 1,638 eligible samples from Locus Lab, 84% were classified as HR-positive/HER2 negative, 12% HER2-positive, and 4% triple-negative. In 1,386 HR-positive/HER2 negative samples, 83% were HER2-zero, and 17% (CI95% 15%-19%) were HER2-low (1+ in 79% and 2+ with ISH negative in 21%). In 70 triple-negative samples, 62% were HER2-zero and 38% (CI95% 27%-51%) were HER2-low (1+ in 44% and 2+ with ISH negative in 56%). HER2-low positivity was 17% in the subset of in-house samples (N=1.090) and 16% in external referrals (P=0.41). In the independent cohort, out of 441 samples from IRA Lab, 80% were HR-positive/HER2 negative, 12% HER2-positive and 8% triple negative. In 352 HR positive/HER2 negative samples, 80% were HER2-zero and 20% (CI95% 16%-25%) were HER2-low. In 36 triple-negative samples, 72% were HER2-zero and 28% (CI95% 14%-45%) were HER2-low.

Conclusions: Different from another Brazilian cohort where the prevalence of HER2-low was 50% with monoclonal anti-HER2 antibodies (Reinert et al., SABCS 2020), our data suggests that the reduced proportion of samples with HER2-low status may be related to antibody clone sensitivity and not linked to preanalytical factors or local ancestry/ cancer biology. Indeed, a recent Italian cohort also had lower than expected prevalence of HER2-low in surgical specimens using anti-HER2 Dako A0485 assay on Omnis instrument (Rossi et al., Breast Cancer Res Treat 2023). Prior studies have found differential analytical sensitivity of antibodies for HER2-low status, while HER2 score 3+ detection is equivalent (Ruschoff et al., Virchows Archiv 2022). We recommend prospective evaluation of the HER2-low status with companion-diagnostic Ventana 4B5 assay and alternative antibodies and instruments.

PO4-26-08

Prevalence of HER2-low and IHC >0 to < 1+ in breast cancer and its concordance between historical and rescored results: a multi-center, retrospective study in China

Presenting Author(s) and Co-Author(s):

H. Lv. Fudan University Shanghai Cancer Center, United States

J. Yue. Hubei Cancer Hospital, United States

Q. Zhang. The First Hospital of China Medical University, United States

F. Xu. Guangdong Provincial People's Hospital, United States

J. Li. Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

L. Kong. Henan Provincial People's Hospital, United States

P. Gao. Qilu Hospital of Shandong University, United States

G. Zhang. The First Affiliated Hospital of Xi'an Jiaotong University, United States

H. Yang. Guangdong Provincial Hospital of Chinese Medicine, United States

X. Nie. Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, United States

W. Yang. Department of Oncology, Fudan University Shanghai Cancer Center, United States

Background:

With Trastuzumab deruxtecan (T-DXd) changing the anti-HER2 treatment paradigm, HER2-low (defined as IHC2+/ISH- and IHC1+) breast cancer patients have emerged as a new targetable population. The lower threshold for HER2 expression that can benefit from HER2-directed antibody-drug conjugates (ADCs) is still being investigated, such as HER2 immunohistochemistry (IHC) >0 to < 1+ (defined as IHC 0 with incomplete and faint staining in $\leq 10\%$ of tumor cells) in the DESTINY-Breast06 trial. Accurate determination of HER2 scores has become a critical topic in clinical discussions, given its clinical relevance to HER2-directed treatment strategies. Hence, we conduct this study (HER2-PATH, NCT05203458) to evaluate the distribution of HER2 status including HER2 IHC >0 to < 1+ in Chinese patients with breast cancer. Concordance between rescored and historical results was also analyzed.

Methods:

A retrospective study was conducted in breast cancer patients who underwent surgery at 10 sites in China between July 2021 and July 2022. Archived HER2 IHC slides from these patients were subjected to rescoring by a review committee comprising two readers and one adjudicator. The two readers independently evaluated each slide blinded to the historical scores. If their results matched, the recorded outcome was considered final. In cases of disagreement, the adjudicator made the final judgment. All slides were stained using Ventana 4B5 and scored following the ASCO/CAP 2018 guidelines, including the addition of the IHC >0< 1+ as defined in the DESTINY-Breast06 trial. The prevalence of the rescored HER2 status was calculated, and the concordance between the historical and rescored HER2 status was assessed using the Cohen's Kappa coefficient.

Results:

A total of 2868 patients were included in the analysis. The rescored results categorized 682 (23.8%) patients as HER2 IHC 0, 871 (30.4%) patients as IHC 1+, 800 (27.9%) patients as IHC 2+, and 515 (18.0%) patients as IHC 3+. The rates of HER2-positive, HER2-low, and HER2 IHC 0 (including HER2 null and HER2 IHC >0 to < 1+) were 21.8%, 54.3% and 23.9%,

respectively. Notably, the prevalence of HER2-low was numerically higher in the HR-positive subgroup compared to the HR-negative subgroup (60.2% vs 30.6%). Furthermore, the prevalence of HER2 IHC >0 to < 1+ and HER2 null was 10.6% and 13.2% among all patients, respectively. Among the HR-positive subgroup, the prevalence of HER2 IHC >0 to < 1+ was 10.9%, while the rate was 9.1% among the HR-negative subgroup. Overall, there was an 83.1% concordance between the historical and rescored results for HER2 IHC scores. The concordance rate for IHC 1+ was numerically lower (74.5%) compared to IHC 0 (85.2%), IHC 2+ (81.4%), and IHC 3+ (98.6%). However, considering that 12.0% of IHC 1+ patients turned into IHC 2+ with limited impact on HER2-low diagnosis, the concordance rate for HER2-low remained as 91.6%.

Conclusion:

HER2-low prevalence in Chinese breast cancer patients was found to be consistent with global data, while additional 10.6% of patients were identified as HER2 IHC >0 to < 1+, which is currently being investigated in a randomized controlled trial comparing T-DXd with SoC. To our knowledge, this is the first study to report the prevalence of HER2-low, including HER2 IHC >0 to < 1+, in the Chinese breast cancer population based on rescored results. The concordance of HER2-low between the historical and rescored results was 91.6%, indicating that most cases could be reproducibly classified.

Table: Rescored HER2 Expression Level

Items	Total patients (N=2868)
Rescored HER2 IHC scores	
0	682 (23.8%)
null	379 (13.2%)
IHC >0 to <1+	303 (10.6%)
1+	871 (30.4%)
2+	800 (27.9%)
3+	515 (18.0%)
Total	2868
FISH results for IHC 2+	
FISH-	681 (86.4%)
FISH+	107 (13.6%)
Missing	12
Total	800
HER2 status based on the rescores	
HER2 IHC 0	682 (23.9%)
HER2-low [#]	1552 (54.3%)
HER2 positive [*]	622 (21.8%)
Missing	12
Total	2868

^{*}HER2 positive: defined as IHC score 3+ and 2+/ISH+;

[#]HER2-low: defined as IHC score 2+/ISH- and 1+;

PO4-26-09

The Advantage of Artificial-Intelligence in HER2 IHC 0 and 1+ Scoring in Breast Cancer

Presenting Author(s) and Co-Author(s):

M. Li. Fudan University Shanghai Cancer Center, United States

H. Lv. Fudan University Shanghai Cancer Center, United States

Y. Zhao. Westlake Universtiy, United States

C. Zhu. Westlake Universtiy, United States

H. Li. Northwest University, United States

M. Lin. HangZhou DiYingJia Technology Co.,Ltd., United States

W. Yang. Department of Oncology, Fudan University Shanghai Cancer Center, United States

Background:

Trastuzumab deruxtecan has substantially changed the treatment of HER2-low breast cancer, emphasizing the need for accurate differentiation between HER2 immunohistochemistry (IHC) scores of 0 and 1+. However, the current accuracy of HER2 IHC 0 and 1+ scoring in real-world is inadequate. Artificial intelligence (AI) has emerged as a potential solution to improve interpretation accuracy. We developed an AI algorithm based on whole slide images (WSI) to quantitatively assess HER2 expression and its role in interpreting HER2 IHC scores of 0 and 1+.

Methods:

Our three-phase AI analysis framework involved segmenting tumor areas (excluding ductal carcinoma in situ), detecting and classifying tumor cells based on membrane staining patterns, and grading HER2 IHC scores according to the 2018 ASCO/CAP HER2 guideline. The AI tool was trained using 6012 patches annotated by experienced pathologists. Performance evaluation was conducted using a test dataset comprising 265 slides. A total of 141 HER2 IHC slides (27 IHC 0 and 114 IHC 1+) from patients diagnosed with invasive breast cancer at Fudan University Shanghai Cancer Center in 2021 were included. Two pretrained expert pathologists independently rescored the HER2 slides, followed by analysis using the AI tool. All inconsistent cases were also reviewed by a third senior pathologist. Interobserver agreement between the pathologists and concordance between the pathologists and the AI interpretation results were assessed. We also explored potential ranges where HER2 interpretation by pathologists exhibited inconsistency or inaccuracy.

Results:

The HER2 AI algorithm showed high performance in interpreting all levels of HER2 expression, with an overall kappa value of 0.85. For HER2 IHC 0 and 1+ cases, the AI model demonstrated high sensitivities (0.839 and 0.914) and specificities (0.983 and 0.890) (Table 1). After the rescoring process, 51 cases were reclassified as IHC 0 and 90 cases as IHC 1+. The overall agreement rate between the historical and re-scoring results was 73.05% (103/141). The agreement rate between the AI and re-scoring results was 91.49% (129/141) (Table 2), indicating comparable interpretation capabilities between the AI model and well-trained pathologists. The interobserver agreement between the two pathologists was 83.69% (118/141), with agreement rates of 88.23% (45/51) for IHC 0 and 81.11% (73/90) for IHC 1+. Analyzing the inconsistent cases (n=12) between IHC 0 and IHC 1+, we examined the percentage of weak and incomplete expression provided by the AI. In 9 out of 12 cases, the AI provided the same results as the third senior pathologist, suggesting that AI could assist in

interpretation within this range. We identified a range of 2.83% to 24.98% as a "grey-zone," where even well-trained pathologists provided inconsistent results.

Conclusion:

Our study demonstrates the excellent performance of an AI-based tool for scoring HER2 IHC 0 and 1+. The AI model exhibits comparable capabilities to well-trained pathologists in interpreting HER2 expression. Additionally, we identified a "grey-zone" among pathologists, highlighting the limitations of manual subjective interpretation. AI assistance within this zone may help mitigate subjective variations.

Table 1. Correlation between pathologist read and AI read of HER2 immunohistochemistry.

Table 1. Correlation between pathologist read and AI read of HER2 immunohistochemistry.

		AI			
		HER2 0	HER2 1+	HER2 2+	HER2 3+
Pathologist	HER2 0	68	13	0	0
	HER2 1+	3	75	4	0
	HER2 2+	0	7	35	2
	HER2 3+	0	0	1	57

Table 2. Correlation between pathologist rescored and AI read of HER2 immunohistochemistry.

Table 2. Correlation between pathologist rescored and AI read of HER2 immunohistochemistry.

		AI	
		HER2 0	HER2 1+
Pathologist	HER2 0	45	6
Rescoring	HER2 1+	6	84

PO4-27-01

COVID-19 Vaccination Behavior and Outcomes in Breast Cancer Patients in comparison with other Cancer types

Presenting Author(s) and Co-Author(s):

H. Polimera. Penn State Cancer Institute, United States

E. Guare. Penn State College of Medicine, United States

L. Pomerantz. Penn State College of Medicine, United States

M. Vasekar. Penn State Cancer Institute, United States

j. Zhu. Penn State Cancer Institute, United States

m. Joshi. Penn State Cancer Institute, United States

Background: Cancer(ca) is a known risk factor for severe COVID-19 (C19) disease, related morbidity, and mortality. Ca patients (pts) were largely excluded from clinical trials evaluating the safety and efficacy of the 3 FDA-approved C19 vaccines (vax). Breast cancer (Bca) is the most commonly diagnosed non-skin ca, and accounts for ~ 30% of all new female cancers each year. The pandemic has led to disruptions in Bca care including screening, diagnosis, treatment, and follow-up which will likely have an impact on Bca mortality. We aim to study behavior and outcomes regarding C19 vax in Bca pts comparison to non-Bca pts.

Methods: In our prospective and observational single center study; adult ca pts (18-89 years) seen in clinics from Nov 2021-Sept 2022 were randomly interviewed using telephone surveys after a verbal consent. Type of ca and therapy data were collected from medical records. The survey included C19 disease status, vax status positive (+) or negative (-), reason for vax status, side effects (s.e), and their perspective on impact on ca Rx or ca progression. The primary objective was to identify the rate of vaccination in adult ca pts. Secondary objectives were to quantify C19 vax acceptance vs. hesitance, identify s.e of C19 vax and effect of C19 vax on outcomes in Bca and non-Bca pts.

Results: N=170 [Bca 45 (26.5%) and non-Bca 125 (73.5%)]. Among Bca pts: 40 (88.9%) were ER+, 34 (75.5%) PR+, and 9 (20%) HER2+. Of them, 20 (44.4%) pts received cytotoxic chemotherapy and 39 (86.7%) pts received hormonal therapy alone. Refer to Table 1 for key outcomes data. Top 3 risk factors for serious C19+ in Bca pts were age >65yr (42.2%), BMI >30 (42.2%) and smoking (24.4%); and in non Bca pts: age >65yr (52%), BMI >30 (34.4%) and immunocompromised state (23.2%). Top 3 reasons for C19 vax (+) in Bca pts: protection against C19+ for self (82.2%), for others (37.8%) and provider recommendation (46.7%). The main reasons for vax hesitancy in C19 vax (-) Bca pts: fear of side effects (4.4%), prior C19 infection (4.4%) and don't trust the research behind it (2.2%). The common s.e of C19 vax in Bca pts were fatigue (40%), injection site inflammation (35.6%) and body aches (31.1%). Also, 13.3% of Bca pts developed lymphadenopathy. A total of 71.1% Bca pts developed 'minor s.e' from C19 vax, compared to 33.1% in non-Bca pts (p=0.0001). However, none of Bca pts reported progression of the disease or delay in cancer Rx or outcome due to C-19 vax.

Conclusion: Majority of the Bca pts were vaccinated against C19 and tolerated it well. Even though significantly higher number of Bca pts had side effects, they were minor and did not impact Bca outcomes. Oncologists should discuss the importance of C19 vax in the context of ca.

Table1. Outcomes data

Patient characteristics	Breast malignancy n=45 (26.5%)	Non- Breast malignancies n=125 (73.5%)	P-value
Female	43 (95.6%)	45 (36%)	<0.0001*
Male	2 (4.4%)	80 (64%)	
Age (years, mean ± SD)	60.5±13.9	62.5± 15.3	0.4416
C19 Infection +	16 (35.6%)	33 (26.4%)	0.255
C19 Infection + (requiring hospitalization)	1 (2.2%)	8 (8.8%)	0.3038
C 19 vax rate	43 (95.6%)	103 (82.4%)	0.1096
C 19 Vax side effects	32 (71.1%)	41 (33.1%)	0.0001*
Received Booster	34 (75.6%)	49 (57%)	0.0383*
Cancer status: Progression of disease	5 (11.1%)	27 (21.6%)	0.2729
Cancer disease status changed due to C19 vax	0(0%)	1 (0.8%)	1

PO4-27-02

Pandemic Shifts: How did elective breast cancer care change?

Presenting Author(s) and Co-Author(s):

H. Wang. UT Austin, United States

G. Reece. MD Anderson Cancer Center / Department of Plastic and Reconstructive Surgery, United States

M. Bordes. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Markey. The University of Texas at Austin, Austin, Texas, United States

A. Hoffman. UT Austin, United States

Introduction: As the COVID-19 pandemic began, concerns arose that timely utilization of elective breast cancer care would decrease due to state moratoriums, travel restrictions, or fear, resulting in poorer long-term outcomes. Advances in telemedicine provided a new avenue for care; however, rapid implementation brought concerns about variable uptake and disparities. To support longitudinal clinical and epidemiological studies, this analysis described elective breast cancer care utilization during the first year of the pandemic, including patient, hospital, and geographic barriers and facilitators. Methods: The Multidisciplinary Breast Reconstruction Research Program team reviewed all breast cancer surgeries and procedures at The University of Texas MD Anderson Cancer Center during the pre-pandemic (March 1, 2019 to February 29, 2020) and pandemic (March 1, 2020 to February 28, 2021) periods. The team identified procedures that were deemed elective or preference-sensitive, and summarized the timeline of pandemic milestones and changes, including the implementation of telemedicine appointments. A data analyst summarized the distributions of completed, canceled, rescheduled, and never completed procedures. T tests and analyses of variance tested differences between the pre-pandemic and pandemic year. Generalized linear models assessed patient, hospital, and geographic factors that correlated with successful access to, and completion of, procedures. Two focus groups reviewed data and informed the interpretation of results. Results: During the first pandemic year, 30 breast care procedures were identified that were postponed during March-April, July-August, and December-January. Surprisingly, no decrease in overall utilization of elective care procedures was observed; in fact, 19% more elective breast cancer care surgeries and procedures were scheduled (4752 pre-pandemic vs 4003 pandemic) in 13% more episodes of care (2723 pre-pandemic vs 2415 pandemic). As expected, rescheduling of procedures increased 98% (from 14% pre-pandemic to 27% pandemic); however, the majority of procedures were able to be completed by the end of the year (72% pre-pandemic, 73% pandemic). Telemedicine did not significantly mediate successful completion, as the majority of procedures were prophylactic or reconstructive surgeries. However, extended hours ($p = 0.03$) and proximity to the hospital facilitated access and successful completion of care ($p < 0.01$). The most common procedures that were not able to be performed within the first year of the pandemic were autologous breast reconstruction, revision, and mastopexy. Notably, patients reported slightly improved rates of anxiety and depression during the initial pandemic year (11% vs 14%, $p = 0.04$), possibly due to relative privation or comparison bias. Clinicians and patients/survivors noted several “lessons learned” that may inform access and preference-sensitive care delivery. Conclusions: Despite three periods of state-mandated discontinuation of elective care procedures, the majority of patients were able to access and successfully complete elective breast cancer care during the first year of the COVID-19 pandemic. Future studies and initiatives may use this information to explore innovations in care delivery and short- and long-term effects on health outcomes.

PO4-27-03

Real-World Evidence: Impact of Margin Involvement on Overall Survival Following Breast Cancer Surgery – A Single-Center Analysis at Charité University Medical Center Berlin

Presenting Author(s) and Co-Author(s):

M. Beck. Charité University Medical Center Berlin, Germany, United States

K. Weiler. Charité University Medical Center Berlin, Germany, United States

S. Ossmann. Charité University Medical Center Berlin, Germany, United States

V. Kiver. Charité University Medical Center Berlin, Germany, United States

J. Blohmer. Charité - Universitätsmedizin Berlin, Germany

Introduction: Limited data is available regarding the impact of margin involvement following surgery for early-stage breast cancer on distant recurrence and overall survival (OS). We therefore conducted a retrospective single-center analysis to provide further real-world evidence of margin status on OS. Methods: We systematically evaluated patients who underwent surgical intervention for early breast cancer or carcinoma in situ at Charité University Medical Center Berlin between 2006 and 2022. Our study cohort included individuals with a minimum follow-up period of 6 months and documented margin status. Patients with secondary tumors were excluded from this comprehensive analysis. Results: In our analysis, we included a total of 3767 patients, with a median follow-up duration of 72.2 months. Among these, 3443 patients underwent surgery for invasive breast cancer, while 324 patients underwent surgery for carcinoma in situ. The median overall survival (OS) for the entire cohort was 63.7 months. Specifically, patients who achieved clear margins after primary surgery exhibited a median OS of 63.5 months (n=3068), and those with free margins after secondary surgery had a median OS of 65.2 months (n=610). Conversely, patients with definitively involved margins experienced a shorter median OS of 58.6 months (n=89). The multivariate analysis revealed a statistical trend toward adverse survival outcomes for patients with definitive involved margins (Hazard Ratio 1.55; 95% CI: 0.93-2.56; p=0.090), with no statistically significant difference observed between clear margins following primary or secondary surgery. Notably, patients who underwent breast-conserving surgery demonstrated a significantly improved OS (HR 0.45; 95% CI 0.37-0.45; p< 0.001). Higher rates of margin involvement were observed in patients with hormone receptor-positive tumors and carcinoma in situ, while lower rates were noted in triple-negative breast cancer and after neoadjuvant chemotherapy. Implication: Our findings suggest that involved margins may be associated with a limited overall survival. Notably, patients who underwent breast-conserving therapy exhibited more favorable outcomes in our analysis, underscoring the oncologic safety of this procedure.

PO4-27-04

GRACE-trial: A randomized active-controlled trial for vulvovaginal atrophy in breast cancer patients on endocrine therapy

Presenting Author(s) and Co-Author(s):

G. Vergauwen. Ghent University Hospital, United States

P. Cools. Ghent University, United States

H. Denys. Department of Medical Oncology, Ghent University Hospital, Belgium, United States

T. Fiers. Ghent University Hospital, United States

K. van de Vijver. Department of Pathology, University Hospital Ghent, Ghent, Belgium, United States

L. Veldeman. Ghent University Hospital, United States

H. Verstraelen. Ghent University Hospital, United States

Background: Breast cancer is the most common cancer type in women worldwide. Due to hormone receptor positivity in the majority of the breast cancer tumors is endocrine therapy a crucial part in the treatment landscape of breast cancer. Selective estrogen-receptor modulators or aromatase inhibitors are the used treatment options for endocrine therapy. These medicines generate a hypoestrogenic environment by reducing circulating estrogen or by altering the effect of estrogen on tissue cells by receptor blockade. As a common side effect, vulvovaginal atrophy occurs in a majority of breast cancer patients using endocrine therapy. Vulvovaginal atrophy has a significant impact on physical and psychological wellbeing due to negative influence on quality-of-life, self-esteem and sexuality. As a consequence, adherence of endocrine therapy for the standard duration of 5 to 10 years is challenging, resulting in higher rates of therapy interruption, leading to poorer prognosis with shorter distant disease free survival. The standard treatment for vulvovaginal atrophy in postmenopausal women is based on the use of local hormonal treatment. However, when a patient has a history of breast cancer, delay of treatment and undertreatment are ubiquitous. Methods & design: In this first ever prospective randomized trial breast cancer patients on endocrine therapy with vulvovaginal atrophy will be treated with the available local treatment modalities with a 1:1:1:1 randomization: estrogen, dehydroepiandrosterone, moisturizers and a co-treatment of estrogen and probiotics. Patient-reported outcomes measurements will be implemented to investigate the efficacy of the implemented treatments. These outcome measures include symptom evaluation, impact on quality-of-life and sexuality. Safety of the treatments will be evaluated by assessing systemic sex hormones concentrations. Previous research indicated no increased recurrence risk, yet no randomized trials comparing the different modalities have been published. Primary objectives: Two primary objectives have been determined. Firstly, the efficacy of the different treatment modalities will be assessed. The assessment will be based on patient-reported outcome measurements (PROMs) and clinical evaluations such as vaginal pH and the vaginal maturation index, the latter a direct microscopic evaluation of the vaginal epithelium. Secondly, safety of the different groups will be assessed. Evaluation will be done by measuring sex hormone concentrations systemically, which will be a surrogate for safety evaluation. Secondary objectives: The secondary objective in this study is the identification of microbial alterations after treatment initiation. Identification of these alterations can help in further understanding of the pathophysiology of vulvovaginal atrophy and potentially create opportunities for new treatment strategies towards vulvovaginal atrophy in breast cancer patients on endocrine therapy. Registration: The current study is registered at the European Union Clinical Trials Register (EudraCT number 2021-001921-31). Trial status: Recruitment for

the study was commenced in May 2022. At time of manuscript submission, patient recruitment was ongoing.

PO4-27-05

A phase I open-label dose escalation trial of FWD1802 as monotherapy and in combination with palbociclib in patients with ER+/HER2- unresectable locally advanced or metastatic breast cancer with or without ESR1 mutations

Presenting Author(s) and Co-Author(s):

L. Zeng. Shenzhen Forward Pharmaceuticals Co. Ltd., China (People's Republic)

J. Liu. Shenzhen Forward Pharmaceuticals Co. Ltd., China (People's Republic)

D. Wu. Shenzhen Forward Pharmaceuticals Co. Ltd., China (People's Republic)

H. Ge. Shenzhen Forward Pharmaceuticals Co. Ltd., China (People's Republic)

Z. Bian. Shenzhen Forward Pharmaceuticals Co. Ltd., China (People's Republic)

C. Zhu. Shenzhen Forward Pharmaceuticals Co. Ltd., China (People's Republic)

Background: Estrogen receptor (ER) signaling sits at center of the tumor biology in ER+/HER2- breast cancers. Current standard of care involves hormone therapy with agents including selective estrogen receptor modulators (SERMs), selective estrogen receptor degraders (SERDs), and aromatase inhibitors (AIs). Unfortunately, most patients eventually develop resistance to these therapies. Mutations in estrogen receptor 1 (ESR1) are partially responsible for the acquired resistance. Mutated estrogen receptors are still sensitive to fulvestrant but with a much less sensitivity. In January 2023, elacestrant received its first approval for the treatment of postmenopausal women or adult men with breast cancer harboring ESR1 mutations in US. However, there is still great unmet medical need for this population. FWD1802 is a third-generation oral SERD for ER-positive breast cancer patients. It binds competitively to ER, with a much higher affinity than that of fulvestrant. Preclinically, FWD1802 alone and in combination with palbociclib exhibits significant anti-tumor activity in the ER+/HER2- models and in ESR1-mutated models in vitro and in vivo. This ongoing phase I study is to assess the safety, tolerability, pharmacokinetics (PK) and clinical activity of FWD1802 as monotherapy and in combination with palbociclib in ER+/HER2- unresectable locally advanced or metastatic breast cancer with or without ESR1 mutations. Methods: This clinical study (CTR20232130) consists of three parts: monotherapy dose escalation (Part A), dose escalation in combination with palbociclib (Part B) and monotherapy dose expansion in ESR1-mutated patients (Part C). A conventional "3+3" design is used for this study. Approximately a total of 129 patients will be enrolled. FWD1802 is administered orally daily. In monotherapy dose escalation study (Part A), at each dose level, a single ascending dose (SAD) is followed by a 28-day continuous multiple ascending dose (MAD) period (defined as 1 cycle). In Part B dose, palbociclib (125 mg daily) is administered on a 28-day treatment cycle with 21-day on treatment and 7-day off treatment, along with the 28-day treatment cycle of FWD1802. The primary objectives include dose limiting toxicity (DLT), maximum tolerated dose (MTD), safety, tolerability, and the recommended phase 2 dose (RP2D) of FWD1802. Secondary objectives include pharmacokinetics characteristics of FWD1802 and its major metabolite as monotherapy and in combination with palbociclib. Preliminary anti-tumor activity including objective response rate (ORR), duration of response (DoR), disease control rate (DCR) and progression-free survival (PFS) will also be evaluated. DLT evaluation will be conducted after the first cycle of multi-dose period, and tumor assessment will be conducted every 8 weeks by investigators according to RECIST version 1.1. Patients with ER+/HER2- unresectable locally advanced or metastatic breast cancer with or without ESR1 mutation are eligible for the enrollment. Enrolled patients should have progressed disease, or failed from previous therapy, or intolerable or inaccessible to standard therapy. In addition, patients with ECOG score ≤ 1 and with adequate renal, cardiac,

hepatic, and hematologic function are eligible for enrollment. The monotherapy dose escalation (Part A) is currently ongoing. The dose selection for Part B and Part C will be based on the data from the ongoing Part A.

Clinical trial information: CTR20232130.

Research Sponsor: Shenzhen Forward Pharmaceuticals Co., Ltd. (FORWARD PHARMA).

PO4-27-06

Design of Active Phase 3 ENABLAR-2 Study Evaluating Enobosarm +/- Abemaciclib in Patients with AR+ER+HER2- 2nd-Line Metastatic Breast Cancer Following Tumor Progression on an Estrogen Blocking Agent Plus Palbociclib or Ribociclib

Presenting Author(s) and Co-Author(s):

K. Rinn. CCNW, Washington, United States

H. Linden. University of Washington, Fred Hutchison Cancer Center, Seattle, Washington, United States

L. Schwartzberg. William N. Pennington Cancer Institute - Renown Health, United States

G. Barnette. Veru Inc., United States

D. Rodriguez. Veru Inc., United States

I. Shalev. Veru Inc., United States

M. Steiner. Veru Inc., United States

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

Background: Targeting the androgen receptor (AR) with an oral selective agonist, enobosarm, is a novel approach to overcome ER and CDK4/6 resistance to suppress metastatic breast cancer (mBC). Preclinical studies in CDK4/6 inhibitor and estrogen blocking agent resistant PDX mBC models demonstrated that enobosarm alone or in combination with another CDK 4/6 inhibitor suppressed PDX mBC growth. In a subgroup analysis from a Phase 2 study, enobosarm demonstrated efficacy in the treatment of AR+ ER+ HER2- metastatic breast cancer in patients who had tumor progression on estrogen blocking agent and a CDK 4/6 inhibitor with a best overall response rate of 30% (2CRs and 1 PR). A Phase 3 ENABLAR-2 multi-center, open label, study evaluating enobosarm +/- abemaciclib is open and active for the treatment of HR+HER2- mBC. Methods: The two-staged Phase 3 ENABLAR-2, open-label, randomized, multicenter study is being conducted in AR+ER+ HER2- 2nd-line mBC who have progressed on estrogen blocking agent plus palbociclib or ribociclib. In the Stage 1 of the study (160 patients), five treatment arms will be assessed with the primary efficacy endpoint of ORR: enobosarm 9 mg QD, enobosarm 1 mg QD + abemaciclib, enobosarm 3 mg QD + abemaciclib, enobosarm 9 mg QD + abemaciclib, and an estrogen blocking agent, active control (a nonsteroidal AI, exemestane +/- everolimus, or SERD). Secondary efficacy endpoints include progression-free survival (PFS). In Stage 2 of the study, patients will be randomized to receive enobosarm +/- abemaciclib (based on outcome of ORR in Stage 1) or estrogen blocking agent, active control, with the primary endpoint of PFS and secondary efficacy endpoints including, ORR, CBR, OS, as well as changes in quality-of-life measurements (SPPB, EORTC-QLQ, body composition measured by DEXA). Randomization will be stratified by AR% nuclei staining and by line of treatment for metastatic disease. Subjects will receive study drug until disease progression is observed. Preliminary Results: To date, 3 patients have been treated with enobosarm 9 mg in combination with abemaciclib. The combination therapy was well tolerated with no new safety findings. There were no drug-drug interactions between enobosarm and abemaciclib. Two patients have achieved BOR of a partial response with up to 79% and 56% reduction in their target lesion recorded by local reads on day 224 post-treatment initiation (PTI). The third patient has achieved a stable disease and continues to receive treatment (on

study 10+ months). Conclusions: Preliminary data of efficacy and safety of enobosarm in combination with abemaciclib are encouraging. The Phase 3 ENABLAR-2 study is underway to further evaluate enobosarm monotherapy or in abemaciclib combination therapy in 2nd-line metastatic breast cancer population. Clinical trial information: NCT05065411. Research Sponsor: Veru Inc

PO4-27-07

A Phase 3, randomized, open-label study of upfront camizestrant vs standard endocrine therapy as adjuvant treatment for ER-positive/HER2-negative early breast cancer with intermediate-high or high risk of recurrence (CAMBRIA-2)

Presenting Author(s) and Co-Author(s):

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

I. Gioni. Late Development Oncology R&D, AstraZeneca, Cambridge, UK, United Kingdom

S. Johnston. Late Development Oncology R&D, AstraZeneca, Cambridge, UK, United States

T. Klinowska. AstraZeneca, Cambridge, United Kingdom

I. Mayer. Late Development Oncology R&D, AstraZeneca, Gaithersburg, NJ, USA, United States

R. Nunes. Late Development Oncology R&D, AstraZeneca, Gaithersburg, NJ, USA, United States

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

M. Stuart. Late Development Oncology R&D, AstraZeneca, Cambridge, UK, United Kingdom

A. Quintana. Late Development Oncology R&D, AstraZeneca, Cambridge, UK, United States

A. Walding. Late Development Oncology R&D, AstraZeneca, Cambridge, UK, United Kingdom

M. Gnant. Medical University of Vienna, Wien, Austria

Background: Camizestrant is a next-generation oral selective estrogen receptor (ER) degrader and pure ER antagonist being investigated in early and advanced breast cancer (BC). In postmenopausal women with advanced ER-positive/human epidermal growth factor receptor 2 (HER2)-negative BC and disease recurrence or progression on or after ≤ 1 endocrine therapy (ET) in the advanced setting, camizestrant significantly prolonged progression-free survival compared with fulvestrant in the Phase 2 SERENA-2 trial.

Camizestrant may also provide benefit in the early BC setting. Following locoregional therapy (surgery \pm radiotherapy), standard adjuvant treatment of ET with or without chemotherapy and/or a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) has shown significant benefit in decreasing the risk of recurrence of stage I–III ER-positive/HER2-negative BC. However, BC recurrence as incurable metastatic disease is still common. Thus, adjuvant therapeutic options with improved clinical outcomes are needed.

The CAMBRIA-2 study (NCT05952557) aims to assess whether upfront camizestrant can improve outcomes compared with standard ET as adjuvant treatment in patients with ER-positive/HER2-negative early BC with an intermediate-high or high risk of recurrence after definitive locoregional therapy. Trial design: This ongoing Phase 3, randomized, open-label study is enrolling women (pre-, peri-, or postmenopausal) and men with ER-positive/HER2-negative (HER2-negative status defined as immunohistochemistry 0, or 1+, or in situ hybridization-negative) early BC who are at intermediate-high or high risk of recurrence (as defined in the protocol) after having completed definitive locoregional therapy (surgery \pm radiotherapy) \pm (neo)adjuvant systemic chemotherapy, and who have no evidence of disease. Patients may have received up to 12 weeks of (neo)adjuvant ET prior to randomization. Patients are randomized (1:1) to receive camizestrant 75 mg \pm abemaciclib \pm luteinizing

hormone-releasing hormone (LHRH) agonist or standard ET of the investigator's choice (any aromatase inhibitor or tamoxifen) ± abemaciclib ± LHRH agonist for up to 7 years. The primary endpoint is invasive BC-free survival (IBCFS) (Standardized Definitions for Efficacy End Points [STEEP] 2.0 criteria). Secondary endpoints include invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) (STEEP 2.0 criteria), overall survival, safety, and health-related quality of life. Primary endpoint analysis will use a stratified log-rank test adjusting for stratification factors, assuming a two-sided significance level of 5%. Approximately 5500 patients will be randomized. Clinical trial identification: NCT05952557 Editorial acknowledgment: Writing assistance was provided by Clare Davis of BOLDSCIENCE Inc., funded by AstraZeneca. Legal entity responsible for the study: AstraZeneca Funding: This study was supported by AstraZeneca.

PO4-27-08

A Phase II Multi-Institutional Study of Concurrent Radiotherapy, Palbociclib, and Hormone Therapy for Treatment of Bone Metastasis in Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

M. Torres. Winship Cancer Institute of Emory University, Atlanta, Georgia, United States

J. Lin. Winship Cancer Institute of Emory University, United States

S. Friend. Winship Cancer Institute of Emory University, United States

C. Xiao. Nell Hodgson Woodruff School of Nursing, Emory University, United States

Y. Cao. Winship Cancer Institute of Emory University, United States

S. Kahn. Department of Radiation Oncology, Winship Cancer Institute, Emory University, United States

K. Godette. Department of Radiation Oncology, Winship Cancer Institute, Emory University, United States

S. Hanasoge. Department of Radiation Oncology, Winship Cancer Institute, Emory University, United States

D. Yu. Department of Radiation Oncology, Winship Cancer Institute, Emory University, United States

T. Eng. Department of Radiation Oncology, Winship Cancer Institute, Emory University, United States

M. Cheney. Radiation Oncology Division, Spectrum Healthcare Partners, United States

N. Wiggers. Northside Hospital Cancer Institute, United States

A. Pippas. John B. Amos Cancer Center, Piedmont Columbus Regional, United States

K. Gogineni. Emory University Hospital, Atlanta, GA, United States

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

D. Schuster. Winship Cancer Institute of Emory University, Georgia, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

A. Miller. Department of Psychiatry and Behavioral Sciences, Emory University, United States

J. Felger. Department of Psychiatry and Behavioral Sciences, Emory University, United States

J. Switchenko. Winship Cancer Institute of Emory University, United States

A. Zelnak. Northside Hospital, United States

K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

M. Bhave. Emory University School of Medicine, Atlanta, Georgia, United States

Background: This Phase II study aimed to determine the efficacy and safety of administering palliative radiotherapy (RT) to bone metastases (mets) in patients (pts) receiving concurrent palbociclib and hormone therapy (HT) for hormone receptor positive, Her2/neu negative breast cancer. The primary endpoint was response rate 3 months after RT. Methods: Pts with painful bone mets or asymptomatic bone mets with risk for impending clinical event were treated with RT to 30 Gy in 10 fractions or 20 Gy in 5 fractions with concurrent palbociclib and HT. Change in maximum pain score on the Brief Pain Inventory was used to assess pain response 3 months post RT relative to baseline. Among pts with asymptomatic bone lesions, response was defined

as prevention of a clinical event (e.g., bone fracture) without evidence of local tumor growth on surveillance imaging. Patient reported outcomes (PROs) of fatigue, depression, anxiety, and quality of life were collected. Blood-based biomarkers were examined to determine their relationship with response and PROs. Using a non-inferiority study design, a sample size of at least 33 pts was needed to achieve 80% power to detect a non-inferiority proportion of 60% using a one-sided binomial test and assuming a Type I error of 0.05. Results: Among 38 patients enrolled, 79% had painful bone mets. 35 pts completed baseline and 3-month post RT assessments. 61% and 37% of pts received aromatase inhibitors and fulvestrant, respectively, with palbociclib. Median age was 60 years (31-83) and 25% of pts were non-Hispanic Black. The majority (72%) of pts received 5 fraction RT and 69% received RT to one bone region. 29 patients (83%) were responders [95% CI: 66%-93%, $p=.003$]. Median progression free survival (PFS) was 30.4 months (1.3 - 44.0). Three-year PFS and overall survival were 45.6% and 67.2%, respectively. Grade 3 neutropenia developed in 4 (11%), 4 (11%), and 7 (20%) pts at end of RT, 1 month, and 3 months post RT, respectively. No pts developed Grade 4 neutropenia. One patient developed Grade 3 gastrointestinal toxicity during RT, another developed Grade 3 dyspnea 1 month post XRT, and another developed a bone fracture 6 months after RT. >While patient reported measures of fatigue, depression, and overall quality of life did not significantly change during or after RT relative to baseline, pain scores (i.e., BPI pain severity and interference, BM22 pain characteristics and pain site subscales, EORTC C15 pain) significantly decreased 3 months post XRT relative to baseline. Heightened inflammatory marker levels (e.g., TNFR2, IL1ra, CRP, TNF alpha) were significantly associated with worse symptoms of fatigue (MFI) and depression (HADS), increased pain interference (BPI), and lower overall quality of life (SF-36), controlling for age and time using mixed effect models. Patients with improved pain symptoms and lower pain scores had significantly lower inflammatory marker levels relative to baseline (e.g., interleukin-6). Conclusions: Our study demonstrated high rates of response to concurrent RT with palbociclib and HT with acceptable levels of toxicity. These results suggest that RT to bone mets effectively alleviates pain in patients taking palbociclib and pain response to treatment is associated with decreased inflammatory markers. RT may be given to pts receiving palbociclib and HT for breast cancer. Clinical Trial Identification: NCT03691493

PO4-27-10

A Systematic Review and Meta-analysis of Diagnostic Performance of Fluorescein Guided Sentinel Lymph Node Biopsy in Early Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Yadav. NSCB Medical College Jabalpur, JABALPUR, Madhya Pradesh, India

B. S. NSCB Medical College Jabalpur, Jabalpur, Madhya Pradesh, India

S. Khadka. BPKIHS Dharan Nepal, DHARAN, Nepal

D. Sharma. NSCB Medical College Jabalpur, Jabalpur, Madhya Pradesh, India

C. Jha. AIIMS PATNA, PATNA, Bihar, India

G. Agarwal. SGPGIM Lucknow, Lucknow, Uttar Pradesh, India

M. Singh. JLN Medical College RAIPUR, RAIPUR, Chhattisgarh, India

A. SRIVASTAVA. Subharti Institute of Cancer Management and Research, MEERUT, Uttar Pradesh, India

A. Goyal. Royal Derby Hospital, United States

Background: Evaluation of axillary lymph nodes status in cN0 axilla is performed by sentinel lymph node biopsy (SLNB) utilizing a combination of radioactive isotope and blue dye . There is a paucity of radioactive tracer in many countries of transitional economies. Hence, alternatives to isotope have been explored, viz. indocyanine green (ICG), superparamagnetic iron oxide nanoparticles and Fluorescein Sodium (FS). This systematic review and meta-analysis, evaluates the diagnostic performance of Fluorescein Sodium guided SLNB. Objectives: The objective was to evaluate the diagnostic performance of Fluorescein Sodium for sentinel lymph node biopsy in early breast cancer. Methods: PRISMA 2020 guidelines were followed for this meta-analysis. Eligibility criteria: Studies where SLNB was performed using Fluorescein Sodium for breast carcinoma. Information sources: PubMed, EMBASE, Cochrane library and online clinical trial registers Risk of bias: Articles were assessed for risk of bias using the QUADAS-2 tool. Synthesis of results: The main summary measures were pooled detection rate and pooled false negative rate using random effects model. In order to describe heterogeneity, we constructed summary receiver operating characteristic (SROC) curves with 95% prediction regions, estimated using bivariate meta-analysis with a test level random effect only, and forest plots. Calculations were performed using the Meta-Disc v1.4 program (available from <https://metadisc.software.informer.com/1.4/>). Results: Out of 45 studies found on initial systematic search, 7 studies were found eligible and were included in the meta-analysis based on data on 332 patients. The pooled detection rate was 93.2% (95% confidence interval [CI] 87% to 97%). The heterogeneity (I^2 value) of the pooled detection rate was 71%. Five validation studies were included for pooling the false negative rate (FNR) and included a total of 211 patients. The pooled FNR was 5.6% (95% CI ; 2.9 to 9.07). Five validation studies were included for sensitivity, specificity, diagnostic odds ratio, LR+ and LR- meta-analysis. With regards to the identification of SLN the pooled sensitivity was 80% [(95% CI, 68% to 89%); $I^2=79.8$]; specificity was 98% [(95% CI, 95% to 100%); $I^2=0.0$]. The likelihood ratio for a positive test LR+ was 23.2 [(95% CI, 5.91 to 95.18); $I^2=0.0$] and likelihood ratio for a negative test a LR- of 0.41 [(95% CI, 0.16 to 1.05); $I^2=88.1$]. The diagnostic Odds ratio OR was 76.94 (95% CI, 15.88 to 372.79). Diagnostic accuracy as measured by SROC was 99.08%. Q index was 0.96. Publication bias for pooled detection rate as per Egger's test was -2.2 (p= 0.66) and for FNR was 1.85 (p=0.29). Visual inspection of summary ROC curve and of forest plots did not show significant heterogeneity. Conclusion: Fluorescein guided SLNB is an affordable option

for detection of lymph node metastases in cN0 patients with early breast cancer. It achieves a high detection rate of 93% with a false negative rate of 5.6% for the detection of axillary lymph node metastasis. We recommend larger multinational trials to confirm its high detection rate with low false negativity.

PO4-27-11

Fat grafting is oncologically safe during implant-based breast reconstruction and mastectomy after radiotherapy for breast cancer or Hodgkin Lymphoma: results of a multicentric study.

Presenting Author(s) and Co-Author(s):

C. Listorti. Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, Milan, Lombardia, Italy

C. Vernieri. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Lombardia, Italy

F. Barretta. Biostatistics for Clinical Research, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, Milan, Lombardia, Italy

C. Osio. Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, Milan, Lombardia, Italy

I. Maugeri. Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, Milan, Lombardia, Italy

F. Pilotta. Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, Milan, Lombardia, Italy

C. Ferraris. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy

M. Gennaro. Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, Milan, Lombardia, Italy

G. Martelli. Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, Milan, Lombardia, Italy

M. Visaggio. Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy, Milan, Lombardia, Italy

G. Bianchi. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy

S. Di Cosimo. Biomarker Unit, Department of Applied Research and Technological Development, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

G. Scaperrotta. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy

M. De Santis. Radiation Oncology 1, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy, United States

D. Tognali. Breast Unit, Ospedale GB Morgagni, Forlì, AUSL Romagna, Italy, Emilia-Romagna, Italy

A. Romeo. Istituto di Ricovero e Cura a Carattere Scientifico, Meldola (FC), Italy, Emilia-Romagna, Italy

M. Mingozzi. Breast Unit, Ospedale GB Morgagni, Forlì, AUSL Romagna, Italy, Emilia-Romagna, Italy

F. Marongiu. Breast Unit, Ospedale GB Morgagni, Forlì, AUSL Romagna, Italy, Emilia-Romagna, Italy

A. Curcio. Breast Unit, Ospedale GB Morgagni, Forlì, AUSL Romagna, Italy, Emilia-Romagna, Italy

S. Folli. Fondazione IRCCS Istituto Nazionale dei Tumori, Italy

Background. Fat grafting during or after mastectomy could promote the regeneration of irradiated tissues, thus improving tissue softness, increasing patient comfort and ameliorating

quality of life. However, there are no conclusive data about the oncological safety of fat grafting, especially in terms of risk of tumor recurrences. The most appropriate timing of adipose tissue transplant is also debated, especially in patients with locoregional breast cancer (BC) recurrence undergoing salvage mastectomy and implant-based breast reconstruction after breast conserving surgery and radiotherapy.

Methods. We conducted a prospective, multicentric Italian study to investigate the oncological safety of fat grafting between June 2007 and March 2022. One hundred sixty-three patients who had previously received radiotherapy, either as adjuvant treatment after breast conservative surgery (N=154), or as a treatment of Hodgkin Lymphoma (N=9), underwent mastectomy (simple mastectomy, NAC-sparing and skin-sparing mastectomy) and implant-based, two-stage breast reconstruction. Inclusion criteria were: age between 25 and 75 years, absence of concomitant malignancies, grade 2 or 3 of Breast post Radiotherapy Reconstruction with ExpAnder Score Test (B.R.R.E.A.S.T. score) (Tab 1). Patient BMI, hypertension, smoking history, diabetes and having received neoadjuvant chemotherapy were not considered as exclusion criteria. Contextual mastectomy and expander positioning were performed during first stage (stage I), while substitution of the expander with definitive implant occurred during second stage (stage II). Fat grafting could be performed during stage I, between stage I and II surgery, or during stage II.

Results. One hundred sixty-nine mastectomy procedures (six bilateral) and first-stage implant-based reconstructions with expander were performed either as prophylactic surgery (N=23) or for the treatment of primary or recurrent BC (N=146). Thirty-four patients had ductal carcinoma in situ, whereas 112 patients had invasive disease, including: 17 patients with Luminal A BC, 67 patients with Luminal B HER2-negative BC, 3 patients with Luminal B HER-2 positive BC, 7 patients with HER-2 positive BC and 18 patients had triple-negative BC. One hundred thirty-six (80.5%) patients received at least one fat grafting. Eighty-six patients (52.8%) have received second-stage definitive implant. With a median time of observation of 25.1 months, we observed four locoregional cancer recurrences (2.4%), one of which in axillary lymph nodes. All tumor recurrences occurred in patients who had received fat grafting. Eight patients (4.9%) developed distant metastases (liver, lung, lymph nodes, and bone metastases); of these, four patients (50%) had received fat grafting. No death events occurred.

Conclusion. Fat grafting after radiotherapy of the breast is associated with a low incidence of locoregional tumor recurrences and distant metastases. Although our findings need to be confirmed in larger, multicentric clinical studies, fat grafting is a safe and useful technique that can be proposed for breast reconstruction after irradiation.

Breast post Radiotherapy Reconstruction with ExpAnder Score Test, B.R.R.E.A.S.T score.

B.R.R.E.A.S.T score	Pinch test \geq 0.5 cm	Skin teleangectasia or severe dyschromia
1	No	Any
2	Yes	Moderate
3	Yes	No

Based on our experience, we thought to include two tissue characteristics (Pinch test \geq 0.5 cm and presence/absence of skin teleangectasia or severe dyschromia) in a pre-operative, clinically useful, and ready-to-use score to assess soft tissue adequacy as recommended by NCCN guidelines, that we called Breast post Radiotherapy Reconstruction with ExpAnder Score Test (B.R.R.E.A.S.T. score). In our study, two-stage implant-based breast reconstruction and adipose tissue transplant with regenerative intent were performed in patients with Pinch test \geq 0.5 cm but moderate skin teleangectasia or dyschromia (B.R.R.E.A.S.T. score 2) and in patients with Pinch test \geq 0.5 cm and absence of skin teleangectasia or severe dyschromia (B.R.R.E.A.S.T. score 3). Patients with skin teleangectasia or dyschromia and Pinch test $<$ 0.5 cm (B.R.R.E.A.S.T. score 1) were not enrolled in our study as they did not undergo alloplastic breast reconstruction but they underwent autologous reconstruction (data not shown).

PO4-27-12

Increasing DAXX as a Novel Approach to Inhibit Breast Cancer Stem Cells and Estrogen Receptor-positive Tumor Recurrence

Presenting Author(s) and Co-Author(s):

C. Osipo. Loyola University Chicago, United States

D. Wyatt. Loyola University Chicago, United States

K. Albain. Loyola University Chicago Stritch School of Medicine, Cardinal Bernardin Cancer Center, United States

Background: Resistance to endocrine therapy (ET; tamoxifen, aromatase inhibitors, AI, or fulvestrant) in ER+ breast cancer (BC) could be due to survival of breast cancer stem cells (BCSCs). BCSCs contribute to relapse of ER+ BC. We discovered a novel and potent anti-BCSC gene, Death Associated Protein 6 (DAXX) through a pre-surgical biomarker window study combining ET plus a Notch inhibitor [MK-0752, a g-secretase inhibitor (GSI)]. We also found that ET enhances the BCSC population by decreasing DAXX protein levels. In this current study, we measured DAXX protein levels in ER+ PDX tumors and human tumor tissues treated with ET. We determined the mechanism by which ET regulates DAXX expression at the level of protein stability. The goal of this study was to identify novel therapeutic strategies to prevent ET-mediated degradation of the DAXX protein, eliminate BCSCs, and prevent ER+ recurrence. Methods: ER+ BC cell lines (MCF-7 and T47D), an ER+ PDX BCM 5097 tumor line, and human breast cancer tumor samples were used. The ER+ PDX tumor (BCM 5097) was implanted into NSG mice and passaged into female athymic, nude mice-supplemented with an estradiol capsule. After one week, the estradiol capsule was removed from 10 mice, to mimic the use of AI. The remaining 10 mice retained the estradiol capsule. Tumor area was measured weekly up to 50 weeks. Western blotting detected ER α , the stem cell factor Notch4, and DAXX levels. Immunohistochemistry (IHC) detected DAXX protein levels. ER+ human tumor samples were collected prior to and after neoadjuvant treatment with ET (N=11) or chemotherapy (N=14) and stained for the DAXX protein. Correlations were made between DAXX and Ki67. Full length and deletion mutants of DAXX were expressed in ER+ BC cells. BCSCs were measured using the mammosphere forming assay. Liquid chromatography followed by mass spectrometry were used to detect phosphorylated residues of DAXX in response to ET. Kinases that phosphorylate these residues on DAXX were identified using PhosphoSite.org. ER+ cells were treated with kinase inhibitors for AURKA (alisertib), AURKB (barasertib), CK1 (CK-IN-1), or CK2 (CX-4945) and DAXX protein was detected by western blotting. BCSC survival was measured using mammosphere forming assay. Based on results from the kinase inhibitor screen, barasertib was selected for pre-clinical testing in mice. ER+ MCF-7 xenograft tumors were treated with vehicle or barasertib in vivo up to 120 days. Results: DAXX protein levels decreased in ER+ PDX tumors in response to ET. Similar trends were detected in human tumor tissue after ET or chemotherapy alone. DAXX protein levels inversely correlated with Ki67 in ER+ human tumor samples. Analysis of DAXX deletion mutants demonstrated that amino acids 400-740 of the DAXX protein were required to inhibit BCSC survival. This region of the DAXX protein had high levels of phosphorylated residues in response to ET. Only the AURKB (barasertib) inhibitor increased DAXX protein expression and inhibited BCSCs in a DAXX-dependent manner. Barasertib inhibited growth of ER+ MCF-7 tumor xenografts compared to the vehicle control. After treatment ceased, tumor recurrence was measured up to 120 days. Regrowth of tumors was partially delayed in response to barasertib. Conclusions: ET decreased DAXX protein levels in ER+ PDX and human tumors. Downregulation of the DAXX protein by ET was through activation of AURKB and hyper-

phosphorylation of DAXX which resulted in protein degradation and enhanced survival of BCSCs. Therefore, Inhibition of AURKB using barasertib partially restored DAXX expression, inhibited BCSCs, and delayed tumor recurrence. A combination approach of ET plus an AURKB inhibitor might be a novel therapeutic strategy to prevent ER+ breast cancer relapse by increasing DAXX in order to eradicate BCSCs. Support: Breast Cancer Research Foundation

PO4-28-01

Molecular profiling revealed activation of cytokine signaling and suppression of lipid metabolism as the hallmarks of doxorubicin-resistant TNBC

Presenting Author(s) and Co-Author(s):

V. Radhakrishnan. Qatar Biomedical Research Institute, Hamad Bin Khalifa University (HBKU), Doha, Ad Dawhah, Qatar

N. Alajez. Qatar Biomedical Research Institute, Hamad Bin Khalifa University (HBKU), Doha, Qatar

Background: Chemotherapeutic resistance observed in triple-negative breast cancer (TNBC) poses a substantial clinical hurdle, emphasizing the imperative to enhance our comprehension of the underlying mechanisms with the aim of potentially mitigating or reversing this phenomenon. Methods: Doxorubicin-resistant (DoxR) TNBC models (MDA-MB-231 and BT-549) were established through continuous exposure to increasing concentrations of doxorubicin. RNA-Seq was conducted using the Illumina platform, while bioinformatics analyses were performed using CLC genomics workbench 20.2 and iDEP.91. Colony forming unit (CFU), flow cytometry and fluorescent microscopy were used to assess cell proliferation, cell cycle distribution, and cell death, respectively. Western blotting was used to confirm the expression and phosphorylation of protein targets. Ingenuity pathway analysis (IPA) and STRING database v 11.5 were used for network and pathway analyses, while Kaplan-Meier Plotter was used for survival analyses. Results: Herein, we provide a comprehensive functional and transcriptomic characterization of DoxR TNBC models, revealing multiple affected signaling networks and functional categories. The defense and immune response, response to stress, response to cytokine and external stimulus and cytokine-mediated signaling pathways were among the top activated, while suppression of cholesterol, sterol and lipid biosynthesis and metabolism were the hallmarks of DoxR cells. Upstream regulator analysis revealed IL-1B cytokine network activation in DoxR cells. Concordantly, disease and function analysis on the downregulated genes in DoxR TNBC cells revealed the most pronounced enrichment in pathways associated with cell invasion, colony formation, as well as lipid and carbohydrate metabolism. A number of upregulated genes were validated by qRT-PCR, which correlated with unfavorable overall survival (OS). Functionally, DoxR cells exhibited remarkable suppression of cell proliferation, as evidenced by diminished CFU potential, sphere formation and growth under 3D organoid culture, and cell migration. Although DoxR TNBC cells exhibited a slow cell cycling under normal culture conditions, wild-type TNBC cells exhibited remarkable arrest in the G2M phase when exposed to doxorubicin, which was less evident in DoxR TNBC models, suggesting DoxR cells undergo a quiescent state in response to chemotherapeutic challenge. In agreement with those data, increased phosphorylation of CHK2 and p53 proteins was remarkable in DoxR cells, thus promoting cellular dormancy. Conclusion: Our data revealed cellular dormancy and suppression of lipid metabolism as the hallmark associated with doxorubicin-resistant TNBC cells. On the other hand, cytokine signaling and stress response were the most enriched functional categories in DoxR TNBC cells. Therapeutic targeting to reverse the quiescent state or suppression of cytokine signaling networks could enhance the efficacy of doxorubicin-based therapeutics.

PO4-28-02

Adipocyte Progenitor-Mediated Effects on Mammary Cancer Cells

Presenting Author(s) and Co-Author(s):

J. Sunder Singh. The University of Texas at Dallas, Richardson, Texas, United States

P. Joshi. The University of Texas at Dallas, United States

E. Unger. The University of Texas at Dallas, United States

Treatment challenges in breast cancer arise from significant heterogeneity found within breast tumors and the surrounding microenvironment. The tumor microenvironment presents a complex ecosystem which comprises diverse stromal cells including immune, endothelial and fibroblast cell lineages and the extracellular matrix that support tumor progression. Adipocytes represent an abundant cell population in the normal breast and prior studies have reported a crosstalk between adipocytes and mammary cancer cells. De-differentiation of adipocytes into adipocyte progenitor-like cells is linked to a pro-tumorigenic microenvironment in mouse mammary tumors. We have previously demonstrated that adipocyte progenitors in the murine mammary stroma have the capacity to generate epithelial lineages during mammary epithelial growth. The influence of adipocyte progenitors in the mammary tumor microenvironment is not known. In this study, we investigated the effects of adipocyte progenitors on mammary cancer cells and their interactions using the 3T3-L1 adipocyte precursor (AP) cell line and the EO771 syngeneic mammary cancer (MCA) cell line. AP and MCA cell lines were co-cultured, after which MCA cell growth, invasion and migration were assessed using established in vitro assays. MCA cells cultured alone were also exposed to AP-conditioned media to determine whether secreted factors derived from APs could modulate MCA cells. AP cells were found to alter the behavior of MCA cells, affecting their cell proliferation, migration, and cellular phenotype. This work infers the potential of adipocyte progenitors to regulate mammary cancer growth and progression, which warrants further investigation into their fate and role in vivo during mammary tumorigenesis. **Keywords:** breast cancer, adipocyte progenitors, tumor microenvironment

PO4-28-03

Investigating the role of extracellular vesicles in tumor-stromal cell interactions in early-stage breast cancer invasion.

Presenting Author(s) and Co-Author(s):

M. Schmidtmann. University of Notre Dame, United States

G. Richmond. University of Notre Dame, United States

S. Jayman. University of Notre Dame, United States

J. Clancy. University of Notre Dame, United States

C. D'Souza-Schorey. University of Notre Dame, United States

Ductal carcinoma in situ (DCIS) is the most common form of early-stage breast cancer. Anywhere from 10%–30% of DCIS cases progress to invasive ductal carcinoma (IDC), resulting in poor prognosis and clinical challenges. Still, the cellular basis of this DCIS transition remains poorly understood. To escape the primary site during local invasion, DCIS cells navigate through the extracellular matrix and a diverse collection of stromal cells in the surrounding microenvironment. Cancer associated fibroblasts (CAFs) are a stromal cell population that can facilitate tumor invasion in part through extracellular matrix remodeling. CAFs at the primary tumor are largely derived from fibroblasts that have been reprogrammed to an activated state. In addition, several physical, cellular and metabolic changes within the tumor microenvironment (TME) are known to alter the breast cancer invasive capacity. Here we report that forced inhibition of cell invasion, by blocking the activity of known regulators of cell invasion in the ductal epithelial cell line, MCF10ADCIS.com, (herein referred to as DCIS.com), is accompanied by a marked reduction in extracellular vesicle (EV) secretion. Moreover, we show that DCIS.com cells conditioned with secreted EVs exhibit significantly enhanced invasive capacity relative to naïve DCIS.com cells. It is now well documented that breast and other tumor cells release heterogeneous populations of EVs that can function as mediators of intercellular communication in the tumor microenvironment. EVs contain a host of bioactive cargo, such as membrane and cytosolic proteins, various RNA species including microRNAs, as well as dsDNA. These shed vesicles may deposit paracrine information and can also be taken up by stromal cells such as fibroblasts causing the recipient cells to undergo phenotypic changes that profoundly impact various facets of tumor progression. Conversely, EVs shed from stromal cells also affect tumor cell behavior. This unique form of intercellular crosstalk helps condition the TME and promotes both invasive and metastatic activity. In this regard, we found that incubation of human fibroblast cells with EVs shed from tumor cells leads to a loss of SMAD-7 expression (previously implicated in CAF reprogramming), and this loss is abrogated when shedding cells are depleted of miR-21 or regulators of miRNA trafficking to surface-derived EVs. Further, using spheroid invasion assays we demonstrate that fibroblast-derived EVs facilitate directed and leader-follower modes of migration, suggesting the possibility that CAFs likely deposit chemotactic cues to promote directional movement in DCIS. While the regulation of this behavior is still being explored, our observations suggest that EVs, in addition to facilitating distal proteolysis, may also support both autocrine and paracrine signaling during cell invasion. Finally, we are investigating how these pathways may also contribute to the 'field effect' of breast cancerization, a poorly understood process that introduces genetic and phenotypic changes in normal epithelia, potentially contributing to disease onset and/or recurrence.

PO4-28-04

Curcumin inhibits breast cancer cell proliferation by regulating ciRS-7/miR-7-5p/CKS2 axis

Presenting Author(s) and Co-Author(s):

A. Abuaisa. Istanbul University, Institute of Graduate Studies in Health Sciences, Genetics Department, Istanbul/ Turkey, Istanbul, Turkey

M. Kaya. Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Medical Genetics, Istanbul/Turkey, Istanbul, Turkey

I. Suer. Istanbul University, Istanbul Faculty of Medicine, Medical Genetics Department, Istanbul/Turkey, Istanbul, Turkey

S. Emiroglu. Istanbul University, Istanbul Faculty of Medicine, Department of General Surgery, Division of Breast Surgery, Istanbul/Turkey, Istanbul, Turkey

F. Abanoz. Istanbul University, Institute of Graduate Studies in Health Sciences, Genetics Department, Istanbul/ Turkey, Istanbul, Turkey

M. Tukenmez. Istanbul University, Istanbul Faculty of Medicine, Department of General Surgery, Division of Breast Surgery, Istanbul/Turkey, Istanbul, Turkey

N. Cabioğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Bakırköy, Istanbul, Turkey

M. Muslumanoğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey

K. Cefle. Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Medical Genetics, Istanbul/Turkey, Istanbul, Turkey

S. Palanduz. Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Medical Genetics, Istanbul/Turkey, Istanbul, Turkey

S. Ozturk. Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Medical Genetics, Istanbul/Turkey, Istanbul, Turkey

Background Breast cancer (BC) is the most common cancer in women worldwide. Curcumin is a polyphenolic turmeric-derived compound that has anti-proliferative and anti-tumor properties in different cancer types by acting on multiple molecules. Circular RNAs (circRNAs) are non-coding, single-stranded, covalently closed RNA molecules that act as regulators of the microRNA (miRNA) activity. Recent studies show that circRNAs are potential contributors to the onset and progression of many cancer types. CircRNA ciRS-7 acts as an oncogene and accelerates tumor progression by competitively suppressing miR-7-5p in BC. However, whether curcumin can regulate ciRS-7 to inhibit BC progression is still unclear. **Method** Breast Cancer cell lines (MCF-7 and T47D) and normal epithelial cell line (MCF-10A) were cultivated and treated with Curcumin (5µM, 10 µM, 20 µM) or DMSO as a control. Also, the cell lines were transfected with ciRS-7 siRNA, miR-7-5p mimic, and their non-targeted controls. The cell viability was detected by Cell Viability Detection Kit-8 (CVDK-8) using an ELISA plate reader. To detect cell migration, scratch assay was performed after 24hs of transfection and a phase contrast microscope was used to acquire images. The effect on apoptosis was detected by Annexin V-FITC Apoptosis Detection Kit using flow cytometry. Potential target genes of miR-7-5p were identified by searching for the overlapping genes in miRNet and miRTarBase v8 with the overexpressed genes in BC patient tissue samples in the TCGA database. Quantitative real-time polymerase chain reaction (qRT-PCR) was used to detect the expression of ciRS-7, miR-7-5p, and the selected genes. qRT-PCR experiments were performed in duplicate and the

$2^{-\Delta\Delta Ct}$ method was used for relative quantitation analysis. Results Curcumin treatment, depending on the increased doses, decreased cell proliferation through inducing apoptosis in MCF-7 and T47D cancer cells. Curcumin's anti-proliferative effect was shown to be quite restricted on normal MCF-10A cells, as compared to MCF-7 and T47D cancer cells. In MCF-7 and T47D cells treated with curcumin, cell migration was dramatically inhibited. Curcumin has very little influence on the migration of MCF-10A cells. In both cancer cell group that was transfected with ciRS-7 siRNA and miR-7-5p mimic, it was observed that apoptosis was increased, proliferation was suppressed, and migration was decreased compared to its control groups. Moreover, the expression of ciRS-7 was found to be significantly decreased in the curcumin-treated group, while miR-7-5p was shown to be significantly higher. CKS2 gene one of the possible target genes of miR-7-5p that was identified by using in silico approaches, was also downregulated in curcumin-treated BC cell lines compared to its control group. ciRS-7 and CKS2 expression levels were found to be downregulated, whereas miR-7-5p expression level was found to be elevated in MCF-7 and T47D cells that were transfected with ciRS-7 siRNA. Additionally, CKS2 gene expression was found to be downregulated in miR-7-5p mimic transfected cells. Conclusion Curcumin is derived from the turmeric plant (*Curcuma longa*) and has been used since 3000 B.C. as a food additive. Nowadays, curcumin is one of the most essential anti-cancer substances that was examined. However, investigations on the influence of curcumin on the circRNA-miRNA-mRNA axis are scarce. Curcumin has been demonstrated to inhibit proliferation and induce apoptosis of BC cells via the ciRS-7/miR-7-5p/CKS2 axis in the present study. Keywords Breast Cancer, Curcumin, ciRS-7, miR-7-5p, CKS2

PO4-28-05

Prolactin drives labile iron transfer from macrophages to breast cancer cells through CD44

Presenting Author(s) and Co-Author(s):

R. Farrell. Texas Tech University, United States

N. Pascuzzi. Texas Tech University, United States

Y. Chen. National Kaohsiung University of Science and Technology, United States

M. Torres. Texas Tech University, United States

M. kim. Texas Tech University, United States

L. Gollahon. Texas Tech University, United States

K. Chen. Texas Tech University, United States

Cancer cells are “ferrophilic” and exhibit great dependence on iron. While iron metabolism is closely related to tumor development, the source of iron and the mechanisms cancer cells adopt to actively acquire iron is not well understood. In the present study, we discovered a novel function of the lactating hormone, prolactin, in the regulation of iron transport. In breast cancer cells using mouse triple negative breast cancer cell lines EO771 and Py230 for demonstration, prolactin stimulation increased intracellular labile iron pool. Analyses of gene expression involved in iron transport revealed dramatic induction of CD44, a surface receptor for iron bound hyaluronan. Other genes involved in iron uptake including transferrin receptor (TFRC), CD163 and divalent metal transporter 1 (DMT1) were not changed. The utilization of neutralizing antibodies against CD44 significantly blocked prolactin mediated labile iron pool accumulation in breast cancer cells. In contrast to what was found in breast cancer cells, prolactin had the opposite impact on immune macrophages. Prolactin treatment increased ferroportin (FPN I, iron exporter) but had no influence on all iron uptake transporters leading to net iron release by macrophages. To further determine if the iron released by macrophages can be a direct source of iron utilized by breast cancer cells, we conducted co-culture work of macrophages with pre-stained labile iron pool and breast cancer cells without any iron staining and found a gradual increase of fluorescent iron pool developed in breast cancer cells over time. In conclusion, our work presents a multidisciplinary regulation of iron transport among prolactin, macrophages, and cancer cells. The novel regulatory role of prolactin to drive iron flow can provide new information on fine-tuning immune responses in tumor microenvironment and potentially benefit the development of novel therapeutics.

PO4-28-06

A Single-minded-2s/Sirtuin interaction in the regulation of mitochondrial dynamics across normal mammary development and ER+ BC progression

Presenting Author(s) and Co-Author(s):

H. Carter. Texas A&M University, United States

Characterizing the mechanisms underlying the regulation of cellular differentiation and mitochondrial dynamics are critical to understanding normal development and breast cancer in the mammary gland. Our previous studies have highlighted the significance of Single-minded-2s (Sim2s), a member of the bHLH/PAS family, in regulating mitochondrial dynamics during mammary gland development and the progression of estrogen receptor-positive (ER+) breast cancer. Sim2s is temporally regulated, with maximal expression occurring during mid-lactation. Cross-fostered pups nursed by mice over-expressing Sim2s under the mouse mammary tumor virus (MMTV-Sim2s) display significantly higher weights by mid-lactation compared to pups nursed by control dams. Overexpression of Sim2s leads to alterations in mitochondrial morphology and dynamics, characterized by increased OPA1 expression and decreased DRP1 levels, resulting in enhanced mitochondrial fusion and elongation. Furthermore, we have extended our investigations to an ER+ breast cancer cell line (MCF7). We have identified SIM2s as a tumor suppressor expressed in mammary epithelial cells, known to inhibit epithelial-mesenchymal transition (EMT) and metastasis. In our previous studies, we discovered that loss of SIM2s expression in the MCF7 cell line promotes mitochondrial fragmentation, as evidenced by a decrease in OPA1 expression and an increase in DRP1 levels. In conjunction with these findings, literature suggests that sirtuins also play a role in the regulation of mitochondrial dynamics similar to Sim2s. Specifically, there is an upregulation of Sirtuin 1 in cancer when Sim2 is lost, while Sirtuin 3 increases during differentiation and normal development progression. Therefore, our aim is to elucidate the potential interaction between Single-minded-2s and sirtuins, a family of NAD⁺-dependent deacetylases, in the regulation of mitochondrial dynamics. We hypothesize that Sim2s may modulate mitochondrial function through its association with sirtuins, thereby influencing normal mammary gland development and breast cancer progression.

PO4-28-07

SLC26A9 promotes triple-negative breast cancer progression by regulating lipid metabolism

Presenting Author(s) and Co-Author(s):

Y. Zhou. Department of General Surgery, Affiliated Hospital of Zunyi Medical University, United States

H. Wang. Affiliated Hospital of Zunyi Medical University, China (People's Republic)

Z. Zhou. Breast and Thyroid Surgery, Department of General Surgery, The Affiliated Hospital of Zunyi Medical University, Zunyi, China, United States

X. Liu. Affiliated Hospital of Zunyi Medical University, China (People's Republic)

B. Tuo. Department of Gastroenterology, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, United States

T. Li. Breast and Thyroid Surgery, Department of General Surgery, The Affiliated Hospital of Zunyi Medical University, Zunyi, China, United States

Background:

The disturbance of lipid metabolism in the microenvironment plays an important role in the occurrence and development of triple-negative breast cancer(TNBC). SLC26A9, a member of the SLC26A family of anion transporters, is involved in breast oncogenesis. However, the effect of SLC26A9 in triple-negative breast cancer on lipid metabolism in the tumor microenvironment remains unclear.

Methods:

Bioinformatics, tissue microarrays and TNBC cell lines were used to detect the expression of SLC26A9 and its clinical significance. By altering the expression of SLC26A9 gene in TNBC cells, the effects of SLC26A9 on the regulation of lipid metabolism, cell biological behavior and its related molecular mechanisms in the TNBC microenvironment were explored using adoptive staining techniques, flow cytometric analysis and animal models.

Results:

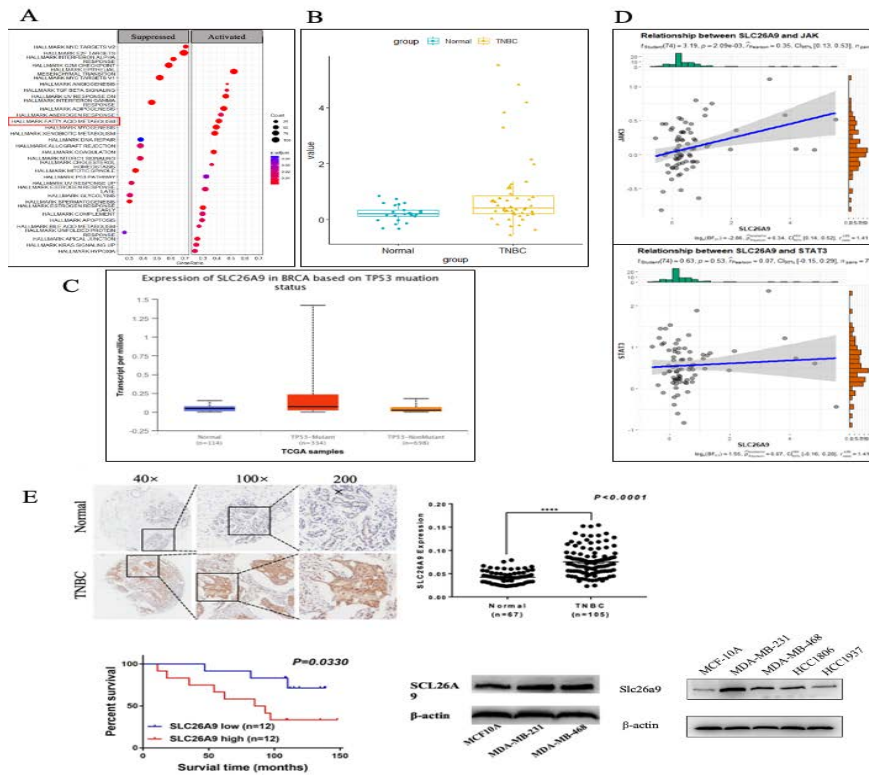
We found by tissue microarray (TNBC=105 cases, Nor=67 cases) that the expression of SLC26A9 was significantly up-regulated in BC compared to paracancerous tissues, where SLC26A9 expression was higher in TNBC, and the same results were obtained in BC cell lines. Secondly, we found that SCL26A9 was positively correlated with lipid metabolism status in TNBC microenvironment and possessed a close association with P53 mutation by analyzing GEO and TCGA databases. Therefore, we used two cell lines (MDA-MB-231, MDA-MB-468) in which SCL26A9 was highly expressed in TNBC cell lines. It was demonstrated by oil red O staining and lipid fluorescence staining that knockdown/silencing of SLC26A9 diminished the ability of MDA-MB-231 and MDA-MB-468 cells to uptake and utilize lipids, especially for metabolites such as neutral lipids: triglycerides, lipid droplets, and steroidal substances. Then we demonstrated by using fatty acid flow cytometric analysis that knockdown/silencing of SLC26A9 significantly reduced the utilization and production of fatty acids in MDA-MB-231 and MDA-MB-468 cells, which are the key metabolic indicators of cancer cells as well as important energy-providing substances for cancer progression. Therefore, we further verified functionally that cell proliferation, migration, invasion and anti-apoptosis were significantly inhibited in in vitro after knockdown/silencing of SLC26A9, and in vivo tumorigenesis was significantly inhibited in BALB/c nude mice in in vivo. In addition, the expression of markers of lipid

metabolic activity (FASN, ACLY) was reduced after knockdown/silencing of SLC26A9 in MDA-MB-231 cells by Western Blot, and the reduced expression of FASN and ACLY mainly inhibited the ab initio synthesis, uptake and utilization of fatty acids in TNBC cells, which in turn regulated the proliferation and invasion of TNBC. Mechanistically, SLC26A9 silencing/knockdown inhibited the synthesis, uptake, and utilization of multiple metabolites of lipids in TNBC, which combined with the TCGA database results revealed the activation of the key signaling pathway, the JAK-STAT3 signaling pathway, to promote the progression of TNBC.

Conclusion(s):

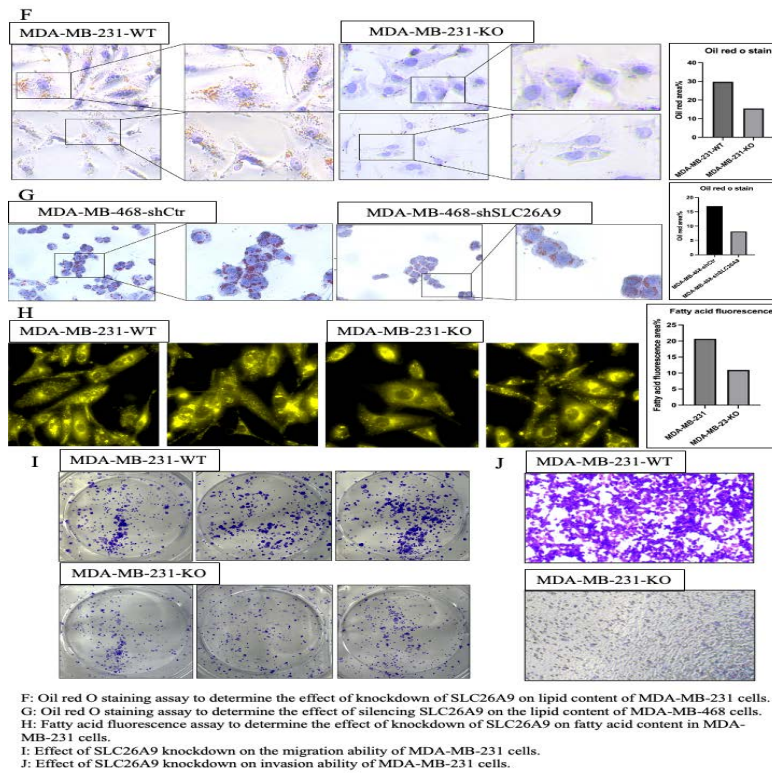
SLC26A9 is involved in the disturbance of lipid metabolism in the TNBC microenvironment and regulates the progression of TNBC. The search for new SLC26A9 inhibitors is expected to provide a new direction for the treatment of TNBC, but the exact molecular mechanisms need to be further explored.

SLC26A9 upregulation in TNBC leads to a poor prognosis by referencing lipid metabolism in the TNBC microenvironment Wench.

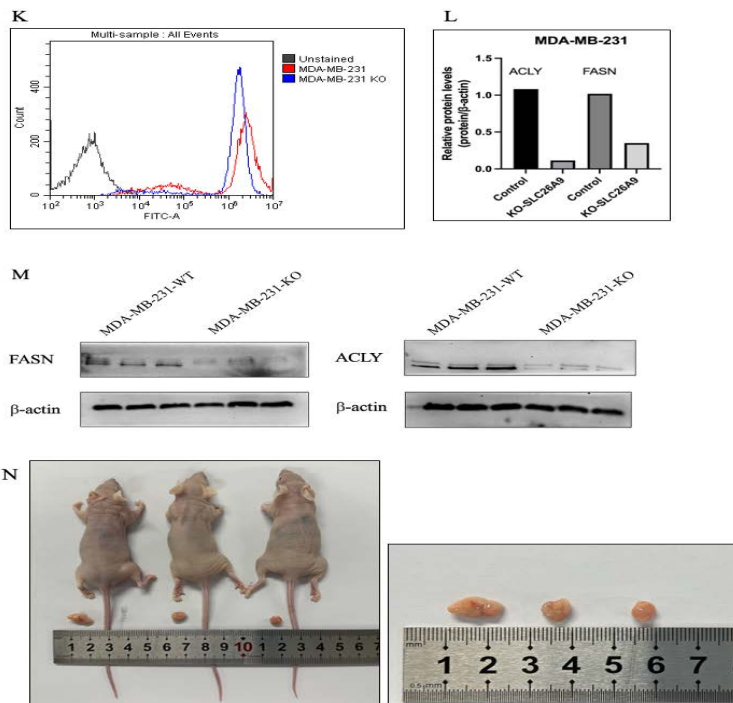


A: Analysis of SLC26A9 correlation with lipid metabolism in GEO database.
 B: Correlation analysis of SLC26A9 with paraneoplastic tissues in triple-negative breast cancer in GEO database.
 C: Correlation analysis of SLC26A9 with P53 in breast cancer in TCGA database.
 D: Correlation analysis of SLC26A9 with JAK-STAT3 signaling pathway in TCGA database.
 E: Expression of SLC26A9 in triple-negative breast cancer and paraneoplastic tissues in tissue microarrays; relationship between SLC26A9 and survival rate of breast cancer; expression of SLC26A9 in cell lines (MDA-MB-231, MDA-MB-468).

SLC26A9 is involved in lipid metabolism disorders and cell biological functions in the TNBC microenvironment in vivo.



SLC26A9 is involved in disordered lipid metabolism in the TNBC microenvironment.



PO4-28-08

Unraveling the Role of BRCA1-BARD1 E3 Ubiquitin Ligase in DNA Repair: A Promise for Enhanced Chemotherapy Outcomes

Presenting Author(s) and Co-Author(s):

W. Li. UT Health San Antonio, United States

M. Wang. UT SouthWest, United States

N. Tomimatsu. UT Health San Antonio, United States

J. Ji. UT Health San Antonio, United States

S. Alejo. UT Health San Antonio, United States

G. Sareddy. UT Health San Antonio, United States

S. Burma. UT Health San Antonio, United States

R. Klevit. University of Washington, United States

W. Zhao. UT Health San Antonio, United States

BACKGROUND: BRCA1, a central player in gynecological cancers, collaborates with BARD1 to shape a potent complex pivotal for DNA binding and ubiquitin E3 ligase activities. This complex impacts a myriad of biological pathways. Notably, BRCA1-BARD1's role in tumor suppression and homology-directed DNA repair (HDR) has been spotlighted. Our innovative approach used RING-domain mutations to craft ligase-dead BRCA1-BARD1 mutants, hypothesizing that these mutants would offer fresh insights into the DNA repair dynamics of BRCA1-BARD1. **METHODS:** Full length BRCA1-BARD1 or truncated mutants, and histones were purified from *E. coli*. or insect cells. Nucleosomes were assembled for in vitro ubiquitylation reaction and binding assays. Stable mammalian cell lines HeLa and MDA-MB-436 that express wild type or mutant forms of BRCA1 and BARD1 were established for a host of analyses, including cellular fractionation, foci analysis, Proximity ligation assay (PLA), comet assays and clonogenic survival assays with various DNA damage agents. **RESULTS:** By systematic biochemical screening and a series of in vitro assays, we generated a truly BRCA1-BARD1 E3 dead mutant, BRCA1^{I26A, L63A, K65A}-BARD1 (BRCA1-E3d), which lacks E3 ligase activity but possesses all other known attributes such as retention of BRCA1-BARD1 heterodimeric structure formation, DNA binding, and intact RAD51-mediated recombinase activity. To our surprise, we discovered that previously described BRCA1-BARD1 RING-domain mutant (BRCA1-I26A) still possessed ubiquitylation activity not found in BRCA1-E3d. To determine the biological significance of these mutants, cells stably expressing BRCA1-E3d were treated with various DNA-damaging agents and shown to more sensitive than WT or previously identified mutants. DNA repair pathway reporter assays determined these cells were deficient in various repair pathways compared to their BRCA1-WT counterparts. Further studies demonstrate that BRCA1-BARD1 E3 ligase is required for DNA resection during HDR, as evidenced in reduced levels of DNA repair-related foci formation such as RPA, RAD51 and CtIP in BRCA1-E3d cells. Furthermore, compared to BRCA1-WT cells, BRCA1-E3d cells were more sensitive to DNA damage reagents after depletion of 53BP1, which indicates BRCA1-BARD1 E3 ligase function also contributes to later stages of DNA repair completion. **CONCLUSIONS:** Our work dispels prevailing ambiguities surrounding BRCA1-BARD1 E3 ligase functions, underscoring its paramountcy in genome repair. This trailblazing research not only enriches our understanding but also beckons therapeutic interventions targeting tumor suppression. The unveiling of BRCA1-BARD1 E3 ligase's intricate regulatory dynamics

combined with our novel mutants paves the way for an exciting new era in cancer therapeutics, hinting at superior treatments to enhance patient recovery.

PO4-28-09

Upregulation of the immune checkpoint protein B7-H3 is associated with an immune suppressive microenvironment in progression from in situ to invasive lobular breast cancer

Presenting Author(s) and Co-Author(s):

L. Bennett. University of Texas Southwestern Medical Center, Dallas, Texas, United States

S. Sahoo. University of Texas Southwestern Medical Center, United States

C. Lewis. University of Texas Southwestern Medical Center, United States

I. Raman. University of Texas Southwestern Medical Center, Dallas, Texas, United States

C. Frerich. ut southwestern medical center, United States

G. Chen. University of Texas Southwestern Medical Center, United States

M. Xu. University of Texas Southwestern Medical Center, United States

S. Conzen. University of Texas Southwestern Medical Center, United States

Invasive lobular breast cancer (ILC) is an understudied subtype of breast cancer characterized by late recurrence, metastasis to serosal surfaces including the peritoneum, and poor long-term outcomes. Lobular carcinoma in situ (LCIS) is a non-obligate precursor to ILC but is associated with a 30% increased risk of developing ILC. Therefore, understanding the underlying changes that occur in the invasive lobular cells as well as their tumor microenvironment (TME) during the transition from LCIS to ILC is critical for the development of novel therapeutic targets that could be used in early disease. To address this, we used combined spatial whole genome transcriptomics and a 97-protein proteomics assay to examine the spatial molecular profiles of coexistent LCIS and ILC. PanCK-positive tumor cells and panCK-negative stromal cells were segmented and analyzed separately for both RNA and protein. Despite the close spatial proximity of LCIS and ILC, there were notable differences in gene and protein expression in the tumor cells as well as the tumor microenvironment (TME). RNA profiling revealed significant upregulation of genes encoding essential components of the extracellular matrix, including type I, 3 and 5 collagens, small leucine-rich proteoglycans biglycan (BGN) and lumican (LUM), periostin (POSTN) and secreted protein acidic and cysteine rich (SPARC). Metalloprotease genes MMP2 and MMP11 were also upregulated. Genes highly expressed in the LCIS tumor compartment were KRT5, KRT14 KRT17 and MYLK which are highly expressed in myoepithelial cells at the periphery of the LCIS. One of the most upregulated proteins in ILC cells was B7 homology 3 protein (B7-H3) or Cluster of Differentiation 276 (CD276). B7-H3 is a transmembrane immunoregulatory protein belonging to the B7 family (that also includes PD-L1 and PD-L2). This immune checkpoint protein is overexpressed in many tumors but is barely expressed in normal cells. B7-H3 has been associated with several aspects of cancer progression, such as evasion of tumor immune surveillance and metastasis, and is strongly linked to poor prognosis in cancer. Compared to the LCIS TME, B7-H3 was also the most upregulated protein in the ILC TME along with the tumor-promoting M1 macrophage marker CD68 and the regulatory T-cell marker FOXP3. The lymphocyte marker CD45 was downregulated as well as T-cell proteins CD3, CD40 and granzyme B. Moreover, CD27, a memory B-cell marker was most highly expressed in the TME surrounding LCIS compared to ILC. Overall, these molecular profiles support a transition to a toward a much more immunosuppressive environment for invasive tumor cells compared to LCIS. Based on these data, our working hypothesis is that upregulation of B7-H3 on lobular tumor cells promotes invasion allowing interaction with laminins, integrins and other ECM proteins in the basement membrane and the interstitial membrane as LCIS acquire invasive properties of ILC.

Furthermore, upregulation of B7-H3 on CD3+ HLA-DR+ expressing antigen presenting cells also promotes a suppressive immune microenvironment by inhibiting T-cell proliferation and downregulating cytokine production. In sum, these strongly concurrent spatial transcriptome and protein data suggest that B7-H3 and the immune suppressive network of ILC may be a promising target for early stage lobular breast cancer. B7-H3 Inhibitors could be explored in the neoadjuvant setting to evaluate the efficacy of immunotherapy in primary ILC.

PO4-28-10

Single-Cell Transcriptomic Assessment of Stromal and Immune Crosstalk on Breast Cancer Invasion Using 3D Tumor-On-Chip Model

Presenting Author(s) and Co-Author(s):

K. Ravi. Arizona State University, United States

L. Sakala. Arizona State University, United States

J. Park. Arizona State University, United States

J. LaBaer. Arizona State University, United States

M. Nikkhah. Arizona State University, United States

Introduction: Our understanding of cancer has evolved over the last decades, with treatments increasingly targeting stromal cells in the tumor microenvironment (TME). The TME comprises transformed cancer cells and various non-cancerous cell types such as fibroblasts, macrophages, and endothelial cells. Despite this understanding, disrupting the tumor-stromal interactions are not targeted mainstream, as the stromal cells in the TME are genetically stable and can induce both beneficial and adverse effect on tumorigenesis. Thus, ex vivo tumor models that can faithfully recapitulate these critical tumor-stroma interactions are required to mechanistically understand the multifaceted reaction occurring within the TME. In this study, we established an innovative and multi-cellular TME on-a-chip model and assessed the synergistic effect of patient-derived Cancer Associated Fibroblast (CAF's) and macrophages ($M\phi$) on breast cancer progression. **Materials and Methods:** The influence of stromal components on cancer progression was assessed using the microfluidic model that allows spatial organization of various cell types. Tri-culture invasion model was established using Sum159 breast cancer cells, patient-derived CAFs, and THP-1 derived naïve ($M\phi$) macrophages. Sum159 mixed with collagen and Matrigel forms the tumor region, while CAF's and $M\phi$ embedded in collagen form the stromal region. Functional and real-time assessments such as migration, morphometric analysis, and proliferation studies were conducted to understand the stromal influence on cancer cells. Gene expression analysis on an array of macrophage activation genes was performed to identify the polarized state of the macrophages after cellular interactions. Finally, Single Cell-RNA sequencing was carried out to unveil the drivers of stromal-immune crosstalk on invasion. **Results and Discussion:** Using the TME on-a-chip model, we compared cancer cell invasion across 4 different culture conditions namely monoculture (Sum only), co-culture (Sum+CAF, Sum+ $M\phi$) and tri-culture (Sum+CAF+ $M\phi$). Cancer cell migration was significantly increased in the triculture condition compared to others and stromal components also enhanced cancer cell proliferation. Hierarchical clustering of migration and morphological changes demonstrated that the co-culture conditions grouped together while CAF+ $M\phi$ exerted the highest influence on cell migration and clustered separately. To understand the bi-directional communication between tumor and stroma, we assessed the polarized states of naïve macrophages using qPCR. Gene expression analysis showed that tumor-educated macrophages showed characteristics of M1 and M2 phenotypes and communicated reciprocally with tumor cells. Finally, to investigate the molecular mechanics of complex cellular interactions, we performed sc-RNA sequencing on cells extracted from the device and 2D cells (controls). Unsupervised clustering identified 11 different clusters, categorizing cells as Sum159 (tumor cells), CAFs (Stromal), and $M\phi$ (Immune) based on cell-specific markers. Notably, we observed a noticeable shift in the clusters of Sum159 cells between 2D and 3D samples, emphasizing the difference between these two cultures. **Conclusion:** Using the TME on-a-chip, we confirmed the critical influence of microenvironmental components on tumor progression through functional assessment. Gene-expression analysis revealed bi-directional

communication between noncancerous stromal components and tumor cells highlighting the importance of microenvironmental crosstalk. Furthermore, sc-RNA sequencing revealed the differences between 2D and 3D cultures. Ongoing work aims to perform transcriptomic and bioinformatic analysis on the sc-RNA sequencing data to gain a deeper understanding of the multifaceted communication within our platform.

PO4-28-11

Murine Breast Cancer Cell Culture Supernatant Induces CAF-like and TAM-like Traits in Normal Cells

Presenting Author(s) and Co-Author(s):

B. Sapkota. Louisiana State University, United States

N. Chintalaramulu. Louisiana State University, United States

A. Pandit. Louisiana State University, United States

S. Thota. Louisiana State University, United States

R. Begum. Louisiana State University, United States

J. Francis. Louisiana State University, United States

Several studies in the past have demonstrated the role of cell-to-cell interaction (crosstalk) between tumor cells and normal (nontumorigenic) cells in cancer progression and metastasis. Within the tumor microenvironment (TME), these interactions have a potential to transform the phenotypes and the behaviors of normal cells. Application of the 2D in-vitro cultures has been limited due to its inability to replicate the complex in-vivo TME. Conditioned Medium (CM) obtained from cultured cancer cells contains secreted growth factors that potentially regulate the phenotype and the functionality of normal cells. In this study, a culture of normal murine fibroblast NIH3T3 and macrophage RAW 264.7 cells with conditioned medium (CM) obtained from malignant mammary epithelial 4T1 cells (4T1CM) resulted in an altered phenotype with increased cell viability. 4T1CM treated NIH3T3 and RAW 264.7, in comparison with the respective control cells, resulted in an upregulation of the genes including- α -smooth muscle actin (α SMA), IL-10, CD206, and vascular endothelial growth factor (VEGF). In addition, 4T1.CM treated NIH3T3 showed an EMT phenotype as indicated by the regulation of EMT markers such as, E-cadherin, β -catenin, N-cadherin, and Vimentin. Interestingly, an upregulation of cyclooxygenase-2 (COX-2) and programmed death-ligand 1 (PDL-1) was observed in 4T1CM treated RAW 264.7, a tendency towards exhibiting an inhibitory immune response. Intriguingly, NIH3T3 cells conditioned with 4T1CM demonstrated an upregulation of stemness markers including- sex determining region Y-box 2, and Aldehyde dehydrogenase. Collectively, our study suggested a role for 4T1CM in transforming the normal NIH3T3 and RAW 264.7 into cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs). RNAseq experiments are underway to map differentially expressed genes (DEGs) that potentially regulate the 4T1CM induced transformation of NIH3T3 and RAW 264.7 cells. Furthermore, invitro drug testing in 3D model of these transformed cells to target the pathway intermediates may provide novel therapeutic intervention strategies.

PS13-01

Worse Prognosis for Breast Cancer in the Second and Third Trimesters and Shortly Postpartum: An Update of the Dutch Pregnancy-Associated Breast Cancer Cohort

Presenting Author(s) and Co-Author(s):

C. Bakhuis. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

C. Van Doijeweert. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

B. Suelmann. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

J. Verloop. Netherlands Comprehensive Cancer Organisation, Netherlands

P. Westenend. PALDordrecht, Dordrecht, Zuid-Holland, Netherlands

S. Linn. Netherlands Cancer Institute, Amsterdam, Netherlands

P. Van Diest. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

E. Van der Wall. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

Rationale: Pregnancy-Associated Breast Cancer (PABC), often defined as breast cancer during pregnancy (PrBC) or in the first year postpartum (PPBC), is known for its aggressive histopathology and higher stage at diagnosis. In a previous study of the nationwide Dutch PABC Cohort, we observed an impaired survival for patients diagnosed in the second and third trimester of pregnancy. However, the etiology of these differences, and how this relates to the patients diagnosed with breast cancer in the postpartum period (PPBC) or after an abortion (AABC), remains to be elucidated. While we are exploring the etiologic hypotheses, we updated and expanded our database to compare these specific PABC subgroups. **Methods:** All pathology reports of invasive breast carcinoma between January 1st 1988 and July 1st 2022 were screened for pregnancy-related keywords to find all patients diagnosed with PrBC, PPBC or AABC within one year after childbirth or an interrupted pregnancy (induced abortion or miscarriage before a gestational age of 24 weeks). A local patient series provided 22 additional cases. Pregnant patients were subdivided by gestational trimester at time of diagnosis. The different PrBC, PPBC and AABC subgroups were compared by histopathology, clinical characteristics and outcome. **Results:** 787 patients were included, of whom 60% were pregnant during their diagnosis. Median age at diagnosis was 34 years. In line with our previous findings, a large majority (68%) of patients had a Bloom & Richardson (B&R) grade III tumor and 37% of tumors were triple negative. Moreover, over a third of patients presented with lymph node metastases (38%). We observed two distinct groups based on histopathology and prognosis: group A, consisting of three patient groups: (I) patients diagnosed in the first trimester of pregnancy, (II) patients diagnosed between 6-12 months postpartum, and (III) patients diagnosed after an abortion, and group B, consisting of two patient groups, (I) patients diagnosed in the second or third trimester of pregnancy or (II) within 6 months after childbirth. Compared to group A, patients in group B more often had B&R grade III tumors: (73% vs. 60%, $p=0.002$) and more frequently had triple negative tumors (43% vs. 28% in group A, $p<0.001$). Survival was significantly worse for patients in group B (5-year OS 67,3% versus 88.2%, $p<0.001$). In a multivariable analysis, corrected for grade, type of surgery and overall stage, these differences upheld with an HR of 1.515 (95% CI 1,012 – 2,268). **Conclusions:** With this extensive update of our nationwide Dutch PABC cohort, we show that especially PrBC patients diagnosed in the second and third trimesters and PPBC patients within six months after childbirth exhibit unfavorable tumor characteristics, with an associated worse prognosis. This highlights the need for in-depth analyses in these specific groups of PABC patients to elucidate the etiologic mechanisms involved.

PS13-02

Clinical Outcome and Patients' Characteristics of Breast Cancer Diagnosed During Pregnancy: A Retrospective Single Institutional Study

Presenting Author(s) and Co-Author(s):

M. ELSHENAWY. King Faisal Specialist Hospital & Research Center, United States

E. Haque. College of Medicine, Alfaisal University, United States

A. Badran. King Faisal Specialist Hospital & Research Center, Saudi Arabia

A. AISayed. King Faisal Specialist Hospital and Research Center, Saudi Arabia

T. Twegieri. King Faisal Specialist Hospital and Research Center, Saudi Arabia

D. Ajarim. King Faisal Specialist Hospital and Research Center, Saudi Arabia

W. Khayal. King Faisal Specialist Hospital & Research Center, United States

O. Al Malik. King Faisal Specialist Hospital & Research Center, United States

A. Al Hefdhi. King Faisal Specialist Hospital & Research Center, United States

T. El Hassan. King Faisal Specialist Hospital & Research Center, United States

S. Akhtar. King Faisal Specialist Hospital & Research Center, United States

M. Al Zahrani. King Faisal Specialist Hospital & Research Center, United States

S. Al Aklabi. King Faisal Specialist Hospital & Research Center, United States

K. Suleman. King Faisal Specialist Hospital and Research Center, Riyadh, Ar Riyad, Saudi Arabia

Background: Breast cancer (BC) is considered the second most common malignancy affecting pregnant women. Treatment of this condition is complex due to the potential risks it poses to both the fetus and mother. In this study, we report on the incidence, clinicopathological characteristics, management, and the outcomes of patients diagnosed with breast cancer during pregnancy in a tertiary care institution in Saudi Arabia. **Patients and methods:** This is a single-institution retrospective cohort analysis. We reviewed the medical records of all breast cancer cases in pregnant women that were diagnosed and treated at a tertiary care center in Saudi Arabia, during the period from 2001 to 2017. We used Fisher's exact test, chi-square, and Kaplan-Meier (KM) method for various analyses. Demographic data, treatment received, response, and prognostic factors were analyzed. The study was approved by the institutional review board at our center. **Results:** One hundred seventy-three patients met the search criteria. Median age at diagnosis was 34 (IQR: 30 – 38) years. Of these patients, 100 (58%) had invasive ductal carcinoma (IDC), 42 (24%) had IDC with ductal carcinoma in situ (DCIS), and 15 (20%) had other types. One hundred forty-two (82%) had pathological grades 2 and 3. Hormone receptors were positive in 90 (52%) patients, negative in 79 (45.7) patients and unknown in 4 (2.3%) patients. Her2/neu receptor status was positive in 67 (38.7%) patients and negative in 96(55.5%) patients. Forty five (26%) patients had triple negative disease. Stages I, II, III and IV were identified in 7(4%) , 47 (27.2%), 54 (31.3%) and 51 (29.5%) patients respectively. Ninety (52%) and 75 (43%) patients received neoadjuvant and adjuvant anthracycline, platinum or taxane based chemotherapy. After being implemented in different international and our institutional guidelines, anti-Her2/neu therapies were given in 35 (20.2%) patients. The median overall survival (OS) was 127 months. Univariate analysis had shown statistically significant correlation between clinical stage, hormonal status, and overall survival. **Conclusion:** Breast cancer diagnosed during pregnancy is associated with poor outcomes. Breast cancer awareness and screening programs are essential for early detection and proper

management thereby leading to better outcomes.

PS13-03

Safety of taxane chemotherapy for the treatment of breast cancer during pregnancy: an international cohort study

Presenting Author(s) and Co-Author(s):

A. Ferrigno Guajardo. Yale University School of Medicine, New Haven, Connecticut, United States

B. Vaca-Cartagena. Hospital Zambrano Hellion - TecSalud, Tecnologico de Monterrey, United States

E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

C. Bousrih. Gustave Roussy, Villejuif, France

O. Oke. MD Anderson Cancer Center, United States

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

F. Peccatori. Fertility and Procreation Unit, IEO European Institute of Oncology IRCCS, Milan, Italy

W. Muñoz-Montaño. Instituto Nacional de Cancerología, Mexico

A. Cabrera-Garcia. Hospital Regional de Alta Especialidad de Ixtapaluca, Mexico

M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy

L. Corrales. Centro de Investigación y Manejo del Cáncer (CIMCA), United States

A. Becerril-Gaitan. University of Texas Health Science Center, United States

T. Sella. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Newman. Brigham and Women's Hospital Boston/Harvard Medical School, United States

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

A. Martinez. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

C. Ortiz. Breast Cancer Program. Vall d'Hebron Institute of Oncology/Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

L. Joval-Ramentol. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

G. Scarfone. Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Italy

B. Buonomo. Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Italy

F. Lara-Medina. Instituto Nacional de Cancerología, Mexico

J. Sanchez. Hospital Regional de Alta Especialidad de Ixtapaluca, Mexico

L. Arecco. School of Medicine, University of Genova, United States

A. Ramos-Esquivel. Hospital San Juan de Dios, Caja Costarricense de Seguro Social, Costa Rica

S. Susnjar. Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

G. Morgan. Skåne University Hospital, United States

C. Villarreal-Garza. Tecnologico de Monterrey, Nuevo Leon, Mexico

H. Azim. School of Medicine, Monterrey Institute of Technology, Monterrey, Nuevo Leon, Mexico

Introduction: The addition of taxanes to anthracycline-based chemotherapy regimens offers increased odds of survival in breast cancer (BC) patients. However, some clinicians defer their use in pregnant patients due to limited evidence supporting safety during gestation. The aim of this study is to describe the prevalence of maternal and neonatal adverse events in BC patients exposed to taxane-containing regimens during pregnancy. **Methods:** This is an international cohort study of BC patients treated with taxane chemotherapy during pregnancy. Inclusion criteria were age ≥ 18 years, treatment in a participating center (n=10), and completion of pregnancy. **Results:** A total of 103 women with a median age of 34 years (range 21-44) were included, of whom the majority (91/101; 90.1%) were also exposed to anthracyclines. The median gestational age at initiation of any chemotherapy agent was 16 weeks (range 4-34), while that of taxanes was 28 weeks (range 12-37). Paclitaxel was the most frequently used taxane (100/103; 97.1%), most prescribed as an 80 mg/m² weekly infusion. All cases were singleton pregnancies except for one twin gestation. The overall live birth rate was 98.0% (100/102). Median gestational age at delivery was 37 weeks (range 32 to 40), with 36/83 live births being preterm (gestational age of < 37 weeks; 43.4%). Median birth weight was 2700 grams (range 1440-4000). The prevalence of grade 3 to 4 adverse events, obstetric complications, and neonatal outcomes are shown in the Table. A total of 56/58 (96.6%) of neonates had a 5-minute Apgar score ≥ 7 and 14/88 (15.9%) were admitted to a neonatal intensive care unit. Follow-up beyond the neonatal period was available for 28 neonates (median 42 months, range 1-228), of which reported adverse events were: cardiac abnormality (n=1), speech disorder (n=1), renal dysfunction (n=1), and femoral anteversion (n=1). **Conclusion:** The use of taxane-containing chemotherapy during pregnancy does not seem to increase the risk of obstetric and neonatal complications. Our findings support the use of taxanes during gestation when clinically indicated.

Table 1. Reported adverse events with gestational use of taxane-containing chemotherapy regimens.

Outcome	N (%)
Maternal grade 3-4 adverse events (n=103)	
Hypersensitivity reaction	3 (2.9)
Neutropenia	3 (2.9)
Thrombocytopenia	1 (1.0)
Nausea / vomiting	1 (1.0)
Obstetric complications (n=94)	
Intrauterine growth restriction	8 (8.5)
Preterm premature rupture of membranes	5 (5.3)
Gestational diabetes	5 (5.3)
Hypertensive disorders of pregnancy	4 (4.3)
Oligohydramnios	2 (2.1)
Placental abruption	1 (1.1)
Neonatal complications (n=88)	
Small for gestational age (n=70)	17 (24.3)
Hyperbilirubinemia	11 (12.5)
Respiratory distress syndrome	5 (5.7)
Hypoglycemia	5 (5.7)
Need for respiratory support	4 (4.3)
Congenital malformation	2 (2.3)
Neonatal sepsis	2 (2.3)
Necrotizing enterocolitis	1 (1.1)

PS13-04

Frequent Intra-Tumoral Hypoxia in Pregnancy-Associated Breast Cancer

Presenting Author(s) and Co-Author(s):

C. Bakhuis. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

C. Van Dooijeweert. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

B. Suelmann. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

P. Westenend. PALDordrecht, Dordrecht, Zuid-Holland, Netherlands

S. Linn. Netherlands Cancer Institute, Amsterdam, Netherlands

E. Van der Wall. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

P. Van Diest. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

Rationale: Breast cancer is the most common malignancy in pregnant women, occurring in approximately 1:3000 pregnancies. Breast cancer diagnosed during pregnancy or after childbirth is also known as Pregnancy-Associated Breast Cancer (PABC). PABC is known for exhibiting several unfavorable prognostic tumor characteristics, such as an advanced tumor stage at diagnosis, high histologic grade and frequent hormone receptor negativity. Most probably, several interplaying mechanisms may promote the tumor progression and adverse clinical outcome of PABC. One of these mechanisms may be the presence of hypoxia, a relative state of low intra-tumoral oxygen levels which is a known marker of adverse outcome in breast cancer. However, the occurrence and prognostic consequences of the presence of intra-tumoral hypoxia in PABC have not been studied yet. **Methods:** We constructed a cohort with histopathological, clinical, and outcome data of patients diagnosed with breast cancer during pregnancy (PrBC) or within one year after childbirth (PPBC) in the Netherlands between 1988 and 2022. Next, tissue blocks of all patients were collected from the participating Dutch pathology laboratories. Using H&E stained slides of the tumor tissue blocks, we selected suitable donor sites for a tissue micro array (TMA). Slides from these TMAs were stained for three important hypoxia-associated proteins: glucose transporter-1 (Glut-1), carbonic anhydrase IX (CAIX) and hypoxia-inducible factor-1 α (HIF-1 α). Expression was scored by an expert breast pathologist blinded by clinicopathologic data. **Results:** For a total of 195 PrBC and PPBC patients, we were able to assess the expression of Glut-1, CAIX and HIF-1 α on tumor cells. Patients had a median age of 33 years at diagnosis, whilst a large majority had a Bloom & Richardson grade III tumor (76%) with frequent hormone receptor negativity (50%). Expression of hypoxia-associated proteins was frequent, with 61% of the tumors expressing Glut-1, 30% expressing CAIX and 56% expressing HIF-1 α . In total, 153 (78%) of the tumors expressed at least one of the hypoxia-associated proteins. We observed a significantly worse 5-year overall survival for patients with intra-tumoral hypoxia in comparison to patients without intra-tumoral hypoxia (70% vs. 90%, $p=0.046$). **Conclusions:** We show that the presence of intra-tumoral hypoxia in PABC is common, with 78% of tumors expressing at least one of the studied hypoxia-associated proteins. Importantly, patients with tumors overexpressing hypoxia-markers have a significantly worse survival. This shows that intra-tumoral hypoxia may be an important underlying carcinogenic mechanism in PABC, and might be a promising novel therapeutic target in this patient group.

PS13-07

Systemic therapy in geriatric patients with triple negative breast cancer: a National Cancer Database analysis

Presenting Author(s) and Co-Author(s):

Y. Chamorro. Miami Cancer Institute, Miami, Florida, United States

M. Rubens. Miami Cancer Institute, United States

M. Roy. Miami Cancer Institute, Baptist Health of South Florida, United States

N. Dempsey. Miami Cancer Institute, Baptist Health of South Florida, United States

R. Mahtani. Miami Cancer Institute, Plantation, Florida, United States

M. Ahluwalia. Miami Cancer Institute, United States

L. Carcas. Miami Cancer Institute, United States

A. Sandoval-Leon. Miami Cancer Institute, Miami, Florida, United States

Background Breast cancer (BC) incidence increases with age and is the leading cause of new cancer diagnosis among women in the United States. Although the median age of diagnosis is 63 years (yrs.), over a third of patients diagnosed, and about half of BC mortality in Western societies are in patients over 70 yrs. old. Overall, outcomes for early-stage BC have improved. Despite the lower incidence of triple negative BC (TNBC) (12%-15%) the 5-year survival is 8% to 16% lower than in hormone receptor-positive BC. With the improved life expectancy in the US and the increased incidence of BC as patients age, it is of vital importance to know how to treat BC in the elderly. Unfortunately, optimal management of BC among the elderly has not been adequately studied due to underrepresentation in clinical trials. Furthermore, there is limited information of the potential toxicity and real benefit of chemotherapy in older patients.

Methods This is a retrospective analysis of data collected from the National Cancer Database (NCDB), a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, during the years 2004 to 2019. All women ≥ 65 yrs with early stage TNBC (stages I-III) were included in the analysis. Patients were categorized into three treatment groups – those who did not receive chemotherapy (No-CT), those who received chemotherapy (CT), and those who received chemotherapy and immunotherapy (CTIO). After adjusting for multiple variables including race, insurance, Charlson-Deyo score, stage at diagnosis, and receipt of loco-regional therapy, using the log rank P value, the age cutoff over which the survival rates were not significantly different between two treatment groups (No-CT and CT/CTIO) was identified. The main outcome of this study was all-cause mortality.

Results A total of 11,416 women with TNBC were included in the analysis. Of these, 4105 (36.0%) received No-CT, while 7311 (64.0%) received CT/CTIO. Log rank P values showed that above 81 years, there was no survival benefit between No-CT and CT/CTIO. A further analysis categorized patients into two groups – those between 65-80 yrs and those ≥ 81 yrs. old. Cox proportional regression analysis showed that among patients between 65-80 yrs. all-cause mortality was significantly lower among patients in the CT/CTIO group compared to those in the No-CT group (hazard ratio [HR], 0.52; CI: 0.45-0.60). However, among patients ≥ 81 yrs old, there was no significant difference in all-cause mortality between the treatment groups (hazard ratio [HR], 0.84; CI: 0.67-1.05).

Conclusions: Among patients who were >81 yrs old with early-stage TNBC, those who received treatment with CT/CTIO did not have an overall survival benefit as compared to those who received No-CT. Limitations of this study includes the small number of patients >81 yr old who received chemotherapy which could explain why we were not able to identify a statistically significant benefit of CT/CTIO. Another limitation is that we were not able to assess breast cancer specific mortality. However, this analysis highlights the

importance of individualizing treatment recommendations in older patients, who may not garner the same benefit of treatment as younger patients. Additional studies are required to clarify contributing factors and to help optimize the management of geriatric patients with TNBC. Acknowledgement: The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Table 1. Patient characteristics based on treatment.

Characteristics	No CT (n=4105, 36.0%)	CT/CTIO (n=7311, 64.0%)	P value
CT, n (%)	---	7080 (96.8%)	
CT/CTIO, n (%)	---	231 (3.2%)	
Age, n (%)			<0.001
65-69 y	731 (17.8%)	3076 (42.1%)	
70-74 y	849 (20.7%)	2348 (32.1%)	
75-79 y	864 (21.0%)	1275 (17.4%)	
80-84 y	806 (19.6%)	487 (6.7%)	
≥85 y	855 (20.8%)	125 (1.7%)	
Race, n (%)			0.152
White	2956 (74.1%)	5208 (72.4%)	
Black	743 (18.6%)	1405 (19.5%)	
Hispanic	151 (3.8%)	324 (4.5%)	
Other	140 (3.5%)	258 (3.6%)	
Insurance, n (%)			<0.001
Public	3636 (89.4%)	6314 (87.1%)	
Private	416 (10.2%)	905 (12.5%)	
None	13 (0.3%)	34 (0.5%)	
Charlson–Deyo score, n (%)			<0.001
0	2904 (70.7%)	5517 (75.5%)	
1	643 (15.7%)	1163 (15.9%)	
2	298 (7.3%)	354 (4.8%)	
3	260 (6.3%)	277 (3.8%)	
Stage			<0.001
I	2410 (58.7%)	3034 (41.5%)	
II	1089 (26.5%)	2549 (34.9%)	
III	606 (14.8%)	1728 (23.6%)	
Regional Lymph Node Surgery, n (%)	3245 (79.2%)	6805 (93.2%)	<0.001
Surgery, n (%)	3737 (91.2%)	7009 (96.0%)	<0.001
Radiation, n (%)	1848 (45.0%)	4803 (65.7%)	<0.001

PS13-08

Chemotherapy in geriatric patients with early stage HER2+ breast cancer: A National Cancer Database analysis.

Presenting Author(s) and Co-Author(s):

R. Mahtani. Miami Cancer Institute, Plantation , Florida, United States

A. Sandoval-Leon. Miami Cancer Institute, Miami, Florida, United States

Y. Chamorro. Miami Cancer Institute, Miami, Florida, United States

M. Rubens. Miami Cancer Institute, United States

M. Roy. Miami Cancer Institute, Baptist Health of South Florida, United States

L. Carcas. Miami Cancer Institute, United States

N. Dempsey. Miami Cancer Institute, Baptist Health of South Florida, United States

M. Ahluwalia. Miami Cancer Institute, United States

Background Breast cancer (BC) incidence increases with age and women ≥ 65 years account for almost half of BC related mortality. Life expectancy has increased in the US due to improvements in medical care, and therefore the number of older patients with a BC diagnosis is also expected to increase. The population of individuals ≥ 80 years in the US is growing and now comprises more than 9 million. Approximately 15% of BC are human epidermal growth factor receptor 2 amplified (HER2+). The combination of chemotherapy with trastuzumab +/- pertuzumab compared with trastuzumab alone has been shown to be cost-effective in patients 70 years and older but trastuzumab monotherapy could be considered as an option in certain patients. Nevertheless, there is limited guidelines on how to properly care for the geriatric population with HER2+ BC. **Methods** We conducted a retrospective analysis of data collected from the National Cancer Database (NCDB). NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Women ≥ 65 years with stage I, II and III HER2+ BC were included in the analysis. Patients were categorized into three treatment groups – those who did not receive chemotherapy or monoclonal antibodies (no-CT/mAbs), those who received chemotherapy in combination with monoclonal antibodies (CT/mAbs) and those who received monoclonal antibodies alone (mAbs). Using the Logrank P value, we explored the age cut off for which survival rates were not significantly different between treatment groups. Two comparisons were done: no-CT/mAbs vs CT/mAbs and CT/mAbs vs mAbs. The main outcome of this study was all-cause mortality. **RESULTS:** For the first comparison, a total of 9,924 HER2+ early-stage BC patients were included. Of these, 3,052 (30.8%) received no-CT/mAbs, while 6,872 (69.2%) received CT/mAbs. Kaplan Meier curves comparing mortality by treatment in the whole sample showed that those in the CT/mAbs group had significantly improved survival, compared to the no-CT/mAbs group (Logrank $P < 0.001$). The 1-year and 3-year survival rates were significantly higher in the CT/mAbs, compared to no-CT/mAbs. Cox proportional regression analysis showed that in the whole sample all-cause mortality was significantly lower among patients in the CT/mAbs group, compared to those in the no-CT/mAbs group (hazard ratio [HR], 0.48; CI: 0.41-0.57). However, the Logrank P values showed that there was no age cut off over which CT/mAbs did not improve survival compared to No-CT/mAbs. For the second comparison, a total of 7,457 patients were included. Of these 6,872 (92.2%) receive CT/mAbs and 585 (7.8%) received mAbs. The 1-year and 3-year survival rates were significantly higher in the CT/mAbs compared to the mAbs. The Logrank P values showed that there was no age cut off over which CT/mAbs did not improve survival compared to mAbs. **Conclusion** Chemotherapy in combination with HER2 directed monoclonal antibodies showed a survival benefit in elderly patients, irrespective

of age, when compared to no-CT/mAb and mAb alone. These data highlight the importance of individualizing treatment recommendations and not forgoing standard therapy based merely on age. Limitations of the analysis include lack of available information on BC specific mortality. Also, the benefit that we identified could be secondary to selection bias. Additional studies are needed to improve the treatment in elderly patients with HER2+ BC. Acknowledgement The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Table 1. Logrank P values for survival comparison between those who received CT/mAbs and No-CT/mAbs by age cut-off.

Age cut-off	Logrank P value
Age ≥65 years	<0.001
Age ≥66 years	<0.001
Age ≥67 years	<0.001
Age ≥68 years	<0.001
Age ≥69 years	<0.001
Age ≥70 years	<0.001
Age ≥71 years	<0.001
Age ≥72 years	<0.001
Age ≥73 years	<0.001
Age ≥74 years	<0.001
Age ≥75 years	<0.001
Age ≥76 years	<0.001
Age ≥77 years	<0.001
Age ≥78 years	<0.001
Age ≥79 years	<0.001
Age ≥80 years	<0.001
Age ≥81 years	<0.001
Age ≥82 years	<0.001
Age ≥83 years	<0.001
Age ≥84 years	<0.001
Age ≥85 years	<0.001
Age ≥86 years	<0.001
Age ≥87 years	0.001
Age ≥88 years	0.014
Age ≥89 years	0.022
Age ≥90 years	0.016

PS13-09

Molecular and immunological landscape of sex-based differences in breast cancer: a distinct disease in men.

Presenting Author(s) and Co-Author(s):

D. Trapani. European Institute of Oncology, IRCCS, University of Milano, Milan, Lombardia, Italy

S. Deshmukh. Caris Life Sciences, United States

S. Wu. Caris Life Sciences, United States

J. Xiu. Caris Life Sciences, United States

P. Walker. Caris Life Sciences, United States

P. Advani. Mayo Clinic, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

C. Nabhan. 2. Caris Life Sciences, Phoenix, Arizona, United States

G. Sledge Jr. Caris Life Sciences, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Leone. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Breast cancer (BC) in males represents a rare clinical entity, accounting about 1% of all breast malignancies diagnosed every year. Emerging evidence suggest that a gender medicine approach is critical in the research and treatment of cancer, based on the possibility that sex hormones, molecular differences, immune system, and other factors might play a crucial role in disease management. Here, we characterized molecular and immune differences between male BC (MaBC) and female BC (FeBC) across BC subtypes. Methods: 10,728 BC samples (male, n=137; female, n=10591) were analysed by next-generation sequencing (592, NextSeq; WES, NovaSeq), Whole Transcriptome Sequencing (WTS; NovaSeq) (Caris Life Sciences, Phoenix, AZ). Tumor mutational burden (TMB) totaled somatic mutations per tumor (high ≥ 10 mt/MB). Microsatellite-instability (MSI) was tested by IHC and NGS. Immune cell fractions were calculated by deconvolution of WTS: Quantiseq. Real world treatment-associated survival was extracted from insurance claims and calculated from sample collection to last contact using Kaplan-Meier estimates. Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q < 0.05$). Results: MaBC represented higher HR+/HER2+ (6.61% vs 4.76%), HR+/HER2- (80.17% vs 60.66%) and lower HR-/HER2+ (1.65% vs 3.5%), TNBC (11.57% vs 31.08%) molecular subtypes compared to FeBC. Compared to HR+/HER2+ FeBC, MaBC had higher frequency of CHEK2, RAD51B, TSC1 mutation (Table 1) and RAR α (100% vs 13.61%), DAXX (10% vs 0.16%) copy number alteration (all $p < 0.05$). HR+/HER2- MaBC had higher frequency of BRCA2, FOXA1, CREBBP, FLCN mutation (Table 1), and FGF3 (21.62% vs 14.31%), MRE11 (1.75% vs 0.23%), MEN1 (1.75% vs 0.13%) copy number alteration, but lower frequency of TP53, CHD1, ESR1 and AKT1 mutation (Table 1) (all $p < 0.05$). HR-/HER2+ MaBC had higher frequency of BRCA1 ($p < 0.05$) mutation (Table 1). Male TNBC had higher frequency of CDKN2A, KMT2D, STK11, ASXL1, MYC, NF2, PPM1D, WT1, EPHA2, AMER1, ARHGAP35

mutation (Table 1) and BCL6 (4.35% vs 0.05%) copy number alteration, but lower frequency of TP53 mutation (all $p < 0.05$) (Table 1). MaBC had higher AR protein expression (82.5% vs 60%) but lower frequency of fusion variant-AR (0.7% vs 3.9%) (all $p < 0.05$) compared to FeBC. There was no difference in TMB high (7.1% vs 8.4%, $p = 0.5$) and dMMR/MSI-H (1.8% vs 0.8%, $p = 0.1$). Analysis of inferred immune cell infiltrates showed that MaBC had increased immune cell infiltration of B cells (5.8% vs 5.3%) and M2 M ϕ (4.9% vs 4.3%), but decreased infiltration of DC (2% vs 2.6%) (all $p < 0.05$). MaBC had increased expression of MHC class II gene HLA-DQB2 (FC: 1.3), but decreased expression of immune-related genes CD274 (FC: 1.2), IDO (FC: 1.4), IL1A (FC: 1.3) and IL12A (FC: 1.5) (all $p < 0.05$). Correlative analyses with survival will be presented at the meeting. Conclusions: These data indicate that MaBC has a differential mutational frequency, copy number alteration, immune gene expression and immune cell infiltration and overall survival compared to their FeBC counterparts. A better understanding of these sex-based differences with additional research may help inform disease outcomes, provide a rationale for tailored therapeutic approaches and design future treatments.

Table 1. Mutation frequency in male and female breast cancer

	Features	Female (%)	Male (%)	Change %	p-value	q-value
HR+/HER2+	CHEK2	1.73	20	18.27	0.02	0.26
	RAD51B	0.3	10	9.7	0.04	0.54
	TSC1	0	10	10	0.01	0.25
HR+/HER2-	TP53	31.79	5.13	-26.66	0	0
	BRCA2	4.55	13.49	8.94	0	0
	CDH1	16.56	3.94	-12.62	0	0
	ESR1	14.41	3.08	-11.33	0	0.01
	FOXA1	2.2	6.11	3.91	0.01	0.18
	FLCN	0.15	1.55	1.4	0.02	0.31
	AKT1	4.71	0.78	-3.93	0.04	0.46
HR-/HER2+	BRCA1	0.6	25	24.4	0.03	0.43
TNBC	TP53	84.69	58.33	-26.36	0	0.05
	MYC	0.05	4.17	4.12	0.02	0.26
	CDKN2A	1.46	13.04	11.58	0	0.1
	KEAP1	0.43	8.33	7.9	0.01	0.11
	KMT2D	2.76	16.67	13.91	0	0.09
	NF2	0.61	8.33	7.72	0.01	0.19
	PPM1D	0.05	10	9.95	0.01	0.19
	ASXL1	0.73	9.52	8.79	0.01	0.21
	WT1	0.07	4.17	4.1	0.02	0.33
	EPHA2	0.21	9.09	8.88	0.03	0.4
	STK11	1.18	8.33	7.15	0.03	0.46
	AMER1	0.16	4.17	4.01	0.04	0.53
	ARHGAP35	0.15	18.18	18.03	0	0.01

PS13-01

Worse Prognosis for Breast Cancer in the Second and Third Trimesters and Shortly Postpartum: An Update of the Dutch Pregnancy-Associated Breast Cancer Cohort

Presenting Author(s) and Co-Author(s):

C. Bakhuis. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

C. Van Doijeweert. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

B. Suelmann. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

J. Verloop. Netherlands Comprehensive Cancer Organisation, Netherlands

P. Westenend. PALDordrecht, Dordrecht, Zuid-Holland, Netherlands

S. Linn. Netherlands Cancer Institute, Amsterdam, Netherlands

P. Van Diest. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

E. Van der Wall. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

Rationale:

Pregnancy-Associated Breast Cancer (PABC), often defined as breast cancer during pregnancy (PrBC) or in the first year postpartum (PPBC), is known for its aggressive histopathology and higher stage at diagnosis. In a previous study of the nationwide Dutch PABC Cohort, we observed an impaired survival for patients diagnosed in the second and third trimester of pregnancy. However, the etiology of these differences, and how this relates to the patients diagnosed with breast cancer in the postpartum period (PPBC) or after an abortion (AABC), remains to be elucidated. While we are exploring the etiologic hypotheses, we updated and expanded our database to compare these specific PABC subgroups.

Methods:

All pathology reports of invasive breast carcinoma between January 1st 1988 and July 1st 2022 were screened for pregnancy-related keywords to find all patients diagnosed with PrBC, PPBC or AABC within one year after childbirth or an interrupted pregnancy (induced abortion or miscarriage before a gestational age of 24 weeks). A local patient series provided 22 additional cases. Pregnant patients were subdivided by gestational trimester at time of diagnosis. The different PrBC, PPBC and AABC subgroups were compared by histopathology, clinical characteristics and outcome.

Results:

787 patients were included, of whom 60% were pregnant during their diagnosis. Median age at diagnosis was 34 years. In line with our previous findings, a large majority (68%) of patients had a Bloom & Richardson (B&R) grade III tumor and 37% of tumors were triple negative. Moreover, over a third of patients presented with lymph node metastases (38%). We observed two distinct groups based on histopathology and prognosis: group A, consisting of three patient groups: (I) patients diagnosed in the first trimester of pregnancy, (II) patients diagnosed between 6-12 months postpartum, and (III) patients diagnosed after an abortion, and group B, consisting of two patient groups, (I) patients diagnosed in the second or third trimester of pregnancy or (II) within 6 months after childbirth. Compared to group A, patients in group B more often had B&R grade III tumors: (73% vs. 60%, $p=0.002$) and more frequently had triple negative tumors (43% vs. 28% in group A, $p<0.001$). Survival was significantly worse for patients in group B (5-year OS 67,3% versus 88.2%, $p<0.001$). In a multivariable analysis, corrected for grade, type of surgery and overall stage, these differences upheld with an HR of 1.515 (95% CI 1,012 – 2,268).

Conclusions:

With this extensive update of our nationwide Dutch PABC cohort, we show that especially PrBC patients diagnosed in the second and third trimesters and PPBC patients within six months after childbirth exhibit unfavorable tumor characteristics, with an associated worse prognosis. This highlights the need for in-depth analyses in these specific groups of PABC patients to elucidate the etiologic mechanisms involved.

Disclosure(s):

Carsten F.J Bakhuis: No financial relationships to disclose

Carmen Van Doijeweert, MD, PhD: No financial relationships to disclose

Poster Spotlight Session 13: Special Populations: Pregnancy, Male and Geriatric Patients

Presenting Author(s) and Co-Author(s):

K. Lee. Moffitt Cancer Center, Tampa, Florida, United States

Disclosure(s):

Kimberley Lee, MD, MHS: No financial relationships to disclose

PS13-02

Clinical Outcome and Patients' Characteristics of Breast Cancer Diagnosed During Pregnancy: A Retrospective Single Institutional Study

Presenting Author(s) and Co-Author(s):

M. ELSHENAWY. King Faisal Specialist Hospital & Research Center, United States

E. Haque. College of Medicine, Alfaisal University, United States

A. Badran. King Faisal Specialist Hospital & Research Center, Saudi Arabia

A. AlSayed. King Faisal Specialist Hospital and Research Center, Saudi Arabia

T. Twegieri. King Faisal Specialist Hospital and Research Center, Saudi Arabia

D. Ajarim. King Faisal Specialist Hospital and Research Center, Saudi Arabia

W. Khayal. King Faisal Specialist Hospital & Research Center, United States

O. Al Malik. King Faisal Specialist Hospital & Research Center, United States

A. Al Hefdhhi. King Faisal Specialist Hospital & Research Center, United States

T. El Hassan. King Faisal Specialist Hospital & Research Center, United States

S. Akhtar. King Faisal Specialist Hospital & Research Center, United States

M. Al Zahrani. King Faisal Specialist Hospital & Research Center, United States

S. Al Aklabi. King Faisal Specialist Hospital & Research Center, United States

K. Suleman. King Faisal Specialist Hospital and Research Center, Riyadh, Ar Riyad, Saudi Arabia

Background:

Breast cancer (BC) is considered the second most common malignancy affecting pregnant women. Treatment of this condition is complex due to the potential risks it poses to both the fetus and mother. In this study, we report on the incidence, clinicopathological characteristics, management, and the outcomes of patients diagnosed with breast cancer during pregnancy in a tertiary care institution in Saudi Arabia.

Patients and methods:

This is a single-institution retrospective cohort analysis. We reviewed the medical records of all breast cancer cases in pregnant women that were diagnosed and treated at a tertiary care center in Saudi Arabia, during the period from 2001 to 2017. We used Fisher's exact test, chi-square, and Kaplan-Meier (KM) method for various analyses. Demographic data, treatment received, response, and prognostic factors were analyzed. The study was approved by the institutional review board at our center.

Results:

One hundred seventy-three patients met the search criteria. Median age at diagnosis was 34 (IQR: 30 – 38) years. Of these patients, 100 (58%) had invasive ductal carcinoma (IDC), 42 (24%) had IDC with ductal carcinoma in situ (DCIS), and 15 (20%) had other types. One hundred forty-two (82%) had pathological grades 2 and 3. Hormone receptors were positive in 90 (52%) patients, negative in 79 (45.7) patients and unknown in 4 (2.3%) patients. Her2/neu receptor status was positive in 67 (38.7%) patients and negative in 96(55.5%) patients. Forty five (26%) patients had triple negative disease. Stages I, II, III and IV were identified in 7(4%) , 47 (27.2%), 54 (31.3%) and 51 (29.5%) patients respectively. Ninety (52%) and 75 (43%) patients received neoadjuvant and adjuvant anthracycline, platinum or taxane based

chemotherapy. After being implemented in different international and our institutional guidelines, anti-Her2/neu therapies were given in 35 (20.2%) patients. The median overall survival (OS) was 127 months. Univariate analysis had shown statistically significant correlation between clinical stage, hormonal status, and overall survival.

Conclusion:

Breast cancer diagnosed during pregnancy is associated with poor outcomes. Breast cancer awareness and screening programs are essential for early detection and proper management thereby leading to better outcomes.

Disclosure(s):

Kausar Suleman, MD: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Astra zeneca (Terminated), MSD (Terminated), Novartis (Terminated)

PS13-03

Safety of taxane chemotherapy for the treatment of breast cancer during pregnancy: an international cohort study

Presenting Author(s) and Co-Author(s):

A. Ferrigno Guajardo. Yale University School of Medicine, New Haven, Connecticut, United States

B. Vaca-Cartagena. Hospital Zambrano Hellion - TecSalud, Tecnológico de Monterrey, United States

E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

C. Bousrih. Gustave Roussy, Villejuif, France

O. Oke. MD Anderson Cancer Center, United States

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

F. Peccatori. Fertility and Procreation Unit, IEO European Institute of Oncology IRCCS, Milan, Italy

W. Muñoz-Montaño. Instituto Nacional de Cancerología, Mexico

A. Cabrera-Garcia. Hospital Regional de Alta Especialidad de Ixtapaluca, Mexico

M. Lambertini. University of Genova - San Martino Hospital, Genova, Liguria, Italy

L. Corrales. Centro de Investigación y Manejo del Cáncer (CIMCA), United States

A. Becerril-Gaitan. University of Texas Health Science Center, United States

T. Sella. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Newman. Brigham and Women's Hospital Boston/Harvard Medical School, United States

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

A. Martinez. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

C. Ortiz. Breast Cancer Program. Vall d'Hebron Institute of Oncology/Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

L. Joval-Ramentol. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

G. Scarfone. Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Italy

B. Buonomo. Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Italy

F. Lara-Medina. Instituto Nacional de Cancerología, Mexico

J. Sanchez. Hospital Regional de Alta Especialidad de Ixtapaluca, Mexico

L. Arecco. School of Medicine, University of Genova, United States

A. Ramos-Esquivel. Hospital San Juan de Dios, Caja Costarricense de Seguro Social, Costa Rica

S. Susnjar. Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

G. Morgan. Skåne University Hospital, United States

C. Villarreal-Garza. Tecnológico de Monterrey, Nuevo Leon, Mexico

H. Azim. School of Medicine, Monterrey Institute of Technology, Monterrey, Nuevo Leon, Mexico

Introduction:

The addition of taxanes to anthracycline-based chemotherapy regimens offers increased odds of survival in breast cancer (BC) patients. However, some clinicians defer their use in pregnant patients due to limited evidence supporting safety during gestation. The aim of this study is to describe the prevalence of maternal and neonatal adverse events in BC patients exposed to taxane-containing regimens during pregnancy.

Methods:

This is an international cohort study of BC patients treated with taxane chemotherapy during pregnancy. Inclusion criteria were age ≥ 18 years, treatment in a participating center (n=10), and completion of pregnancy.

Results:

A total of 103 women with a median age of 34 years (range 21-44) were included, of whom the majority (91/101; 90.1%) were also exposed to anthracyclines. The median gestational age at initiation of any chemotherapy agent was 16 weeks (range 4-34), while that of taxanes was 28 weeks (range 12-37). Paclitaxel was the most frequently used taxane (100/103; 97.1%), most prescribed as an 80 mg/m² weekly infusion. All cases were singleton pregnancies except for one twin gestation. The overall live birth rate was 98.0% (100/102). Median gestational age at delivery was 37 weeks (range 32 to 40), with 36/83 live births being preterm (gestational age of < 37 weeks; 43.4%). Median birth weight was 2700 grams (range 1440-4000). The prevalence of grade 3 to 4 adverse events, obstetric complications, and neonatal outcomes are shown in the Table. A total of 56/58 (96.6%) of neonates had a 5-minute Apgar score ≥ 7 and 14/88 (15.9%) were admitted to a neonatal intensive care unit. Follow-up beyond the neonatal period was available for 28 neonates (median 42 months, range 1-228), of which reported adverse events were: cardiac abnormality (n=1), speech disorder (n=1), renal dysfunction (n=1), and femoral anteversion (n=1).

Conclusion:

The use of taxane-containing chemotherapy during pregnancy does not seem to increase the risk of obstetric and neonatal complications. Our findings support the use of taxanes during gestation when clinically indicated.

Table 1. Reported adverse events with gestational use of taxane-containing chemotherapy regimens.

Outcome	N (%)
Maternal grade 3-4 adverse events (n=103)	
Hypersensitivity reaction	3 (2.9)
Neutropenia	3 (2.9)
Thrombocytopenia	1 (1.0)
Nausea / vomiting	1 (1.0)
Obstetric complications (n=94)	
Intrauterine growth restriction	8 (8.5)
Preterm premature rupture of membranes	5 (5.3)
Gestational diabetes	5 (5.3)
Hypertensive disorders of pregnancy	4 (4.3)
Oligohydramnios	2 (2.1)
Placental abruption	1 (1.1)
Neonatal complications (n=88)	
Small for gestational age (n=70)	17 (24.3)
Hyperbilirubinemia	11 (12.5)
Respiratory distress syndrome	5 (5.7)
Hypoglycemia	5 (5.7)
Need for respiratory support	4 (4.3)
Congenital malformation	2 (2.3)
Neonatal sepsis	2 (2.3)
Necrotizing enterocolitis	1 (1.1)

Disclosure(s):

Ana S. Ferrigno Guajardo, MD: No financial relationships to disclose

Erica L. Mayer, MD, MPH: Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Novartis Pharma GmbH (Ongoing)

Matteo Lambertini, MD, PhD: Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Eli Lilly and Co (Ongoing), Exact Sciences Corporation (Ongoing), Gilead (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), SeaGen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Daiichi-Sankyo (Ongoing), Eli Lilly and Co (Ongoing), Gilead (Ongoing), IPSEN (Ongoing), Knights Pharmaceuticals (Ongoing), Libbs (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), Sandoz (Ongoing), Takeda Pharmaceuticals, Ltd. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Gilead (Ongoing); Travel grant: Daiichi-Sankyo (Ongoing), Gilead (Ongoing)

Barbara Pistilli, MD: Advisory Committee/Board Member: LILLY (Ongoing), Novartis Pharma GmbH (Ongoing)

Hatem A. Azim, MD, PhD, Jr.: Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): PierreFabre (Terminated, May 31, 2022)

PS13-04

Frequent Intra-Tumoral Hypoxia in Pregnancy-Associated Breast Cancer

Presenting Author(s) and Co-Author(s):

C. Bakhuis. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

C. Van Doijeweert. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

B. Suelmann. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

P. Westenend. PALDordrecht, Dordrecht, Zuid-Holland, Netherlands

S. Linn. Netherlands Cancer Institute, Amsterdam, Netherlands

E. Van der Wall. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

P. Van Diest. University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

Rationale:

Breast cancer is the most common malignancy in pregnant women, occurring in approximately 1:3000 pregnancies. Breast cancer diagnosed during pregnancy or after childbirth is also known as Pregnancy-Associated Breast Cancer (PABC). PABC is known for exhibiting several unfavorable prognostic tumor characteristics, such as an advanced tumor stage at diagnosis, high histologic grade and frequent hormone receptor negativity. Most probably, several interplaying mechanisms may promote the tumor progression and adverse clinical outcome of PABC. One of these mechanisms may be the presence of hypoxia, a relative state of low intra-tumoral oxygen levels which is a known marker of adverse outcome in breast cancer. However, the occurrence and prognostic consequences of the presence of intra-tumoral hypoxia in PABC have not been studied yet.

Methods:

We constructed a cohort with histopathological, clinical, and outcome data of patients diagnosed with breast cancer during pregnancy (PrBC) or within one year after childbirth (PPBC) in the Netherlands between 1988 and 2022. Next, tissue blocks of all patients were collected from the participating Dutch pathology laboratories. Using H&E stained slides of the tumor tissue blocks, we selected suitable donor sites for a tissue micro array (TMA). Slides from these TMAs were stained for three important hypoxia-associated proteins: glucose transporter-1 (Glut-1), carbonic anhydrase IX (CAIX) and hypoxia-inducible factor-1 α (HIF-1 α). Expression was scored by an expert breast pathologist blinded by clinicopathologic data.

Results:

For a total of 195 PrBC and PPBC patients, we were able to assess the expression of Glut-1, CAIX and HIF-1 α on tumor cells. Patients had a median age of 33 years at diagnosis, whilst a large majority had a Bloom & Richardson grade III tumor (76%) with frequent hormone receptor negativity (50%). Expression of hypoxia-associated proteins was frequent, with 61% of the tumors expressing Glut-1, 30% expressing CAIX and 56% expressing HIF-1 α . In total, 153 (78%) of the tumors expressed at least one of the hypoxia-associated proteins. We observed a significantly worse 5-year overall survival for patients with intra-tumoral hypoxia in comparison to patients without intra-tumoral hypoxia (70% vs. 90%, $p=0.046$).

Conclusions:

We show that the presence of intra-tumoral hypoxia in PABC is common, with 78% of tumors expressing at least one of the studied hypoxia-associated proteins. Importantly, patients with tumors overexpressing hypoxia-markers have a significantly worse survival. This shows that

intra-tumoral hypoxia may be an important underlying carcinogenic mechanism in PABC, and might be a promising novel therapeutic target in this patient group.

Disclosure(s):

Carsten F.J Bakhuis: No financial relationships to disclose

Carmen Van Dooijeweert, MD, PhD: No financial relationships to disclose

PS13-07

Systemic therapy in geriatric patients with triple negative breast cancer: a National Cancer Database analysis

Presenting Author(s) and Co-Author(s):

Y. Chamorro. Miami Cancer Institute, Miami, Florida, United States

M. Rubens. Miami Cancer Institute, United States

M. Roy. Miami Cancer Institute, Baptist Health of South Florida, United States

N. Dempsey. Miami Cancer Institute, Baptist Health of South Florida, United States

R. Mahtani. Miami Cancer Institute, Plantation , Florida, United States

M. Ahluwalia. Miami Cancer Institute, United States

L. Carcas. Miami Cancer Institute, United States

A. Sandoval-Leon. Miami Cancer Institute, Miami, Florida, United States

Background

Breast cancer (BC) incidence increases with age and is the leading cause of new cancer diagnosis among women in the United States. Although the median age of diagnosis is 63 years (yrs.), over a third of patients diagnosed, and about half of BC mortality in Western societies are in patients over 70 yrs. old. Overall, outcomes for early-stage BC have improved. Despite the lower incidence of triple negative BC (TNBC) (12%-15%) the 5-year survival is 8% to 16% lower than in hormone receptor-positive BC. With the improved life expectancy in the US and the increased incidence of BC as patients age, it is of vital importance to know how to treat BC in the elderly. Unfortunately, optimal management of BC among the elderly has not been adequately studied due to underrepresentation in clinical trials. Furthermore, there is limited information of the potential toxicity and real benefit of chemotherapy in older patients.

Methods

This is a retrospective analysis of data collected from the National Cancer Database (NCDB), a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, during the years 2004 to 2019. All women ≥ 65 yrs with early stage TNBC (stages I-III) were included in the analysis. Patients were categorized into three treatment groups – those who did not receive chemotherapy (No-CT), those who received chemotherapy (CT), and those who received chemotherapy and immunotherapy (CTIO). After adjusting for multiple variables including race, insurance, Charlson-Deyo score, stage at diagnosis, and receipt of loco-regional therapy, using the log rank P value, the age cutoff over which the survival rates were not significantly different between two treatment groups (No-CT and CT/CTIO) was identified. The main outcome of this study was all-cause mortality

Results

A total of 11,416 women with TNBC were included in the analysis. Of these, 4105 (36.0%) received No-CT, while 7311 (64.0%) received CT/CTIO. Log rank P values showed that above 81 years, there was no survival benefit between No-CT and CT/CTIO. A further analysis categorized patients into two groups – those between 65-80 yrs and those ≥ 81 yrs. old. Cox proportional regression analysis showed that among patients between 65-80 yrs. all-cause mortality was significantly lower among patients in the CT/CTIO group compared to those in the No-CT group (hazard ratio [HR], 0.52; CI: 0.45-0.60). However, among patients ≥ 81 yrs old, there was no significant difference in all-cause mortality between the treatment groups (hazard ratio [HR], 0.84; CI: 0.67-1.05).

Conclusions:

Among patients who were >81yrs old with early-stage TNBC, those who received treatment with CT/CTIO did not have an overall survival benefit as compared to those who received No-CT. Limitations of this study includes the small number of patients >81yr old who received chemotherapy which could explain why we were not able to identify a statistically significant benefit of CT/CTIO. Another limitation is that we were not able to assess breast cancer specific mortality. However, this analysis highlights the importance of individualizing treatment recommendations in older patients, who may not garner the same benefit of treatment as younger patients. Additional studies are required to clarify contributing factors and to help optimize the management of geriatric patients with TNBC.

Acknowledgement:

The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Table 1. Patient characteristics based on treatment.

Characteristics	No CT (n=4105, 36.0%)	CT/CTIO (n=7311, 64.0%)	P value
CT, n (%)	---	7080 (96.8%)	
CT/CTIO, n (%)	---	231 (3.2%)	
Age, n (%)			<0.001
65-69 y	731 (17.8%)	3076 (42.1%)	
70-74 y	849 (20.7%)	2348 (32.1%)	
75-79 y	864 (21.0%)	1275 (17.4%)	
80-84 y	806 (19.6%)	487 (6.7%)	
≥85 y	855 (20.8%)	125 (1.7%)	
Race, n (%)			0.152
White	2956 (74.1%)	5208 (72.4%)	
Black	743 (18.6%)	1405 (19.5%)	
Hispanic	151 (3.8%)	324 (4.5%)	
Other	140 (3.5%)	258 (3.6%)	
Insurance, n (%)			<0.001
Public	3636 (89.4%)	6314 (87.1%)	
Private	416 (10.2%)	905 (12.5%)	
None	13 (0.3%)	34 (0.5%)	
Charlson–Deyo score, n (%)			<0.001
0	2904 (70.7%)	5517 (75.5%)	
1	643 (15.7%)	1163 (15.9%)	
2	298 (7.3%)	354 (4.8%)	
3	260 (6.3%)	277 (3.8%)	
Stage			<0.001
I	2410 (58.7%)	3034 (41.5%)	
II	1089 (26.5%)	2549 (34.9%)	
III	606 (14.8%)	1728 (23.6%)	
Regional Lymph Node Surgery, n (%)	3245 (79.2%)	6805 (93.2%)	<0.001
Surgery, n (%)	3737 (91.2%)	7009 (96.0%)	<0.001
Radiation, n (%)	1848 (45.0%)	4803 (65.7%)	<0.001

Disclosure(s):

Reshma L. Mahtani, DO: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing)

Ana Sandoval-Leon, MD: Advisory Committee/Board Member: Merck & Co., Inc. (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated), Gilead (Terminated), Guardant Health Inc. (Terminated), Menarini/Stemline (Terminated), Oncocyte, Inc (Terminated), Sanofi Aventis (Terminated), Sermonix Pharmaceuticals Inc. (Terminated)

PS13-08

Chemotherapy in geriatric patients with early stage HER2+ breast cancer: A National Cancer Database analysis.

Presenting Author(s) and Co-Author(s):

R. Mahtani. Miami Cancer Institute, Plantation , Florida, United States

A. Sandoval-Leon. Miami Cancer Institute, Miami, Florida, United States

Y. Chamorro. Miami Cancer Institute, Miami, Florida, United States

M. Rubens. Miami Cancer Institute, United States

M. Roy. Miami Cancer Institute, Baptist Health of South Florida, United States

L. Carcas. Miami Cancer Institute, United States

N. Dempsey. Miami Cancer Institute, Baptist Health of South Florida, United States

M. Ahluwalia. Miami Cancer Institute, United States

Background

Breast cancer (BC) incidence increases with age and women ≥ 65 years account for almost half of BC related mortality. Life expectancy has increased in the US due to improvements in medical care, and therefore the number of older patients with a BC diagnosis is also expected to increase. The population of individuals ≥ 80 years in the US is growing and now comprises more than 9 million. Approximately 15% of BC are human epidermal growth factor receptor 2 amplified (HER2+). The combination of chemotherapy with trastuzumab +/- pertuzumab compared with trastuzumab alone has been shown to be cost-effective in patients 70 years and older but trastuzumab monotherapy could be considered as an option in certain patients. Nevertheless, there is limited guidelines on how to properly care for the geriatric population with HER2+ BC.

Methods

We conducted a retrospective analysis of data collected from the National Cancer Database (NCDB). NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Women ≥ 65 years with stage I, II and III HER2+ BC were included in the analysis. Patients were categorized into three treatment groups – those who did not receive chemotherapy or monoclonal antibodies (no-CT/mAbs), those who received chemotherapy in combination with monoclonal antibodies (CT/mAbs) and those who received monoclonal antibodies alone (mAbs). Using the Logrank P value, we explored the age cut off for which survival rates were not significantly different between treatment groups. Two comparisons were done: no-CT/mAbs vs CT/mAbs and CT/mAbs vs mAbs. The main outcome of this study was all-cause mortality.

RESULTS:

For the first comparison, a total of 9,924 HER2+ early-stage BC patients were included. Of these, 3,052 (30.8%) received no-CT/mAbs, while 6,872 (69.2%) received CT/mAbs. Kaplan Meier curves comparing mortality by treatment in the whole sample showed that those in the CT/mAbs group had significantly improved survival, compared to the no-CT/mAbs group (Logrank $P < 0.001$). The 1-year and 3-year survival rates were significantly higher in the CT/mAbs, compared to no-CT/mAbs. Cox proportional regression analysis showed that in the whole sample all-cause mortality was significantly lower among patients in the CT/mAbs group, compared to those in the no-CT/mAbs group (hazard ratio [HR], 0.48; CI: 0.41-0.57). However, the Logrank P values showed that there was no age cut off over which CT/mAbs did not

improve survival compared to No-CT/mAbs. For the second comparison, a total of 7,457 patients were included. Of these 6,872 (92.2%) receive CT/mAbs and 585 (7.8%) received mAbs. The 1-year and 3-year survival rates were significantly higher in the CT/mAbs compared to the mAbs. The Logrank P values showed that there was no age cut off over which CT/mAbs did not improve survival compared to mAbs.

Conclusion

Chemotherapy in combination with HER2 directed monoclonal antibodies showed a survival benefit in elderly patients, irrespective of age, when compared to no-CT/mAb and mAb alone. These data highlight the importance of individualizing treatment recommendations and not forgoing standard therapy based merely on age. Limitations of the analysis include lack of available information on BC specific mortality. Also, the benefit that we identified could be secondary to selection bias. Additional studies are needed to improve the treatment in elderly patients with HER2+ BC.

Acknowledgement

The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Table 1. Logrank P values for survival comparison between those who received CT/mAbs and No-CT/mAbs by age cut-off.

Age cut-off	Logrank P value
Age ≥65 years	<0.001
Age ≥66 years	<0.001
Age ≥67 years	<0.001
Age ≥68 years	<0.001
Age ≥69 years	<0.001
Age ≥70 years	<0.001
Age ≥71 years	<0.001
Age ≥72 years	<0.001
Age ≥73 years	<0.001
Age ≥74 years	<0.001
Age ≥75 years	<0.001
Age ≥76 years	<0.001
Age ≥77 years	<0.001
Age ≥78 years	<0.001
Age ≥79 years	<0.001
Age ≥80 years	<0.001
Age ≥81 years	<0.001
Age ≥82 years	<0.001
Age ≥83 years	<0.001
Age ≥84 years	<0.001
Age ≥85 years	<0.001
Age ≥86 years	<0.001
Age ≥87 years	0.001
Age ≥88 years	0.014
Age ≥89 years	0.022
Age ≥90 years	0.016

Disclosure(s):

Reshma L. Mahtani, DO: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing)

Ana Sandoval-Leon, MD: Advisory Committee/Board Member: Merck & Co., Inc. (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated), Gilead (Terminated), Guardant Health Inc. (Terminated), Menarini/Stemline (Terminated), Oncocyte, Inc (Terminated), Sanofi Aventis (Terminated), Sermonix Pharmaceuticals Inc. (Terminated)

PS13-09

Molecular and immunological landscape of sex-based differences in breast cancer: a distinct disease in men.

Presenting Author(s) and Co-Author(s):

D. Trapani. European Institute of Oncology, IRCCS, University of Milano, Milan, Lombardia, Italy

S. Deshmukh. Caris Life Sciences, United States

S. Wu. Caris Life Sciences, United States

J. Xiu. Caris Life Sciences, United States

P. Walker. Caris Life Sciences, United States

P. Advani. Mayo Clinic, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

C. Nabhan. 2. Caris Life Sciences, Phoenix, Arizona, United States

G. Sledge Jr. Caris Life Sciences, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

J. Leone. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background:

Breast cancer (BC) in males represents a rare clinical entity, accounting about 1% of all breast malignancies diagnosed every year. Emerging evidence suggest that a gender medicine approach is critical in the research and treatment of cancer, based on the possibility that sex hormones, molecular differences, immune system, and other factors might play a crucial role in disease management. Here, we characterized molecular and immune differences between male BC (MaBC) and female BC (FeBC) across BC subtypes.

Methods:

10,728 BC samples (male, n=137; female, n=10591) were analysed by next-generation sequencing (592, NextSeq; WES, NovaSeq), Whole Transcriptome Sequencing (WTS; NovaSeq) (Caris Life Sciences, Phoenix, AZ). Tumor mutational burden (TMB) totaled somatic mutations per tumor (high ≥ 10 mt/MB). Microsatellite-instability (MSI) was tested by IHC and NGS. Immune cell fractions were calculated by deconvolution of WTS: Quantiseq. Real world treatment-associated survival was extracted from insurance claims and calculated from sample collection to last contact using Kaplan-Meier estimates. Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q < 0.05$).

Results:

MaBC represented higher HR+/HER2+ (6.61% vs 4.76%), HR+/HER2- (80.17% vs 60.66%) and lower HR-/HER2+ (1.65% vs 3.5%), TNBC (11.57% vs 31.08%) molecular subtypes compared to FeBC. Compared to HR+/HER2+ FeBC, MaBC had higher frequency of CHEK2, RAD51B, TSC1 mutation (Table 1) and RAR α (100% vs 13.61%), DAXX (10% vs 0.16%) copy

number alteration (all $p < 0.05$). HR+/HER2- MaBC had higher frequency of BRCA2, FOXA1, CREBBP, FLCN mutation (Table 1), and FGF3 (21.62% vs 14.31%), MRE11 (1.75% vs 0.23%), MEN1 (1.75% vs 0.13%) copy number alteration, but lower frequency of TP53, CHD1, ESR1 and AKT1 mutation (Table 1) (all $p < 0.05$). HR-/HER2+ MaBC had higher frequency of BRCA1 ($p < 0.05$) mutation (Table 1). Male TNBC had higher frequency of CDKN2A, KMT2D, STK11, ASXL1, MYC, NF2, PPM1D, WT1, EPHA2, AMER1, ARHGAP35 mutation (Table 1) and BCL6 (4.35% vs 0.05%) copy number alteration, but lower frequency of TP53 mutation (all $p < 0.05$) (Table 1). MaBC had higher AR protein expression (82.5% vs 60%) but lower frequency of fusion variant-AR (0.7% vs 3.9%) (all $p < 0.05$) compared to FeBC. There was no difference in TMB high (7.1% vs 8.4%, $p = 0.5$) and dMMR/MSI-H (1.8% vs 0.8%, $p = 0.1$). Analysis of inferred immune cell infiltrates showed that MaBC had increased immune cell infiltration of B cells (5.8% vs 5.3%) and M2 M ϕ (4.9% vs 4.3%), but decreased infiltration of DC (2% vs 2.6%) (all $p < 0.05$). MaBC had increased expression of MHC class II gene HLA-DQB2 (FC: 1.3), but decreased expression of immune-related genes CD274 (FC: 1.2), IDO (FC: 1.4), IL1A (FC: 1.3) and IL12A (FC: 1.5) (all $p < 0.05$). Correlative analyses with survival will be presented at the meeting.

Conclusions:

These data indicate that MaBC has a differential mutational frequency, copy number alteration, immune gene expression and immune cell infiltration and overall survival compared to their FeBC counterparts. A better understanding of these sex-based differences with additional research may help inform disease outcomes, provide a rationale for tailored therapeutic approaches and design future treatments.

Table 1. Mutation frequency in male and female breast cancer

	Features	Female (%)	Male (%)	Change %	p-value	q-value
HR+/HER2+	CHEK2	1.73	20	18.27	0.02	0.26
	RAD51B	0.3	10	9.7	0.04	0.54
	TSC1	0	10	10	0.01	0.25
HR+/HER2-	TP53	31.79	5.13	-26.66	0	0
	BRCA2	4.55	13.49	8.94	0	0
	CDH1	16.56	3.94	-12.62	0	0
	ESR1	14.41	3.08	-11.33	0	0.01
	FOXA1	2.2	6.11	3.91	0.01	0.18
	FLCN	0.15	1.55	1.4	0.02	0.31
	AKT1	4.71	0.78	-3.93	0.04	0.46
HR-/HER2+	BRCA1	0.6	25	24.4	0.03	0.43
	TP53	84.69	58.33	-26.36	0	0.05
TNBC	MYC	0.05	4.17	4.12	0.02	0.26
	CDKN2A	1.46	13.04	11.58	0	0.1
	KEAP1	0.43	8.33	7.9	0.01	0.11
	KMT2D	2.76	16.67	13.91	0	0.09
	NF2	0.61	8.33	7.72	0.01	0.19
	PPM1D	0.05	10	9.95	0.01	0.19
	ASXL1	0.73	9.52	8.79	0.01	0.21
	WT1	0.07	4.17	4.1	0.02	0.33
	EPHA2	0.21	9.09	8.88	0.03	0.4
	STK11	1.18	8.33	7.15	0.03	0.46
	AMER1	0.16	4.17	4.01	0.04	0.53
	ARHGAP35	0.15	18.18	18.03	0	0.01

Disclosure(s):

Dario Trapani, MD: No financial relationships to disclose

Nancy U. Lin, MD: Consulting Fees (e.g., advisory boards): Affinia Therapeutics (Ongoing), Aleta Biopharma (Ongoing), AstraZeneca (Ongoing), Blueprint Medicine (Ongoing), Daiichi-Sankyo (Ongoing), Genentech / Roche (Ongoing), Janssen (Ongoing), Menarini/Stemline (Ongoing), Olema Pharmaceuticals (Ongoing), Prelude Therapeutics (Ongoing), Reverie Labs (Ongoing), SeaGen (Ongoing), Voyager Therapeutics (Ongoing); Independent Contractor: Artera (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Genentech / Roche (Ongoing), Menarini/Stemline (Ongoing), Merck (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing), SeaGen (Ongoing), Zion Pharmaceuticals (Ongoing)

Giuseppe Curigliano, Prof, MD, PhD: Advisory Committee/Board Member: Menarini Silicon Biosystems (Terminated); Consulting Fees (e.g., advisory boards): Astra Zeneca, Roche, Novartis, Biocad, R-Pharm, Eisai, Eli Lilly, Pfizer, MSD, BMS (Terminated), Gilead (Terminated), PFS Genomics/Exact Sciences (Terminated)

Stephanie L. Graff, MD: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Terminated, April 1, 2023)

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd. (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

PS14-01

Immune related adverse events in patients ≥ 65 years vs. < 65 years with breast cancer treated with immunotherapy

Presenting Author(s) and Co-Author(s):

N. Vidula. Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, United States

J. Hutchinson. Massachusetts General Hospital, United States

A. McLaren. Massachusetts General Hospital, United States

L. Ryan. Cancer Center, Massachusetts General Hospital, United States

A. Niemierko. Massachusetts General Hospital, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background: Pembrolizumab is approved for early/advanced triple negative breast cancer (TNBC), and atezolizumab was previously approved for advanced TNBC. Toxicity of immunotherapy (IO) and immune related adverse events (irAEs) in patients ≥ 65 years with TNBC is not described in detail in results from registration trials (KEYNOTE 522, KEYNOTE 355, and IMPassion130), where patients ≥ 65 years were a minority. Understanding real-world IO toxicity and irAEs in patients with breast cancer ≥ 65 years may inform clinical decision making.

Methods:

We studied IO toxicity and irAEs in patients with breast cancer ≥ 65 years vs. < 65 years (at IO start) who received IO at an academic institution. A retrospective review was conducted to identify IO toxicity and irAEs (classified by CTCAE v 5.0). Cohorts were compared with Pearson's chi-squared test (categorical variables) and Wilcoxon rank-sum test (continuous variables). Results: Cohorts had 25 patients ≥ 65 years (median age 73 years, interquartile range (IQR) 69-74 years) and 104 patients < 65 years (median age 48 years, IQR 39-56 years). Stage I-III/IV breast cancer distribution was 36%/64% for ≥ 65 years and 68%/32% for < 65 years. Baseline ECOG performance status was mainly 0-1 in both cohorts. IO was mainly pembrolizumab (≥ 65 years: 96%; < 65 years: 83% for first IO regimen) vs. atezolizumab. Table 1 depicts characteristics of IO toxicity. IO duration was longer in patients < 65 years. While rates of IO interruption for toxicity and discontinuation for toxicity were numerically higher in patients ≥ 65 years, these findings did not reach statistical significance, possibly due to the sample size. Similar overall rates of irAEs were seen (≥ 65 years: 72%; < 65 years: 65%, $p=0.47$) but there were differences in the types of irAEs. Patients < 65 years had more transaminitis (≥ 65 years: 12%; < 65 years: 33%, $p=0.04$), and grade 2-3 hypothyroidism (among patients developing hypothyroidism, ≥ 65 years: grade 1- 75%, grade 2- 25%, grade 3- 0%; < 65 years: grade 1- 11%, grade 2- 79%, grade 3- 11%, $p=0.017$). Conversely, patients ≥ 65 years had higher rates of irAE nephritis (≥ 65 years: 12%; < 65 years: 1%, $p=0.004$); notably, none of the patients had baseline chronic kidney disease. Rates of full resolution of irAEs were similar between cohorts (≥ 65 years: 67%; < 65 years: 57%, $p=0.47$), but patients ≥ 65 years had more steroid use for management of first irAE while patients < 65 years required more thyroid hormone supplementation (first irAE management distribution, ≥ 65 years: steroids- 71%, thyroid hormone- 7%, supportive care- 21%; < 65 years: steroids- 31%, thyroid hormone- 25%, supportive care- 44%, $p=0.025$). Late onset irAEs and deaths from irAEs were rare in both cohorts, with 1 irAE related death in the cohort ≥ 65 years. Conclusions: In this real-

world cohort, similar overall rates of irAEs were observed in patients ≥ 65 years and < 65 years. However, patients ≥ 65 years had higher rates of irAE nephritis and steroid use for irAEs, while patients < 65 years had more transaminitis and higher grade hypothyroidism, requiring more thyroid hormone supplementation. Given these age specific differences, validation in a larger cohort is merited.

Table 1. Characteristics of IO toxicity.

Variable (median, IQR OR #, %)	≥ 65 years (69-74)	< 65 years (39-56)	p value
IO duration (months)	2.3 (1.6-4.4)	5.4 (2.1-10.7)	0.006
IO interruption for toxicity	4 (16%)	7 (7%)	0.14
IO dose # at toxicity interruption	2 (2-4)	5 (2-6)	0.31
IO discontinuation for toxicity	4 (16%)	7 (7%)	0.14

PS14-02

Real-world analysis comparing Black and White patients with triple-negative breast cancer receiving therapy per KEYNOTE-522

Presenting Author(s) and Co-Author(s):

M. Hofherr. Washington University, St. Louis, Missouri, United States
A. Davis. Washington University in St Louis School of Medicine, United States
S. January. BJC, United States
E. Owen. BJC, United States
F. Raheem. Mayo Clinic, United States
L. Mina. Mayo Clinic, United States
S. Arunachalam Karikalan. Mayo Clinic Arizona, Phoenix, Arizona, United States
L. Lyons. Lexington Medical Cancer Center, United States
M. Watson Rose. Lexington Medical Cancer Center, United States
K. Madden. Lexington Medical Cancer Center, United States
J. Hsin. City of Hope, United States
A. Keegan. City of Hope, United States
W. Yu. City of Hope, United States
S. Kraft. University of Michigan, United States
A. Schepers. University of Michigan, United States
E. Armgardt. Northwestern, United States
D. Mazewski. Northwestern, United States
A. Svoboda. Northwestern, United States
K. Harwood. Mayo, United States
J. Taraba. Mayo Clinic, United States
Y. Resnick. NEW ECS, United States
S. Hummert. Huntsman Cancer Institute, United States
L. Grate. UC Health, United States
S. Keisner. UAMS, United States
J. Hobbs. Avera Cancer Institute, United States
T. Davis. UW Cancer Center, United States
K. Bastian. PHCI, United States
D. Minikel. ProHealthCare Institute, United States
W. Adler. SALUD, United States
T. White. UMN, United States
A. Singh Sandu. Kettering Health, United States
F. Boulbol. Community Medical, United States
K. Finch. Columbus Regional Health, United States
K. Clifton. Washington University in St Louis School of Medicine, United States

Abstract Title: Real-world analysis comparing Black and White patients with triple-negative breast cancer receiving therapy per KEYNOTE-522 **Background:** KEYNOTE-522 was a randomized, double-blind, placebo-controlled phase 3 trial which resulted in the FDA approval of pembrolizumab with neoadjuvant chemotherapy for patients with newly diagnosed, high-risk, early-stage triple-negative breast cancer (TNBC). Despite the significant improvement in pathological complete response (pCR) and event-free survival rates across all patients, the landmark trial included only 4.5% Black patients. It is essential to assess outcomes in representative treatment populations. We assessed real-world toxicity and treatment outcomes across Black and White patients who received standard-of-care treatment per KEYNOTE-522. **Methods:** In this retrospective, multicenter study, we examined patients with early-stage TNBC who received planned treatment per KEYNOTE-522 as standard-of-care (SOC) therapy. 16 sites were included in the analysis. IRB approval was obtained from each participating site. Number and length of treatment delays, treatment-related toxicities (both chemotherapy and immune-related) of all grades, and pCR rate were collected from the electronic medical record of each participating site, and deidentified data were shared for central analysis. **Results:** Of the 577 patients who initiated treatment with chemotherapy and immunotherapy, 534 patients were included in this analysis with 105 patients who self-identified as Black (19.7%) and 429 who self-identified as White (80.3%). There were no statistically significant differences in clinical and pathological characteristics between the two groups. White women were more likely to have grade 3+ immune-related adverse events (irAEs) compared to Black women (33.8% vs 20.9%, $P=0.011$). There was no significant difference across Black and White patients with respect to grade 3+ chemotherapy-related adverse events. Out of the 444 patients who have completed surgery, no difference in pCR rate was observed between Black and White women (45/86 52.3% vs 200/358 55.9%) ($p = 0.6$). The authors also saw no difference in the rates of hospitalizations between Black and White women (39% vs 36% $p = 0.5$), and rates of acute care utilization (38% vs 38% $p = 0.9$). **Conclusions:** We report safety and efficacy across Black and White women in a real-world analysis of patients who received treatment per KEYNOTE-522. Notably, White patients had a significantly higher frequency of grade 3+ irAEs, although the reason for this finding is unclear based on this analysis. Black patients had similar pCR rates and rates of treatment-related hospitalizations compared to White patients. Assessment of outcomes and toxicity by race in clinical trials and real-world analyses are critical in drug development.

PS14-03

Delayed and post-treatment immune toxicities in patients with breast cancer receiving immune checkpoint inhibitors.

Presenting Author(s) and Co-Author(s):

S. Jacob. University of California, San Francisco, California, United States

S. Fisch. University of California, San Francisco, United States

C. Face. University of California, San Francisco, United States

L. Huppert. University of California, San Francisco, Oakland, California, United States

Z. Quandt. University of California, San Francisco, United States

L. Quintal. University of California, San Francisco, United States

M. Melisko. University of California at San Francisco, San Francisco, California, United States

M. Majure. University of California, San Francisco, United States

J. Chien. University of California, San Francisco, San Francisco, California, United States

A. Blaes. University of Minnesota, Minneapolis, Minnesota, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

Background: Immune checkpoint inhibitors (ICI) have improved outcomes in patients (pts) with breast cancer, however identification and management of immune-related adverse events (irAE) remains challenging. Delayed irAE have been observed, occurring even after ICI cessation. Prior analyses of delayed irAE have focused on patients with melanoma, lung, and head & neck cancer but data in patients with breast cancer are lacking. Methods: We identified pts with breast cancer who received ICI at our institution between 2012 and 2022 using pharmacy administration records. Charts were reviewed for delayed and post-treatment irAE. Delayed irAE were defined as occurring >90 days after ICI start; post-treatment irAE were defined as occurring >60 days after ICI discontinuation. Events were categorized as irAE if provider notes indicated that the toxicity was related to or possibly related to ICI. Results: 320 consecutive pts with breast cancer (219 metastatic, 96 localized disease) underwent treatment with ICI, of which 79 (25%) developed delayed irAE (40 with metastatic disease, 39 with localized disease). 54 pts had triple negative breast cancer (TNBC), 22 had hormone receptor positive (HR+) disease, and 4 had HER2+ disease. 44 pts received ICI on a clinical trial. The median number of ICI doses was 8, and the median length of follow-up after the first ICI infusion with 29 months. For delayed irAE, median time to onset was 183 days (range 91-1800 days) with a total of 103 delayed irAE events (see table). 24 pts (7.5%) developed a post-treatment irAE with a total of 27 events. For post-treatment irAE, median time to onset was 112 days after ICI cessation (range 69-1100 days) and median time on ICI was 63 days (range 22-1724 days). 11 of 24 patients who experienced a post-treatment irAE also experienced an irAE while on treatment. Hypothyroidism, colitis, adrenal insufficiency, and hepatitis were the most common irAE at all time points. Rash primarily occurred while still on ICI. All irAE at any time point either self-resolved, resolved with systemic steroids, or continued with indefinite hormone replacement. 45 irAE required systemic steroids, not including hydrocortisone replacement for adrenal insufficiency. There were no grade 4 or 5 irAEs. Conclusions: This is the first evaluation of delayed/post-treatment irAE in a large cohort of patients with breast cancer. 79 pts (25%) experienced delayed irAEs occurring \geq 90 days after ICI start, with median time to onset of 183 days. 89% of patients with delayed irAE also experienced an irAE at an earlier time point, indicating that early irAE may be a risk for delayed irAE. 24 pts (7.5%) experienced post-

treatment irAE with median onset of 121 days after ICI cessation. Diagnosis of delayed irAE requires heightened awareness and prompt treatment. Future work is needed to identify key clinical and molecular markers that predict risk for delayed irAE to better inform treatment & monitoring.

Parameter	Number of pts (%)	
Total pts receiving an ICI	320	
Delayed irAE	79 (25)	
>1 delayed irAE	21 (27% of pts with delayed irAE)	
Patients with delayed irAEs who also had irAE occurring < 90 days after ICI start	70 (89% of pts with delayed irAE)	
Post-treatment irAE	24 (7.5)	
Types of delayed irAE (>90 days after ICI start)	Any Grade	Grade 3
Hypothyroidism	24 (23)	1 (1)
Colitis/Diarrhea	19 (18)	3 (3)
Rash	14 (14)	0
Adrenal Insufficiency/Hypophysitis	11 (11)	4 (4)
Hepatitis	10 (10)	3 (3)
Pneumonitis	4 (4)	1 (1)
Arthralgia	4 (4)	0
Diabetes mellitus	3 (3)	0
Mucositis	2 (2)	1 (1)
Neuropathy	2 (2)	0
Neutropenia	2 (2)	1 (1)
Bronchitis	1 (1)	0
Fever	1 (1)	0
Neuromuscular Weakness	1 (1)	0
Autoimmune Hemolytic Anemia	1 (1)	1 (1)
Myocarditis	1 (1)	1 (1)
Acid Reflux	1 (1)	0
Sarcoidosis	1 (1)	0
Vitiligo	1 (1)	0
Types of post-treatment irAE (>60 days post ICI cessation)	Any Grade	Grade 3
Hypothyroidism	7 (26)	2 (7)
Colitis	7 (26)	3 (11)
Adrenal Insufficiency/Hypophysitis	6 (22)	1 (4)
Hepatitis	4 (15)	3 (11)
Arthralgia	1 (4)	0
Neuropathy	1 (4)	0
Neutropenia	1 (4)	1 (4)
Rash	1 (4)	0

PS14-05

Safety evaluation from the KEYNOTE-522 study of neoadjuvant pembrolizumab (or placebo) plus chemotherapy followed by adjuvant pembrolizumab (or placebo) in patients with early triple-negative breast cancer (TNBC)

Presenting Author(s) and Co-Author(s):

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

R. Dent. National Cancer Centre Singapore, Singapore

L. Pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

H. McArthur. UT Southwestern, Dallas, Texas, United States

S. Kuemmel. West German Study Group, Moenchengladbach, Germany; Breast Unit, Kliniken Essen-Mitte, Essen, Germany; Charité - Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany

C. Denkert. Institut für Pathologie, Philipps Universität Marburg und Universitätsklinikum Marburg (UKGM), Germany

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

R. Hui. Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia

M. Takahashi. Hokkaido University, Sapporo, Japan

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

Y. Zhu. Merck & Co., Inc., Rahway, New Jersey, United States

X. Zhang. Merck & Co., Inc., Rahway, New Jersey, United States

W. Pan. Merck & Co., Inc., Rahway, New Jersey, United States

V. Karantza. Merck Sharp & Dohme LLC, Rahway, New Jersey, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

Background: In KEYNOTE-522 (NCT03036488), neoadjuvant (neoadj) pembrolizumab (pembro) + chemotherapy (chemo) followed by adjuvant (adj) pembro led to statistically significant and clinically meaningful improvements in the primary endpoints, pCR and EFS, vs neoadj placebo (pbo) + chemo followed by adj pbo in patients (pts) with newly diagnosed, high-risk, early TNBC. In the safety population at preplanned interim analysis 4 (IA4), treatment-related AEs in the combined phases (neoadj + adj) occurred in 98.9% of pts with pembro + chemo/pembro and 99.7% of pts with pbo + chemo/pbo; immune-mediated AEs of any grade occurred in 33.5% and 11.3% of pts, respectively. We report additional safety findings, beyond the already reported safety results, on immune-mediated AEs and management in the combined phases from IA4 of KEYNOTE-522. Methods: Eligible pts were randomized 2:1 to receive neoadj pembro 200 mg or pbo Q3W + paclitaxel-carboplatin for 4 cycles and then

doxorubicin or epirubicin + cyclophosphamide for 4 cycles. After definitive surgery, pts received radiation therapy as indicated + adj pembro 200 mg or pbo Q3W for up to 9 cycles. Safety was assessed in all randomized pts who received ≥ 1 dose, underwent surgery, or both. AEs were monitored throughout the study and for 30 d post-treatment (90 d for serious AEs). Results: At IA4 (data cut-off: March 23, 2021), median treatment duration was 13.3 (range, 0-21.9) mo with pembro + chemo/pembro (n = 783) and 13.6 (range, 0-19.8) mo with pbo + chemo/pbo (n = 389). Of 341 pts with immune-mediated AEs and infusion reactions in the pembro + chemo/pembro arm (most events occurred in neoadj phase), 224 had grade 1-2 events and 117 had grade 3–5 events. The most common immune-mediated AEs with pembro + chemo/pembro were hypothyroidism (15.1%) and severe skin reactions (5.7%); infusion reactions occurred in 18.0% of pts (table). Of 118 pts with hypothyroidism, median time to onset was 105 d (range, 7–510 d) and 106 were treated with thyroid replacement, suggesting an endocrine abnormality and need for continued thyroid replacement. Of 45 pts with severe skin reactions, median time to onset was 64 d (range, 4–479 d) and 28 were treated with corticosteroids. Of 141 pts with infusion reactions, median time to onset was 16 d (range, 1–458 d) and 85 were treated with corticosteroids. Other immune-mediated AEs of interest with pembro + chemo/pembro were adrenal insufficiency (2.6%), pneumonitis (2.2%), and hypophysitis (1.9%); most of these events were grade 2–3. All 20 pts with adrenal insufficiency were treated with hormone replacement. Of 17 pts with pneumonitis, median time to onset was 167 d (range, 22-537 d) and 12 were treated with corticosteroids; median episode duration was 92 d. Of 15 pts with hypophysitis, 14 were treated with corticosteroids. Conclusion: In pts with newly diagnosed, high-risk, early TNBC, neoadj pembro + chemo followed by adj pembro had a manageable safety profile that was generally consistent with the known safety profiles of pembro and the chemo regimens. Most immune-mediated AEs and infusion reactions were grade 1-2, manageable with treatment interruption, corticosteroids, and/or hormone replacement therapy, and did not result in treatment discontinuation. Together with the efficacy findings, our results support neoadj pembro + chemo followed by adj pembro as a standard of care regimen for these pts.

Table

Table. Summary of immune-mediated AEs and infusion reactions* in combined phases (neoadj + adj)

	Pembro + chemo/pembro n = 783	Pbo + chemo/pbo n = 389
Immune-mediated AEs and infusion reactions		
Infusion reactions	141 (18.0)	45 (11.6)
Severe skin reactions	118 (15.1)	22 (5.7)
Hypothyroidism	45 (5.7)	4 (1.0)
Hyperthyroidism	41 (5.2)	7 (1.8)
Adrenal insufficiency	20 (2.6)	0
Pneumonitis	17 (2.2)	6 (1.5)
Thyroiditis	16 (2.0)	5 (1.3)
Hypophysitis ^b	15 (1.9)	1 (0.3)
Colitis	13 (1.7)	3 (0.8)
Hepatitis	11 (1.4)	3 (0.8)
Nephritis	7 (0.9)	0
Myocarditis	5 (0.6)	0
Pancreatitis	5 (0.6)	0
Myositis	4 (0.5)	0
Type 1 diabetes mellitus	4 (0.5)	0
Vasculitis	4 (0.5)	0
Encephalitis	2 (0.3)	0
Uveitis	2 (0.3)	0
Myasthenic syndrome	1 (0.1)	0
Sarcoidosis	1 (0.1)	0
Immune-mediated AEs and infusion reactions leading to dose reduction ^c		
Chemo ^d	1 (0.1)	0
Immune-mediated AEs and infusion reactions leading to treatment interruption		
Pembro/pbo	43 (5.5)	9 (2.3)
Chemo ^d	88 (11.2)	25 (6.4)
Immune-mediated AEs and infusion reactions leading to treatment discontinuation		
Pembro/pbo	61 (7.8)	4 (1.0)
Chemo ^d	45 (5.7)	7 (1.8)

Results are n (%) of pts.

*Immune-mediated AEs and infusion reactions were based on a list of terms specified at the time of analysis and were included regardless of attribution to study treatment or immune relatedness by the investigator; related terms were included.

^bIncludes 5 pts with hypopituitarism.

^cDose reduction was not allowed for pembro/pbo.

^dChemo was administered during the neoadj phase only.

PS14-06

Real-World Analysis of Adverse Events in Patients with Triple Negative Breast Cancer Receiving Therapy per KEYNOTE-522

Presenting Author(s) and Co-Author(s):

M. Hofherr. Washington University, St. Louis, Missouri, United States
K. Clifton. Washington University in St Louis School of Medicine, United States
S. January. BJC, United States
E. Owen. BJC, United States
F. Raheem. Mayo Clinic, United States
L. Mina. Mayo Clinic, United States
S. Arunachalam Karikalan. Mayo Clinic Arizona, Phoenix, Arizona, United States
L. Lyons. Lexington Medical Cancer Center, United States
M. Watson Rose. Lexington Medical Cancer Center, United States
K. Madden. Lexington Medical Cancer Center, United States
J. Hsin. City of Hope, United States
A. Keegan. City of Hope, United States
W. Yu. City of Hope, United States
S. Kraft. University of Michigan, United States
A. Schepers. University of Michigan, United States
E. Armgardt. Northwestern, United States
D. Mazewski. Northwestern, United States
A. Svoboda. Northwestern, United States
K. Harwood. Mayo, United States
J. Taraba. Mayo Clinic, United States
Y. Resnick. NEWECS, United States
S. Hummert. Huntsman Cancer Institute, United States
L. Grate. UC Health, United States
S. Keisner. UAMS, United States
J. Hobbs. Avera Cancer Institute, United States
T. Davis. UW Cancer Center, United States
K. Bastian. PHCI, United States
D. Minikel. ProHealthCare Institute, United States
T. White. UMN, United States
W. Adler. UMAS, United States
A. Singh Sandu. Kettering Health, United States
F. Boulbol. Community Medical, United States
K. Finch. Columbus Regional Health, United States
A. Davis. Washington University in St Louis School of Medicine, United States

Title: Real-world analysis of adverse events in patients with triple-negative breast cancer receiving therapy per KEYNOTE-522 **Background:** KEYNOTE-522 was a randomized, double-blind, placebo-controlled phase 3 trial which resulted in the FDA approval of pembrolizumab with neoadjuvant chemotherapy for patients (pts) with newly diagnosed, high-risk, early-stage triple-negative breast cancer (TNBC). Given the improvement in pathological complete response (pCR) and event-free survival rates, this regimen has emerged as standard-of-care (SOC) therapy. To date, real world outcome analyses are limited. **Methods:** In this retrospective, multicenter study, we examined pts with early-stage TNBC who received planned treatment per KEYNOTE-522 as SOC. 16 sites were included in the analysis. IRB approval was obtained from each participating site. Number and length of treatment delays, treatment related toxicities (both chemotherapy and immune-related) of all grades, and pCR rate were collected from the electronic medical record of each participating site, and deidentified data were shared for central analysis. **Results:** 577 pts were included in this analysis. The median age of the cohort was 52 [range 27-77]. 457 pts had T1-2 disease and 139 had T3-4 disease. 316 pts had N0 disease and 261 had N1-3 disease. 506 pts had baseline ECOG 0, 62 had ECOG 1, and 9 had ECOG 2-3. Of the 482 patients who had surgery at the time of this analysis, 219 patients had pCR (54.5%) and 192 pts were still receiving treatment. 217 patients (37%) had an adverse drug event (ADE) causing dose reductions and 228 patients (39.5%) had to discontinue treatment early. There were 360 unplanned care visits, with 91 patients having 2+ visits. 66 patients had hospitalizations due to the regimen with 102 total hospitalizations. 179 (31%) of patients had grade 3+ immune related adverse events (irAEs), including many that are rare and potentially serious. 317 (54%) had an immune related adverse effect (see Table 1). There was no significant difference in the frequency of grade 3+ irAE based on age or body mass index. We observed no difference in residual disease between patients who discontinued treatment early and those who did not. However, if patients had an ADR causing a dose reduction, pts were significantly more likely to have residual disease (P=0.039) **Conclusions:** In a multicenter real-world analysis, the KEYNOTE-522 regimen was associated with a high frequency of dose reductions, early treatment discontinuations, ER visits, and hospitalizations. This may have accounted for a lower pCR rate than observed in the landmark clinical trial. Most grade 3+ irAEs occurred at greater frequency in our real-world analysis. Providers should carefully monitor for toxicity to ensure optimal patient outcomes.

Table 1

Immune-related adverse events (N=577)	Immune Related Adverse Events of Any Grade	Grade 3+ Immune Related Adverse Events
Elevated ALT	137 (23.7%)	21 (3.6%)
Immune-Related rash	135 (23.4%)	27 (4.6%)
Elevated AST	126 (21.8%)	21 (3.6%)
Hepatitis	115 (19.9%)	23 (3.9%)
Hypothyroidism	106 (18%)	30 (5.2%)
Myalgias	91 (15.7%)	12 (2.0%)
Arthralgia	86 (14.9%)	9 (1.6%)
Pruritis	63 (10.9%)	14 (2.4%)
Primary Adrenal Insufficiency	45 (7.8%)	32 (5.5%)
Colitis	30 (5.2%)	22 (3.8%)
Vision Changes	28 (4.8%)	5 (0.8%)
AKI	24 (4.1%)	6 (1.0%)
Pneumonitis	21 (3.6%)	11 (1.9%)
Hyperthyroidism	10 (1.7%)	8 (1.4%)
Inflammatory Arthritis	9 (1.6%)	2 (0.3%)
Thyroiditis	9 (1.6%)	4 (0.6%)
Hypophysitis	8 (1.4%)	2 (0.3%)
Type I Diabetes	8 (1.4%)	6 (1.0%)
Bullous Dermatitis	7 (1.2%)	1 (0.1%)
Myocarditis	6 (1.0%)	2 (0.3%)
DKA	5 (0.8%)	5 (0.8%)
Transverse Myelitis	4 (0.6%)	0 (0.0%)
Myositis	4 (0.6%)	2 (0.3%)
Encephalitis	4 (0.6%)	2 (0.3%)
Pancreatitis	4 (0.7%)	3 (0.5%)
ILD	3 (0.5%)	2 (0.3%)

PS14-07

Exploring Circulating Leukocyte RNA Expression: Implications for Treatment Outcomes and Immune-Related Adverse Events in Patients with Triple Negative Breast Cancer Enrolled in the GeparNuevo Trial

Presenting Author(s) and Co-Author(s):

H. Hübner. Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Bayern, Germany

M. Ruebner. Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich-Alexander-University Erlangen-Nürnberg, Germany

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

C. Denkert. Institut für Pathologie, Philipps Universität Marburg und Universitätsklinikum Marburg (UKGM), Germany

H. Sinn. Pathologie, Universitätsklinikum, Heidelberg, Germany

M. Braun. Rotkreuzklinikum München, Germany

T. Karn. Universitätsklinikum Frankfurt, Frankfurt am Main, Germany

B. Sinn. Institut für Pathologie, Charité Berlin, Germany

D. Zahm. SH Wald-Klinikum Gera, Germany

J. Thomalla. Institut für Versorgungsforschung in der Oncologie Koblenz am Rhein, Germany

J. Huober. Kantonsspital St.Gallen, Brustzentrum, Departement Interdisziplinäre medizinische Dienste, St. Gallen, Switzerland

C. Hanusch. Rotkreuzklinikum München, Germany

M. Untch. AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany, Berlin, United States

C. Solbach. University Hospital Frankfurt, Frankfurt, Germany

T. Link. Department of Gynecology and Obstetrics, Technische Universität Dresden, Dresden, Germany

N. Filmann. German Breast Group, Neu-Isenburg, Germany

J. Rey. GBG Forschungs GmbH, Germany

J. Holtschmidt. German Breast Group, Neu-Isenburg, Germany

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

Abstract Exploring Circulating Leukocyte RNA Expression: Implications for Treatment Outcomes and Immune-Related Adverse Events in Patients with Triple Negative Breast Cancer Enrolled in the GeparNuevo Trial Background: Significant research has been conducted on the influence of immune checkpoint inhibitor therapy on tumor microenvironment, particularly with regard to tumor-infiltrating immune cells. Nevertheless, our understanding of the circulating immune repertoire and its association with treatment outcomes remains limited. Consequently, our subproject of the GeparNuevo trial aimed to explore the RNA phenotype of circulating

leukocytes and its impact on overall survival (OS), and adverse events of patients enrolled in the GeparNuevo trial (Loibl S et al. *Annals Oncol* 2022). Methods: The GeparNuevo phase II trial focused on the effects of neoadjuvant nab-paclitaxel followed by epirubicin/cyclophosphamide (nabP-EC) chemotherapy combined with the anti-PD-L1 immune checkpoint inhibitor durvalumab versus placebo in patients with non-metastatic triple-negative breast cancer. RNA-stabilizing PAXgene tubes were used to collect blood samples prior to treatment initiation. RNA was extracted from circulating leukocytes of 117 patients and analyzed using a custom NanoString nCounter CodeSet, including 290 immune-related target genes. The associations between 16 immune cell scores, 26 immune signaling scores, 31 individual gene expression patterns, OS, and immune-related adverse events (irAEs) were analyzed. Results: Univariate Cox regression analysis using continuous scores revealed a significant correlation between PIP3 activates AKT signaling, T cells, CDK2, and TIMP1 expression with OS in the placebo arm. Higher expression of PIP3 activates AKT signaling, T cells, and CDK2, as well as lower expression of TIMP1, were associated with prolonged survival. Notably, T cell scores and CDK2 expression exhibited a significant interaction with the treatment arm ($p=0.0489$ and 0.0210 , respectively). Multivariate Cox regression analysis demonstrated a significant association of DPP4, ICOS and MYC expression with OS. Additionally, CDK2, CDKN2A, F5 and HLA-DRA expression were linked to the presence of irAEs. In the durvalumab arm, TNFR2 non canonical NF κ B pathway signaling, CDK2 and CDKN2A expression showed an inverse association with the occurrence of irAEs. Conclusions: Our study provides preliminary evidence that RNA derived from circulating leukocytes may serve as a potential biomarker for predicting treatment outcomes and identifying patients prone to develop side effects during standard-of-care chemotherapy or immune checkpoint therapy. These findings highlight the potential utility of peripheral immune cell RNA profiling in improving treatment strategies and patient management. Further research and validation are necessary to fully comprehend the clinical significance and broader implications of these findings. Key words: Breast cancer, immune phenotype, immune checkpoint Funding Source: This study was funded by Walter Schulz Stiftung and the clinical trial was funded by AstraZeneca and Celgene.

PS14-08

Safety evaluation from the KEYNOTE-355 study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy in patients with previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

Z. Nowecki. Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland

D. Cescon. Princess Margaret Cancer Centre/UHN, Toronto, Ontario, Canada

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

M. Yusof. Cancer Center, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

C. Gallardo. Oncology Institute, Arturo Lopez Perez Foundation, Santiago, Chile

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

X. Zhou. Merck & Co., Inc., Rahway, New Jersey, United States

X. Zhang. Merck & Co., Inc., Rahway, New Jersey, United States

W. Pan. Merck & Co., Inc., Rahway, New Jersey, United States

V. Karantza. Merck Sharp & Dohme LLC, Rahway, New Jersey, United States

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Spain

Background: In KEYNOTE-355 (NCT02819518), pembrolizumab (pembro) + chemotherapy (chemo) led to statistically significant and clinically meaningful improvements in PFS and OS (primary endpoints) vs placebo (pbo) + chemo in patients (pts) with previously untreated PD-L1 positive advanced TNBC (combined positive score ≥ 10). In the overall safety population at final analysis, treatment-related AEs occurred in 96.3% of pts in the pembro + chemo arm and 95.0% of pts in the pbo + chemo arm; immune-mediated AEs occurred in 26.5% and 6.4% of pts, respectively. We report additional safety information, beyond the already reported safety results, on immune-mediated AEs and management from the final analysis of KEYNOTE-355. **Methods:** Eligible pts were randomized 2:1 to receive pembro 200 mg or pbo Q3W for up to 35 cycles + investigator's choice of nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin. Safety was assessed in all randomized pts who received ≥ 1 dose of study treatment. AEs were monitored throughout the study and for 30 d post-treatment (90 d for serious AEs). **Results:** At final analysis (data cut-off: June 15, 2021), median treatment duration was 6.1 (range, 0.0–48.8) mo in the pembro + chemo arm (n = 562) and 5.3 (range, 0.0–51.5) mo in the pbo + chemo arm (n = 281). Of 157 pts with immune-mediated AEs and infusion reactions in the pembro + chemo arm, 125 had grade 1-2 events and 32 had grade 3-4 events; none were grade 5. The most common immune-mediated AEs with pembro + chemo were hypothyroidism (15.8%) and hyperthyroidism (4.3%); infusion reactions occurred in 3.7% of pts (table). Of 89

pts with hypothyroidism, median time to onset was 105 d (range, 19–707 d) and 70 were treated with thyroid replacement, suggesting an endocrine abnormality and need for continued thyroid replacement. Of 24 pts with hyperthyroidism, median time to onset was 53.5 d (range, 20–209 d) and 2 were treated with corticosteroids. Of 21 pts with infusion reactions, median time to onset was 147 d (range, 1–729 d) and 10 were treated with corticosteroids. Other immune-mediated AEs of interest in the pembro + chemo arm were pneumonitis (2.5%) and adrenal insufficiency (1.4%); most of these events were grade 2–3. Of 14 pts with pneumonitis, median time to onset was 99.5 d (range, 29–288 d) and 11 were treated with corticosteroids; median episode duration was 56 d. All 8 pts with adrenal insufficiency were treated with hormone replacement. There were no reports of hypophysitis. Conclusion: In pts with previously untreated advanced TNBC, pembro + chemo had a manageable safety profile that was generally consistent with the known safety profiles of pembro and the chemo regimens. Most immune-mediated AEs and infusion reactions were grade 1-2, manageable with treatment interruption, corticosteroids, and/or hormone replacement therapy, and did not result in discontinuation of study treatment. Together with the efficacy findings, our results support pembro + chemo as a standard of care regimen for these pts.

Table. Summary of immune-mediated AEs and infusion reactions^a

	Pembro + chemo n = 562	Pbo + chemo n = 281
Immune-mediated AEs and infusion reactions		
Hypothyroidism	89 (15.8)	9 (3.2)
Hyperthyroidism	24 (4.3)	3 (1.1)
Infusion reactions	21 (3.7)	14 (5.0)
Pneumonitis	14 (2.5)	0
Colitis	10 (1.8)	4 (1.4)
Severe skin reactions	10 (1.8)	1 (0.4)
Adrenal insufficiency	8 (1.4)	0
Thyroiditis	7 (1.2)	0
Hepatitis	5 (0.9)	2 (0.7)
Myositis	3 (0.5)	0
Nephritis	3 (0.5)	0
Uveitis	2 (0.4)	0
Vasculitis	2 (0.4)	1 (0.4)
Guillain-Barre Syndrome	1 (0.2)	0
Myocarditis	1 (0.2)	0
Pancreatitis	1 (0.2)	0
Type 1 diabetes mellitus	1 (0.2)	0
Immune-mediated AEs and infusion reactions leading to dose reduction ^b		
Chemo	1 (0.2)	0
Immune-mediated AEs and infusion reactions leading to treatment interruption		
Pembro/pbo	36 (6.4)	2 (0.7)
Chemo	38 (6.8)	9 (3.2)
Immune-mediated AEs and infusion reactions leading to treatment discontinuation		
Pembro/pbo	14 (2.5)	0
Chemo	13 (2.3)	3 (1.1)

Results are n (%) of pts.

^aImmune-mediated AEs and infusion reactions were based on a list of terms specified at the time of analysis and were included regardless of attribution to study treatment or immune relatedness by the investigator; related terms were included.

^bDose reduction was not allowed for pembro/pbo.

PS14-01

Immune related adverse events in patients ≥ 65 years vs. < 65 years with breast cancer treated with immunotherapy

Presenting Author(s) and Co-Author(s):

N. Vidula. Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, United States

J. Hutchinson. Massachusetts General Hospital, United States

A. McLaren. Massachusetts General Hospital, United States

L. Ryan. Cancer Center, Massachusetts General Hospital, United States

A. Niemierko. Massachusetts General Hospital, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

Background:

Pembrolizumab is approved for early/advanced triple negative breast cancer (TNBC), and atezolizumab was previously approved for advanced TNBC. Toxicity of immunotherapy (IO) and immune related adverse events (irAEs) in patients ≥ 65 years with TNBC is not described in detail in results from registration trials (KEYNOTE 522, KEYNOTE 355, and IMPassion130), where patients ≥ 65 years were a minority. Understanding real-world IO toxicity and irAEs in patients with breast cancer ≥ 65 years may inform clinical decision making.

Methods:

We studied IO toxicity and irAEs in patients with breast cancer ≥ 65 years vs. < 65 years (at IO start) who received IO at an academic institution. A retrospective review was conducted to identify IO toxicity and irAEs (classified by CTCAE v 5.0). Cohorts were compared with Pearson's chi-squared test (categorical variables) and Wilcoxon rank-sum test (continuous variables).

Results:

Cohorts had 25 patients ≥ 65 years (median age 73 years, interquartile range (IQR) 69-74 years) and 104 patients < 65 years (median age 48 years, IQR 39-56 years). Stage I-III/IV breast cancer distribution was 36%/64% for ≥ 65 years and 68%/32% for < 65 years. Baseline ECOG performance status was mainly 0-1 in both cohorts. IO was mainly pembrolizumab (≥ 65 years: 96%; < 65 years: 83% for first IO regimen) vs. atezolizumab. Table 1 depicts characteristics of IO toxicity. IO duration was longer in patients < 65 years. While rates of IO interruption for toxicity and discontinuation for toxicity were numerically higher in patients ≥ 65 years, these findings did not reach statistical significance, possibly due to the sample size. Similar overall rates of irAEs were seen (≥ 65 years: 72%; < 65 years: 65%, $p=0.47$) but there were differences in the types of irAEs. Patients < 65 years had more transaminitis (≥ 65 years: 12%; < 65 years: 33%, $p=0.04$), and grade 2-3 hypothyroidism (among patients developing hypothyroidism, ≥ 65 years: grade 1- 75%, grade 2- 25%, grade 3- 0%; < 65 years: grade 1- 11%, grade 2- 79%, grade 3- 11%, $p=0.017$). Conversely, patients ≥ 65 years had higher rates of irAE nephritis (≥ 65 years: 12%; < 65 years: 1%, $p=0.004$); notably, none of the patients had baseline chronic kidney disease. Rates of full resolution of irAEs were similar between cohorts (≥ 65 years: 67%; < 65 years: 57%, $p=0.47$), but patients ≥ 65 years had more steroid use for management of first irAE while patients < 65 years required more thyroid hormone supplementation (first irAE management distribution, ≥ 65 years: steroids- 71%, thyroid

hormone- 7%, supportive care- 21%; < 65 years: steroids- 31%, thyroid hormone- 25%, supportive care- 44%, p=0.025). Late onset irAEs and deaths from irAEs were rare in both cohorts, with 1 irAE related death in the cohort ≥65 years.

Conclusions:

In this real-world cohort, similar overall rates of irAEs were observed in patients ≥65 years and < 65 years. However, patients ≥65 years had higher rates of irAE nephritis and steroid use for irAEs, while patients < 65 years had more transaminitis and higher grade hypothyroidism, requiring more thyroid hormone supplementation. Given these age specific differences, validation in a larger cohort is merited.

Table 1. Characteristics of IO toxicity.

Variable (median, IQR OR #, %)	≥65 years (69-74)	<65 years (39-56)	p value
IO duration (months)	2.3 (1.6-4.4)	5.4 (2.1-10.7)	0.006
IO interruption for toxicity	4 (16%)	7 (7%)	0.14
IO dose # at toxicity interruption	2 (2-4)	5 (2-6)	0.31
IO discontinuation for toxicity	4 (16%)	7 (7%)	0.14

Disclosure(s):

Neelima Vidula, MD: Advisory Committee/Board Member: Aadi Biopharma (Terminated, December 5, 2023), Gilead (Terminated, December 5, 2023), Stemline Therapeutics (Terminated, December 5, 2023), TerSera (Terminated, December 5, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Daehwa (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer, Inc. (Ongoing)

Aditya Bardia, MD, MPH: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Menarini/Stemline (Ongoing)

Poster Spotlight Session 14: Setting Expectations for Toxicities Related to I/O Therapy

Presenting Author(s) and Co-Author(s):

W. Gradishar. Robert H. Lurie Comprehensive Cancer Center, Northwestern University,
Chicago, Illinois, United States

Disclosure(s):

William Gradishar, MD: No financial relationships to disclose

PS14-02

Real-world analysis comparing Black and White patients with triple-negative breast cancer receiving therapy per KEYNOTE-522

Presenting Author(s) and Co-Author(s):

M. Hofherr. Washington University, St. Louis, Missouri, United States
A. Davis. Washington University in St Louis School of Medicine, United States
S. January. BJC, United States
E. Owen. BJC, United States
F. Raheem. Mayo Clinic, United States
L. Mina. Mayo Clinic, United States
S. Arunachalam Karikalan. Mayo Clinic Arizona, Phoenix, Arizona, United States
L. Lyons. Lexington Medical Cancer Center, United States
M. Watson Rose. Lexington Medical Cancer Center, United States
K. Madden. Lexington Medical Cancer Center, United States
J. Hsin. City of Hope, United States
A. Keegan. City of Hope, United States
W. Yu. City of Hope, United States
S. Kraft. University of Michigan, United States
A. Schepers. University of Michigan, United States
E. Armgardt. Northwestern, United States
D. Mazewski. Northwestern, United States
A. Svoboda. Northwestern, United States
K. Harwood. Mayo, United States
J. Taraba. Mayo Clinic, United States
Y. Resnick. NEW ECS, United States
S. Hummert. Huntsman Cancer Institute, United States
L. Grate. UC Health, United States
S. Keisner. UAMS, United States
J. Hobbs. Avera Cancer Institute, United States
T. Davis. UW Cancer Center, United States
K. Bastian. PHCI, United States
D. Minikel. ProHealthCare Institute, United States
W. Adler. SALUD, United States
T. White. UMN, United States
A. Singh Sandu. Kettering Health, United States
F. Boulbol. Community Medical, United States
K. Finch. Columbus Regional Health, United States
K. Clifton. Washington University in St Louis School of Medicine, United States

Abstract

Title:

Real-world analysis comparing Black and White patients with triple-negative breast cancer receiving therapy per KEYNOTE-522

Background: KEYNOTE-522 was a randomized, double-blind, placebo-controlled phase 3 trial which resulted in the FDA approval of pembrolizumab with neoadjuvant chemotherapy for patients with newly diagnosed, high-risk, early-stage triple-negative breast cancer (TNBC). Despite the significant improvement in pathological complete response (pCR) and event-free survival rates across all patients, the landmark trial included only 4.5% Black patients. It is essential to assess outcomes in representative treatment populations. We assessed real-world toxicity and treatment outcomes across Black and White patients who received standard-of-care treatment per KEYNOTE-522.

Methods:

In this retrospective, multicenter study, we examined patients with early-stage TNBC who received planned treatment per KEYNOTE-522 as standard-of-care (SOC) therapy. 16 sites were included in the analysis. IRB approval was obtained from each participating site. Number and length of treatment delays, treatment-related toxicities (both chemotherapy and immune-related) of all grades, and pCR rate were collected from the electronic medical record of each participating site, and deidentified data were shared for central analysis.

Results:

Of the 577 patients who initiated treatment with chemotherapy and immunotherapy, 534 patients were included in this analysis with 105 patients who self-identified as Black (19.7%) and 429 who self-identified as White (80.3%). There were no statistically significant differences in clinical and pathological characteristics between the two groups. White women were more likely to have grade 3+ immune-related adverse events (irAEs) compared to Black women (33.8% vs 20.9%, $P=0.011$). There was no significant difference across Black and White patients with respect to grade 3+ chemotherapy-related adverse events. Out of the 444 patients who have completed surgery, no difference in pCR rate was observed between Black and White women (45/86 52.3% vs 200/358 55.9%) ($p = 0.6$). The authors also saw no difference in the rates of hospitalizations between Black and White women (39% vs 36% $p = 0.5$), and rates of acute care utilization (38% vs 38% $p = 0.9$).

Conclusions:

We report safety and efficacy across Black and White women in a real-world analysis of patients who received treatment per KEYNOTE-522. Notably, White patients had a significantly higher frequency of grade 3+ irAEs, although the reason for this finding is unclear based on this analysis. Black patients had similar pCR rates and rates of treatment-related hospitalizations compared to White patients. Assessment of outcomes and toxicity by race in clinical trials and real-world analyses are critical in drug development.

Disclosure(s):

Mara Hofherr, PharmD: Consulting Fees (e.g., advisory boards): Astra Zeneca, Roche, Novartis, Biocad, R-Pharm, Eisai, Eli Lilly, Pfizer, MSD, BMS (Terminated); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Merck & Co., Inc. (Ongoing)

PS14-03

Delayed and post-treatment immune toxicities in patients with breast cancer receiving immune checkpoint inhibitors.

Presenting Author(s) and Co-Author(s):

S. Jacob. University of California, San Francisco, California, United States

S. Fisch. University of California, San Francisco, United States

C. Face. University of California, San Francisco, United States

L. Huppert. University of California, San Francisco, Oakland, California, United States

Z. Quandt. University of California, San Francisco, United States

L. Quintal. University of California, San Francisco, United States

M. Melisko. University of California at San Francisco, San Francisco, California, United States

M. Majure. University of California, San Francisco, United States

J. Chien. University of California, San Francisco, San Francisco, California, United States

A. Blaes. University of Minnesota, Minneapolis, Minnesota, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

Background:

Immune checkpoint inhibitors (ICI) have improved outcomes in patients (pts) with breast cancer, however identification and management of immune-related adverse events (irAE) remains challenging. Delayed irAE have been observed, occurring even after ICI cessation. Prior analyses of delayed irAE have focused on patients with melanoma, lung, and head & neck cancer but data in patients with breast cancer are lacking.

Methods:

We identified pts with breast cancer who received ICI at our institution between 2012 and 2022 using pharmacy administration records. Charts were reviewed for delayed and post-treatment irAE. Delayed irAE were defined as occurring >90 days after ICI start; post-treatment irAE were defined as occurring >60 days after ICI discontinuation. Events were categorized as irAE if provider notes indicated that the toxicity was related to or possibly related to ICI.

Results:

320 consecutive pts with breast cancer (219 metastatic, 96 localized disease) underwent treatment with ICI, of which 79 (25%) developed delayed irAE (40 with metastatic disease, 39 with localized disease). 54 pts had triple negative breast cancer (TNBC), 22 had hormone receptor positive (HR+) disease, and 4 had HER2+ disease. 44 pts received ICI on a clinical trial. The median number of ICI doses was 8, and the median length of follow-up after the first ICI infusion was 29 months. For delayed irAE, median time to onset was 183 days (range 91-1800 days) with a total of 103 delayed irAE events (see table). 24 pts (7.5%) developed a post-treatment irAE with a total of 27 events. For post-treatment irAE, median time to onset was 112 days after ICI cessation (range 69-1100 days) and median time on ICI was 63 days (range 22-1724 days). 11 of 24 patients who experienced a post-treatment irAE also experienced an irAE while on treatment. Hypothyroidism, colitis, adrenal insufficiency, and hepatitis were the most common irAE at all time points. Rash primarily occurred while still on ICI. All irAE at any time point either self-resolved, resolved with systemic steroids, or continued with indefinite hormone replacement. 45 irAE required systemic steroids, not including hydrocortisone replacement for

adrenal insufficiency. There were no grade 4 or 5 irAEs.

Conclusions:

This is the first evaluation of delayed/post-treatment irAE in a large cohort of patients with breast cancer. 79 pts (25%) experienced delayed irAEs occurring ≥ 90 days after ICI start, with median time to onset of 183 days. 89% of patients with delayed irAE also experienced an irAE at an earlier time point, indicating that early irAE may be a risk for delayed irAE. 24 pts (7.5%) experienced post-treatment irAE with median onset of 121 days after ICI cessation. Diagnosis of delayed irAE requires heightened awareness and prompt treatment. Future work is needed to identify key clinical and molecular markers that predict risk for delayed irAE to better inform treatment & monitoring.

Parameter	Number of pts (%)	
Total pts receiving an ICI	320	
Delayed irAE	79 (25)	
>1 delayed irAE	21 (27% of pts with delayed irAE)	
Patients with delayed irAEs who also had irAE occurring < 90 days after ICI start	70 (89% of pts with delayed irAE)	
Post-treatment irAE	24 (7.5)	
Types of delayed irAE (>90 days after ICI start)	Any Grade	Grade 3
Hypothyroidism	24 (23)	1 (1)
Colitis/Diarrhea	19 (18)	3 (3)
Rash	14 (14)	0
Adrenal Insufficiency/Hypophysitis	11 (11)	4 (4)
Hepatitis	10 (10)	3 (3)
Pneumonitis	4 (4)	1 (1)
Arthralgia	4 (4)	0
Diabetes mellitus	3 (3)	0
Mucositis	2 (2)	1 (1)
Neuropathy	2 (2)	0
Neutropenia	2 (2)	1 (1)
Bronchitis	1 (1)	0
Fever	1 (1)	0
Neuromuscular Weakness	1 (1)	0
Autoimmune Hemolytic Anemia	1 (1)	1 (1)
Myocarditis	1 (1)	1 (1)
Acid Reflux	1 (1)	0
Sarcoidosis	1 (1)	0
Vitiligo	1 (1)	0
Types of post-treatment irAE (>60 days post ICI cessation)	Any Grade	Grade 3
Hypothyroidism	7 (26)	2 (7)
Colitis	7 (26)	3 (11)
Adrenal Insufficiency/Hypophysitis	6 (22)	1 (4)

Hepatitis	4 (15)	3 (11)
Arthralgia	1 (4)	0
Neuropathy	1 (4)	0
Neutropenia	1 (4)	1 (4)
Rash	1 (4)	0

Disclosure(s):

Saya Jacob, MD: No financial relationships to disclose

Laura Huppert, MD: Consulting Fees (e.g., advisory boards): AstraZenica (Ongoing)

Jo Chien, MD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Amgen Inc. (Ongoing), Merck & Co., Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), SeaGen (Ongoing)

Anne Blaes, MD MS: No financial relationships to disclose

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

PS14-05

Safety evaluation from the KEYNOTE-522 study of neoadjuvant pembrolizumab (or placebo) plus chemotherapy followed by adjuvant pembrolizumab (or placebo) in patients with early triple-negative breast cancer (TNBC)

Presenting Author(s) and Co-Author(s):

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

R. Dent. National Cancer Centre Singapore, Singapore

L. Pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

H. McArthur. UT Southwestern, Dallas, Texas, United States

S. Kuemmel. West German Study Group, Moenchengladbach, Germany; Breast Unit, Kliniken Essen-Mitte, Essen, Germany; Charité - Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany

C. Denkert. Institut für Pathologie, Philipps Universität Marburg und Universitätsklinikum Marburg (UKGM), Germany

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

R. Hui. Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia

M. Takahashi. Hokkaido University, Sapporo, Japan

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

Y. Zhu. Merck & Co., Inc., Rahway, New Jersey, United States

X. Zhang. Merck & Co., Inc., Rahway, New Jersey, United States

W. Pan. Merck & Co., Inc., Rahway, New Jersey, United States

V. Karantza. Merck Sharp & Dohme LLC, Rahway, New Jersey, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

Background:

In KEYNOTE-522 (NCT03036488), neoadjuvant (neoadj) pembrolizumab (pembro) + chemotherapy (chemo) followed by adjuvant (adj) pembro led to statistically significant and clinically meaningful improvements in the primary endpoints, pCR and EFS, vs neoadj placebo (pbo) + chemo followed by adj pbo in patients (pts) with newly diagnosed, high-risk, early TNBC. In the safety population at preplanned interim analysis 4 (IA4), treatment-related AEs in the combined phases (neoadj + adj) occurred in 98.9% of pts with pembro + chemo/pembro and 99.7% of pts with pbo + chemo/pbo; immune-mediated AEs of any grade occurred in 33.5% and 11.3% of pts, respectively. We report additional safety findings, beyond the already reported safety results, on immune-mediated AEs and management in the combined phases from IA4 of KEYNOTE-522.

Methods:

Eligible pts were randomized 2:1 to receive neoadj pembro 200 mg or pbo Q3W + paclitaxel-

carboplatin for 4 cycles and then doxorubicin or epirubicin + cyclophosphamide for 4 cycles. After definitive surgery, pts received radiation therapy as indicated + adj pembro 200 mg or pbo Q3W for up to 9 cycles. Safety was assessed in all randomized pts who received ≥ 1 dose, underwent surgery, or both. AEs were monitored throughout the study and for 30 d post-treatment (90 d for serious AEs).

Results:

At IA4 (data cut-off: March 23, 2021), median treatment duration was 13.3 (range, 0-21.9) mo with pembro + chemo/pembro (n = 783) and 13.6 (range, 0-19.8) mo with pbo + chemo/pbo (n = 389). Of 341 pts with immune-mediated AEs and infusion reactions in the pembro + chemo/pembro arm (most events occurred in neoadj phase), 224 had grade 1-2 events and 117 had grade 3–5 events. The most common immune-mediated AEs with pembro + chemo/pembro were hypothyroidism (15.1%) and severe skin reactions (5.7%); infusion reactions occurred in 18.0% of pts (table). Of 118 pts with hypothyroidism, median time to onset was 105 d (range, 7–510 d) and 106 were treated with thyroid replacement, suggesting an endocrine abnormality and need for continued thyroid replacement. Of 45 pts with severe skin reactions, median time to onset was 64 d (range, 4–479 d) and 28 were treated with corticosteroids. Of 141 pts with infusion reactions, median time to onset was 16 d (range, 1–458 d) and 85 were treated with corticosteroids. Other immune-mediated AEs of interest with pembro + chemo/pembro were adrenal insufficiency (2.6%), pneumonitis (2.2%), and hypophysitis (1.9%); most of these events were grade 2–3. All 20 pts with adrenal insufficiency were treated with hormone replacement. Of 17 pts with pneumonitis, median time to onset was 167 d (range, 22-537 d) and 12 were treated with corticosteroids; median episode duration was 92 d. Of 15 pts with hypophysitis, 14 were treated with corticosteroids.

Conclusion:

In pts with newly diagnosed, high-risk, early TNBC, neoadj pembro + chemo followed by adj pembro had a manageable safety profile that was generally consistent with the known safety profiles of pembro and the chemo regimens. Most immune-mediated AEs and infusion reactions were grade 1-2, manageable with treatment interruption, corticosteroids, and/or hormone replacement therapy, and did not result in treatment discontinuation. Together with the efficacy findings, our results support neoadj pembro + chemo followed by adj pembro as a standard of care regimen for these pts.

Table

Table. Summary of immune-mediated AEs and infusion reactions* in combined phases (neoadj + adj)

	Pembro + chemo/pembro n = 783	Pbo + chemo/pbo n = 389
Immune-mediated AEs and infusion reactions		
Infusion reactions	141 (18.0)	45 (11.6)
Hypothyroidism	118 (15.1)	22 (5.7)
Severe skin reactions	45 (5.7)	4 (1.0)
Hyperthyroidism	41 (5.2)	7 (1.8)
Adrenal insufficiency	20 (2.6)	0
Pneumonitis	17 (2.2)	6 (1.5)
Thyroiditis	16 (2.0)	5 (1.3)
Hypophysitis ^b	15 (1.9)	1 (0.3)
Colitis	13 (1.7)	3 (0.8)
Hepatitis	11 (1.4)	3 (0.8)
Nephritis	7 (0.9)	0
Myocarditis	5 (0.6)	0
Pancreatitis	5 (0.6)	0
Myositis	4 (0.5)	0
Type 1 diabetes mellitus	4 (0.5)	0
Vasculitis	4 (0.5)	0
Encephalitis	2 (0.3)	0
Uveitis	2 (0.3)	0
Myasthenic syndrome	1 (0.1)	0
Sarcoidosis	1 (0.1)	0
Immune-mediated AEs and infusion reactions leading to dose reduction ^c		
Chemo ^d	1 (0.1)	0
Immune-mediated AEs and infusion reactions leading to treatment interruption		
Pembro/pbo	43 (5.5)	9 (2.3)
Chemo ^d	88 (11.2)	25 (6.4)
Immune-mediated AEs and infusion reactions leading to treatment discontinuation		
Pembro/pbo	61 (7.8)	4 (1.0)
Chemo ^d	45 (5.7)	7 (1.8)

Results are n (%) of pts.

*Immune-mediated AEs and infusion reactions were based on a list of terms specified at the time of analysis and were included regardless of attribution to study treatment or immune relatedness by the investigator; related terms were included.

^bIncludes 5 pts with hypopituitarism.

^cDose reduction was not allowed for pembro/pbo.

^dChemo was administered during the neoadj phase only.

Disclosure(s):

Javier Cortés, MD, PhD: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), Astrazeneca (Ongoing), Bioasis (Ongoing), BiolInvent Pharma (Ongoing), Boehringer Ingelheim (Ongoing), BridgeBio (Ongoing), Clovis Oncology (Ongoing), Daiichi-Sankyo (Ongoing), Ellipses (Ongoing), Expres2ion Biotechnologies (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gemoab (Ongoing), Gilead (Ongoing), HiberCell (Ongoing), Jazz Pharmaceuticals (Ongoing), Leuko (Ongoing), Lilly (Ongoing), Menarini (Ongoing), Merck Sharp&Dhome (Ongoing), Reveal Genomics, S.L. (Ongoing), Scorpion Therapeutics (Ongoing), Seattle genetics (Ongoing), Zymeworks Inc. (Ongoing); honoraria: Lilly (Ongoing), Novartis (Ongoing); honoraria, research funding to the institution, travel and expenses: Astrazeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Europe Ltd. (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Merck Sharp&Dhome (Ongoing), Pfizer, Inc. (Ongoing); honoraria, travel and expenses: Gilead (Ongoing), Steamline Therapeutics (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1 (Ongoing), MAJ3 Capital (Ongoing), Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. (Ongoing); research funding to the institution: Ariad pharmaceuticals (Ongoing), Baxalta GMBH/Servier Affaires (Ongoing), Bayer Pharmaceuticals (Ongoing), Guardant Health Inc. (Ongoing), IQVIA Inc. (Ongoing), Piquar Therapeutics (Ongoing), Queen Mary University of London (Ongoing); stock (relative): Leuko (Ongoing)

Lajos pusztai, MD, DPhil: Consulting Fees (e.g., advisory boards): Natera Inc (Ongoing)

Heather McArthur, MD, MPH: Consulting Fees (e.g., advisory boards): Crown Bioscience (Ongoing), Daiichi Sankyo |Astrazeneca (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer (Ongoing), Seattle Genetics/Seagen (Ongoing)

Carlos H. Barrios, MD: Consulting Fees (e.g., advisory boards): AstraZenca (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai, Inc (Ongoing), Gilead Science (Ongoing), Loxo@Lilly (Ongoing), MSD Pharma (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), Zodiac (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Amgen Inc. (Ongoing), AstraZenca (Ongoing), Aveo (Ongoing), Bayer Pharmaceuticals (Ongoing), BMS (Ongoing), Celgene (Ongoing), Daiichi-Sankyo (Ongoing), Exelixis, Inc. (Ongoing), Gilead Science (Ongoing), GSK (Ongoing), ICON (Ongoing), IQVIA Inc. (Ongoing), Janssen Biotech (Ongoing), Labcorp (Ongoing), Loxo@Lilly (Ongoing), MerkSerono (Ongoing), MSD Pharma (Ongoing), Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncopeptides, Orion Pharma, Ose Pharma, (Ongoing), Novartis International AG (Ongoing), Novocure (Ongoing), Nuvisan (Ongoing), OBI Pharma Inc. (Ongoing), Parexel International (Ongoing), Pfizer, Inc. (Ongoing), PharmaMar (Ongoing), Polyphor (Ongoing), PPD Global (Ongoing), PsiOxus (Ongoing), Regeneron Pharmaceuticals Inc. (Ongoing), Roche/GNE (Ongoing), Sanofi Aventis (Ongoing), SeaGen (Ongoing), Servier (Ongoing), Syneos Health (Ongoing), Takeda Pharmaceuticals, Ltd. (Ongoing), TRIO (Ongoing), Worldwide (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): MedSIR (Ongoing), Thummi (Ongoing)

Vassiliki Karantza, MD, PhD: Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Merck Sharp & Dohme (MSD) (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Merck Sharp & Dohme (MSD) (Ongoing)

Joyce O'Shaughnessy, MD: Consulting Fees (e.g., advisory boards): Agendia (Ongoing), Aptitude Health (Ongoing), AstraZeneca (Ongoing), Carrick Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), ELY LILLY (Ongoing), F. Hoffman La Roche Ltd (Ongoing), G1-Therapeutics (Ongoing), Genentech (Ongoing), Loxo@Lilly (Ongoing), Merck Sharp & Dohme, Lda. (Ongoing), Novartis (Ongoing), Ontada (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Samsung Bioepis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing), Synthon (Ongoing)

Peter Schmid, MD, PhD: Consulting Fees (e.g., advisory boards): Eli Lilly & Company (Ongoing), Gilead Science (Ongoing)

PS14-06

Real-World Analysis of Adverse Events in Patients with Triple Negative Breast Cancer Receiving Therapy per KEYNOTE-522

Presenting Author(s) and Co-Author(s):

M. Hofherr. Washington University, St. Louis, Missouri, United States
K. Clifton. Washington University in St Louis School of Medicine, United States
S. January. BJC, United States
E. Owen. BJC, United States
F. Raheem. Mayo Clinic, United States
L. Mina. Mayo Clinic, United States
S. Arunachalam Karikalan. Mayo Clinic Arizona, Phoenix, Arizona, United States
L. Lyons. Lexington Medical Cancer Center, United States
M. Watson Rose. Lexington Medical Cancer Center, United States
K. Madden. Lexington Medical Cancer Center, United States
J. Hsin. City of Hope, United States
A. Keegan. City of Hope, United States
W. Yu. City of Hope, United States
S. Kraft. University of Michigan, United States
A. Schepers. University of Michigan, United States
E. Armgardt. Northwestern, United States
D. Mazewski. Northwestern, United States
A. Svoboda. Northwestern, United States
K. Harwood. Mayo, United States
J. Taraba. Mayo Clinic, United States
Y. Resnick. NEW ECS, United States
S. Hummert. Huntsman Cancer Institute, United States
L. Grate. UC Health, United States
S. Keisner. UAMS, United States
J. Hobbs. Avera Cancer Institute, United States
T. Davis. UW Cancer Center, United States
K. Bastian. PHCI, United States
D. Minikel. ProHealthCare Institute, United States
T. White. UMN, United States
W. Adler. UMAS, United States
A. Singh Sandu. Kettering Health, United States
F. Boulbol. Community Medical, United States
K. Finch. Columbus Regional Health, United States
A. Davis. Washington University in St Louis School of Medicine, United States

Title:

Real-world analysis of adverse events in patients with triple-negative breast cancer receiving therapy per KEYNOTE-522

Background:

KEYNOTE-522 was a randomized, double-blind, placebo-controlled phase 3 trial which resulted in the FDA approval of pembrolizumab with neoadjuvant chemotherapy for patients (pts) with newly diagnosed, high-risk, early-stage triple-negative breast cancer (TNBC). Given the improvement in pathological complete response (pCR) and event-free survival rates, this regimen has emerged as standard-of-care (SOC) therapy. To date, real world outcome analyses are limited.

Methods:

In this retrospective, multicenter study, we examined pts with early-stage TNBC who received planned treatment per KEYNOTE-522 as SOC. 16 sites were included in the analysis. IRB approval was obtained from each participating site. Number and length of treatment delays, treatment related toxicities (both chemotherapy and immune-related) of all grades, and pCR rate were collected from the electronic medical record of each participating site, and deidentified data were shared for central analysis.

Results:

577 pts were included in this analysis. The median age of the cohort was 52 [range 27-77]. 457 pts had T1-2 disease and 139 had T3-4 disease. 316 pts had N0 disease and 261 had N1-3 disease. 506 pts had baseline ECOG 0, 62 had ECOG 1, and 9 had ECOG 2-3. Of the 482 patients who had surgery at the time of this analysis, 219 patients had pCR (54.5%) and 192 pts were still receiving treatment. 217 patients (37%) had an adverse drug event (ADE) causing dose reductions and 228 patients (39.5%) had to discontinue treatment early. There were 360 unplanned care visits, with 91 patients having 2+ visits. 66 patients had hospitalizations due to the regimen with 102 total hospitalizations. 179 (31%) of patients had grade 3+ immune related adverse events (irAEs), including many that are rare and potentially serious. 317 (54%) had an immune related adverse effect (see Table 1). There was no significant difference in the frequency of grade 3+ irAE based on age or body mass index. We observed no difference in residual disease between patients who discontinued treatment early and those who did not. However, if patients had an ADR causing a dose reduction, pts were significantly more likely to have residual disease (P=0.039)

Conclusions:

In a multicenter real-world analysis, the KEYNOTE-522 regimen was associated with a high frequency of dose reductions, early treatment discontinuations, ER visits, and hospitalizations. This may have accounted for a lower pCR rate than observed in the landmark clinical trial. Most grade 3+ irAEs occurred at greater frequency in our real-world analysis. Providers should carefully monitor for toxicity to ensure optimal patient outcomes.

Table 1

Immune-related adverse events (N=577)	Immune Related Adverse Events of Any Grade	Grade 3+ Immune Related Adverse Events
Elevated ALT	137 (23.7%)	21 (3.6%)
Immune-Related rash	135 (23.4%)	27 (4.6%)
Elevated AST	126 (21.8%)	21 (3.6%)
Hepatitis	115 (19.9%)	23 (3.9%)
Hypothyroidism	106 (18%)	30 (5.2%)
Myalgias	91 (15.7%)	12 (2.0%)
Arthralgia	86 (14.9%)	9 (1.6%)
Pruritis	63 (10.9%)	14 (2.4%)
Primary Adrenal Insufficiency	45 (7.8%)	32 (5.5%)
Colitis	30 (5.2%)	22 (3.8%)
Vision Changes	28 (4.8%)	5 (0.8%)
AKI	24 (4.1%)	6 (1.0%)
Pneumonitis	21 (3.6%)	11 (1.9%)
Hyperthyroidism	10 (1.7%)	8 (1.4%)
Inflammatory Arthritis	9 (1.6%)	2 (0.3%)
Thyroiditis	9 (1.6%)	4 (0.6%)
Hypophysitis	8 (1.4%)	2 (0.3%)
Type I Diabetes	8 (1.4%)	6 (1.0%)
Bullous Dermatitis	7 (1.2%)	1 (0.1%)
Myocarditis	6 (1.0%)	2 (0.3%)
DKA	5 (0.6%)	5 (0.8%)
Transverse Myelitis	4 (0.6%)	0 (0.0%)
Myositis	4 (0.6%)	2 (0.3%)
Encephalitis	4 (0.6%)	2 (0.3%)
Pancreatitis	4 (0.7%)	3 (0.5%)
ILD	3 (0.5%)	2 (0.3%)

Disclosure(s):

Mara Hofherr, PharmD: Consulting Fees (e.g., advisory boards): Astra Zeneca, Roche, Novartis, Biocad, R-Pharm, Eisai, Eli Lilly, Pfizer, MSD, BMS (Terminated); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Merck & Co., Inc. (Ongoing)

PS14-07

Exploring Circulating Leukocyte RNA Expression: Implications for Treatment Outcomes and Immune-Related Adverse Events in Patients with Triple Negative Breast Cancer Enrolled in the GeparNuevo Trial

Presenting Author(s) and Co-Author(s):

H. Hübner. Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Bayern, Germany

M. Ruebner. Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich-Alexander-University Erlangen-Nürnberg, Germany

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

C. Denkert. Institut für Pathologie, Philipps Universität Marburg und Universitätsklinikum Marburg (UKGM), Germany

H. Sinn. Pathologie, Universitätsklinikum, Heidelberg, Germany

M. Braun. Rotkreuzklinikum München, Germany

T. Karn. Universitätsklinikum Frankfurt, Frankfurt am Main, Germany

B. Sinn. Institut für Pathologie, Charité Berlin, Germany

D. Zahm. SH Wald-Klinikum Gera, Germany

J. Thomalla. Institut für Versorgungsforschung in der Oncologie Koblenz am Rhein, Germany

J. Huober. Kantonsspital St.Gallen, Brustzentrum, Departement Interdisziplinäre medizinische Dienste, St. Gallen, Switzerland

C. Hanusch. Rotkreuzklinikum München, Germany

M. Untch. AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany, Berlin, United States

C. Solbach. University Hospital Frankfurt, Frankfurt, Germany

T. Link. Department of Gynecology and Obstetrics, Technische Universität Dresden, Dresden, Germany

N. Filmann. German Breast Group, Neu-Isenburg, Germany

J. Rey. GBG Forschungs GmbH, Germany

J. Holtschmidt. German Breast Group, Neu-Isenburg, Germany

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

Abstract

Exploring Circulating Leukocyte RNA Expression: Implications for Treatment Outcomes and Immune-Related Adverse Events in Patients with Triple Negative Breast Cancer Enrolled in the GeparNuevo Trial

Background:

Significant research has been conducted on the influence of immune checkpoint inhibitor

therapy on tumor microenvironment, particularly with regard to tumor-infiltrating immune cells. Nevertheless, our understanding of the circulating immune repertoire and its association with treatment outcomes remains limited. Consequently, our subproject of the GeparNuevo trial aimed to explore the RNA phenotype of circulating leukocytes and its impact on overall survival (OS), and adverse events of patients enrolled in the GeparNuevo trial (Loibl S et al. *Annals Oncol* 2022).

Methods:

The GeparNuevo phase II trial focused on the effects of neoadjuvant nab-paclitaxel followed by epirubicin/cyclophosphamide (nabP-EC) chemotherapy combined with the anti-PD-L1 immune checkpoint inhibitor durvalumab versus placebo in patients with non-metastatic triple-negative breast cancer. RNA-stabilizing PAXgene tubes were used to collect blood samples prior to treatment initiation. RNA was extracted from circulating leukocytes of 117 patients and analyzed using a custom NanoString nCounter CodeSet, including 290 immune-related target genes. The associations between 16 immune cell scores, 26 immune signaling scores, 31 individual gene expression patterns, OS, and immune-related adverse events (irAEs) were analyzed.

Results:

Univariate Cox regression analysis using continuous scores revealed a significant correlation between PIP3 activates AKT signaling, T cells, CDK2, and TIMP1 expression with OS in the placebo arm. Higher expression of PIP3 activates AKT signaling, T cells, and CDK2, as well as lower expression of TIMP1, were associated with prolonged survival. Notably, T cell scores and CDK2 expression exhibited a significant interaction with the treatment arm ($p=0.0489$ and 0.0210 , respectively). Multivariate Cox regression analysis demonstrated a significant association of DPP4, ICOS and MYC expression with OS. Additionally, CDK2, CDKN2A, F5 and HLA-DRA expression were linked to the presence of irAEs. In the durvalumab arm, TNFR2 non canonical NF κ B pathway signaling, CDK2 and CDKN2A expression showed an inverse association with the occurrence of irAEs.

Conclusions:

Our study provides preliminary evidence that RNA derived from circulating leukocytes may serve as a potential biomarker for predicting treatment outcomes and identifying patients prone to develop side effects during standard-of-care chemotherapy or immune checkpoint therapy. These findings highlight the potential utility of peripheral immune cell RNA profiling in improving treatment strategies and patient management. Further research and validation are necessary to fully comprehend the clinical significance and broader implications of these findings.

Key words: Breast cancer, immune phenotype, immune checkpoint

Funding Source: This study was funded by Walter Schulz Stiftung and the clinical trial was funded by AstraZeneca and Celgene.

Disclosure(s):

Hanna Hübner: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): LEO Pharma (Ongoing), Novartis Pharma GmbH (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Novartis Pharma GmbH (Ongoing)

Sibylle Loibl, MD, PhD: Advisory Committee/Board Member: GSK, Pfizer, Novartis (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo

(Ongoing); Consulting Fees (e.g., advisory boards): GSK, Pfizer, Novartis (Ongoing), Menarini/Stemline (Ongoing), MSD Co., Ltd. (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Licences for VM Ki67 Quantifier: VM Scope GmbH (Ongoing); patents pending: EP14153692.0 ,EP21152186.9 , EP19808852.8 , (Ongoing)

PS14-08

Safety evaluation from the KEYNOTE-355 study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy in patients with previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

Z. Nowecki. Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland

D. Cescon. Princess Margaret Cancer Centre/UHN, Toronto, Ontario, Canada

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

M. Yusof. Cancer Center, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

C. Gallardo. Oncology Institute, Arturo Lopez Perez Foundation, Santiago, Chile

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

X. Zhou. Merck & Co., Inc., Rahway, New Jersey, United States

X. Zhang. Merck & Co., Inc., Rahway, New Jersey, United States

W. Pan. Merck & Co., Inc., Rahway, New Jersey, United States

V. Karantza. Merck Sharp & Dohme LLC, Rahway, New Jersey, United States

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

Background:

In KEYNOTE-355 (NCT02819518), pembrolizumab (pembro) + chemotherapy (chemo) led to statistically significant and clinically meaningful improvements in PFS and OS (primary endpoints) vs placebo (pbo) + chemo in patients (pts) with previously untreated PD-L1 positive advanced TNBC (combined positive score ≥ 10). In the overall safety population at final analysis, treatment-related AEs occurred in 96.3% of pts in the pembro + chemo arm and 95.0% of pts in the pbo + chemo arm; immune-mediated AEs occurred in 26.5% and 6.4% of pts, respectively. We report additional safety information, beyond the already reported safety results, on immune-mediated AEs and management from the final analysis of KEYNOTE-355.

Methods:

Eligible pts were randomized 2:1 to receive pembro 200 mg or pbo Q3W for up to 35 cycles + investigator's choice of nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin. Safety was assessed in all randomized pts who received ≥ 1 dose of study treatment. AEs were monitored throughout the study and for 30 d post-treatment (90 d for serious AEs).

Results:

At final analysis (data cut-off: June 15, 2021), median treatment duration was 6.1 (range, 0.0–

48.8) mo in the pembro + chemo arm (n = 562) and 5.3 (range, 0.0–51.5) mo in the pbo + chemo arm (n = 281). Of 157 pts with immune-mediated AEs and infusion reactions in the pembro + chemo arm, 125 had grade 1-2 events and 32 had grade 3-4 events; none were grade 5. The most common immune-mediated AEs with pembro + chemo were hypothyroidism (15.8%) and hyperthyroidism (4.3%); infusion reactions occurred in 3.7% of pts (table). Of 89 pts with hypothyroidism, median time to onset was 105 d (range, 19–707 d) and 70 were treated with thyroid replacement, suggesting an endocrine abnormality and need for continued thyroid replacement. Of 24 pts with hyperthyroidism, median time to onset was 53.5 d (range, 20–209 d) and 2 were treated with corticosteroids. Of 21 pts with infusion reactions, median time to onset was 147 d (range, 1–729 d) and 10 were treated with corticosteroids. Other immune-mediated AEs of interest in the pembro + chemo arm were pneumonitis (2.5%) and adrenal insufficiency (1.4%); most of these events were grade 2–3. Of 14 pts with pneumonitis, median time to onset was 99.5 d (range, 29–288 d) and 11 were treated with corticosteroids; median episode duration was 56 d. All 8 pts with adrenal insufficiency were treated with hormone replacement. There were no reports of hypophysitis.

Conclusion:

In pts with previously untreated advanced TNBC, pembro + chemo had a manageable safety profile that was generally consistent with the known safety profiles of pembro and the chemo regimens. Most immune-mediated AEs and infusion reactions were grade 1-2, manageable with treatment interruption, corticosteroids, and/or hormone replacement therapy, and did not result in discontinuation of study treatment. Together with the efficacy findings, our results support pembro + chemo as a standard of care regimen for these pts.

Table. Summary of immune-mediated AEs and infusion reactions^a

	Pembro + chemo n = 562	Pbo + chemo n = 281
Immune-mediated AEs and infusion reactions		
Hypothyroidism	89 (15.8)	9 (3.2)
Hyperthyroidism	24 (4.3)	3 (1.1)
Infusion reactions	21 (3.7)	14 (5.0)
Pneumonitis	14 (2.5)	0
Colitis	10 (1.8)	4 (1.4)
Severe skin reactions	10 (1.8)	1 (0.4)
Adrenal insufficiency	8 (1.4)	0
Thyroiditis	7 (1.2)	0
Hepatitis	5 (0.9)	2 (0.7)
Myositis	3 (0.5)	0
Nephritis	3 (0.5)	0
Uveitis	2 (0.4)	0
Vasculitis	2 (0.4)	1 (0.4)
Guillain-Barre Syndrome	1 (0.2)	0
Myocarditis	1 (0.2)	0
Pancreatitis	1 (0.2)	0
Type 1 diabetes mellitus	1 (0.2)	0
Immune-mediated AEs and infusion reactions leading to dose reduction ^b		
Chemo	1 (0.2)	0
Immune-mediated AEs and infusion reactions leading to treatment interruption		
Pembro/pbo	36 (6.4)	2 (0.7)
Chemo	38 (6.8)	9 (3.2)
Immune-mediated AEs and infusion reactions leading to treatment discontinuation		
Pembro/pbo	14 (2.5)	0
Chemo	13 (2.3)	3 (1.1)

Results are n (%) of pts.

^aImmune-mediated AEs and infusion reactions were based on a list of terms specified at the time of analysis and were included regardless of attribution to study treatment or immune relatedness by the investigator; related terms were included.

^bDose reduction was not allowed for pembro/pbo.

Disclosure(s):

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck &

Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

Peter Schmid, MD, PhD: Consulting Fees (e.g., advisory boards): Eli Lilly & Company (Ongoing), Gilead Science (Ongoing)

David W. Cescon, MD, PhD: Advisory Committee/Board Member: Inivata/NeoGenomics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co. Ltd. (Ongoing), Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), GlaxoSmithKline (Ongoing), Inflex Ltd (Ongoing), Lilly (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer, Inc. (Ongoing), SAGA Diagnostics (Ongoing); Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Gilead Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing), GlaxoSmithKline (Ongoing), Guardant Health Inc. (Ongoing), Inivata/NeoGenomics (Ongoing), Knight Therapeutics (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), ProteinQure (Ongoing), Roche (Ongoing)

Carlos H. Barrios, MD: Consulting Fees (e.g., advisory boards): AstraZenca (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai, Inc (Ongoing), Gilead Science (Ongoing), Loxo@Lilly (Ongoing), MSD Pharma (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), Zodiac (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Amgen Inc. (Ongoing), AstraZenca (Ongoing), Aveo (Ongoing), Bayer Pharmaceuticals (Ongoing), BMS (Ongoing), Celgene (Ongoing), Daiichi-Sankyo (Ongoing), Exelixis, Inc. (Ongoing), Gilead Science (Ongoing), GSK (Ongoing), ICON (Ongoing), IQVIA Inc. (Ongoing), Janssen Biotech (Ongoing), Labcorp (Ongoing), Loxo@Lilly (Ongoing), MerkSerono (Ongoing), MSD Pharma (Ongoing), Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncopeptides, Orion Pharma, Ose Pharma, (Ongoing), Novartis International AG (Ongoing), Novocure (Ongoing), Nuvisan (Ongoing), OBI Pharma Inc. (Ongoing), Parexel International (Ongoing), Pfizer, Inc. (Ongoing), PharmaMar (Ongoing), Polyphor (Ongoing), PPD Global (Ongoing), PsiOxus (Ongoing), Regeneron Pharmaceuticals Inc. (Ongoing), Roche/GNE (Ongoing), Sanofi Aventis (Ongoing), SeaGen (Ongoing), Servier (Ongoing), Syneos Health (Ongoing), Takeda Pharmaceuticals, Ltd. (Ongoing), TRIO (Ongoing), Worldwide (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): MedSIR (Ongoing), Thummi (Ongoing)

Sherene Loi, MD, PhD: Advisory Committee/Board Member: Bristol-Myers Squibb Company (Ongoing), MSD Co., Ltd. (Ongoing); Consulting Fees (e.g., advisory boards): Aduro Biotech (Ongoing), Amunix (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), MSD Co., Ltd. (Ongoing), Nektar Therapeutics (Ongoing), Novartis International AG (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics (Ongoing); Uncompensated consultant: Aduro Biotech (Ongoing), Amunix (Ongoing), Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International

AG (Ongoing), Pfizer, Inc. (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing)

Vassiliki Karantza, MD, PhD: Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Merck Sharp & Dohme (MSD) (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Merck Sharp & Dohme (MSD) (Ongoing)

Javier Cortés, MD, PhD: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), Astrazeneca (Ongoing), Bioasis (Ongoing), BioInvent Pharma (Ongoing), Boehringer Ingelheim (Ongoing), BridgeBio (Ongoing), Clovis Oncology (Ongoing), Daiichi-Sankyo (Ongoing), Ellipses (Ongoing), Expres2ion Biotechnologies (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gemoab (Ongoing), Gilead (Ongoing), HiberCell (Ongoing), Jazz Pharmaceuticals (Ongoing), Leuko (Ongoing), Lilly (Ongoing), Menarini (Ongoing), Merck Sharp&Dhome (Ongoing), Reveal Genomics, S.L. (Ongoing), Scorpion Therapeutics (Ongoing), Seattle genetics (Ongoing), Zymeworks Inc. (Ongoing); honoraria: Lilly (Ongoing), Novartis (Ongoing); honoraria, research funding to the institution, travel and expenses: Astrazeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Europe Ltd. (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Merck Sharp&Dhome (Ongoing), Pfizer, Inc. (Ongoing); honoraria, travel and expenses: Gilead (Ongoing), Steamline Therapeutics (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1 (Ongoing), MAJ3 Capital (Ongoing), Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. (Ongoing); research funding to the institution: Ariad pharmaceuticals (Ongoing), Baxalta GMBH/Servier Affaires (Ongoing), Bayer Pharmaceuticals (Ongoing), Guardant Health Inc. (Ongoing), IQVIA Inc. (Ongoing), Piquor Therapeutics (Ongoing), Queen Mary University of London (Ongoing); stock (relative): Leuko (Ongoing)

PS15-01

A first-in-human phase 1 study of SIM0270, a brain-penetrant oral selective estrogen receptor degrader (SERD), in patients with ER+/ HER2- locally advanced or metastatic breast cancer

Presenting Author(s) and Co-Author(s):

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

J. Zhang. Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

Q. Zhang. Harbin Medical University Cancer Hospital, United States

Y. Sun. Shandong Cancer Hospital, United States

H. Li. The First Affiliated Hospital of Bengbu Medical College, United States

Y. Yin. Department of Medical Oncology, Jiangsu Province Hospital, Nanjing, China (People's Republic)

Y. Shi. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

W. Li. The Affiliated Hospital of Qingdao University, United States

Y. Liu. The Fourth Hospital of Hebei Medical University, United States

M. Yan. Henan Cancer Hospital, Henan, China

C. Yang. Simcere Zaiming Pharmaceutical Co., Ltd., United States

L. Zhu. Simcere Zaiming Pharmaceutical Co., Ltd., United States

Y. Yang. Simcere Zaiming Pharmaceutical Co., Ltd., United States

L. Xue. Simcere Zaiming Pharmaceutical Co., Ltd., United States

Background: ER+/HER2- breast cancer is the most prevalent subtype, and endocrine-based therapy is the standard treatment. SIM0270 is a brain-penetrant and highly potent oral SERD that has demonstrated ER degradation and robust antitumor activity across various preclinical models, including those with intracranial xenograft tumors.

Methods: This Phase 1 study evaluates the safety, pharmacokinetics and preliminary anti-tumor activity of SIM0270 as monotherapy and/or in combination with palbociclib or everolimus in patients with HR+/HER2- advanced or metastatic breast cancer. The primary objective of the phase 1a study, which consisted of the dose escalation stage and the dose expansion stage, is to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of SIM0270 as monotherapy. A Bayesian Optimal Interval design (BOIN) was adopted. SIM0270 was administered orally daily in 28-day cycles. Here we report preliminary monotherapy data.

Results: As of May 22nd 2023, 45 female patients were enrolled, receiving SIM0270 at dose levels of 10 mg (n=4), 30 mg (n=4), 60 mg (n=9), 90 mg (n=6), 120 mg (n=11), 200 mg (n=5), or 300 mg (n=6). The median age was 56 years (range, 40-73) and ECOG performance status was 0 (18%) or 1 (82%). Most patients were heavily pretreated, with a median of 2 prior endocrine-based therapies (range, 0-5) and a median of 2 prior chemotherapies (range, 0-8). Thirty-one patients (69%) received prior fulvestrant, 42 (93%) received prior aromatase inhibitors, and 28 (62%) received prior CDK4/6 inhibitors. Visceral metastases were present in 33 patients (72%), and brain metastases in 7 patients (16%). The most common TEAEs were

sinus bradycardia (51%), anemia (38%), hypalbuminaemia (31%), hypercholesterolaemia (24%), urinary tract infection (24%), asthenia (24%), electrocardiogram (ECG) QT prolonged (24%), and dizziness (22%). Most of the TEAEs were Grade 1-2. Grade 3 TRAEs were ECG QT prolonged, gamma-glutamyltransferase(γ -GT) increased and dizziness in 2 patients each. All AEs were manageable with dose interruption or reduction, except only 1 patient discontinued treatment of SIM0270 due to TRAE (Grade 3 γ -GT increased). Four patients experienced dose-limiting toxicities (DLTs): 1 with Grade 3 ECG QT prolonged at 200mg dose level, 1 with Grade 3 ECG QT prolonged and 2 with Grade 3 dizziness at 300mg dose level. All DLTs were resolved with dose interruption then reduction. The MTD of single-agent SIM0270 was established as 200mg QD. Pharmacokinetic analysis revealed a $T_{1/2}$ of approximately 70 hours, and the AUC and C_{max} increased in an approximately linear manner with dose escalation. Concentration in cerebrospinal fluid was measured in 1 patient after 41 days treatment of SIM0270, which is consistent with preclinical data and suggested high concentration of SIM0270 in the brain of patients. Among 31 response evaluable patients (per RECIST 1.1 criteria), 4 PRs (3 unconfirmed) were observed, yielding an ORR of 12.9%. Brain lesions were all stable in 4 evaluable patients per RANO-BM criteria. In patients with ESR1 mutations at baseline and samples available for analysis, 4/6(67%) exhibited a reduction or loss of mutant ESR1 upon SIM0270 treatment.

Conclusions: Single-agent SIM0270 was well tolerated and showed favorable antitumor activity in heavily pretreated advanced or metastatic ER+/HER2- breast cancer patients, including those previously treated with CDK4/6 inhibitors and fulvestrant. Phase 1a dose expansion with single-agent SIM0270 is ongoing, and the RP2D will be determined based on further accumulative data of tolerability and efficacy. (NCT05293964)

PS15-02

A Phase I b Study of D-0502 as Monotherapy for Advanced or Metastatic ER-Positive and HER2-Negative Breast Cancer: Results from the Dose-Expansion Stage

Presenting Author(s) and Co-Author(s):

J. Wang. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

T. Sun. Department of Medical Oncology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Key Laboratory of Liaoning Breast Cancer Research, Shenyang, United States

Q. Zhang. Harbin Medical University Cancer Hospital, China (People's Republic)

Y. Shi. Sun Yat-sen University Cancer Center, China (People's Republic)

X. Wang. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

Y. Chen. The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Q. Ouyang. Department of Medical Oncology, Hunan Cancer Hospital, United States

K. Li. Hunan Cancer Hospital, China (People's Republic)

M. Bupathi. Rocky Mountain Cancer Center, US Oncology, Aurora, Colorado, United States

w. Edenfield. Prisma Health, United States

A. L.M. Silber. Yale University, New Haven, Connecticut, United States

H. Zong. The First Affiliated Hospital of Zhengzhou University, China (People's Republic)

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

D. Juric. Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

K. Lathrop. UT Health San Antonio, San Antonio, Texas, United States

Y. Zhang. InventisBio Co., Ltd, United States

K. Stazzone. InventisBio Co., Ltd, China (People's Republic)

Z. Shi. InventisBio Co., Ltd, China (People's Republic)

Y. Wang. InventisBio Co., Ltd, China (People's Republic)

L. Zhang. InventisBio Co., Ltd, China (People's Republic)

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

Background: Endocrine therapy is the mainstay treatment for estrogen receptor (ER)-positive advanced breast cancer (BC). D-0502, an orally bioavailable selective estrogen receptor degrader (SERD), has previously demonstrated antitumor activity in various ER-positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) breast cancer cell lines and xenograft models. The phase I open-label study (NCT03471663) evaluated the safety, tolerability, pharmacokinetics (PK) and efficacy of D-0502 as monotherapy and in combination with palbociclib in female patients with ER+ and HER2- breast cancer. The dose escalation part of D-0502 monotherapy (phase I a) has been presented before (SABCS 2021, PS11-26 Abstract #1348). Here, we present the results of D-0502 monotherapy from the dose-expansion

stage in phase I b study. Methods: In the single-agent dose-expansion stage of phase I b study, patients (n=60) received D-0502 (400 mg QD) in 28-day cycles. Eligible patients included females with confirmed ER+, HER2- locally advanced, or metastatic BC; ECOG 0-1; measurable disease (RECIST v1.1); premenopausal or postmenopausal status; adequate hematologic, hepatic and renal functions. The primary objectives are to characterize the safety of D-0502. The secondary objectives are to evaluate the preliminary anti-tumor activity and the PK characteristic. Results: As of April 07, 2023, 60 female patients were enrolled and treated with 400mg single-agent D-0502. Median age was 57 (range: 32-82) years, 55.0% had an ECOG PS of 1. Disease progression resulting in treatment discontinuation occurred in 66.7% (40/60) of patients, and 6.7% (4/60) of patients discontinued treatment because of AEs. Treatment-related adverse events (TRAEs) were reported in 57 pts (95.0%), most of which were grade 1-2. No grade 4/5 TRAE has been reported. The incidence of serious adverse events was 6.7% (4/60). The most common ($\geq 15\%$) TRAEs included vomiting, dizziness, nausea, increased aspartate aminotransferase and alanine aminotransferase, anaemia, decreased appetite, diarrhoea, and malaise. In the 51 efficacy evaluable patients, 8 patients had partial response (PR) and 27 had stable disease (SD); objective response rate (ORR) and disease control rate (DCR) were 15.7% (8/51) and 68.6% (35/51), respectively. The clinical benefit rate (CBR: CR + PR + SD ≥ 24 weeks) was 47.1% (24/51). The median PFS was 5.6 months (95% CI: 2.0, 10.0). Conclusion: D-0502 monotherapy showed promising antitumor activity and tolerable toxicity in female patients with ER+ and HER2- locally advanced or metastatic BC. Currently this treatment is being evaluated in a phase III study for patients with ER+ and HER2- locally advanced or metastatic BC in China.

PS15-03

Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, plus palbociclib in ER-positive/human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer: phase 1b cohort

Presenting Author(s) and Co-Author(s):

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Hurvitz. Fred Hutchinson Cancer Center, Seattle, Washington, United States

D. Juric. Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

H. Han. H. Lee Moffitt Cancer Center, Tampa, Florida, United States

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

G. Zahrah. Whittingham Cancer Center, Norwalk, Connecticut, United States

R. Nanda. University of Chicago Medicine, Chicago, Illinois, United States

Y. Zhang. Arvinas Operations, Inc., New Haven, Connecticut, United States

W. Tan. Pfizer Inc., La Jolla, California, United States

E. Duperret. Arvinas Operations, Inc., New Haven, Connecticut, United States

E. Zhi. Arvinas Operations, Inc., New Haven, Connecticut, United States

C. Mather. Arvinas, Inc, New Haven, Connecticut, United States

A. Schott. Rogel Cancer Center, University of Michigan Health, Ann Arbor, Michigan, United States

Background: Vepdegestrant (ARV-471) is an oral PROTAC ER degrader. In a phase 1/2 study (NCT04072952), vepdegestrant monotherapy had a favorable safety profile and encouraging clinical activity, and showed robust ER degradation. The phase 1b cohort of this study is evaluating vepdegestrant in combination with the cyclin-dependent kinase (CDK)4/6 inhibitor palbociclib (palbo). In xenograft models, vepdegestrant plus palbo showed substantially greater tumor growth inhibition vs fulvestrant plus palbo, supporting investigation in patients with breast cancer. Methods: Eligible patients for the phase 1b combination cohort had ER+/HER2- locally advanced/metastatic breast cancer and had received ≥ 1 prior endocrine therapy and ≤ 2 chemotherapy regimens for advanced disease; prior CDK4/6 inhibitor treatment was permitted. Vepdegestrant was given orally once daily (QD) continuously at doses of 180 mg (n=2), 200 mg (n=21), 400 mg (n=3), or 500 mg (n=20); palbo 125 mg was given orally QD for 21 days followed by 7 days off treatment in 28-day cycles. The primary endpoints were dose-limiting toxicities (DLTs) in the first cycle and safety (adverse events [AEs] and laboratory abnormalities). Enrollment in these 4 dose levels is complete; we report data as of June 6, 2023. Results: Across 46 patients in the phase 1b cohort, 45 (97.8%) patients were female with a median age of 62.0 y (range: 29–78). Patients had received a median of 4 prior therapies (range: 1–11) in any setting, including 87.0% prior CDK4/6 inhibitors (78.3% prior palbo), 80.4% prior fulvestrant, and 76.1% prior chemotherapy (45.7% in the metastatic setting). There were no DLTs. Treatment-emergent AEs (TEAEs) leading to dose reductions or discontinuation of vepdegestrant occurred in 5 and 4 patients, respectively. TEAEs leading to dose reductions or discontinuation of palbo occurred in 34 and 8 patients, respectively. Grade 3/4 treatment-related AEs (TRAEs) to either vepdegestrant or palbo in $\geq 10\%$ of patients were neutropenia (89.1%), decreased white blood cell count (15.2%), and decreased platelet count (10.9%);

there were no grade 5 TRAEs and no patients had febrile neutropenia. The clinical benefit rate (rate of confirmed complete response, partial response, or stable disease ≥ 24 wks) in patients treated with vepdegestrant plus palbo was 63.0% (95% CI: 47.5–76.8). The objective response rate in evaluable patients with measurable disease at baseline (n=31) was 41.9% (95% CI: 24.5–60.9). Pharmacokinetics (PK) showed dose-dependent exposure for vepdegestrant, consistent with data for vepdegestrant administered as monotherapy; palbo exposure was similar across dose levels of vepdegestrant and modestly higher compared with historical palbo PK data. Circulating tumor DNA levels were evaluated in patients who received vepdegestrant 200 mg QD plus palbo and demonstrated substantial and sustained decreases in ESR1 mutant allele fraction across multiple treatment cycles. Conclusions: The combination of vepdegestrant plus palbo showed promising clinical activity in heavily pretreated patients with ER+/HER2-advanced breast cancer who had received extensive prior treatment. The safety profile of vepdegestrant plus palbo was generally consistent with the known safety profiles of the 2 agents except for an increased occurrence of grade 3/4 neutropenia, which was readily managed with laboratory monitoring and dose reductions of palbo. There is an ongoing study lead-in to the global VERITAC-3 study (NCT05909397) that is evaluating 2 doses of palbo (100 mg and 75 mg) in combination with vepdegestrant 200 mg QD to determine the recommended phase 3 combination to compare with letrozole plus palbo as first-line treatment for ER+/HER2-advanced breast cancer.

PS15-04

A Phase 1b/2 study of palazestrant (OP-1250), an oral complete estrogen receptor antagonist (CERAN) and selective ER degrader (SERD), with palbociclib in ER-positive, HER2-negative, advanced or metastatic breast cancer patients

Presenting Author(s) and Co-Author(s):

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

D. Day. Monash Health and Monash University, Clayton, Victoria, Australia

P. Dinh. 3Crown Princess Mary Cancer Care Centre, Westmead, New South Wales, Australia

M. Slancar. ICON Cancer Centre, Southport, Queensland, Australia

J. Lombard. Calvary Mater Newcastle, Waratah, New South Wales, Australia

V. Ganju. PSEHOG (Peninsula & South Eastern Haematology and Oncology Group), Frankston, Victoria, Australia

N. McCarthy. Icon Cancer Center, Wesley Medical Centre, Auchenflower, Australia

R. Wilson. Olema Oncology, Sydney, Sydney, Australia

D. Faltaos. Olema Oncology, San Francisco, San Francisco, California, United States

G. Mathauda-Sahota. Olema Oncology, San Francisco, San Francisco, California, United States

C. Murphy. Cancer Services Trials Unit, University Hospital Geelong, Barwon Health, Geelong, Victoria, Australia

Background: Palazestrant (OP-1250) is a small molecule oral complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD) that binds the ligand binding domain of ER and completely blocks ER-driven transcriptional activity in both wild-type (ESR1-wt) and mutant (ESR1-mut) forms of ER. In preclinical studies, palazestrant demonstrated improved tumor growth inhibition and shrinkage when combined with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. In a Phase 1/2 monotherapy clinical study in patients with ER-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer, palazestrant was well tolerated with demonstrated antitumor efficacy and favorable pharmacokinetics (PK) supporting once a day (qd) dosing at the recommended Phase 2 dose of 120 mg. In this study, pts received palazestrant at escalating doses of 30, 60, 90, and 120 mg qd in combination with palbociclib (125 mg qd) and no dose-limiting toxicities were observed. Palazestrant did not affect palbociclib PK and no drug–drug interactions (DDIs) occurred. Here we report updates on safety, efficacy, and PK from the ongoing study of palazestrant in combination with palbociclib. Methods: Patients with advanced or metastatic breast cancer with progression on or after ≤ 1 line of endocrine therapy (prior CDK4/6 inhibitor therapy and ≤ 1 chemotherapy allowed) were enrolled to receive oral palazestrant 120 mg qd with oral palbociclib 125 mg qd for 21 of 28 days (NCT0526610). Results: As of May 12, 2023, 33 patients have been treated with palazestrant in combination with palbociclib; 12 pts were dosed in the dose-escalation phase and 21 patients were dosed in the dose-expansion phase of the study. Twenty-two patients (67%) received prior CDK4/6 inhibitor therapy; 15 patients received prior palbociclib. Thirteen of 25 patients (52%) with available baseline ctDNA had an ESR1 mutation. The most common ($\geq 20\%$) treatment-emergent adverse events (TEAEs) were neutropenia, nausea, vomiting, constipation, and diarrhea. Most of these events were grade 1 or 2. The most common grade 3 or 4 related AE was neutropenia (18/33 [55%] were grade 3; 3/33 [9%] were grade 4). The steady-state exposure of palazestrant when dosed with 125 mg palbociclib was consistent with

the monotherapy study. Palbociclib exposure at steady-state was comparable to published monotherapy data when combined with palazestrant at all dose levels tested. As of the data cut-off, there were 4 partial responses (2 confirmed) out of 19 response-evaluable patients, with a clinical benefit rate (CBR) of 42% (8/19) across all patients and 67% (6/9) in patients with ESR1 mutations. Conclusions: Palazestrant and palbociclib dosed in combination were well tolerated with a safety profile consistent with the individual profiles of each drug as monotherapy, and there were no DDIs. Tumor responses and clinical benefit were observed in this population of patients, including those who received prior CDK4/6 inhibitors. Expanding on our previous report, these data provide the rationale to continue advancing the clinical development of palazestrant with the approved dose of palbociclib. Updated data will be presented.

PS15-06

Results of the window-of-opportunity PIONEER trial evaluating addition of the progesterone receptor (PR) agonist megestrol to letrozole for early stage estrogen receptor (ER) positive breast cancer: exploiting ER-PR interaction

Presenting Author(s) and Co-Author(s):

R. Burrell. Department of Oncology, University of Cambridge, Cambridge, England, United Kingdom

S. Kumar. Department of Oncology, University of Cambridge, United States

S. McIntosh. Queen's University Belfast, United States

V. Pitsinis. University of Dundee and Ninewells Hospital Dundee, UK, United Kingdom

P. King. Royal Cornwall Hospital, United States

B. Elsberger. Aberdeen Royal Infirmary, United States

S. Govindarajulu. Southmead Hospital Bristol, United Kingdom

L. Satherley. Cardiff University and University Hospital Llandough, United Kingdom

S. Hadad. Sheffield Teaching Hospitals NHS Foundation Trust, UK, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

J. Abraham. Precision Breast Cancer Institute, Department of Oncology, University of Cambridge / Cambridge University Hospitals NHS Foundation Trust, United States

A. Agrawal. Cambridge University Hospitals NHS Trust, United Kingdom

J. Benson. Cambridge University Hospitals NHS Trust, United Kingdom

D. Cheeseman. CRUK Cambridge Institute, University of Cambridge, United Kingdom

I. Chernukhin. CRUK Cambridge Institute, University of Cambridge, United Kingdom

P. Frouhi. Cambridge University Hospitals NHS Trust, United Kingdom

E. Kleidi. Cambridge University Hospitals NHS Trust, United Kingdom

C. Pike. Cambridge Clinical Cancer Trials Unit, Cambridge University Hospitals NHS Trust, United Kingdom

K. Pinilla. Precision Breast Cancer Institute and CRUK Cambridge Institute, University of Cambridge, Cambridge, United Kingdom

E. Provenzano. Cambridge University Hospitals NHS Trust, UK and Cambridge Biomedical Research Centre (NIHR), United Kingdom

W. Qian. Cambridge Clinical Cancer Trials Unit, Cambridge University Hospitals NHS Trust, United Kingdom

J. Carroll. CRUK Cambridge Institute and Precision Breast Cancer Institute, University of Cambridge, United Kingdom

R. Baird. CRUK Cambridge Centre, University of Cambridge, United Kingdom

Background: Pre-clinical data suggest that combining anti-estrogen treatment with a progesterone receptor agonist leads to greater inhibition of tumor proliferation, due to molecular interactions between ER and PR [1]. A high dose of the PR agonist megestrol (160mg daily) is approved as monotherapy for the treatment of ER positive metastatic breast cancer. A lower dose of megestrol (20-40mg daily) can be an effective treatment for severe hot flashes

associated with endocrine therapy [2] but whether this dose has anti-tumor activity is unknown. The PIONEER trial evaluated the potential anti-proliferative effect of low and high dose megestrol in combination with letrozole, relative to letrozole alone, using a short-term preoperative 'window' trial design assessing the direct effects of the trial treatment on tumor tissue before and after treatment. Methods: Eligible patients were post-menopausal women with histologically confirmed ER+ (Allred \geq 3) HER2 negative breast cancer at least 10mm in size, with an ECOG performance status \leq 2, planned for primary surgery or endocrine therapy. Enrolled patients were randomised 2:3:3 to Arm A: letrozole alone, Arm B: letrozole + lower-dose megestrol (40mg) or Arm C: letrozole + higher-dose megestrol (160mg). Treatment was given for 15 (13-19) days prior to surgery or end of treatment (EOT) core biopsy. The primary endpoint was change in tumor proliferation between baseline and EOT in Arm A vs (Arms B+C combined), measured by Ki67 immunohistochemistry (IHC). Secondary endpoints were comparison of Ki67 change in high versus low dose megestrol arms, absolute Ki67 at EOT, and change in tumor apoptosis (cleaved caspase 3 IHC), proliferation (Aurora Kinase A IHC), PR and androgen receptor expression. Exploratory analysis of ER chromatin binding (ChIP-Seq) was conducted on paired fresh-frozen samples from a subset of patients. Results: A total of 243 patients were randomised from July 2017 to October 2022 with recruitment paused for 3 months at onset of the COVID pandemic. 198 patients completed treatment and had evaluable tissue samples at baseline and EOT (Arm A: n = 51, Arm B: n = 74, Arm C: n = 73). Baseline mean Ki67 values were well balanced. Therapy was well tolerated and adverse events \geq grade 3 were similarly rare across arms (A: 3.3%, B+C: 3.5%). The mean % reduction in Ki67 for each arm was: Arm A (letrozole): 71%, Arm B (letrozole + 40mg megestrol): 79%, Arm C (letrozole + 160mg megestrol): 80%. There was a statistically significantly greater reduction in Ki67 with megestrol combinations (B+C) versus letrozole alone (A) (P = 0.013). Analyses of secondary IHC endpoints and ER ChIP-Seq are ongoing and will be presented. Conclusion: Addition of the PR agonist megestrol enhanced the anti-proliferative effect of letrozole in this window-of-opportunity trial. Megestrol combinations were well tolerated, and the anti-proliferative effect was observed in both low and high dose arms. These data support the potential use of low-dose megestrol as an inexpensive and well-tolerated means of improving aromatase inhibitor efficacy. Low dose megestrol can also ameliorate hot flashes and therefore might be a strategy to improve both treatment adherence and clinical outcomes for patients taking adjuvant endocrine therapy. References 1. Mohammed et al., *Nature* 523: 313–317 (2015) 2. Loprinzi et al., *NEJM* 331: 347-352 (1994)

PS15-07

Proxalutamide plus Endocrine Therapies in Women with HR+/HER2-/AR+ Metastatic Breast Cancer: A Phase Ic Study

Presenting Author(s) and Co-Author(s):

H. Li. Department of Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, Beijing, China (People's Republic)

G. Song. Department of Breast Oncology, Peking University Cancer Hospital & Institute, United States

h. jiang. beijing cancer hospital, United States

x. liang. beijing cancer hospital, United States

X. Wang. Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, United States

H. Yang. Affiliated Hospital of Hebei University, United States

L. Zhang. Department of Medical Oncology, Jiangsu Cancer Hospital, Nanjing, Jiangsu, China (People's Republic)

y. tong. Suzhou Kintor Pharmaceuticals Inc, United States

Proxalutamide plus Endocrine Therapies in Women with HR+/HER2-/AR+ Metastatic Breast Cancer: A Phase Ic Study Huiping Li^{1,*}, Guohong Song¹, Hanfang Jiang¹, Xu Liang¹, Xiaojia Wang², Hua Yang³, Lili Zhang⁴, Youzhi Tong⁵, Zhiming Shao^{6,*} ¹ Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital and Institute, 100142, China; ² Department of Breast Medical Oncology, Zhejiang Cancer Hospital (Department of Breast Medical Oncology), China ³Department of Medical Oncology, Affiliated Hospital of Hebei University; Hebei Key Laboratory of Cancer Radiotherapy and Chemotherapy, China ⁴ Department of Chemotherapy, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, China ⁵ Suzhou Kintor Pharmaceuticals Inc ⁶ Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China, Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China * Corresponding author: Huiping Li, email: huipingli2012@hotmail.com; Zhiming Shao, email: zhimingshao@Fudan.deu.cn

Abstract

Background: Resistance to endocrine therapy (ET) and cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is a major obstacle to the management of hormone-receptor (HR)+/human epidermal growth factor receptor 2 (HER2)- metastatic breast cancer (mBC). Targeting the AR signaling pathway has been demonstrated with promising results in this population. This phase Ic study aimed to assess the safety, efficacy, pharmacokinetic (PK), and pharmacodynamic (PD) characteristics of the combination of proxalutamide, a high-affinity AR antagonist, with ETs in androgen receptor (AR)+/HR+/HER2- mBC. Methods: Patients in part 1 regimen-finding phase received proxalutamide plus specific ETs (letrozole [cohort A], exemestane [cohort B], or

fulvestrant [cohort C]) and were assessed for dose-limiting toxicity (DLT), PK, PD, and anti-tumor activity. Part 2 expansion phase evaluated the safety and efficacy of proxalutamide plus fulvestrant. The primary endpoint was safety and tolerability. Results: Between June 18, 2019, and Sep 15, 2022, 38 (18 in part 1 and 20 in part 2) patients were treated. Efficacy analysis indicated that the ORR was 16.7% (2/12, 95% CI, 2.1%-48.4%) for cohort C and 15.0% (3/20; 95% CI, 3.2%-37.9%) for part 2. Patients achieved a median progression-free survival (PFS) of 6.4 months (95% CI, 2.7-19.3) in cohort C while an mPFS of 11.0 months (95% CI, 5.5- not estimable) in part 2. In part 1, no DLTs were reported. Grade 3 or more treatment-emergent adverse events (TEAEs) were observed in 11 (29.7%) patients (7 [18.9%] in part 1 and 4 [10.8%] in part 2) and mainly included neutrophil count decreased (8.1%) and platelet count decreased (5.4%). Seven (18.9%) had serious AEs (4 [10.8%] in part 1 and 3 [8.1%] in part 2)[1]. PD results showed a greater reduction of estradiol in cohort C compared with that in cohort B. In addition, proxalutamide was absorbed rapidly into the body with the plasma concentrations of proxalutamide and metabolites reaching a nearly steady state on day 29. Patients with AR/ER of ≤ 1 seemed to achieve longer PFS over those of > 1 (8.4 months vs. 4.1 months). Conclusions: These findings suggested favorable clinical outcomes and safety profiles of the combination of proxalutamide and fulvestrant in AR+/HR+/HER2- mBC patients who have progressed on the first-line therapy, and maybe with better efficacy in patients with lower AR/ER ratio. Trial registration: NCT20191063

PS15-08

Final Overall Survival (OS) analysis of the SAKK 21/12 trial. CR1447 in HR+/HER2-metastatic breast cancer and androgen receptor positive triple negative breast cancer.

Presenting Author(s) and Co-Author(s):

M. Vetter. Cancer Center Baselland, Liestal, Basel-Landschaft, Switzerland

H. Lisa. SAKK, United States

K. Rothgiesser. SAKK, United States

W. Schönfeld. Curadis, United States

S. Riniker. Brustzentrum Ostschweiz, United States

R. von Moos. Breast Center, St. Gallen, Switzerland

A. Torjan. Hirslanden Klinik im Park, United States

E. Kralidis. Onkozentrum ZH, United States

M. Rabaglio. Department of Medical Oncology; Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland

M. Fehr. Breast Center Thurgau, Münsterlingen, United States

A. Müller. KSW Breast Center, United States

B. Thürlimann. Swiss Breast Care, Bethanienspital, Zurich, Switzerland

Introduction: CR1447 (4-Hydroxytestosteron) is a compound with aromatase inhibitor and anti-androgen receptor activity and is applied transdermally. We assessed its activity and safety in metastatic breast cancer (mBC). The primary endpoint (disease control rate at week 24) was reported in 2019. We now present the final overall survival (OS) analysis of the trial. **Methods** In cohort A (ER+/HER2-negative metastatic disease), one prior treatment line was allowed and 29 patients (ITT 21 patients) were included. In cohort B (triple negative mBC), eight patients were included. The trial was closed in 2018 due to futility (cohort A) and slow accrual (cohort B). **Results** At data cut-off on 11.04.2023 92% of all patients had died. Median OS for cohort A was 35.4 months (95% CI: 24.6-49.1) in the ITT population and 19.4 months (95% CI: 2.3-36.8) in the non-ITT population (patients with more than one line of endocrine therapy). In cohort B, median OS was 10.8 months (95% CI: 3.3-28.6). Treatment was well tolerated with no new safety signals and the majority of treatment-related adverse events (TRAE) were Grade 1 and 2. The most common TRAEs were dry skin (43%), rash (16%), fatigue (16%) and nausea (16%). **Discussion** Despite the trial being negative in terms of the primary endpoint, cohort A (ITT) had a median OS of 35.4 months. There were no new safety signals. Mutational analysis of AR/ER is ongoing to determine benefit of this treatment in specific subgroups. CR1447 might be a candidate drug to combine with other agents (CDK4/6 inhibitors or other targeted therapies).

PS15-09

Imlunestrant monotherapy and in combination with abemaciclib, with or without an aromatase inhibitor, in estrogen receptor-positive (ER+), HER2-negative (HER2-) advanced breast cancer (aBC): updated results from the EMBER study

Presenting Author(s) and Co-Author(s):

- K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States
E. Lim. Garvan Institute of Medical Research, St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia
R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States
E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States
C. Osborne. Baylor Charles A. Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, Texas, United States
M. Bhave. Emory University School of Medicine, Atlanta, Georgia, United States
P. Kaufman. University of Vermont Cancer Center, Burlington, Vermont, United States
J. Beck. Highlands Oncology Group, Springdale, Arkansas, United States
L. Manso. Hospital Universitario 12 de Octubre, Madrid, Spain
R. Parajuli. University of California, Irvine Medical Center, Orange, California, United States
H. Wang. Department of Surgery, China Medical University Hospital, Taichung, Taiwan
J. Tao. Johns Hopkins University School of Medicine, Baltimore, Maryland, United States
A. Dhakal. University of Rochester Medical Center, Rochester, New York, United States
J. Pierga. Institut Curie & Université Paris Cité, Paris, France
Y. Lu. National Taiwan University Hospital, Taipei, Taiwan.
T. Larson. Minnesota Oncology/Hematology PA, Minneapolis, Minnesota, United States
Y. Jerez Gilarranz. Hospital General Universitario Gregorio Marañón, Madrid, Spain
R. Ismail-Khan. Loxo@Lilly, United States
F. Bacchion. Eli Lilly and Company, Indianapolis, Indiana, United States
C. Karacsonyi. Loxo@Lilly, United States
Y. Li.
S. Estrem. Loxo@Lilly, United States
B. Nguyen. Eli Lilly and Company, Indianapolis, Indiana, United States
M. Beeram. The START Center, United States

Background: Imlunestrant is an oral, brain-penetrant selective estrogen receptor degrader, designed to deliver continuous ER target inhibition, including in ESR1-mutant breast cancer. In the first-in-human dose escalation/expansion (Phase 1a/1b) study of the EMBER trial (NCT04188548), imlunestrant showed favorable safety, pharmacokinetics, and clinical benefit in pre-treated patients with ER+, HER2- aBC when administered as monotherapy (Jhaveri, ASCO 2022) or with abemaciclib ± aromatase inhibitor (AI) (Jhaveri, SABCS 2022). Here, we report updated data from Phase 1a/1b of imlunestrant monotherapy as well as from Phase 1b of imlunestrant with abemaciclib ± AI in EMBER. Methods: Phase 1a/1b enrolled patients with ER+ aBC (prior endocrine therapy (ET) sensitivity or untreated de novo aBC). Prior aBC

therapy allowance was ≤ 3 (no restrictions on the type of prior therapies) in Phase 1a and ≤ 2 (only 1 prior ET) in Phase 1b for patients receiving imlunestrant monotherapy; and ≤ 1 (no prior CDK4/6 inhibitors) in Phase 1b for patients randomized to receive imlunestrant + abemaciclib \pm AI. Key endpoints included safety and tolerability, objective response rate (ORR: complete response (CR) or partial response (PR) in patients with measurable disease), clinical benefit rate (CBR: CR or PR, or stable disease ≥ 24 weeks) per RECIST v1.1, and progression-free survival (PFS). Results: As of March 2023, 114 patients received imlunestrant monotherapy (200mg n=21; 400mg (RP2D) n= 51; ≥ 600 mg n=42), and 85 patients received imlunestrant (400mg n=80; 800 mg n=5) in combination with abemaciclib \pm AI (both at labeled doses). At the RP2D, the most common all-grade/ Grade 3 treatment-emergent adverse events (TEAEs) with imlunestrant monotherapy were fatigue (39%/ 4%), nausea (39%/ 2%), and diarrhea (29%/ 2%). With the combination of imlunestrant + abemaciclib \pm AI, the most common all-grade/ Grade 3 TEAEs were diarrhea (88%/ 9%), nausea (61%/ 0%), fatigue (51%/ 5%), and neutropenia (44%/ 16%). No safety signals of ocular or cardiac toxicity (bradycardia/QTc prolongation) were observed. Baseline characteristics, safety, and preliminary efficacy are presented in Table 1. Combination therapy of imlunestrant and abemaciclib \pm AI improved ORR and CBR. Conclusion: With longer follow-up, imlunestrant alone or in combination with abemaciclib \pm AI continues to demonstrate a tolerable safety profile along with favorable preliminary efficacy in patients with ER+, HER2- aBC. Further data will be presented at the meeting. The Phase 3, EMBER-3 study is ongoing; evaluating imlunestrant, investigator's choice ET, and imlunestrant plus abemaciclib in ET pre-treated ER+, HER2- aBC patients (NCT04975308).

Table. Baseline characteristics, safety and preliminary efficacy

Endpoints	Imlunestrant monotherapy n=114	Imlunestrant + abemaciclib n=42	Imlunestrant + abemaciclib + AI n=43
Visceral disease, n (%)	72 (63)	21 (50)	27 (63)
ESR1 mutation detected in ctDNA, n/ N ^a (%)	53/ 108 (49)	3/ 41 (7)	4/ 40 (10)
Median prior therapies for aBC, n (range)	2 (0-8)	0 (0-1)	0 (0-1)
Fulvestrant, n (%)	59 (52)	2 (5)	2 (5)
CDK 4/6 inhibitors, n (%)	106 (93)	0 (0)	0 (0)
Chemotherapy, n (%)	29 (25)	4 (10)	4 (9)
All-grade/ Grade ≥ 3 TRAEs, n (%)	83 (73)/ 6 (5)	41 (98)/ 15 (36)	40 (93)/ 17 (40)
Nausea	38 (33)/ 0 (0)	21 (50)/ 0 (0)	21 (49)/ 0 (0)
Diarrhea	27 (24)/ 1 (1)	40 (95)/ 4 (10)	31 (72)/ 3 (7)
Dose reductions due to TRAEs, n (%)			
Imlunestrant alone	3 (3)	1 (2)	2 (5)
Abemaciclib alone	-	9 (21)	14 (33)
Imlunestrant + abemaciclib	-	4 (10)	2 (5)
Discontinuation due to TRAEs, n (%)	0 (0)	0 (0)	1 (2)
ORR, n/N (%)	6/76 (8)	9/28 (32)	21/34 (62)
CBR, n (%)	48 (42)	30 (71)	34 (79)
Median time to response, median months (range)	3.58 (0.7, 8.2)	5.45 (1.6, 10.9)	3.65 (1.7, 8.5)

a, in patients with available ctDNA data.

PS15-01

A first-in-human phase 1 study of SIM0270, a brain-penetrant oral selective estrogen receptor degrader (SERD), in patients with ER+/ HER2- locally advanced or metastatic breast cancer

Presenting Author(s) and Co-Author(s):

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

J. Zhang. Fudan University Shanghai Cancer Center, Shanghai, Shanghai, China (People's Republic)

Q. Zhang. Harbin Medical University Cancer Hospital, United States

Y. Sun. Shandong Cancer Hospital, United States

H. Li. The First Affiliated Hospital of Bengbu Medical College, United States

Y. Yin. Department of Medical Oncology, Jiangsu Province Hospital, Nanjing, China (People's Republic)

Y. Shi. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

W. Li. The Affiliated Hospital of Qingdao University, United States

Y. Liu. The Fourth Hospital of Hebei Medical University, United States

M. Yan. Henan Cancer Hospital, Henan, China

C. Yang. Simcere Zaiming Pharmaceutical Co., Ltd., United States

L. Zhu. Simcere Zaiming Pharmaceutical Co., Ltd., United States

Y. Yang. Simcere Zaiming Pharmaceutical Co., Ltd., United States

L. Xue. Simcere Zaiming Pharmaceutical Co., Ltd., United States

Background:

ER+/HER2- breast cancer is the most prevalent subtype, and endocrine-based therapy is the standard treatment. SIM0270 is a brain-penetrant and highly potent oral SERD that has demonstrated ER degradation and robust antitumor activity across various preclinical models, including those with intracranial xenograft tumors.

Methods:

This Phase 1 study evaluates the safety, pharmacokinetics and preliminary anti-tumor activity of SIM0270 as monotherapy and/or in combination with palbociclib or everolimus in patients with HR+/HER2- advanced or metastatic breast cancer. The primary objective of the phase 1a study, which consisted of the dose escalation stage and the dose expansion stage, is to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of SIM0270 as monotherapy. A Bayesian Optimal Interval design (BOIN) was adopted. SIM0270 was administered orally daily in 28-day cycles. Here we report preliminary monotherapy data.

Results:

As of May 22nd 2023, 45 female patients were enrolled, receiving SIM0270 at dose levels of 10 mg (n=4), 30 mg (n=4), 60 mg (n=9), 90 mg (n=6), 120 mg (n=11), 200 mg (n=5), or 300 mg (n=6). The median age was 56 years (range, 40-73) and ECOG performance status was 0 (18%) or 1 (82%). Most patients were heavily pretreated, with a median of 2 prior endocrine-

based therapies (range, 0-5) and a median of 2 prior chemotherapies (range, 0-8). Thirty-one patients (69%) received prior fulvestrant, 42 (93%) received prior aromatase inhibitors, and 28 (62%) received prior CDK4/6 inhibitors. Visceral metastases were present in 33 patients (72%), and brain metastases in 7 patients (16%). The most common TEAEs were sinus bradycardia (51%), anemia (38%), hypalbuminaemia (31%), hypercholesterolaemia (24%), urinary tract infection (24%), asthenia (24%), electrocardiogram (ECG) QT prolonged (24%), and dizziness (22%). Most of the TEAEs were Grade 1-2. Grade 3 TRAEs were ECG QT prolonged, gamma-glutamyltransferase(γ -GT) increased and dizziness in 2 patients each. All AEs were manageable with dose interruption or reduction, except only 1 patient discontinued treatment of SIM0270 due to TRAE (Grade 3 γ -GT increased). Four patients experienced dose-limiting toxicities (DLTs): 1 with Grade 3 ECG QT prolonged at 200mg dose level, 1 with Grade 3 ECG QT prolonged and 2 with Grade 3 dizziness at 300mg dose level. All DLTs were resolved with dose interruption then reduction. The MTD of single-agent SIM0270 was established as 200mg QD. Pharmacokinetic analysis revealed a $T_{1/2}$ of approximately 70 hours, and the AUC and C_{max} increased in an approximately linear manner with dose escalation. Concentration in cerebrospinal fluid was measured in 1 patient after 41 days treatment of SIM0270, which is consistent with preclinical data and suggested high concentration of SIM0270 in the brain of patients. Among 31 response evaluable patients (per RECIST 1.1 criteria), 4 PRs (3 unconfirmed) were observed, yielding an ORR of 12.9%. Brain lesions were all stable in 4 evaluable patients per RANO-BM criteria. In patients with ESR1 mutations at baseline and samples available for analysis, 4/6(67%) exhibited a reduction or loss of mutant ESR1 upon SIM0270 treatment.

Conclusions:

Single-agent SIM0270 was well tolerated and showed favorable antitumor activity in heavily pretreated advanced or metastatic ER+/HER2- breast cancer patients, including those previously treated with CDK4/6 inhibitors and fulvestrant. Phase 1a dose expansion with single-agent SIM0270 is ongoing, and the RP2D will be determined based on further accumulative data of tolerability and efficacy. (NCT05293964)

Disclosure(s):

Jiong Wu: Consulting Fees (e.g., advisory boards): AstraZeneca (Terminated, October 10, 2022), Novartis (Terminated, October 10, 2022); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): F. Hoffman La Roche Ltd (Terminated, February 5, 2023)
Jian Zhang, MD: No financial relationships to disclose

Poster Spotlight Session 15: Novel Nuclear Receptor Targeting Therapies

Presenting Author(s) and Co-Author(s):

L. pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

Disclosure(s):

Lajos pusztai, MD, DPhil: Consulting Fees (e.g., advisory boards): Natera Inc (Ongoing)

PS15-02

A Phase I b Study of D-0502 as Monotherapy for Advanced or Metastatic ER-Positive and HER2-Negative Breast Cancer: Results from the Dose-Expansion Stage

Presenting Author(s) and Co-Author(s):

J. Wang. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

T. Sun. Department of Medical Oncology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Key Laboratory of Liaoning Breast Cancer Research, Shenyang, United States

Q. Zhang. Harbin Medical University Cancer Hospital, China (People's Republic)

Y. Shi. Sun Yat-sen University Cancer Center, China (People's Republic)

X. Wang. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

Y. Chen. The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Q. Ouyang. Department of Medical Oncology, Hunan Cancer Hospital, United States

K. Li. Hunan Cancer Hospital, China (People's Republic)

M. Bupathi. Rocky Mountain Cancer Center, US Oncology, Aurora, Colorado, United States

w. Edenfield. Prisma Health, United States

A. L.M. Silber. Yale University, New Haven, Connecticut, United States

H. Zong. The First Affiliated Hospital of Zhengzhou University, China (People's Republic)

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

D. Juric. Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

K. Lathrop. UT Health San Antonio, San Antonio, Texas, United States

Y. Zhang. InventisBio Co., Ltd, United States

K. Stazzone. InventisBio Co., Ltd, China (People's Republic)

Z. Shi. InventisBio Co., Ltd, China (People's Republic)

Y. Wang. InventisBio Co., Ltd, China (People's Republic)

L. Zhang. InventisBio Co., Ltd, China (People's Republic)

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

Background:

Endocrine therapy is the mainstay treatment for estrogen receptor (ER)-positive advanced breast cancer (BC). D-0502, an orally bioavailable selective estrogen receptor degrader (SERD), has previously demonstrated antitumor activity in various ER-positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) breast cancer cell lines and xenograft models. The phase I open-label study (NCT03471663) evaluated the safety, tolerability, pharmacokinetics (PK) and efficacy of D-0502 as monotherapy and in combination with palbociclib in female patients with ER+ and HER2- breast cancer. The dose escalation part of D-0502 monotherapy (phase I a) has been presented before (SABCS 2021, PS11-26

Abstract #1348). Here, we present the results of D-0502 monotherapy from the dose-expansion stage in phase I b study.

Methods:

In the single-agent dose-expansion stage of phase I b study, patients (n=60) received D-0502 (400 mg QD) in 28-day cycles. Eligible patients included females with confirmed ER+, HER2-locally advanced, or metastatic BC; ECOG 0-1; measurable disease (RECIST v1.1); premenopausal or postmenopausal status; adequate hematologic, hepatic and renal functions. The primary objectives are to characterize the safety of D-0502. The secondary objectives are to evaluate the preliminary anti-tumor activity and the PK characteristic.

Results:

As of April 07, 2023, 60 female patients were enrolled and treated with 400mg single-agent D-0502. Median age was 57 (range: 32-82) years, 55.0% had an ECOG PS of 1. Disease progression resulting in treatment discontinuation occurred in 66.7% (40/60) of patients, and 6.7% (4/60) of patients discontinued treatment because of AEs. Treatment-related adverse events (TRAEs) were reported in 57 pts (95.0%), most of which were grade 1-2. No grade 4/5 TRAE has been reported. The incidence of serious adverse events was 6.7% (4/60). The most common ($\geq 15\%$) TRAEs included vomiting, dizziness, nausea, increased aspartate aminotransferase and alanine aminotransferase, anaemia, decreased appetite, diarrhoea, and malaise. In the 51 efficacy evaluable patients, 8 patients had partial response (PR) and 27 had stable disease (SD); objective response rate (ORR) and disease control rate (DCR) were 15.7% (8/51) and 68.6% (35/51), respectively. The clinical benefit rate (CBR: CR + PR + SD ≥ 24 weeks) was 47.1% (24/51). The median PFS was 5.6 months (95% CI: 2.0, 10.0).

Conclusion:

D-0502 monotherapy showed promising antitumor activity and tolerable toxicity in female patients with ER+ and HER2- locally advanced or metastatic BC. Currently this treatment is being evaluated in a phase III study for patients with ER+ and HER2- locally advanced or metastatic BC in China.

Disclosure(s):

Erika P. Hamilton, MD: Consulting Fees (e.g., advisory boards): Arcus, Arvinas, AstraZeneca, Daiichi Sankyo, Deciphera Pharmaceuticals, Ellipses Pharma, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo, Mersana, Novartis, Orum Therapeutics, Pfizer, Relay Therapeutics, Roche/Genentech, SeaGen, Verascity Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Abbvie, Acerta Pharma, Accutar Biotechnology ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, (Ongoing)

Kate I. Lathrop, MD: No financial relationships to disclose

Binghe Xu, MD: Advisory Committee/Board Member: Astra Zeneca, Novartis (Ongoing)

PS15-03

Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, plus palbociclib in ER–positive/human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer: phase 1b cohort

Presenting Author(s) and Co-Author(s):

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Hurvitz. Fred Hutchinson Cancer Center, Seattle, Washington, United States

D. Juric. Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

H. Han. H. Lee Moffitt Cancer Center, Tampa, Florida, United States

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

G. Zahrah. Whittingham Cancer Center, Norwalk, Connecticut, United States

R. Nanda. University of Chicago Medicine, Chicago, Illinois, United States

Y. Zhang. Arvinas Operations, Inc., New Haven, Connecticut, United States

W. Tan. Pfizer Inc., La Jolla, California, United States

E. Duperret. Arvinas Operations, Inc., New Haven, Connecticut, United States

E. Zhi. Arvinas Operations, Inc., New Haven, Connecticut, United States

C. Mather. Arvinas, Inc, New Haven, Connecticut, United States

A. Schott. Rogel Cancer Center, University of Michigan Health, Ann Arbor, Michigan, United States

Background:

Vepdegestrant (ARV-471) is an oral PROTAC ER degrader. In a phase 1/2 study (NCT04072952), vepdegestrant monotherapy had a favorable safety profile and encouraging clinical activity, and showed robust ER degradation. The phase 1b cohort of this study is evaluating vepdegestrant in combination with the cyclin-dependent kinase (CDK)4/6 inhibitor palbociclib (palbo). In xenograft models, vepdegestrant plus palbo showed substantially greater tumor growth inhibition vs fulvestrant plus palbo, supporting investigation in patients with breast cancer.

Methods:

Eligible patients for the phase 1b combination cohort had ER+/HER2- locally advanced/metastatic breast cancer and had received ≥ 1 prior endocrine therapy and ≤ 2 chemotherapy regimens for advanced disease; prior CDK4/6 inhibitor treatment was permitted. Vepdegestrant was given orally once daily (QD) continuously at doses of 180 mg (n=2), 200 mg (n=21), 400 mg (n=3), or 500 mg (n=20); palbo 125 mg was given orally QD for 21 days followed by 7 days off treatment in 28-day cycles. The primary endpoints were dose-limiting toxicities (DLTs) in the first cycle and safety (adverse events [AEs] and laboratory abnormalities). Enrollment in these 4 dose levels is complete; we report data as of June 6, 2023.

Results:

Across 46 patients in the phase 1b cohort, 45 (97.8%) patients were female with a median age of 62.0 y (range: 29–78). Patients had received a median of 4 prior therapies (range: 1–11) in

any setting, including 87.0% prior CDK4/6 inhibitors (78.3% prior palbo), 80.4% prior fulvestrant, and 76.1% prior chemotherapy (45.7% in the metastatic setting). There were no DLTs. Treatment-emergent AEs (TEAEs) leading to dose reductions or discontinuation of vepdegestrant occurred in 5 and 4 patients, respectively. TEAEs leading to dose reductions or discontinuation of palbo occurred in 34 and 8 patients, respectively. Grade 3/4 treatment-related AEs (TRAEs) to either vepdegestrant or palbo in $\geq 10\%$ of patients were neutropenia (89.1%), decreased white blood cell count (15.2%), and decreased platelet count (10.9%); there were no grade 5 TRAEs and no patients had febrile neutropenia. The clinical benefit rate (rate of confirmed complete response, partial response, or stable disease ≥ 24 wks) in patients treated with vepdegestrant plus palbo was 63.0% (95% CI: 47.5–76.8). The objective response rate in evaluable patients with measurable disease at baseline (n=31) was 41.9% (95% CI: 24.5–60.9). Pharmacokinetics (PK) showed dose-dependent exposure for vepdegestrant, consistent with data for vepdegestrant administered as monotherapy; palbo exposure was similar across dose levels of vepdegestrant and modestly higher compared with historical palbo PK data. Circulating tumor DNA levels were evaluated in patients who received vepdegestrant 200 mg QD plus palbo and demonstrated substantial and sustained decreases in ESR1 mutant allele fraction across multiple treatment cycles.

Conclusions:

The combination of vepdegestrant plus palbo showed promising clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer who had received extensive prior treatment. The safety profile of vepdegestrant plus palbo was generally consistent with the known safety profiles of the 2 agents except for an increased occurrence of grade 3/4 neutropenia, which was readily managed with laboratory monitoring and dose reductions of palbo. There is an ongoing study lead-in to the global VERITAC-3 study (NCT05909397) that is evaluating 2 doses of palbo (100 mg and 75 mg) in combination with vepdegestrant 200 mg QD to determine the recommended phase 3 combination to compare with letrozole plus palbo as first-line treatment for ER+/HER2- advanced breast cancer.

Disclosure(s):

Erika P. Hamilton, MD: Consulting Fees (e.g., advisory boards): Arcus, Arvinas, AstraZeneca, Daiichi Sankyo, Deciphera Pharmaceuticals, Ellipses Pharma, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo, Mersana, Novartis, Orum Therapeutics, Pfizer, Relay Therapeutics, Roche/Genentech, SeaGen, Verascity Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Abbvie, Acerta Pharma, Accutar Biotechnology ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, (Ongoing)

Melinda Telli, MD: Advisory Committee/Board Member: Blueprint Medicine (Terminated, July 20, 2023), Natera, Inc. (Terminated, July 20, 2023), Novartis Pharma GmbH (Terminated, July 20, 2023), Reflexion Medical (Terminated, July 20, 2023), Replicate (Terminated, July 20, 2023), Sanofi Aventis (Terminated, July 20, 2023); Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated, July 20, 2023), Daiichi-Sankyo (Terminated, July 20, 2023), G1 Therapeutics (Terminated, July 20, 2023), Gilead Science (Terminated, July 20, 2023), Guardanth health (Terminated, July 20, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Arvinas (Ongoing), Astra Zeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Genentech-Roche (Ongoing), Hummingbird Biosciences (Ongoing), Merck & Co., Inc. (Ongoing), OncoSec (Ongoing), Pfizer, Inc. (Ongoing)

PS15-04

A Phase 1b/2 study of palazestrant (OP-1250), an oral complete estrogen receptor antagonist (CERAN) and selective ER degrader (SERD), with palbociclib in ER-positive, HER2-negative, advanced or metastatic breast cancer patients

Presenting Author(s) and Co-Author(s):

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

D. Day. Monash Health and Monash University, Clayton, Victoria, Australia

P. Dinh. 3Crown Princess Mary Cancer Care Centre, Westmead, New South Wales, Australia

M. Slancar. ICON Cancer Centre, Southport, Queensland, Australia

J. Lombard. Calvary Mater Newcastle, Waratah, New South Wales, Australia

V. Ganju. PSEHOG (Peninsula & South Eastern Haematology and Oncology Group), Frankston, Victoria, Australia

N. McCarthy. Icon Cancer Center, Wesley Medical Centre, Auchenflower, Australia

R. Wilson. Olema Oncology, Sydney, Sydney, Australia

D. Faltaos. Olema Oncology, San Francisco, San Francisco, California, United States

G. Mathauda-Sahota. Olema Oncology, San Francisco, San Francisco, California, United States

C. Murphy. Cancer Services Trials Unit, University Hospital Geelong, Barwon Health, Geelong, Victoria, Australia

Background:

Palazestrant (OP-1250) is a small molecule oral complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD) that binds the ligand binding domain of ER and completely blocks ER-driven transcriptional activity in both wild-type (ESR1-wt) and mutant (ESR1-mut) forms of ER. In preclinical studies, palazestrant demonstrated improved tumor growth inhibition and shrinkage when combined with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. In a Phase 1/2 monotherapy clinical study in patients with ER-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer, palazestrant was well tolerated with demonstrated antitumor efficacy and favorable pharmacokinetics (PK) supporting once a day (qd) dosing at the recommended Phase 2 dose of 120 mg. In this study, pts received palazestrant at escalating doses of 30, 60, 90, and 120 mg qd in combination with palbociclib (125 mg qd) and no dose-limiting toxicities were observed. Palazestrant did not affect palbociclib PK and no drug–drug interactions (DDIs) occurred. Here we report updates on safety, efficacy, and PK from the ongoing study of palazestrant in combination with palbociclib.

Methods:

Patients with advanced or metastatic breast cancer with progression on or after ≤ 1 line of endocrine therapy (prior CDK4/6 inhibitor therapy and ≤ 1 chemotherapy allowed) were enrolled to receive oral palazestrant 120 mg qd with oral palbociclib 125 mg qd for 21 of 28 days (NCT0526610).

Results:

As of May 12, 2023, 33 patients have been treated with palazestrant in combination with palbociclib; 12 pts were dosed in the dose-escalation phase and 21 patients were dosed in the dose-expansion phase of the study. Twenty-two patients (67%) received prior CDK4/6 inhibitor

therapy; 15 patients received prior palbociclib. Thirteen of 25 patients (52%) with available baseline ctDNA had an ESR1 mutation. The most common ($\geq 20\%$) treatment-emergent adverse events (TEAEs) were neutropenia, nausea, vomiting, constipation, and diarrhea. Most of these events were grade 1 or 2. The most common grade 3 or 4 related AE was neutropenia (18/33 [55%] were grade 3; 3/33 [9%] were grade 4). The steady-state exposure of palazestrant when dosed with 125 mg palbociclib was consistent with the monotherapy study. Palbociclib exposure at steady-state was comparable to published monotherapy data when combined with palazestrant at all dose levels tested. As of the data cut-off, there were 4 partial responses (2 confirmed) out of 19 response-evaluable patients, with a clinical benefit rate (CBR) of 42% (8/19) across all patients and 67% (6/9) in patients with ESR1 mutations.

Conclusions:

Palazestrant and palbociclib dosed in combination were well tolerated with a safety profile consistent with the individual profiles of each drug as monotherapy, and there were no DDIs. Tumor responses and clinical benefit were observed in this population of patients, including those who received prior CDK4/6 inhibitors. Expanding on our previous report, these data provide the rationale to continue advancing the clinical development of palazestrant with the approved dose of palbociclib. Updated data will be presented.

Disclosure(s):

Arlene Chan, MBBS, FRACP, MMED: No financial relationships to disclose

PS15-06

Results of the window-of-opportunity PIONEER trial evaluating addition of the progesterone receptor (PR) agonist megestrol to letrozole for early stage estrogen receptor (ER) positive breast cancer: exploiting ER-PR interaction

Presenting Author(s) and Co-Author(s):

R. Burrell. Department of Oncology, University of Cambridge, Cambridge, England, United Kingdom

S. Kumar. Department of Oncology, University of Cambridge, United States

S. McIntosh. Queen's University Belfast, United States

V. Pitsinis. University of Dundee and Ninewells Hospital Dundee, UK, United Kingdom

P. King. Royal Cornwall Hospital, United States

B. Elsberger. Aberdeen Royal Infirmary, United States

S. Govindarajulu. Southmead Hospital Bristol, United Kingdom

L. Satherley. Cardiff University and University Hospital Llandough, United Kingdom

S. Hadad. Sheffield Teaching Hospitals NHS Foundation Trust, UK, United States

P. Schmid. Barts Cancer Institute, Queen Mary University of London, UK and St Bartholemew's Hospital, United Kingdom

J. Abraham. Precision Breast Cancer Institute, Department of Oncology, University of Cambridge / Cambridge University Hospitals NHS Foundation Trust, United States

A. Agrawal. Cambridge University Hospitals NHS Trust, United Kingdom

J. Benson. Cambridge University Hospitals NHS Trust, United Kingdom

D. Cheeseman. CRUK Cambridge Institute, University of Cambridge, United Kingdom

I. Chernukhin. CRUK Cambridge Institute, University of Cambridge, United Kingdom

P. Frouhi. Cambridge University Hospitals NHS Trust, United Kingdom

E. Kleidi. Cambridge University Hospitals NHS Trust, United Kingdom

C. Pike. Cambridge Clinical Cancer Trials Unit, Cambridge University Hospitals NHS Trust, United Kingdom

K. Pinilla. Precision Breast Cancer Institute and CRUK Cambridge Institute, University of Cambridge, Cambridge, United Kingdom

E. Provenzano. Cambridge University Hospitals NHS Trust, UK and Cambridge Biomedical Research Centre (NIHR), United Kingdom

W. Qian. Cambridge Clinical Cancer Trials Unit, Cambridge University Hospitals NHS Trust, United Kingdom

J. Carroll. CRUK Cambridge Institute and Precision Breast Cancer Institute, University of Cambridge, United Kingdom

R. Baird. CRUK Cambridge Centre, University of Cambridge, United Kingdom

Background:

Pre-clinical data suggest that combining anti-estrogen treatment with a progesterone receptor agonist leads to greater inhibition of tumor proliferation, due to molecular interactions between ER and PR [1]. A high dose of the PR agonist megestrol (160mg daily) is approved as monotherapy for the treatment of ER positive metastatic breast cancer. A lower dose of

megestrol (20-40mg daily) can be an effective treatment for severe hot flashes associated with endocrine therapy [2] but whether this dose has anti-tumor activity is unknown. The PIONEER trial evaluated the potential anti-proliferative effect of low and high dose megestrol in combination with letrozole, relative to letrozole alone, using a short-term preoperative 'window' trial design assessing the direct effects of the trial treatment on tumor tissue before and after treatment.

Methods:

Eligible patients were post-menopausal women with histologically confirmed ER+ (Allred ≥ 3) HER2 negative breast cancer at least 10mm in size, with an ECOG performance status ≤ 2 , planned for primary surgery or endocrine therapy. Enrolled patients were randomised 2:3:3 to Arm A: letrozole alone, Arm B: letrozole + lower-dose megestrol (40mg) or Arm C: letrozole + higher-dose megestrol (160mg). Treatment was given for 15 (13-19) days prior to surgery or end of treatment (EOT) core biopsy. The primary endpoint was change in tumor proliferation between baseline and EOT in Arm A vs (Arms B+C combined), measured by Ki67 immunohistochemistry (IHC). Secondary endpoints were comparison of Ki67 change in high versus low dose megestrol arms, absolute Ki67 at EOT, and change in tumor apoptosis (cleaved caspase 3 IHC), proliferation (Aurora Kinase A IHC), PR and androgen receptor expression. Exploratory analysis of ER chromatin binding (ChIP-Seq) was conducted on paired fresh-frozen samples from a subset of patients.

Results:

A total of 243 patients were randomised from July 2017 to October 2022 with recruitment paused for 3 months at onset of the COVID pandemic. 198 patients completed treatment and had evaluable tissue samples at baseline and EOT (Arm A: n = 51, Arm B: n = 74, Arm C: n = 73). Baseline mean Ki67 values were well balanced. Therapy was well tolerated and adverse events \geq grade 3 were similarly rare across arms (A: 3.3%, B+C: 3.5%). The mean % reduction in Ki67 for each arm was: Arm A (letrozole): 71%, Arm B (letrozole + 40mg megestrol): 79%, Arm C (letrozole + 160mg megestrol): 80%. There was a statistically significantly greater reduction in Ki67 with megestrol combinations (B+C) versus letrozole alone (A) (P = 0.013). Analyses of secondary IHC endpoints and ER ChIP-Seq are ongoing and will be presented.

Conclusion:

Addition of the PR agonist megestrol enhanced the anti-proliferative effect of letrozole in this window-of opportunity trial. Megestrol combinations were well tolerated, and the anti-proliferative effect was observed in both low and high dose arms. These data support the potential use of low-dose megestrol as an inexpensive and well-tolerated means of improving aromatase inhibitor efficacy. Low dose megestrol can also ameliorate hot flashes and therefore might be a strategy to improve both treatment adherence and clinical outcomes for patients taking adjuvant endocrine therapy.

References

1. Mohammed et al., Nature 523: 313–317 (2015)
2. Loprinzi et al., NEJM 331: 347-352 (1994)

Disclosure(s):

Rebecca A. Burrell, MBBS PhD: No financial relationships to disclose

PS15-07

Proxalutamide plus Endocrine Therapies in Women with HR+/HER2-/AR+ Metastatic Breast Cancer: A Phase Ic Study

Presenting Author(s) and Co-Author(s):

H. Li. Department of Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, Beijing, China (People's Republic)

G. Song. Department of Breast Oncology, Peking University Cancer Hospital & Institute, United States

h. jiang. beijing cancer hospital, United States

x. liang. beijing cancer hospital, United States

X. Wang. Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, United States

H. Yang. Affiliated Hospital of Hebei University, United States

L. Zhang. Department of Medical Oncology, Jiangsu Cancer Hospital, Nanjing, Jiangsu, China (People's Republic)

y. tong. Suzhou Kintor Pharmaceuticals Inc, United States

Proxalutamide plus Endocrine Therapies in Women with HR+/HER2-/AR+ Metastatic Breast Cancer: A Phase Ic Study

Huiping Li^{1,*}, Guohong Song¹, Hanfang Jiang¹, Xu Liang¹, Xiaojia Wang², Hua Yang³, Lili Zhang⁴, Youzhi Tong⁵, Zhiming Shao^{6,*}

¹ Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital and Institute, 100142, China;

² Department of Breast Medical Oncology, Zhejiang Cancer Hospital (Department of Breast Medical Oncology), China

³ Department of Medical Oncology, Affiliated Hospital of Hebei University; Hebei Key Laboratory of Cancer Radiotherapy and Chemotherapy, China

⁴ Department of Chemotherapy, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, China
Suzhou Kintor Pharmaceuticals Inc

⁶ Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China, Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

* Corresponding author: Huiping Li, email: huipingli2012@hotmail.com; Zhiming Shao, email: zhimingshao@Fudan.edu.cn **Abstract** Background: Resistance to endocrine therapy (ET) and cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is a major obstacle to the management of hormone-receptor (HR)+/human epidermal growth factor receptor 2 (HER2)- metastatic breast cancer (mBC). Targeting the AR signaling pathway has been demonstrated with promising results in this population. This phase Ic study aimed to assess the safety, efficacy, pharmacokinetic (PK), and pharmacodynamic (PD) characteristics of the combination of

proxalutamide, a high-affinity AR antagonist, with ETs in androgen receptor (AR)+/HR+/HER2-mBC. Methods: Patients in part 1 regimen-finding phase received proxalutamide plus specific ETs (letrozole [cohort A], exemestane [cohort B], or fulvestrant [cohort C]) and were assessed for dose-limiting toxicity (DLT), PK, PD, and anti-tumor activity. Part 2 expansion phase evaluated the safety and efficacy of proxalutamide plus fulvestrant. The primary endpoint was safety and tolerability. Results: Between June 18, 2019, and Sep 15, 2022, 38 (18 in part 1 and 20 in part 2) patients were treated. Efficacy analysis indicated that the ORR was 16.7% (2/12, 95% CI, 2.1%-48.4%) for cohort C and 15.0% (3/20; 95% CI, 3.2%-37.9%) for part 2. Patients achieved a median progression-free survival (PFS) of 6.4 months (95% CI, 2.7-19.3) in cohort C while an mPFS of 11.0 months (95% CI, 5.5- not estimable) in part 2. In part 1, no DLTs were reported. Grade 3 or more treatment-emergent adverse events (TEAEs) were observed in 11 (29.7%) patients (7 [18.9%] in part 1 and 4 [10.8%] in part 2) and mainly included neutrophil count decreased (8.1%) and platelet count decreased (5.4%). Seven (18.9%) had serious AEs (4 [10.8%] in part 1 and 3 [8.1%] in part 2)[1]. PD results showed a greater reduction of estradiol in cohort C compared with that in cohort B. In addition, proxalutamide was absorbed rapidly into the body with the plasma concentrations of proxalutamide and metabolites reaching a nearly steady state on day 29. Patients with AR/ER of ≤ 1 seemed to achieve longer PFS over those of >1 (8.4 months vs. 4.1 months). Conclusions: These findings suggested favorable clinical outcomes and safety profiles of the combination of proxalutamide and fulvestrant in AR+/HR+/HER2- mBC patients who have progressed on the first-line therapy, and maybe with better efficacy in patients with lower AR/ER ratio.

Trial registration: NCT20191063

Disclosure(s):

Hui-Ping Li, SEC: No financial relationships to disclose

PS15-08

Final Overall Survival (OS) analysis of the SAKK 21/12 trial. CR1447 in HR+/HER2-metastatic breast cancer and androgen receptor positive triple negative breast cancer.

Presenting Author(s) and Co-Author(s):

M. Vetter. Cancer Center Baselland, Liestal, Basel-Landschaft, Switzerland

H. Lisa. SAKK, United States

K. Rothgiesser. SAKK, United States

W. Schönfeld. Curadis, United States

S. Riniker. Brustzentrum Ostschweiz, United States

R. von Moos. Breast Center, St. Gallen, Switzerland

A. Torjan. Hirslanden Klinik im Park, United States

E. Kralidis. Onkozentrum ZH, United States

M. Rabaglio. Department of Medical Oncology; Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland

M. Fehr. Breast Center Thurgau, Münsterlingen, United States

A. Müller. KSW Breast Center, United States

B. Thürlimann. Swiss Breast Care, Bethanienspital, Zurich, Switzerland

Introduction:

CR1447 (4-Hydroxytestosteron) is a compound with aromatase inhibitor and anti-androgen receptor activity and is applied transdermally. We assessed its activity and safety in metastatic breast cancer (mBC). The primary endpoint (disease control rate at week 24) was reported in 2019. We now present the final overall survival (OS) analysis of the trial.

Methods

In cohort A (ER+/HER2-negative metastatic disease), one prior treatment line was allowed and 29 patients (ITT 21 patients) were included. In cohort B (triple negative mBC), eight patients were included. The trial was closed in 2018 due to futility (cohort A) and slow accrual (cohort B).

Results

At data cut-off on 11.04.2023 92% of all patients had died. Median OS for cohort A was 35.4 months (95% CI: 24.6-49.1) in the ITT population and 19.4 months (95% CI: 2.3-36.8) in the non-ITT population (patients with more than one line of endocrine therapy). In cohort B, median OS was 10.8 months (95% CI: 3.3-28.6). Treatment was well tolerated with no new safety signals and the majority of treatment-related adverse events (TRAE) were Grade 1 and 2. The most common TRAEs were dry skin (43%), rash (16%), fatigue (16%) and nausea (16%).

Discussion

Despite the trial being negative in terms of the primary endpoint, cohort A (ITT) had a median OS of 35.4 months. There were no new safety signals. Mutational analysis of AR/ER is ongoing to determine benefit of this treatment in specific subgroups. CR1447 might be a candidate drug to combine with other agents (CDK4/6 inhibitors or other targeted therapies).

Disclosure(s):

Marcus Vetter, PD MD: I am the PI in the trial sponsored by Curadis: Curadis Darmstadt Germany (Terminated)

PS15-09

Imlunestrant monotherapy and in combination with abemaciclib, with or without an aromatase inhibitor, in estrogen receptor-positive (ER+), HER2-negative (HER2-) advanced breast cancer (aBC): updated results from the EMBER study

Presenting Author(s) and Co-Author(s):

- K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States
E. Lim. Garvan Institute of Medical Research, St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia
R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States
E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States
C. Osborne. Baylor Charles A. Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, Texas, United States
M. Bhave. Emory University School of Medicine, Atlanta, Georgia, United States
P. Kaufman. University of Vermont Cancer Center, Burlington, Vermont, United States
J. Beck. Highlands Oncology Group, Springdale, Arkansas, United States
L. Manso. Hospital Universitario 12 de Octubre, Madrid, Spain
R. Parajuli. University of California, Irvine Medical Center, Orange, California, United States
H. Wang. Department of Surgery, China Medical University Hospital, Taichung, Taiwan
J. Tao. Johns Hopkins University School of Medicine, Baltimore, Maryland, United States
A. Dhakal. University of Rochester Medical Center, Rochester, New York, United States
J. Pierga. Institut Curie & Université Paris Cité, Paris, France
Y. Lu. National Taiwan University Hospital, Taipei, Taiwan.
T. Larson. Minnesota Oncology/Hematology PA, Minneapolis, Minnesota, United States
Y. Jerez Gilarranz. Hospital General Universitario Gregorio Marañón, Madrid, Spain
R. Ismail-Khan. Loxo@Lilly, United States
F. Bacchion. Eli Lilly and Company, Indianapolis, Indiana, United States
C. Karacsonyi. Loxo@Lilly, United States
Y. Li.
S. Estrem. Loxo@Lilly, United States
B. Nguyen. Eli Lilly and Company, Indianapolis, Indiana, United States
M. Beeram. The START Center, United States

Background:

Imlunestrant is an oral, brain-penetrant selective estrogen receptor degrader, designed to deliver continuous ER target inhibition, including in ESR1-mutant breast cancer. In the first-in-human dose escalation/expansion (Phase 1a/1b) study of the EMBER trial (NCT04188548), imlunestrant showed favorable safety, pharmacokinetics, and clinical benefit in pre-treated patients with ER+, HER2- aBC when administered as monotherapy (Jhaveri, ASCO 2022) or with abemaciclib ± aromatase inhibitor (AI) (Jhaveri, SABCS 2022). Here, we report updated data from Phase 1a/1b of imlunestrant monotherapy as well as from Phase 1b of imlunestrant with abemaciclib ± AI in EMBER.

Methods:

Phase 1a/1b enrolled patients with ER+ aBC (prior endocrine therapy (ET) sensitivity or untreated de novo aBC). Prior aBC therapy allowance was ≤ 3 (no restrictions on the type of prior therapies) in Phase 1a and ≤ 2 (only 1 prior ET) in Phase 1b for patients receiving imlunestrant monotherapy; and ≤ 1 (no prior CDK4/6 inhibitors) in Phase 1b for patients randomized to receive imlunestrant + abemaciclib \pm AI. Key endpoints included safety and tolerability, objective response rate (ORR: complete response (CR) or partial response (PR) in patients with measurable disease), clinical benefit rate (CBR: CR or PR, or stable disease ≥ 24 weeks) per RECIST v1.1, and progression-free survival (PFS).

Results:

As of March 2023, 114 patients received imlunestrant monotherapy (200mg n=21; 400mg (RP2D) n= 51; ≥ 600 mg n=42), and 85 patients received imlunestrant (400mg n=80; 800 mg n=5) in combination with abemaciclib \pm AI (both at labeled doses). At the RP2D, the most common all-grade/ Grade 3 treatment-emergent adverse events (TEAEs) with imlunestrant monotherapy were fatigue (39%/ 4%), nausea (39%/ 2%), and diarrhea (29%/ 2%). With the combination of imlunestrant + abemaciclib \pm AI, the most common all-grade/ Grade 3 TEAEs were diarrhea (88%/ 9%), nausea (61%/ 0%), fatigue (51%/ 5%), and neutropenia (44%/ 16%). No safety signals of ocular or cardiac toxicity (bradycardia/QTc prolongation) were observed. Baseline characteristics, safety, and preliminary efficacy are presented in Table 1. Combination therapy of imlunestrant and abemaciclib \pm AI improved ORR and CBR.

Conclusion:

With longer follow-up, imlunestrant alone or in combination with abemaciclib \pm AI continues to demonstrate a tolerable safety profile along with favorable preliminary efficacy in patients with ER+, HER2- aBC. Further data will be presented at the meeting. The Phase 3, EMBER-3 study is ongoing; evaluating imlunestrant, investigator's choice ET, and imlunestrant plus abemaciclib in ET pre-treated ER+, HER2- aBC patients (NCT04975308).

Table. Baseline characteristics, safety and preliminary efficacy

Endpoints	Imlunestrant monotherapy n=114	Imlunestrant + abemaciclib n=42	Imlunestrant + abemaciclib + AI n=43
Visceral disease, n (%)	72 (63)	21 (50)	27 (63)
ESR1 mutation detected in ctDNA, n/N ^a (%)	53/ 108 (49)	3/ 41 (7)	4/ 40 (10)
Median prior therapies for aBC, n (range)	2 (0-8)	0 (0-1)	0 (0-1)
Fulvestrant, n (%)	59 (52)	2 (5)	2 (5)
CDK 4/6 inhibitors, n (%)	106 (93)	0 (0)	0 (0)
Chemotherapy, n (%)	29 (25)	4 (10)	4 (9)
All-grade/ Grade ≥ 3 TRAEs, n (%)	83 (73)/ 6 (5)	41 (98)/ 15 (36)	40 (93)/ 17 (40)
Nausea	38 (33)/ 0 (0)	21 (50)/ 0 (0)	21 (49)/ 0 (0)
Diarrhea	27 (24)/ 1 (1)	40 (95)/ 4 (10)	31 (72)/ 3 (7)
Dose reductions due to TRAEs, n (%)			
Imlunestrant alone	3 (3)	1 (2)	2 (5)
Abemaciclib alone	-	9 (21)	14 (33)
Imlunestrant + abemaciclib	-	4 (10)	2 (5)
Discontinuation due to TRAEs, n (%)	0 (0)	0 (0)	1 (2)
ORR, n/N (%)	6/76 (8)	9/28 (32)	21/34 (62)
CBR, n (%)	48 (42)	30 (71)	34 (79)
Median time to response, median months (range)	3.58 (0.7, 8.2)	5.45 (1.6, 10.9)	3.65 (1.7, 8.5)

a, in patients with available ctDNA data.

Disclosure(s):

Komal Jhaveri, MD, FACP: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), AstraZeneca (Ongoing), Blueprint Medicines (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Jounce Therapeutics (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Menarini/Stemline (Ongoing), Novartis (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing), Sun Pharma Advanced Research Company Ltd (Ongoing), TAIHO Oncology (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Context Therapeutics (Ongoing), Debio Pharmaceuticals (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck Pharmaceuticals (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Puma Biotechnology, Inc (Ongoing), Zymeworks Inc. (Ongoing)

Cynthia Ma, MD, PhD: Advisory Committee/Board Member: Puma Biotechnology, Inc (Ongoing); Authorship/Article Publication: Wolters Kluwer/UpToDate (Ongoing); Consulting Fees (e.g., advisory boards): Agendia (Ongoing), AstraZeneca (Ongoing), Athenex (Ongoing), Bayer Healthcare (Ongoing), Biovica (Ongoing), Eisai (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), Inivata (Ongoing), Jacobio (Ongoing), Natera (Ongoing), Novartis (Ongoing), Olaris (Ongoing), OncoSignal (Ongoing), Pfizer (Ongoing), Phillips Electronics (Ongoing), Puma Biotechnology, Inc (Ongoing), Sanofi (Ongoing), Seattle Genetics (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): PlusOne Heath GmbH (Ongoing); Filled out Surveys for Tempus regarding these tests. Did not impact clinical or research activity.: Tempus (Ongoing); Royalty: Wolters Kluwer/UpToDate (Ongoing)

Erika P. Hamilton, MD: Consulting Fees (e.g., advisory boards): Arcus, Arvinas, AstraZeneca, Daiichi Sankyo, Deciphera Pharmaceuticals, Ellipses Pharma, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo, Mersana, Novartis, Orum Therapeutics, Pfizer, Relay Therapeutics, Roche/Genentech, SeaGen, Verascity Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Abbvie, Acerta Pharma, Accutar Biotechnology ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, (Ongoing)

PS16-02

Efficacy and safety of first-line atezolizumab + bevacizumab + paclitaxel in patients with advanced triple-negative breast cancer: the ATRACTIB phase 2 trial.

Presenting Author(s) and Co-Author(s):

M. Gion. Ramón y Cajal University Hospital, Madrid, Madrid, Spain

P. Cortez-Castedo. IOB Institute of Oncology, Hospital Ruber Internacional, Quiron Group, Madrid, Spain

I. Blancas. Medical Oncology Dept, University Hospital San Cecilio, Granada, Spain

A. Cortés. Hospital Universitario Ramón y Cajal, Madrid (Spain); ONCARE, United States

F. Marmé. Med. Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany

S. Blanch. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US. Fundación Instituto Valenciano de Oncología, Valencia, Spain, United States

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

N. Díaz. San Juan de Alicante University Hospital, Alicante, Comunidad Valenciana, Spain

I. Calvo-plaza. MD Anderson Cancer Center, Madrid, Spain

S. Recalde. ICO Hospitalet - Moises Broggi Hospital, Barcelona, Catalonia, Spain

A. Martínez-Bueno. Hospital Universitari Dexeus, Barcelona, Spain

M. Ruiz-Borrego. Virgen del Rocío Hospital, Sevilla, Andalucia, Spain

E. Llabres. Hospital Universitario Insular de Gran Canarias, Spain

M. Taberner. University Hospital La Ribera, Alzira, Comunidad Valenciana, Spain

M. de Laurentiis. National Cancer Institute (IRCCS) Pascale Foundation, Napoli, Campania, Italy

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

J. Repkova. Sant Joan de Reus University Hospital, Tarragona, Catalonia, Spain

A. Antón. Miguel Servet University Hospital, Zaragoza, Aragon, Spain

J. Gligorov. Institut Universitaire de Cancérologie AP-HP Sorbonne Université, Paris, Ile-de-France, France

S. de la Cruz. Navarra University Hospital, Navarra, Spain, Navarra, Spain

O. Hoffmann. University Hospital Essen, Germany

J. Medioni. Georges Pompidou European Hospital, Paris, Ile-de-France, France

M. Phillips. Barts Cancer Institute, Queen Mary University of London, London, England, United Kingdom

M. Sampayo-Cordero. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

D. Alcalá-López. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

J. Pérez-García. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Catalonia, Spain

A. Llombart-Cussac. Arnau de Vilanova Hospital, Valencia, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US, Comunidad Valenciana, Spain

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

BACKGROUND Triple-negative breast cancer (TNBC) is an aggressive tumor characterized by poor outcomes and new treatment strategies are urgently required. The programmed cell death-ligand 1 (PD-L1) antibody (Ab) atezolizumab (ATZ) combined with first-line (1L) nab-paclitaxel (nab-PTX) is approved in multiple countries for the treatment of PD-L1-positive patients (pts) with advanced TNBC (aTNBC) based on a significant improvement in progression-free survival (PFS) and a numerically higher and clinically meaningful median overall survival (OS). A synergism between antiangiogenic therapy and immunotherapy (IO)-based strategies has been observed preclinically and in different tumor types, but data in aTNBC is lacking. **METHODS** ATRACTIB (NCT04408118) is an international, open-label, single-arm, phase 2 trial evaluating the efficacy and safety of 1L ATZ + BVZ + PTX for pts with aTNBC, regardless of their tumors' PD-L1 status. Adult pts with untreated, unresectable locally advanced/metastatic TNBC were included. Pts who had received (neo)adjuvant taxane-based chemotherapy (CT) and/or IO and/or an antiangiogenic agent had to have had a relapse with a disease-free interval beyond 12 months (mo). Pts received intravenous ATZ 840 mg + BVZ 10 mg/kg on days (D)1 and D15 + PTX 90 mg/m² on D1, 8, and 15 of every 28-day cycle until disease progression, intolerable toxicity, death, or patient withdrawal. Tumor assessments were performed every 8 weeks for the first 12 mo and every 12 weeks thereafter. Baseline PD-L1 expression was centrally assessed using 22C3 (combined positive score [CPS]) and SP142 (expression on tumor-infiltrating immune cells [ICs]) Abs. The primary endpoint was investigator-assessed PFS by RECIST v.1.1. Key secondary endpoints included OS, objective response rate (ORR), clinical benefit rate (CBR), duration of response (DoR), and safety. Median PFS was analyzed with exponential maximum likelihood estimation (H0: ≤7.0 mo; HA: ≥9.5 mo). We estimated that enrolling 100 pts would provide 80% power at one-sided α nominal level of 5%, assuming a 10% drop-out rate. **RESULTS** Between October 2020 and May 2022, 100 female pts from 28 centers across 5 European countries were included. Median age was 55.0 years (32.0 - 84.0), 57.0% of pts had visceral disease, 46.0% had ≥3 metastatic sites, and 70.0% had received prior treatment for early BC (taxane-based CT in 87.1% of them). A total of 82 and 85 tumor samples out of 100 pts were available for PD-L1 assessment using 22C3 and SP142 assays, respectively. Most pts had PD-L1-negative tumors (87.8% with 22C3 [CPS < 10] and 97.6% with SP142 [expression on < 1% positive of ICs]). At data cutoff (15th September 2023), 23 pts were still on therapy. With a median follow-up of 16.7 mo (1.1 - 34.1), median PFS was 11.0 mo (95% CI, 9.0 - 13.2). OS data were immature at data cutoff, with 30 events. Estimated 18-month OS was 69.4% (95% CI, 58.4% - 78.1%). ORR was 63.0% (95% CI, 52.8% - 72.4%), CBR was 79.0% (95% CI, 69.7% - 86.5%), and median DoR was 10.0 mo (95% CI, 7.2 - 13.8). Regarding safety, the most common treatment-emergent adverse events (TEAEs) were peripheral neuropathy (68.0%) and fatigue (62.0%). Grade (G) 3/4 treatment-related TEAEs occurred in 47.0% of pts, mainly peripheral neuropathy (13.0%) and neutropenia (12.0%). Any-grade immune-related TEAEs, thrombosis or embolism, and bleeding occurred in 13.0% (5.0%; G≥3), 4.0% (1.0%; G≥3), and 10.0% (0.0%; G≥3) of pts, respectively. There were no drug-related deaths. **CONCLUSIONS** 1L ATZ + BVZ + PTX demonstrated encouraging anti-tumor activity in aTNBC pts, most of them presenting with PD-L1-negative tumors. Median PFS seems to be much higher compared with that previously reported with other IO-based regimens in a similar patient population. The safety profile was consistent with the known safety data of ATZ and BVZ combined with CT, without significant added toxicity. These results merit further

research of this combination for PD-L1-negative aTNBC.

PS16-01

Comparison of an Atezolizumab monotherapy window followed by Atezolizumab and chemotherapy vs. Atezolizumab and chemotherapy alone in triple negative breast cancer (TNBC) – final analysis of the neoadjuvant neoMono trial

Presenting Author(s) and Co-Author(s):

H. Kolberg. Department of Gynecology and Obstetrics, Marienhospital Bottrop, Bottrop, Nordrhein-Westfalen, Germany

J. Schumacher. palleos healthcare GmbH, Germany

R. Erber. University Hospital Erlangen, Germany

M. Braun. Rotkreuzklinikum München, Germany

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

E. Grischke. Universitäts-Frauenklinik Tübingen, Eberhard Karls University, Tübingen, Germany

C. Schem. Mammazentrum am Krankenhaus Jerusalem, Hamburg, Germany

M. Lux. St. Vincenz-Kliniken Paderborn, Germany

M. Deryal. CaritasKlinikum Saarbrücken, Germany

O. Hoffmann. University Hospital Essen, Germany

B. Heinrich. HOP - Hämatologisch-onkologische Praxis Augsburg, Germany

G. Kunz. Department of Gynecology and Obstetrics, Johannes-Hospital Dortmund, Germany

K. Lübbe. Diakovere Henriettenstift, Breast Center, Hannover, Germany

P. Krabisch. Department of Gynecology and Obstetrics, Klinikum Chemnitz, Germany

A. Hartmann. University Hospital Erlangen, Germany

P. Raeth. palleos healthcare GmbH, Germany

S. Kasimir-Bauer. University Hospital Essen, Germany

C. Kolberg-Liedtke. University Hospital Essen, Germany

Background:

Improvement of systemic therapy of TNBC still is a medical need. Exploratory data from the neoadjuvant GeparNuevo trial suggested a benefit from an immune checkpoint inhibitor (ICI) monotherapy window in TNBC. The neoMono trial prospectively analyzed whether the addition of a preceding Atezolizumab monotherapy window prior to Atezolizumab and chemotherapy (CTX) improves pCR rates among patients (pts) with early TNBC. In an interim analysis after 100 pCR events, patients with unselected TNBC did not show a significant benefit from an Atezolizumab monotherapy window, while an exploratory analysis suggested a highly clinically relevant benefit among pts with PD-L1 positive TNBC. Here we present the final primary endpoint analysis.

Methods:

NeoMono is a phase 2 randomized multicenter trial that was planned to recruit a maximum of 458 female and male pts with primary TNBC (defined as ER/PR < 10% and HER2 negative) with tumor stages cT1c – cT4d (cN0 and cN+). As the protocol mandated termination of trial recruitment based on the results of the interim analysis, the final ITT population was limited to 359 pts. PD-L1 status had to be identifiable by central pathology by means of the VENTANA

PD-L1 (SP142) assay and was defined by PD-L1 expression on immune cells (IC). Neoadjuvant treatment in both study arms consisted of Atezolizumab 1200 mg every 3 weeks in addition to neoadjuvant CTX (12 x Carboplatin/Paclitaxel q1w followed by 4x Epirubicin/Cyclophosphamide q3w). Combination therapy in arm A was preceded by an Atezolizumab monotherapy window of 840 mg once two weeks prior to initiation of combination therapy, while patients in arm B received no immune monotherapy window.

Study goals are to compare the efficacy of neoadjuvant CTX + Atezolizumab with versus without a two-week atezolizumab monotherapy window preceding CTX + ICI (primary endpoint: pCR) and to identify biomarkers for response and resistance through analysis of sequential tissue and liquid biopsies. The neoMono statistical design uses Bayesian posterior probabilities (uniform prior distribution) and logistic regression to analyze the primary endpoint.

Results:

180 pts in arm A and 179 in arm B from 34 study sites were included in the final primary endpoint analysis. Demographics and baseline characteristics as well as drug exposure were well-balanced in both arms. Posterior mean pCR rates in the ITT population in study arms A and B were 65.7% (95% high posterior density interval (HPDI): 58.5%, 72.5%) and 69% (62.2%, 75.9%), respectively. In an exploratory analysis stratified by PD-L1 IC status (negative: < 1% versus positive: ≥ 1%), pCR rates in arm A were 91.5% in the PD-L1 IC-positive group and 56.1% in the PD-L1 IC-negative group, the corresponding pCR rates in arm B were 82.2% and 64.5%, respectively. In a multivariate analysis of the ITT population including tumor size, nodal status, tumor grade, age and PD-L1 status, the odds ratio for achieving a pCR was 4.77 ($p < 0.001$) for PD-L1-positive and 2.36 ($p=0.023$) for grade 3 tumors.

In an exploratory analysis including HER2 status, odds for achieving a pCR were significantly higher for patients with HER2-negative (IHC 0) vs. HER2-low tumors (OR 1.73, $p=0.036$).

No new safety signals were observed.

Conclusion:

The final primary endpoint analysis of the neoMono trial demonstrated the highest pCR rates ever reported in a phase II/III trial in TNBC. While a significant impact of an ICI monotherapy window on the pCR rate after combination of CTX + ICI in an unselected ITT population could not be demonstrated, neoMono indicates for the first time in a randomized prospective setting that patients with immune active TNBC might derive particular benefit from a preceding ICI monotherapy window. The results of the neoMono trial are mainly justifying the conduction of a confirmative trial in immune active TNBC. However, our results underscore the potential role of pre-therapeutic ICI monotherapy window as part of future therapeutic concepts in TNBC.

Disclosure(s):

Hans-Christian Kolberg, MD PhD: Advisory Committee/Board Member: Agendia (Terminated, June 14, 2023); Consulting Fees (e.g., advisory boards): Amgen (Terminated, August 13, 2023), Carl Zeiss Meditec (Terminated, August 13, 2023), Daiichi-Sankyo (Terminated, August 13, 2023), Exact Sciences (Genomic Health) (Terminated, August 13, 2023), F. Hoffman La Roche Ltd (Terminated, August 13, 2023), Gilead Science (Terminated, August 13, 2023), MSD Oncology (Terminated, August 13, 2023), Novartis Pharma GmbH (Terminated, August 13, 2023), Onkowissen (Terminated, August 13, 2023), SeaGen (Terminated, August 13, 2023); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Agendia (Terminated, August 13, 2023), Carl Zeiss Meditec (Terminated, August 13, 2023), Daiichi-Sankyo (Terminated, August 13, 2023), Novartis Pharma GmbH

(Terminated, August 13, 2023), SeaGen (Terminated, August 13, 2023); Lectures: F. Hoffman La Roche Ltd (Terminated, October 25, 2023); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Phaon Scientific GmbH (Ongoing), Theraclion SA (Ongoing)

Poster Spotlight Session 16: Enhancing Immunotherapy for Triple Negative Breast Cancer: Novel therapies and Biomarkers

Presenting Author(s) and Co-Author(s):

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

Disclosure(s):

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AtraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

PS16-02

Efficacy and safety of first-line atezolizumab + bevacizumab + paclitaxel in patients with advanced triple-negative breast cancer: the ATRACTIB phase 2 trial.

Presenting Author(s) and Co-Author(s):

M. Gion. Ramón y Cajal University Hospital, Madrid, Madrid, Spain

P. Cortez-Castedo. IOB Institute of Oncology, Hospital Ruber Internacional, Quiron Group, Madrid, Spain

I. Blancas. Medical Oncology Dept, University Hospital San Cecilio, Granada, Spain

A. Cortés. Hospital Universitario Ramón y Cajal, Madrid (Spain); ONCARE, United States

F. Marmé. Med. Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany

S. Blanch. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US. Fundación Instituto Valenciano de Oncología, Valencia, Spain, United States

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

N. Díaz. San Juan de Alicante University Hospital, Alicante, Comunidad Valenciana, Spain

I. Calvo-plaza. MD Anderson Cancer Center, Madrid, Spain

S. Recalde. ICO Hospitalet - Moises Broggi Hospital, Barcelona, Catalonia, Spain

A. Martínez-Bueno. Hospital Universitari Dexeus, Barcelona, Spain

M. Ruiz-Borrego. Virgen del Rocío Hospital, Sevilla, Andalucia, Spain

E. Llabres. Hospital Universitario Insular de Gran Canarias, Spain

M. Taberner. University Hospital La Ribera, Alzira, Comunidad Valenciana, Spain

M. de Laurentiis. National Cancer Institute (IRCCS) Pascale Foundation, Napoli, Campania, Italy

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

J. Repkova. Sant Joan de Reus University Hospital, Tarragona, Catalonia, Spain

A. Antón. Miguel Servet University Hospital, Zaragoza, Aragon, Spain

J. Gligorov. Institut Universitaire de Cancérologie AP-HP Sorbonne Université, Paris, Ile-de-France, France

S. de la Cruz. Navarra University Hospital, Navarra, Spain, Navarra, Spain

O. Hoffmann. University Hospital Essen, Germany

J. Medioni. Georges Pompidou European Hospital, Paris, Ile-de-France, France

M. Phillips. Barts Cancer Institute, Queen Mary University of London, London, England, United Kingdom

M. Sampayo-Cordero. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

D. Alcalá-López. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Barcelona, Catalonia, Spain

J. Pérez-García. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Catalonia, Spain

A. Llombart-Cussac. Arnau de Vilanova Hospital, Valencia, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US, Comunidad Valenciana, Spain

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US; Department of Medicine, Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Madrid, Spain., Barcelona, Catalonia, Spain

BACKGROUND

Triple-negative breast cancer (TNBC) is an aggressive tumor characterized by poor outcomes and new treatment strategies are urgently required. The programmed cell death-ligand 1 (PD-L1) antibody (Ab) atezolizumab (ATZ) combined with first-line (1L) nab-paclitaxel (nab-PTX) is approved in multiple countries for the treatment of PD-L1-positive patients (pts) with advanced TNBC (aTNBC) based on a significant improvement in progression-free survival (PFS) and a numerically higher and clinically meaningful median overall survival (OS). A synergism between antiangiogenic therapy and immunotherapy (IO)-based strategies has been observed preclinically and in different tumor types, but data in aTNBC is lacking.

METHODS

ATRACTIB (NCT04408118) is an international, open-label, single-arm, phase 2 trial evaluating the efficacy and safety of 1L ATZ + BVZ + PTX for pts with aTNBC, regardless of their tumors' PD-L1 status.

Adult pts with untreated, unresectable locally advanced/metastatic TNBC were included. Pts who had received (neo)adjuvant taxane-based chemotherapy (CT) and/or IO and/or an antiangiogenic agent had to have had a relapse with a disease-free interval beyond 12 months (mo).

Pts received intravenous ATZ 840 mg + BVZ 10 mg/kg on days (D)1 and D15 + PTX 90 mg/m² on D1, 8, and 15 of every 28-day cycle until disease progression, intolerable toxicity, death, or patient withdrawal. Tumor assessments were performed every 8 weeks for the first 12 mo and every 12 weeks thereafter.

Baseline PD-L1 expression was centrally assessed using 22C3 (combined positive score [CPS]) and SP142 (expression on tumor-infiltrating immune cells [ICs]) Abs.

The primary endpoint was investigator-assessed PFS by RECIST v.1.1. Key secondary endpoints included OS, objective response rate (ORR), clinical benefit rate (CBR), duration of response (DoR), and safety. Median PFS was analyzed with exponential maximum likelihood estimation (H0: ≤ 7.0 mo; HA: ≥ 9.5 mo). We estimated that enrolling 100 pts would provide 80% power at one-sided α nominal level of 5%, assuming a 10% drop-out rate.

RESULTS

Between October 2020 and May 2022, 100 female pts from 28 centers across 5 European countries were included. Median age was 55.0 years (32.0 - 84.0), 57.0% of pts had visceral disease, 46.0% had ≥ 3 metastatic sites, and 70.0% had received prior treatment for early BC (taxane-based CT in 87.1% of them). A total of 82 and 85 tumor samples out of 100 pts were available for PD-L1 assessment using 22C3 and SP142 assays, respectively. Most pts had PD-L1-negative tumors (87.8% with 22C3 [CPS < 10] and 97.6% with SP142 [expression on < 1% positive of ICs]).

At data cutoff (15th September 2023), 23 pts were still on therapy. With a median follow-up of

16.7 mo (1.1 - 34.1), median PFS was 11.0 mo (95% CI, 9.0 - 13.2). OS data were immature at data cutoff, with 30 events. Estimated 18-month OS was 69.4% (95% CI, 58.4% - 78.1%). ORR was 63.0% (95% CI, 52.8% - 72.4%), CBR was 79.0% (95% CI, 69.7% - 86.5%), and median DoR was 10.0 mo (95% CI, 7.2 - 13.8).

Regarding safety, the most common treatment-emergent adverse events (TEAEs) were peripheral neuropathy (68.0%) and fatigue (62.0%). Grade (G) 3/4 treatment-related TEAEs occurred in 47.0% of pts, mainly peripheral neuropathy (13.0%) and neutropenia (12.0%). Any-grade immune-related TEAEs, thrombosis or embolism, and bleeding occurred in 13.0% (5.0%; G \geq 3), 4.0% (1.0%; G \geq 3), and 10.0% (0.0%; G \geq 3) of pts, respectively. There were no drug-related deaths.

CONCLUSIONS

1L ATZ + BVZ + PTX demonstrated encouraging anti-tumor activity in aTNBC pts, most of them presenting with PD-L1-negative tumors. Median PFS seems to be much higher compared with that previously reported with other IO-based regimens in a similar patient population. The safety profile was consistent with the known safety data of ATZ and BVZ combined with CT, without significant added toxicity. These results merit further research of this combination for PD-L1-negative aTNBC.

Disclosure(s):

Maria Gion, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo/Astra Zeneca (Terminated), Gilead Science (Terminated), Novartis (Terminated), Pfizer (Terminated); Travel: F. Hoffman La Roche Ltd (Terminated)

Javier Cortés, MD, PhD: No relevant disclosure to display

PS16-03

Intratumoral dosing of INT230-6 in Early-Stage Breast Cancer Patients Induces Tumor Cell Necrosis and Immunomodulatory Effects: A Phase II Randomized Window-Of-Opportunity Study – the INVINCIBLE Trial

Presenting Author(s) and Co-Author(s):

A. Arnaout. Ottawa Hospital/Ottawa Hospital Research Institute/Ontario Institute of Cancer Research, Ottawa, Ontario, Canada

L. Bender. Intensity Therapeutics, Westport, Connecticut, United States

M. Hopkins. Ontario Institute for Cancer Research, Canada

V. Lopez Ozuna. Ottawa Hospital Research Institute, Canada

L. Liao. Ontario Institute for Cancer Research, Canada

S. Robertson. Ottawa Hospital, Ottawa, Ontario, Canada

V. Talebian. Ontario Institute for Cancer Research, Canada

K. Keyhanian. Ottawa Hospital, Canada

A. Awan. The Ottawa Hospital Cancer Centre, Canada

F. Abbate. Intensity Therapeutics, Inc., United States

I. Walters. Intensity Therapeutics, westport, Connecticut, United States

G. Pond. McMaster University, United States

J. Bartlett. Ontario Institute of Cancer Research, United States

L. Radvanyi. Ontario Institute for Cancer Research, Canada

M. Spears. Diagnostic Development, Ontario Institute for Cancer Research, Toronto. Ontario, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

Background:

Larger tumors pose an increased risk for breast cancer (BC) recurrence post-surgery. In addition, most BC outside of the triple negative subtype are considered immunological quiescent and minimally responsive to immunotherapies. One potential method to combat disease recurrence risk and induce immune activation pre-surgery is through a local therapy that could cause cell death to expose tumor antigens, provide adjuvants for anti-tumor immune priming, and thus potentially increase responsiveness to immunotherapies or rates of pathological complete response in combination with chemotherapy. We have conducted a randomized, Phase 2 presurgical Window-Of-Opportunity trial for intratumoral (IT) INT230-6 comprising vinblastine, cisplatin and a diffusion enhancer (SHAO) in patients with early-stage operable BC, the INVINCIBLE trial (NCT04781725). Previous in vivo and clinical studies demonstrated that INT230-6 induces cancer cell death and halts replication while maturing dendritic cells and recruiting T-cells into the tumor. In this trial, IT injections of INT230-6 were conducted to 1) evaluate the safety of regional cytotoxic use on BC, 2) assess the drug's ability to cause necrosis, 3) assess immune response within the tumor, microenvironment and systemically prior to surgical resection, and 4) understand the genetic pathways involved in immune activity.

Methods:

Women awaiting surgery for newly diagnosed early-stage intermediate or high-grade T1-T2 invasive BC were recruited to the trial. The study has two parts. Part I was a randomized (2:1)

open label trial comparing 1-3 doses of INT230-6 injected weekly versus no treatment prior to surgery to evaluate safety, feasibility, and optimal drug dosing. Part II was a double-blinded randomized (2:1) trial where patients received one IT dose of INT230-6 vs saline injection IT.

Results:

We successfully recruited 91 patients with age ranges of 40-77 yrs (mean of 60 yrs) with tumor size ranging from 1.1 - 4.8 cm (mean 2.5 cm; SD 0.9 cm). The most common (>10%) AEs were injection site pain, injection site reaction and nausea/vomiting. Approximately 90% of AEs were grade 1. In the study INT230-6 induced necrosis in 64% of subjects (37 out of 58, range 0 to 100%); whereas saline induced partial necrosis in 25% of patients (5 out of 20, range 0 to 10%). The table below shows the results of necrosis for INT230-6 use in the entire study compared to saline injection for all subjects and those with tumors of size T2.

A single injection of INT230-6 caused necrosis in various histologies, including invasive lobular carcinoma. Gene expression analysis showed significant differential gene expression between the baseline biopsy and surgical specimens using INT230-6. Pathway analysis identified genes associated with TCR signaling, B cells and T cell activation that were significantly upregulated in the post INT230-6 treatment samples. There was a relative increase in CD4 and CD8 T cells and B and mast cells.

Conclusion:

Preliminary evidence shows that a single dose of INT230-6 can cause significant intratumoral necrosis compared to saline especially in tumors >2. cm. INT230-6 stimulates an immune response in breast cancers prior to surgery with minimal adverse effects and good tolerability. Given its immune activation properties, INT230-6 shows promising potential in future breast cancer neoadjuvant studies.

Table 1: INVINCIBLE Study Tumor Necrosis Results

INT230-6 IT injection	(N)	Average tumor size (cm)	% subjects with necrosis	Average % necrosis
All subjects	58	2.5	64%	19.3
Tumors T2 (>2 cm)	39	2.1	74%	25
Saline IT injection				
All subjects	20	2.1	25%	0.86
Tumors T2 (>2 cm)	7	2.4	14%	0.14
p-value for necrosis: INT230-6 compared to saline				
All subjects	0.003			
Tumors T2 (>2 cm)	0.021			

Intratumoral INT230-6 injection compared to IT saline injection

Disclosure(s):

Angel Arnaout, MD: No financial relationships to disclose

PS16-04

Denosumab as an enhancer of the immune infiltrate in hormone receptor-positive early breast cancer. Subgroup analysis from the D-Biomark window-of-opportunity clinical trial (NCT03691311)

Presenting Author(s) and Co-Author(s):

A. Vethencourt. Institut Català d'Oncologia, Oncology Department, Barcelona, Spain. Insitut d'Investigació Biomèdica Bellvitge IDIBELL, Barcelona, Catalonia, Spain

E. Trinidad. Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, Barcelona, Spain

E. Dorca. University Hospital of Bellvitge and Institut Català d'Oncologia, Pathology Department, Barcelona, Spain

A. Petit. University Hospital of Bellvitge and Institut Català d'Oncologia, Pathology Department, Barcelona, Spain

T. Soler-Monsó. University Hospital of Bellvitge and Institut Català d'Oncologia, Pathology Department, Barcelona, Spain

A. Stradella. Institut Català d'Oncologia, Oncology Department, Barcelona, Spain

C. Capo. Viladecans Hospital. Institut Català d'Oncologia, Gynecology Service and breast unit, Barcelona, Spain

A. Urriticoechea. Oncologikoa, United States

M. Matas. Althaia Xarxa Assistencial Universitària, Oncology Department, Barcelona, Manresa, Spain

G. Pérez-Chacon. Spanish National Cancer Research Center (CNIO), Madrid, Spain

M. Jimenez. Spanish National Cancer Research Center (CNIO), Madrid, Spain

M. Ciscar. Spanish National Cancer Research Center (CNIO), Madrid, Spain

E. Brizzi. Hospital Universitario La Paz, Pathology Department, Madrid, Spain

G. Soria Alcaide. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

G. Gomez. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

E. Piñeiro. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

E. Purcheras. University Hospital of Bellvitge and Institut Català d'Oncologia, Pathology Department, Barcelona, Spain

A. Garcia. Hospital of Bellvitge and Institut Català d'Oncologia , Gynecology Service and breast unit, Barcelona, Spain

A. Iserte. Insitut d'Investigació Biomèdica Bellvitge IDIBELL, Barcelona, Spain

M. Pla. Hospital of Bellvitge and Institut Català d'Oncologia , Gynecology Service and breast unit., Barcelona, Spain

M. Campos. Hospital of Bellvitge and Institut Català d'Oncologia , Gynecology Service and breast unit., Barcelona, Spain

M. Gil-Gil. Institut Català d'Oncología, Insitut d'Investigació Biomèdica Bellvitge. GEICAM Spanish Breast Cancer Group, United States

S. Pernas. SOLTI Cancer Research Group, Barcelona, Spain Institut Catala d'Oncologia; IDIBELL, L'Hospitalet, Barcelona, Spain

E. Gonzalez-Suarez. Spanish National Cancer Research Center (CNIO), Madrid , Spain. IDIBELL, Institut d'Investigacio Biomédica de Bellvitge, Barcelona, Spain

C. Faló. Institut Català d'Oncologia, Oncology Department, Barcelona, Spain

Background:

The receptor activator of nuclear factor κ B (RANK) signaling pathway has emerged as a therapeutic target in breast cancer (BC). Recent studies indicate that inhibition of the RANK pathway induces tumor cell differentiation and may enhance the anti-tumor immune response. The D-Biomark clinical trial aims to evaluate the antitumor (antiproliferative and proapoptotic) and immunomodulatory effects of denosumab in HER2-negative early BC.

Methods:

Patients with early HER2-negative BC scheduled for primary surgery were randomized in a 2:1 ratio to receive two doses of 120 mg denosumab on days 1 and 8 vs no treatment before surgery.

Immunohistochemistry (IHC) was used to assess Ki67 (proliferation), cleaved caspase-3 (cell survival), RANK and RANKL. Stromal tumor infiltrating lymphocytes (TILs) and serum markers including free RANKL (sRANKL), tartrate-resistant acid phosphatase 5b (TRACP5b), and osteoprotegerin (OPG) were also analyzed. Paired t-test was used to compare values between core biopsy (biopsy A) and surgical samples (biopsy B). Subgroup analysis by intrinsic subtype was performed on 47 matched cases using PAM50.

Results:

Between July 2019 and May 2021, we enrolled 60 patients, 58 evaluable, including 10 triple-negative breast cancer (TNBC). The clinicopathologic characteristics of the population at the time of enrollment were well balanced, but the TNBC recruited included 5 out of 10 tumors with a more indolent behavior than the typical tumors of this lineage (apocrine tumors, low cell proliferation). Due to this and the small number of cases, no conclusions can be drawn in this subgroup. RANK expression was detected in 19 tumor cases, while 17 cases expressed RANKL. The treated group showed a decrease in sRANKL ($p < 0.000$), indicating denosumab activity, while the control group showed no change ($p=1.0$). OPG levels in the experimental group showed a non-significant increase ($p=0.07$), while TRACP5b remained unchanged. Both groups showed a non-clinically relevant increase in cell proliferation (5 percentage points), control $p=0.04$, experimental $p=0.01$. Subgroup analysis of tumors with RANK+ or RANKL+ tumor cells also showed no reduction in Ki67. Cell survival did not decrease in the overall cohort (control $p=0.05$, experimental $p=0.24$), nor in subgroups or in tumors with RANK+ or RANKL+ tumor cells. Denosumab treatment increased TILs in the overall population (control $p=0.06$, experimental $p=0.0006$) and in the subgroups: RANK+ tumors, RANKL+ tumors, premenopausal and postmenopausal, less so in the TNBC group. The subgroup analysis is shown in Table 1. Analysis by intrinsic subtype showed that in the experimental group there was an increase in cases with a change to luminal A lineage (17%) compared to the control group (6%), suggesting a possible cellular differentiation towards less aggressive tumors. Although the number of patients is small, these changes warrant further investigation and highlight the role of denosumab as an immune activator in these luminal tumors known for their low inflammatory infiltrate.

Conclusion:

Two doses of denosumab prior to surgery did not reduce proliferation or increase apoptosis. However, this short course of denosumab increased TILs in early BC, particularly in luminal

tumors, and may induce tumor cell differentiation into luminal A-like tumors.

Table 1. Analysis by subgroups

RESPONSE VARIABLE	LUMINAL BREAST CANCER N=48				TNBC N=10 *			
	CONTROL	UP/DOWN	EXPERIMENTAL	UP/DOWN	CONTROL	UP/DOWN	EXPERIMENTAL	UP/DOWN
KI 67	0,069	UP	0,081	UP	0,517	UP	0,025	UP
CLEAVED-CASPASE 3	0,114	UP	0,216	DOWN	0,35	UP	0,694	UP
TIL	0,176	UP	0,005	UP	0,237	UP	0,079	UP
	LUMINAL PREMENOPAUSAL N=26				LUMINAL POSTMENOPAUSAL N=22			
KI 67	0,031	UP	0,241	UP	0,314	DOWN	0,146	UP
CLEAVED-CASPASE 3	0,095	UP	0,1687	DOWN	0,899	DOWN	0,689	UP
TILS	0,639	UP	0,048	UP	0,062	UP	0,041	UP
	RANK+ N=19				RANKL+ N=17			
KI 67	0,384	UP	0,060	UP	0,307	DOWN	0,062	UP
CLEAVED-CASPASE 3	0,751	DOWN	0,262	DOWN	0,599	DOWN	0,401	DOWN
TILS	0,120	UP	0,013	UP	0,330	UP	0,048	UP

*The results of the P-values of the comparison between biopsy A and biopsy B, together with the direction of the changes (up or down), are indicated for each parameter and each subgroup. * Note that results for TNBC are inconclusive, as 5/10 are "indolent" TNBC and they are not well balanced.*

Disclosure(s):

ANDREA C. Vethencourt, MD: Invited Speaker, Presentation in clinical or research sessions as a speaker: Eisai Europe Ltd. (Ongoing), Novartis Pharma GmbH (Ongoing); Travel, Accommodations, Support for attending meetings: Pfizer, Lilly, ROCHE, Novartis (Ongoing)

PS16-06

Tumor-infiltrating lymphocytes and pathologic response to neoadjuvant chemotherapy with the addition of platinum and pembrolizumab in TNBC: A single-center real-world study

Presenting Author(s) and Co-Author(s):

M. Kim. Gangnam Severance Hospital, Seoul, Seoul-t'ukpyolsi, Republic of Korea

Y. Kook. Gangnam Severance Hospital, South Korea

S. Baek. Gangnam Severance Hospital, South Korea

J. Kim. Gangnam Severance Hospital, South Korea

S. Moon. Gangnam Severance Hospital, South Korea

S. Lee. Gangnam Severance Hospital, South Korea

J. Kim. Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Background

Previous studies have presented compelling evidence suggesting that the inclusion of platinum agents alongside anthracyclines and taxanes could potentially enhance treatment outcomes in high-risk triple-negative breast cancer (TNBC). Moreover, pembrolizumab has been integrated into clinical practice as a part of standard-of-care for non-metastatic TNBC with high risk. In light of these findings, we undertook a real-world study to investigate the impact of incorporating platinum agents and pembrolizumab on achieving pathologic complete response (pCR) in TNBC patients undergoing neoadjuvant chemotherapy (NAC). Furthermore, we specifically examined the influence of tumor-infiltrating lymphocytes (TILs) on the treatment outcomes.

Patients and Methods

In this real-world study conducted at Gangnam Severance Hospital, Seoul, Republic of Korea, we analyzed a cohort of 398 patients with TNBC who underwent surgery following NAC between March 2007 and November 2022. Among them, 247 patients received an anthracycline-taxanes (A-T), 120 received a carboplatin regimen including A-T, and 31 received a pembrolizumab regimen including A-T-carboplatin as part of their neoadjuvant chemotherapy treatment. TIL was evaluated in biopsied samples prior to NAC according to the guideline of TIL international working group. The high TIL was defined with a cutoff of 50%.

Results

Among the 398 patients analyzed, 87 (21.9%) had high TIL tumors. The pCR rates were 32% in the anthracycline-taxane (A-T) regimen group, 57% in the A-T-carboplatin regimen group, and 68% in the pembrolizumab with A-T-carboplatin regimen group. Within the high TIL group, the pCR rate did not increase with the addition of carboplatin (51.8% in the A-T group and 41.7% in the A-T-carboplatin group), but reached 85.7% with the addition of pembrolizumab and

carboplatin. Among the low TIL group, the pCR rate increased from 26.7% to 61.1% with the addition of carboplatin, but there was no difference in the pCR rate between the carboplatin and pembrolizumab groups (61.1% and 60.9%, respectively). In clinically node-positive patients, the pCR rate significantly increased with pembrolizumab in the high TIL group (40.9% versus 100%, $p=0.035$). However, in low TIL patients, the addition of carboplatin alone significantly increased the pCR rate to 62.3%, whereas the addition of pembrolizumab did not show the same effect.

Conclusions

Our real-world data consistently demonstrates an increased pCR rate with the addition of carboplatin and pembrolizumab. Among patients with high TIL, the addition of carboplatin did not result in an elevated pCR rate. However, the addition of pembrolizumab tended to maximize the pCR rate, surpassing 80%. On the other hand, among patients with low TIL, the addition of carboplatin significantly increased the pCR rate, while the addition of pembrolizumab did not have the same effect. Efforts should be made to improve the response to pembrolizumab-containing regimens for patients with low baseline TIL levels.

Disclosure(s):

Min Ji Kim, MD: No financial relationships to disclose

PS16-07

Tumor infiltrating lymphocyte stratification refines AJCC TNM staging based outcomes of early-stage triple negative breast cancer treated with neoadjuvant anthracycline-free, docetaxel and carboplatin chemotherapy.

Presenting Author(s) and Co-Author(s):

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

R. Yoder. The University of Kansas Cancer Center, United States

R. Salgado. Department of Pathology, GZA-ZNA-Hospitals, Antwerp, Belgium. Division of Research, Peter Mac Callum Cancer Centre, Melbourne, VIC, Australia

M. del Monte-Millán. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

E. Álvarez. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

I. Echavarria. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

J. Staley. The University of Kansas Cancer Center, United States

C. Bueno-Muiño. Medical Oncology Department, Hospital Infanta Cristina (Parla), Fundación de Investigación Biomédica del H.U. Puerta de Hierro, Majadahonda, Madrid, Spain

Y. Jerez Gilarranz. Hospital General Universitario Gregorio Marañón, Madrid, Spain

A. Godwin. University of Kansas Medical Center; Kansas Institute for Precision Medicine; The University of Kansas Cancer Center, United States

M. Cebollero. Anatomical pathology service. Hospital General Universitario Gregorio Marañón. IISGM, Madrid, Spain

O. Bueno. Radiology Service. Hospital General Universitario Gregorio Marañón. IISGM, Madrid, Spain

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

F. Moreno Antón. Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISSC), CIBERONC, Madrid, Spain

U. Bohn. Department of Medical Oncology, Hospital Universitario Dr Negrin, Las Palmas de Gran Canaria, Spain

H. Gómez. Departamento de Medicina Oncológica, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Instituto de Investigaciones en Ciencias Biomedicas, Universidad Ricardo Palma, Lima, Peru

T. Massarrah. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

S. López-Tarruella. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

P. Sharma. University of Kansas Medical Center Westwood, Westwood, Kansas City, Kansas, United States

Background:

Stromal tumor-infiltrating lymphocytes (sTILs) quantification is associated with pathological response to neoadjuvant chemotherapy (NAC) and long term outcomes in setting of adjuvant

anthracycline based chemotherapy. A previous study in TNBC patients treated with adjuvant anthracycline chemotherapy shows that at a cut point of 30%, sTILs can up and downstage traditional AJCC stage groups. Additive impact of sTILs on refining outcomes beyond pathological response and TNM stage for patients treated with anthracycline-free chemotherapy is not known. This study aimed to investigate impact of sTILs on outcomes in a large cohort of TNBC patients treated with Docetaxel plus carboplatin NAC.

Methods:

Patients with stage I (T size > 1cm) to III TNBC scheduled to receive 6 cycles of NAC docetaxel (75 mg/m²) plus carboplatin (AUC 6) (TCb) every 3 weeks from two studies (NCT01560663 and NCT02302742) were combined for this analysis. sTILs were evaluated on pre-treatment H&E slide using standard criteria centrally by one of the investigators (RS). Pathological complete response (pCR) was defined as ypT0/is ypN0. Logistic regression analysis was used to examine the effect of multiple variables on Event free survival (EFS) and overall survival (OS).

Results:

For 474 patients included in this analysis, median age was 52 years, 8% were Black, 13% had germline BRCA1/2 mutation, 44% had clinical Lymph node (LN) positive disease and 13%, 62% and 25% respectively had TNM stage I, II and III disease. Median sTILs were 5% (range 1-95%) and 25% had >30% sTILs. pCR and RCB 0+1 rates were 50.2% and 60.4% respectively. On multivariable analysis, T stage (OR=0.51, p=0.030), nodal status (OR=0.56, p=0.028), Ki67 (OR=2.74, p< 0.001) and sTILs (OR=2.01, p=0.014) were associated with pCR. pCR rate in those with sTILs < 30 vs sTILs >30 was 45.9% and 63.9% respectively (p=0.0014). At median follow-up of 58 months, 5 years EFS was 81.05% in all patients, 93.94% in those with pCR and 68.67% in those without pCR, 5 year OS was 84.83% in all patients, 96.53% in those with pCR and 74.13% in those with residual disease. On multivariate analysis lower T stage, negative LN status and increasing sTILs were associated with better EFS (T stage: HR =1.98, p=0.018; LN status: HR=2.92, p< 0.001; sTILs: HR:0.46, p=0.04) and OS (T stage: HR=1.89, p=0.040; LN status: HR=3.13, p=0.001; sTILs: HR=0.30, p=0.008). At a cut-point of 30%, sTILs up and downstaged anatomic AJCC TNM stage groups (table 1).

Conclusions and Relevance:

In patients treated with anthracycline-free TCb chemotherapy, sTILs were independent predictors of EFS and OS beyond clinicopathological features. Notably, 30% sTILs cut-point stratified outcomes beyond anatomical TNM staging. These, findings can aid in patient stratification for chemotherapy backbone de-escalation in future trials and have the potential to inform patient selection for adjuvant treatment escalation and de-escalation trials.

Tumor infiltrating lymphocyte stratification refines AJCC TNM staging based outcomes of early-stage triple negative breast cancer treated with neoadjuvant anthracycline-free, docetaxel and carboplatin chemotherapy.

TNM (% patients)	sTILs	N	5 years-EFS	Conf. Int.	5 years-OS	Conf. Int.
Stage-I (13%)	<30	22	95.45%	(87.14 - 100%)	100%	(100 - 100%)
	≥30	18	100%	(100 - 100%)	100%	(100 - 100%)
Stage-II (62%)	<30	164	82.24%	(76.33 - 88.61%)	88.69%	(83.73 - 93.95%)
	≥30	74	90.37%	(83.84 - 97.42%)	92.53%	(86.42 - 99.06%)
Stage-III (25%)	<30	67	55.24%	(44.26 - 68.95%)	56.36%	(45.02 - 70.57%)
	≥30	29	82.46%	(69.59 - 97.71%)	85.92%	(74.02 - 99.74%)

Table 1: EFS and overall survival based on combined TNM stage and sTILs

Disclosure(s):

Miguel Martín, MD, PhD: Advisory Committee/Board Member: Eli Lilly, Exelixis, Faron Pharmaceuticals Ltd, Forma Therapeutics, Gamamabs, Genentech, Glaxosmithkline, H3 Biomedicine (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Novartis Pharma GmbH (Ongoing); Consulting Fees (e.g., advisory boards): daichii-Sankyo (Ongoing), Gilead (Ongoing), Pfizer, Inc. (Ongoing), Seagen Inc (Ongoing)

Priyanka Sharma, MD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Boston Scientific (Ongoing), Cipla Limited (Ongoing), Gilead Sciences (Ongoing), GlaxoSmithKline (GSK) (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Salient Pharmaceuticals (Ongoing), Sanofi (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol Meyer Squibb (Ongoing), Gilead Sciences (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Amgen (Ongoing), Gilead Sciences (Ongoing), Janssen (Johnson and Johnson) (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), Sanofi (Ongoing)

PS16-08

Histologic Pattern and Outcomes in High-Grade Metaplastic Breast Cancer Compared to Triple-Negative Ductal Breast Cancer Counterparts: A Single Institution Retrospective Study

Presenting Author(s) and Co-Author(s):

A. Matusz-Fisher. Karmanos Cancer Institute, McLaren Northern, Charlevoix, Michigan, United States

A. Chen. Atrium Health, United States

E. Donahue. Atrium Health Levine Cancer Institute, United States

C. Schepel. Atrium Health, United States

M. Wallander. Atrium Health, United States

C. Livasy. Atrium Health Levine Cancer Institute, Charlotte, North Carolina, United States

R. White. Atrium Health Levine Cancer Institute, United States

A. Tan. Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, United States

L. Hadzikadic-Gusic. Atrium Health Levine Cancer Institute, United States

Authors

Ashley Matusz-Fisher, Annabel Chen, Erin Donahue, Courtney Schepel, Michelle Wallander, Chad Livasy, Richard White, Antoinette R. Tan, Lejla Hadzikadic Gusic

Title

Histologic Pattern and Outcomes in High-Grade Metaplastic Breast Cancer Compared to Triple-Negative Ductal Breast Cancer Counterparts: A Single Institution Retrospective Study

Background

Metaplastic breast cancer (MpBC) is a rare and aggressive subtype of breast cancer that presents with high tumor stage and a poor prognosis. MpBC tumors tend to have worse outcomes compared to other non-metaplastic triple-negative breast cancers (TNBC). Although MpBC has been described as chemotherapy resistant, chemotherapy remains a mainstay of treatment.

MpBC tumors can be further characterized by their specific histologic pattern. The existing literature on outcomes of MpBC by histologic pattern is limited, with varying results regarding response rate and overall survival (OS). Identifying a pattern of MpBC that has better response to treatment could help tailor treatment recommendations.

Methods

A retrospective chart review was performed and identified 106 patients with early-stage, high-grade MpBC who were diagnosed at Levine Cancer Institute between January 1, 2010 and September 1, 2021. A matched control cohort (n=106) of patients diagnosed with non-metaplastic TNBC was selected based on propensity score matching on diagnosis date, age at diagnosis, race, pathologic staging, and tumor grade. Patient demographics, tumor characteristics, therapeutic interventions, residual cancer burden (RCB), and outcomes were collected. The associations between the histologic patterns of MpBC and disease characteristics were evaluated using chi-squared tests for categorical variables and Wilcoxon tests for continuous variables. We also examined the differences in RCB scores between the MpBC cohort and the non-metaplastic TNBC cohort who received neoadjuvant chemotherapy.

Additionally, Kaplan-Meier and Cox proportional hazard analysis was performed to assess differences in recurrence free survival (RFS) and OS between the spindle cell/sarcomatous pattern versus all other patterns.

Results

For the entire group (n=212), median age at diagnosis was 58 years (range, 24-92); all patients were female; 66% White, 29% Black, and 5% unknown race. Most tumors were triple-negative (91%); 19%, 56% and 14% with Clinical Stage I, II, and III disease, respectively. A total of 63% of patients underwent radiation treatment and 76% received chemotherapy (43% neoadjuvant and 57% adjuvant). Recurrence after treatment occurred in 16% of all patients. In the MpBC cohort (n=106), the histologic patterns included spindle cell/sarcomatous (34%), squamous (17%), heterologous mesenchymal (31%), mixed (17%), and other (1%). Of those with MpBC who received neoadjuvant chemotherapy (n=32), RCB among the different histologic patterns was assessed. When comparing spindle cell/sarcomatous versus the other histologic patterns combined, there was no significant difference in RCB ($p = 0.81$), although more RCB III scores were recorded in the spindle cell/sarcomatous pattern compared to the other MpBC patterns (40% versus 30%). When assessing RFS and OS by histologic pattern in the entire MpBC cohort, spindle cell/sarcomatous tumors had inferior RFS ($p = 0.0194$) and OS ($p = 0.0039$) compared to the other MpBC patterns combined.

When comparing RCB values between MpBC and non-metaplastic TNBC, there were numerically more RCB-III classes in the MpBC cohort as compared to the non-metaplastic TNBC.

Conclusion

MpBC is an aggressive and difficult breast malignancy to treat. Based on our single institution review, no correlation between RCB and the histologic pattern of MpBC was found, however, RFS and OS were worse among the spindle cell/sarcomatous pattern. Furthermore, the MpBC cohort had numerically higher RCB-III scores than the TNBC control cohort, which is in line with historical data.

Disclosure(s):

Ashley Matusz-Fisher, MD: No financial relationships to disclose

Antoinette R. Tan, MD, MHSc, FACP, FASCO: Consulting Fees (e.g., advisory boards):

Arvinas (Ongoing), Astra Zeneca (Ongoing), G1 Therapeutics (Ongoing), Genentech-Roche (Ongoing), Jazz Pharmaceuticals (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Arvinas (Ongoing), Astra Zeneca (Ongoing), G1-Therapeutics (Ongoing), Genentech-Roche (Ongoing), GSK (Ongoing), Incyclix Bio (Ongoing), Merck & Co., Inc. (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing)

PS16-09

Poster Spotlight Session 16: Enhancing Immunotherapy for Triple Negative Breast Cancer: Novel therapies and Biomarkers

Presenting Author(s) and Co-Author(s):

S. Stecklein. University of Kansas Medical Center; Kansas Institute for Precision Medicine, Kansas City, Kansas, United States

J. White. Ohio State University, Columbus, Ohio, United States

R. Yoder. The University of Kansas Cancer Center, United States

J. Staley. The University of Kansas Cancer Center, United States

Z. Schmitt. University of Kansas Medical Center, United States

A. O'Dea. University of Kansas Medical Center, United States

L. Nye. University of Kansas Medical Center, United States

D. Satelli. University of Kansas Medical Center, United States

G. Crane. University of Kansas Medical Center, United States

R. Madan. University of Kansas Cancer Center, United States

M. O'Neil. University of Kansas Cancer Center, United States

A. Godwin. University of Kansas Medical Center; Kansas Institute for Precision Medicine; The University of Kansas Cancer Center, United States

H. Pathak. University of Kansas Cancer Center, United States

Q. Khan. University of Kansas Medical Center, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

P. Sharma. University of Kansas Medical Center Westwood, Westwood, Kansas City, Kansas, United States

Objectives:

Adjuvant radiotherapy is an important component of curative treatment for triple-negative breast cancer (TNBC). While there are several accepted variations in nominal dose and fractionation, these regimens are generally felt to be radiobiologically equivalent. Molecular radiosensitivity biomarkers have the potential to allow tailoring of physical radiotherapy dose for individual patients. The Radiosensitivity Index (RSI)/Genomic-Adjusted Radiation Dose (GARD) is a gene expression signature that predicts intrinsic radiosensitivity across multiple malignancies, with initial studies demonstrating clinical utility of RSI-GARD in TNBC. Since most TNBC patients will receive neoadjuvant systemic therapy, we sought to understand how neoadjuvant therapy-induced molecular adaptations could alter intrinsic radiosensitivity and RSI-GARD.

Methods:

Total RNA was isolated from pre-treatment and paired surgical specimens (for patients with residual disease (RD)) from TNBC patients treated with chemotherapy on the NeoSTOP (NCT02413320) or chemoimmunotherapy on the NeoPACT (NCT03639948) neoadjuvant trials and was subjected to RNA exome sequencing. The RSI was calculated according to the published algorithm using normalized expression of the 10 genes in this signature (AR, JUN1, STAT1, PRKCB, RELA, ABL1, SUMO1, PAK2, HDAC1, and IRF1). The resulting RSI score was substituted as the surviving fraction (SF) using the linear quadratic model of radiation-

induced cellular lethality assuming a fractional dose of 2.0 Gy and a constant $\beta=0.05 \text{ Gy}^{-2}$ to derive a patient-specific α , which is a coefficient modifying dose-dependent cellular lethality resulting from binary mis-repair of double-strand breaks (DSBs) arising from a single particle track.

Results:

Pre-treatment sequencing data were available for N=200 patients and the overall pathologic complete response (pCR) rate was 56.5%. Paired pre- and post-treatment sequencing data were available for N=58 patients (N=27 from NeoSTOP and N=31 from NeoPACT). One NeoPACT patient had a negative RSI, which led to an undefined α . Under the assumptions of the RSI-substituted LQ model, the median α/β ratio (reflecting sensitivity to fractionation) for all pre-treatment samples was 11.7 Gy. TNBC patients who achieved pCR had a significantly higher pre-treatment α (i.e., higher intrinsic radiosensitivity) compared to patients who had residual disease ($P=0.04$), and this trend was the same for patients treated with chemotherapy ($P=0.31$) or chemoimmunotherapy ($P=0.05$). Importantly, α did not change significantly between paired pre- and post-treatment samples (median change post- vs. pre-treatment= 0.03 Gy^{-1} (range -0.25 to $+0.24 \text{ Gy}^{-1}$; $P=0.26$) in patients with RD, with no difference in subgroups treated with chemotherapy ($P=0.99$) or chemoimmunotherapy ($P=0.10$).

Conclusions:

We found that predicted intrinsic radiosensitivity using the RSI-GARD is associated with pathologic response to neoadjuvant systemic therapy, suggesting that this signature also predicts intrinsic chemosensitivity in TNBC patients. The modeled α/β ratio for all pre-treatment samples was 11.7 Gy, which is substantially higher than empirically determined α/β ratios in studies that were enriched for HR+/HER2- breast cancers. Globally, the RSI-GARD score was not impacted by neoadjuvant systemic therapy, with no significant change in the score in paired pre- and post-treatment samples. These results can inform future testing and implementation of RSI-GARD into prospective trials.

Disclosure(s):

Shane R. Stecklein, MD, PhD: No financial relationships to disclose

Joyce O'Shaughnessy, MD: Consulting Fees (e.g., advisory boards): Agendia (Ongoing), Aptitude Health (Ongoing), AstraZeneca (Ongoing), Carrick Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), ELY LILLY (Ongoing), F. Hoffman La Roche Ltd (Ongoing), G1-Therapeutics (Ongoing), Genentech (Ongoing), Loxo@Lilly (Ongoing), Merck Sharp & Dohme, Lda. (Ongoing), Novartis (Ongoing), Ontada (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Samsung Bioepis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing), Synthron (Ongoing)

Priyanka Sharma, MD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Boston Scientific (Ongoing), Cipla Limited (Ongoing), Gilead Sciences (Ongoing), GlaxoSmithKline (GSK) (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Salient Pharmaceuticals (Ongoing), Sanofi (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol Meyer Squibb (Ongoing), Gilead Sciences (Ongoing), Merck & Co., Inc. (Ongoing), Novartis (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Amgen (Ongoing), Gilead Sciences (Ongoing), Janssen (Johnson and Johnson) (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), Sanofi (Ongoing)

PS16-10

SPATIAL IMMUNE CELL DISTRIBUTION CAN REFINE PROGNOSIS IN EARLY-STAGE ER+/HER2-/LN- BREAST CANCER

Presenting Author(s) and Co-Author(s):

Z. Kinsella. Royal College of Surgeons in Ireland, London, England, United Kingdom

H. Nyarko. Royal College of Surgeons, United States

A. Blümel. Royal College of Surgeons in Ireland/School of Pharmacy and Biomolecular Sciences, Ireland

M. Lucas. St Vincent's University Hospital, United States

D. Kalinska-Lysiak. Royal College of Surgeons in Ireland, United States

C. Gonzalez. University College Dublin, United States

A. Rahman. University College Dublin, United States

J. Fay. Royal College of Surgeons in Ireland, United States

T. O'Grady. Royal College of Surgeons in Ireland, United States

V. Murphy. Cancer Trials Ireland, United States

J. Crown. Saint Vincent's University Hospital, United States

C. Kelly. Mater Private Network, United States

W. Gallagher. UCD/Conway Institute, Ireland

D. O'Connor. Royal College of Surgeons in Ireland/ School of Pharmacy and Biomolecular Sciences, Ireland

Lymphocytic infiltrate is a known prognostic biomarker in estrogen receptor(ER)-negative breast cancers (BCs). Comparatively ER+ disease is putatively cold, however, there exists an infiltrate-rich subset of ER+ tumours with significant spatial heterogeneity and unknown clinical impact. Using serial sections taken from early-stage, ER+/HER2- breast tumours of Irish patients enrolled in the TAILORx trial (n=450), we aimed to investigate the prognostic potential of markers encompassing tumour architecture. Immunohistochemistry for Ki67 and CD45 (leukocyte common-antigen), and staining for haematoxylin and eosin was applied to all sections ^[1]. Classifiers for stromal fraction (SF), stromal-infiltrate (sTIL), Ki67-LI, and their spatial relationships within the tumour were generated using QuPath ^[2] and R Studio. Trained marker classifiers were validated against an expert pathologist (R^2 of M-Score to: CD45%: 0.968, Ki67-LI: 0.814, sTIL: 0.864) to define observed lymphocytes as tumour or stromal-infiltrating, retain only tumour Ki67⁺ density, and to investigate SF. Cohort mean SF was 67.69% (range 16.35 – 98.29%), with marginally significant differences in recurrence prediction for cohort high v low SF by mean (c-index = 0.58, $p < 0.032$), and luminal A disease ($p=0.037$) only. sTILs did not differ significantly between high/low mean SF (Mann-Whitney $p=0.6201$), though sTIL was prognostic in the OncotypeDx intermediate Recurrence Score (RS) category overall ($p=0.0076$). This trend appeared strongest in intermediate RS patients receiving chemo-endocrine therapy (HT+CT) ($p < 0.0001$) vs endocrine therapy (HT) alone ($p=0.86$). Investigating the effects of prescribed therapy on sTIL-derived recurrence risk also revealed significant trends in those patients receiving HT+CT only ($p < 0.00001$) vs HT alone ($p=0.26$). Spatial analysis of sTILs suggest that tumours become more immune excluded as Oncotype Dx RS increases - particularly from intermediate to high RS (Wilcoxon Intermediate v High: $p=0.0077$), with significant differences in survival for high/low tumour-immune hotspots

observed in Intermediate RS, HT+CT treated patients ($p=0.0052$). Further spatial analysis suggests that high normalised frequency of infiltrate ^[method adapted from 3] (within 7 μ m of tumour cells) have negative prognostic impact for premenopausal patients ($p=0.017$), and inter-sectional analysis identifies niche tumour environments where high Ki67-LI colocalize with immune infiltrates ^[methods adapted from 4, 5], most notable in Intermediate RS tumours. Overall these data suggest immune-spatial subsets can be used to refine risk stratification of ER+ breast cancer.

References:

- [1] Lucas, M., Kinsella, Z., Gonzalez, C.A. et al. CD45-positive tumour infiltrating lymphocytes in early-stage hormone-positive, HER2-negative (ER+/HER2-) breast cancer: Correlation with proliferation and prognostic signature scores. Meeting Abstract ASCO Annual Meeting I. 2022.
- [2] Bankhead, P., Loughrey, M.B., Fernandez, J.A. et al. QuPath: Open source software for digital pathology image analysis. *Scientific Reports*. 2017;7:16878.
- [3] Yuan. Y. Modelling the spatial heterogeneity and molecular correlates of lymphocytic infiltration in triple-negative breast cancer. *Journal of the Royal Society Interface*. 2015;12(103):201411532
- [4] Maley, C.C., Koelble, K., Natrajan, R. et al. An ecological measure of immune-cancer colocalization as a prognostic factor for breast cancer. *Breast Cancer Research*. 2022;17(1):131.
- [5] Ord, J.K., Getis, A. Local spatial autocorrelation statistics: Distributional issues and an application. *Geographical Analysis*. 1995;27(4):286-306.

Disclosure(s):

Zak Kinsella, BSc, MSc: No financial relationships to disclose

PS17-01

Key drivers of therapeutic response and resistance to giredestrant from GO39932: a Phase Ia/b study in patients with estrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer

Presenting Author(s) and Co-Author(s):

J. Liang. Genentech, Inc., South San Francisco, California, United States

C. Ong. Genentech, Inc., South San Francisco, California, United States

J. Giltane. Genentech, Inc., South San Francisco, California, United States

J. Aimi. Genentech, Inc., South San Francisco, California, United States

C. Chang. Genentech, Inc., South San Francisco, California, United States

M. Gates. Genentech, Inc., South San Francisco, California, United States

J. Eng-Wong. Genentech, Inc., South San Francisco, California, United States

P. Perez-Moreno. Genentech, Inc., South San Francisco, California, United States

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

E. Lim. Garvan Institute of Medical Research, St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

H. Moore. Genentech, Inc., San Francisco, California, United States

BACKGROUND Several investigational oral selective estrogen receptor antagonists and degraders (SERDs) are under investigation. These were partly developed to benefit patients (pts) with breast cancer (BC) who acquired resistance to standard-of-care (SoC) endocrine therapies (ET); e.g., through gain of ESR1 mutations that enable estrogen-independent ER activity. One such SERD, giredestrant (G), demonstrates activity in pts with ESR1-wild type (WT) or -mutant (m) tumors, and in pts who progressed on other ETs. Results from Phase I/III trials in ER-positive, HER2-negative, locally advanced/metastatic BC (ER+, HER2- LA/mBC) showed that next-generation SERDs had increased activity in ESR1m tumors vs SoC ETs. However, enthusiasm was hindered by heterogeneous responses, driven in part by study design differences. Across acELERA BC (NCT04576455), EMERALD (NCT03778931), SERENA-2 (NCT04214288), and AMEERA-3 (NCT04059484), 30–50% of pts progressed rapidly (< 2 months) when treated with SoC ETs or next-generation SERDs, while others benefited for ≥ 1 year. We present an exploratory biomarker analysis aimed at understanding the mechanistic basis for heterogeneous responses to SERDs in ER+, HER2- LA/mBC, by assessing a Phase Ia/b G cohort (NCT03332797) with paired baseline and on-treatment (tx) biopsies. **METHODS** Pts had ≤ 2 prior therapies for LA/mBC; disease recurrence/progression while on adjuvant ET for ≥ 24 months and/or ET for ER+, HER2- LA/mBC; and tumor response/stable disease for ≥ 6 months. Single-agent dose-escalation stage: 10, 30, 90, or 250 mg G once daily (QD) on Days (D) 1–28 of 28-D cycles (C). Dose-expansion stage: 30, 100, or 250 mg G QD. 100 mg G + 125 mg palbociclib on a 21-D on/7-D off schedule was also explored. Pre-/perimenopausal pts received LHRH agonists. Paired pre- and on-tx (C2D8) tumor biopsies (n = 29) were immunolabeled for ER, progesterone receptor, and Ki67, and assessed via bulk RNA-sequencing. Pre-tx liquid biopsies (n = 85) were evaluated by FoundationOne Liquid CDx assay. To validate our clinical observations, we generated a SERD-resistant MCF7 cell line and tested its sensitivity to other therapies. **RESULTS** We compared fast-progressing pts (FP; progression-free survival [PFS] < 2 months) with those experiencing

long-term benefit (LTB; PFS > 12 months). LTB was significantly associated with high tumor baseline ER pathway activity. Although the benefit of G was of larger magnitude among pts with ESR1m tumors compared with SoC ET in aCeLERA BC, here pts with predominantly ESR1WT tumors received LTB on G tx. At the molecular level, G acted on LTB tumors by suppressing cell cycle- and ER-associated genes. In contrast, G had no effect on the transcriptome of FP tumors, which had lower baseline ER activity than LTB tumors. FP tumors were instead enriched for multiple cancer-associated pathways, e.g., RAS/MAPK and PI3K, which may drive resistance to G and thus enable fast progression. By liquid biopsy, most FP pts (> 90%) did not harbor a mutation in the associated pathway (e.g., NF1, KRAS), and thus could not be identified by genomic profiling alone. FP tumors were instead enriched for multiple cancer-associated pathways by gene expression. We explored these mechanisms further in the SERD-resistant cell line, which was similarly enriched for EGFR and MAPK activation vs standard MCF7 cells. Although cells became resistant to ER-targeted drugs, they acquired sensitivity to EGFR/MAPK inhibitors e.g., gefitinib, cobimetinib. CONCLUSIONS We identified molecular features associated with LTB to G and revealed a set of oncogenic pathways associated with FP pts on tx; demonstrating that these pathways represent acquired dependencies and potential therapeutic targets for SERD-resistant tumors and FP pts.

PS17-02

Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with ESR1 mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial

Presenting Author(s) and Co-Author(s):

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

F. Bidard. Institut Curie, Paris, France

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

P. Aftimos. Institut Jules Bordet, Brussels, Belgium

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

J. Lu. Northwestern University Lurie Comprehensive Cancer Center, Chicago, Illinois, United States

G. Tonini. Menarini Group, United States

K. Theall. Stemline Therapeutics, United States

A. Paoli. Menarini Ricerche, Pomezia, Italy

V. Kaklamani. UT Health San Antonio, San Antonio, Texas, United States

Background: The EMERALD trial reported significantly prolonged progression-free survival (PFS) and a manageable safety profile with elacestrant vs standard of care (SOC) endocrine therapy in patients (pts) with ER+/HER2- ESR1 mutated (ESR1-mut) mBC following progression on prior endocrine therapy (ET). EMERALD is the only pivotal oral SERD clinical trial where prior CDK4/6i usage was mandated. Duration of prior CDK4/6i was shown to be a predictor of efficacy in patients with ESR1 mutations (ESR1-mut) receiving elacestrant, with median PFS (mPFS) for patients with ESR1-mut receiving at least 12 months of CDK4/6i achieved 8.61 months (elacestrant) vs 1.91 months (SOC) (SABCS 2022). This analysis evaluates the clinical benefit of single-agent elacestrant in key clinically relevant subgroups, including biomarkers, usually associated with poorer prognosis. **Methods:** Patients with ER+/HER2- advanced or mBC who previously had 1-2 lines of endocrine therapy, and prior CDK4/6i, were randomized 1:1 to receive elacestrant or SOC (aromatase inhibitor or fulvestrant). A subgroup analysis was performed on patients with ESR1-mut, by prior duration of CDK4/6i plus ET with at least 12 months in the advanced or metastatic setting, with concomitant presence of liver and/or lung metastases, PIK3CA mutations, TP53 mutation, and HER2 low expression. **Results:** Overall, 478 patients were randomized to elacestrant (n=239) or SOC (n=239), 228 pts (47.7%) had ESR1-mut, and 159 pts (71.6%) received at least 12 months of prior CDK4/6i. Out of these 159 pts, 113 pts (71%) had liver and/or lung metastases, 62 pts (39%) had a PIK3CA-mut, 61 pts (38%) had TP53m, and 77 pts (48%) had HER2 low expression. A clinically meaningful improvement in PFS favoring elacestrant compared to SOC was consistent across all relevant subgroups in pts with ESR1-mut. **Conclusions:** Elacestrant showed significantly greater PFS when prior treatment duration with CDK4/6i was at least 12 months, suggesting prior exposure to CDK4/6i is a surrogate marker for endocrine sensitivity. In

this population, elacestrant demonstrated superior efficacy, compared to SOC, even in patients with concomitant PIK3CA or TP53 mutations, expression of HER2 low, or presence of liver and/or lung metastases. These results suggest an active ER-driven pathway for this group despite the presence of other resistance mechanisms, where single-agent oral elacestrant could be an attractive option compared to combination therapies or intravenous HER2 low-targeted ADCs. NCT number: NCT03778931

ER+/HER2-, ESR1-mut patients with ≥ 12 months of prior CDK4/6 inhibitors				
	Patients	Median PFS, months (95% CI)		HR (95% CI)
		Elacestrant	SOC	
All ESR1-mut patients	100% (159)	8.61 (4.14 - 10.84)	1.91 (1.87 - 3.68)	0.410 (0.262 - 0.634)
ESR1-mut and Liver and/or Lung Metastases	71% (113)	7.26 (2.20 - 10.84)	1.87 (1.84 - 1.94)	0.354 (0.209 - 0.589)
ESR1-mut and PIK3CA Mutations ^a	39% (62)	5.45 (2.14 - 10.84)	1.94 (1.84 - 3.94)	0.423 (0.176 - 0.941)
ESR1-mut and TP53 Mutations	38% (61)	8.61 (3.65 - 24.25)	1.87 (1.84 - 3.52)	0.300 (0.132 - 0.643)
ESR1-mut and HER2 Low Expression ^b	48% (77)	9.03 (5.49 - 16.89)	1.87 (1.84 - 3.75)	0.301 (0.142 - 0.604)

a. Includes E545K, H1047R, E542K amongst others b. HER2 IHC 1+, and 2+ with no ISH amplification

PS17-03

Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR positive/HER2-negative advanced breast cancer: exploratory analysis of PFS by AKT pathway gene from the Phase 3 CAPItello-291 trial

Presenting Author(s) and Co-Author(s):

S. Howell. The University of Manchester, Manchester, England, United Kingdom

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

X. Hu. Shanghai Cancer Center, Fudan University, Shanghai, China

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

P. Krivorotko. N.N. Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russia

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain

M. Okera. Adelaide Cancer Centre, Adelaide, Australia

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

M. Toi. Graduate School of Medicine, Kyoto University, Kyoto, Japan

E. Tokunaga. National hospital organization Kyushu Cancer Center, Fukuoka, Japan

L. Zhukova. Loginov Moscow Clinical Scientific Center, Moscow, Russia

A. Lloyd. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

E. de Bruin. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. Egile. Oncology R&D, AstraZeneca, Cambridge, United Kingdom

C. D'Cruz. Oncology R&D, AstraZeneca, Waltham, Massachusetts, United States

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background: In the Phase 3 randomized, double-blind CAPItello-291 trial, the addition of capivasertib (a potent, selective pan-AKT inhibitor) to fulvestrant in patients with aromatase inhibitor-resistant, hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative (HER2- defined as immunohistochemistry [IHC] 0, or 1-positive or IHC2-positive/in situ hybridization-negative) advanced breast cancer (ABC) significantly improved progression-free survival (PFS) versus placebo + fulvestrant (hazard ratio [HR] 0.60, 95%

confidence interval [CI] 0.51–0.71; $p < 0.001$). PFS benefit was observed in patients with detectable AKT pathway alterations (HR 0.50, 95% CI 0.38–0.65; $p < 0.001$) and without (0.70; 95% CI; 0.56–0.88). Here, we report PFS by gene within the AKT pathway-altered population. Methods: Patients were randomized 1:1 to receive fulvestrant (500 mg intramuscularly on days 1 and 15 of cycle 1, and day 1 of each subsequent 28-day cycle) with either placebo or capivasertib (400 mg twice daily; 4 days on, 3 days off). AKT pathway-alteration status (at least one qualifying alteration in the genes PIK3CA, AKT1, or PTEN) was determined post-randomization, using next-generation sequencing in tumor tissue. HRs were calculated using Cox proportional hazards models. Data cut-off Aug 15, 2022. Results: Of the 708 patients randomized to treatment, 289 (41%) had AKT pathway-altered tumors (capivasertib-fulvestrant $n=155$; placebo-fulvestrant $n=134$). In the AKT pathway-altered population, 43% had liver metastases and 40% primary endocrine therapy resistance. Prior therapy for advanced disease included: 89% of patients with ≥ 1 line of prior treatment, 71% with a prior cyclin-dependent kinase 4 and 6 inhibitor, and 18% with prior chemotherapy. Baseline characteristics were broadly balanced between treatment groups. Most patients with an AKT pathway-altered tumor had only one detectable alteration (272/289, 94%). Thirteen patients (capivasertib-fulvestrant $n=4$; placebo-fulvestrant $n=9$) had co-occurring PIK3CA and PTEN alterations, and four patients (capivasertib-fulvestrant $n=2$; placebo-fulvestrant $n=2$) had co-occurring PIK3CA and AKT1 alterations. Consistent PFS benefit of capivasertib-fulvestrant over placebo-fulvestrant was observed across all alterations (Table). The safety profile of capivasertib-fulvestrant in the AKT pathway-altered population was consistent with the overall population. Conclusions: Compared with fulvestrant alone, the addition of capivasertib to fulvestrant provided a consistent PFS benefit across alterations in all three key genes within the AKT pathway in patients with HR-positive/HER2-negative ABC. <https://clinicaltrials.gov/>: NCT04305496 Funding: CAPItello-291 is sponsored by AstraZeneca. Editorial acknowledgment: AstraZeneca-funded medical writing support was provided by Suzanne Patel, Ph.D., from BOLDSCIENCE Inc. Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

Alteration	N (%)	HR* for PFS (95% CI)
Any AKT pathway alteration	289 (100)	0.50 (0.38–0.65)
PIK3CA only	202 (69.9)	0.51 (0.37–0.70)
PTEN only	37 (12.8)	0.43 (0.21–0.88)
AKT1 only	33 (11.4)	0.51 (0.22–1.12)
PIK3CA with/without AKT1/PTEN alterations	219 (75.8)	0.51 (0.37–0.69)
*HR<1 favors capivasertib-fulvestrant over placebo-fulvestrant.		

PS17-04

Clinical and Genomic Features of ER-Positive/HER2-negative Metastatic Breast Cancer in AURORA Molecular Screening Initiative (BIG 14-01): Mechanisms of Endocrine Therapy Resistance and Implications for Adjuvant Approaches

Presenting Author(s) and Co-Author(s):

A. Guerrero. Fundación Instituto Valenciano de Oncología (FIVO). GEICAM Spanish Breast Cancer Group., Valencia, Comunidad Valenciana, Spain

M. Benelli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

A. Irrthum. Breast International Group, Belgium

D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom

L. Ferrando. IRCCS - Ospedale Policlinico San Martino, Italy

D. Romagnoli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

M. Paoli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

A. Llinas. Vall d'Hebron Institute of Oncology (VHIO), Spain

M. Dadiani. Sheba Medical Center, Israel

D. Fimereli. Breast Cancer Translational Research Laboratory J.-C. Heuson, Institut Jules Bordet, Belgium

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

C. Caballero. Breast International Group, Brussels, Belgium

T. Crestani. Breast International Group, Belgium

E. Agostinetto. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Bruxelles, Brussels Hoofdstedelijk Gewest, Belgium

D. Martins-Branco. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Academic Trials Promoting Team (ATPT), Brussels, Belgium

F. Hilbers. NCI, United States

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

M. Balic. Division of Oncology, Department of Internal Medicine, Medical University Graz, Austria

F. Cardoso. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States

C. Sotiriou. Institut Jules Bordet, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

B. Linderholm. Sahlgrenska Academy and University Hospital, Gothenburg, Sweden

E. de Azambuja. Academic Trials Promoting Team and Medical Oncology Department, Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

S. Knox. Europa Donna- The European Breast Cancer Coalition, United States

C. Rotaru. Breast International Group, Belgium

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

N. Davidson. University of Washington, United States

G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy

D. Taylor. Universite catholique de Louvain, CHU UCL Namur—Site Sainte-Elisabeth, Namur, Belgium

J. Canon. Grand Hopital de Charleroi - GHdC site Notre Dame, Belgium

L. Calvo. Oncology Department-Universitary Hospital A Coruña, A Coruña, Galicia, Spain

J. Albanell. Hospital del Mar; IMIM, Barcelona; Pompeu Fabra University, Barcelona; CIBERONC, Spain

M. Colleoni. Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Lombardia, Italy

C. Duhem. Clinique du sein, Centre Hospitalier du Luxembourg, Luxembourg

N. Harbeck. University of Munich, Munich, Bayern, Germany

C. Herremans. , United States

S. Loibl. GBG Forschungs GmbH, Germany

S. Marreaud. EORTC, Belgium

E. Scheepers. Frontier Science Scotland, Kincaig, Kingussie, United Kingdom

A. Raimbault. Breast International Group, Belgium

T. Goulioti. Breast International Group (BIG)-aisbl, Brussels, Belgium

A. Vingiani. Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori, United States

C. Biagioni. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

S. Vosberg. Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Austria

G. Zoppoli. Department of Internal Medicine and Medical Specialties DiMI, University of Genoa, Italy

J. Seoane. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

D. Venet. Breast Cancer Translational Research Laboratory J-C Heuson, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

P. Aftimos. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium

M. Piccart. Institut Jules Bordet, Anderlecht, Brussels Hoofdstedelijk Gewest, Belgium

Background: Up to 30% of patients (pts) with ER-positive early breast cancers develop metastatic relapse. The molecular differences between endocrine therapy (ET)-sensitive and ET-resistant relapses, as well as the impact of specific adjuvant ET-based therapies, remain unclear. Methods: The AURORA program (NCT02102165) analyzed multi-omics data of paired primary (prim) and metastatic (meta) tumor tissue, along with plasma samples, from 1,156 patients with metastatic breast cancer (MBC). Targeted genome sequencing (TGS), RNA sequencing, and circulating tumor DNA analysis were performed. ET-resistance at MBC diagnosis was defined following the 5th ESO-ESMO ABC Guidelines. Results: We studied 628 pts with metastatic ER+/HER2- disease. Patient's median age was 56 years, 133 (21%) were premenopausal, 314 (50%) had ET-resistance at recurrence (9% primary, 41% secondary), 132 (21%) had ET-sensitive recurrence, and the rest were ET-naive recurrences or de novo MBC. Adjuvant treatment was aromatase inhibitor (AI) +/- ovarian function suppression (OFS) in 288

(46%) pts, while 159 (25%) had tamoxifen only (+/- OFS). Gene expression correlation significantly differed ($p < 0.005$) based on ET-resistance in 92 paired samples. ET-sensitive ($n=11$) and de-novo tumors ($n=41$) showed higher correlation than primary ($n=7$) and secondary ET-resistance ($n=32$), regardless of adjuvant ET type. Prim and meta showed concordance in 91% of IHC subtypes and 62% of intrinsic subtypes. Intrinsic subtype showed 9% of prim luminal tumors switching to meta non-luminal, with 66% of Luminal A switching to Luminal B. Neither IHC nor intrinsic subtype switching was associated with the type of adjuvant ET or ET resistance. Pts with meta non-luminal intrinsic subtype (18%) had worse PFS on CDK4/6i (HR 4.0, 95% CI 1.9-8.7) and OS (HR 3.6, 95% CI 2.0-5.7) than luminal subtypes. TGS was performed in 534 meta (365 before 1L, 305 pairs). In meta before 1L, the dN/dS algorithm revealed selection in 17 genes, including TP53, PIK3CA, and ESR1. Mutations (mut) in ESR1, ERBB2, ERBB3, and RB1 among others, were specifically identified in meta. The incidence of ESR1mut was 3% in prim, 12.6% before 1L, 23.4% after 1L, and 4.7% in meta from ET-naïve tumors (Table). Before 1L, ESR1mut was higher after adjuvant AI vs tamoxifen (21% vs. 4%, $p < 0.001$). ESR1mut incidence varied with ET-resistance (16% primary, 19% secondary, 9% sensitive, 4% ET-naïve/de novo, $p < 0.01$). Paired samples showed that ESR1mut were mainly acquired events and associated with higher ER mRNA signaling (hallmark estrogen response) compared to ESR1wt ($p < 0.05$). The agreement between ESR1mut detected in ctDNA and tissue was high before 1L (90%), and slightly lower after 1L (84%). In a multivariate model with relevant clinical factors, ESR1mut were associated with worse OS (HR 1.76, 95% CI 1.2-2.5, $p=0.003$), independently of TP53 and PIK3CA mutational status. Conclusion: AURORA study sheds light on metastatic tumor alterations acquired under anti-cancer therapy, in ER+/HER2-MBC. We observed a high prevalence of acquired ESR1mut prior to the initiation of first-line therapy, particularly in tumors exposed to adjuvant AI or with primary or secondary ET_resistance. The association of ESR1mut with poorer OS underscores the importance of implementing effective adjuvant ET strategies to prevent the emergence of these mutations. Frequency of driver gene mutations in primary and metastatic tumors before 1st-line treatment according to adjuvant ET and type of ET resistance

Gene	Metastatic Tumor, before 1 st line						
	Primary Tumor (%)	Adjuvant AI (%)	Adjuvant Tam (%)	Primary ET-Resistance (%)	Secondary ET-Resistance (%)	ET-sensitive (%)	De novo (%)
PIK3CA	40	34	40	37	32	41	42
TP53	26	24	25	39	25	19	29
ESR1 (all)	3	21	5	16	19	9	4
ESR1 (acquired)	NA	21	2	17	15	7	NA

PS17-06

A phase I trial of the PI3K inhibitor (PI3Ki) copanlisib and fulvestrant in combination with continuous or intermittent abemaciclib in patients with estrogen receptor-positive (ER+), HER2-negative (HER2-) metastatic breast cancer

Presenting Author(s) and Co-Author(s):

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

J. Luo. Washington University in St Louis School of Medicine, United States

J. Moss. University of Kentucky, United States

M. Kwa. New York University, United States

R. Parajuli. University of California, Irvine Medical Center, Orange, California, United States

K. Khoury. O'Neal Comprehensive Cancer Center at the University of Alabama, Birmingham, Alabama, United States

E. Douglas. Atrium Health Wake Forest Baptist Health, United States

A. Frith. Washington University in St Louis School of Medicine, United States

C. Rigden. Washington University in St. Louis School of Medicine, United States

F. Ademuyiwa. Washington University in St Louis School of Medicine, United States

S. Thomas. Washington University in St. Louis School of Medicine, Fenton, Missouri, United States

B. Haas. Washington University in St. Louis School of Medicine, United States

G. Wulf. Harvard Medical School, United States

C. Dees. University of North Carolina, Chapel Hill, North Carolina, United States

R. Said. National Cancer Institute Cancer Therapy Evaluation Program, United States

Background: Activation of the phosphoinositide 3-kinase (PI3K) pathway is a prominent resistance mechanism to endocrine therapy and CDK4/6 inhibition (CDK4/6i) in ER+, HER2- breast cancer. There is reciprocal crosstalk between PI3K and cell cycle regulatory pathways. Triplet therapy that targets ER, CDK4/6, and PI3K prevents or delays disease progression in preclinical models of ER+, HER2- breast cancer. However, the toxicities of triplet therapy hinder its clinical development. Copanlisib (COP) is an intravenous (IV) PI3Ki with potent activity against α and δ isoforms. Intermittent high-dose PI3Ki is expected to be less toxic and more effective than continuous daily dosing. We set out to determine the recommended phase 2 dose (RP2D) for the COP/Fulvestrant (FUL)/Abemaciclib (ABE) combination. Methods: Eligible patients (pts) included men or women with ER+, HER2- metastatic breast cancer (MBC), with no more than 1 prior chemotherapy in the metastatic setting, and no limits on prior endocrine or targeted therapy. Prior FUL, CDK4/6i and PI3K/mTORi were allowed. Pts with HbA1c >8.5% were excluded. Pts received FUL 500 mg IM standard dosing and COP/ABE at assigned doses. Premenopausal women also received a GnRH agonist. Dose-limiting toxicity (DLT) was assessed during the first 28-day cycle. Adverse events (AEs) were graded according to NCI-CTCAE v5.0. Dose escalation/de-escalation was based on continual reassessment (CRM) and the RP2D was defined as the dose with the highest probability of the DLT rate within the acceptable 25~35%. Results: Between June 2020 and June 2023, 24 pts with ER+, HER2- MBC were enrolled. Table 1 shows the dose levels (DLs) and DLTs. The first 10 pts were enrolled to Part A on two consecutive DLs of COP (DL1: 45 mg IV D1 and D15, n=7; DL2: 45 mg IV D1, D8, and D15, n=3), with ABE fixed at 100 mg PO BID continuously. DL2a exceeded the maximum tolerated dose (MTD). DL1a was tolerable based on Cycle 1 AEs. However,

during subsequent cycles, only 1 of the 7 pts in DL1a maintained the intended dose of ABE due to neutropenia, others reduced ABE to 50mg bid (n=5) or discontinued (n=1). This triggered a protocol amendment, adding Part B with ABE administered 5 days on and 2 days off (5-on/2-off) intermittent schedule. 14 pts were enrolled to Part B in 2 consecutive DLs of COP (DL1b: n=7; DL2b: n=7), the same as in Part A. ABE was fixed at 100 mg PO Bid 5-on/2-off. DL2b exceeded the MTD. DL1b was tolerable based on Cycle 1 AEs. In addition, in subsequent cycles, only 1 of 7 pts on DL1b required dose reduction of ABE to 50mg bid. RP2D is therefore defined as DL1b. Grade (G) 4 AEs were rare. The most common all cycle G3 AEs included transient hypertension (45%), rash (30%), anemia (25%), neutropenia (25%), and AST elevation (20%). As of 6/14/2023, 22 pts, with a median of 1 prior metastatic regimen (range 0-5), prior CDK4/6i in 18 (82%), liver mets in 8 (36%), and PIK3CA mutation in 8 (50%) of 16 pts with known mutation status, were evaluable for response. There were 5 partial responses and 3 stable diseases lasting for ≥24 weeks. Clinical benefit rate was 36.4% (8/22, 95%CI: 17.19% ~ 59.34%). Responses were observed in pts regardless of prior CDK4/6i, FUL, or PIK3CA mutation. Conclusion: COP/FUL/intermittent ABE can be safely administered with fair overall tolerability. Preliminary anti-tumor activity was observed, which will be further examined in the randomized phase II trial (NCT 03939897).

Table 1

Table 1	Dose Level	Abeaciclib (PO)	Copanlisib (IV)	No. Enrolled (DLT evaluable)	No. DLT	DLT
Part A	Dose Level 1a (starting dose)	100 mg Bid continuously	45 mg IV D1 and D15	7 (6)	1	Grade 3 ANC, less than 75% abemaciclib dose received
	Dose Level 2a	100 mg Bid continuously	45 mg IV D1, D8 and D15	3 (3)	2	1 Grade 3 rash 1 Grade 3 hyperbilirubinemia
Part B	Dose Level 1b (starting dose)	100 mg Bid 5-on/2-off weekly	45 mg IV D1 and D15	7 (6)	1	Grade 3 rash
	Dose Level 2b	100 mg Bid 5-on/2-off weekly	45 mg IV D1, D8 and D15	7 (5)	2	1 Grade 3, new onset atrial fibrillation 1 Grade 3 rash

Dose-limiting Toxicities by Dose Level

PS17-07

Interim analysis of giredestrant + inavolisib in MORPHEUS Breast Cancer: a Phase Ib/II study of giredestrant treatment combinations in estrogen receptor-positive, HER2-negative, locally advanced/metastatic breast cancer

Presenting Author(s) and Co-Author(s):

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

M. Gion. Ramón y Cajal University Hospital, Madrid, Madrid, Spain

C. Hernando. Hospital Clínico Universitario de Valencia, Valencia, Spain

K. Jung. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Not Applicable, Republic of Korea

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

G. Vidal. The West Clinic, Germantown, United States, United States

S. Vatandoust. Flinders Centre for Innovation in Cancer, Flinders University, Bedford Park, South Australia, Australia

J. Zhu. Genentech, Inc., South San Francisco, California, United States

R. Schwab. Genentech, Inc., South San Francisco, California, United States

H. Ngo. Genentech, Inc., South San Francisco, California, United States

E. Ferreira. Roche Products Limited, Welwyn Garden City, United Kingdom

A. Collier. Genentech, Inc., South San Francisco, California, United States

V. Breton. F. Hoffmann-La Roche Ltd, Canada

BACKGROUND Patients with estrogen receptor-positive metastatic breast cancer (ER+ mBC) almost always progress on first-line endocrine therapy (ET), which is usually combined with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Finding effective ET combinations after progression following CDK4/6is remains a challenge. Giredestrant (GIR) is a highly potent, nonsteroidal, oral, selective ER antagonist and degrader. Inavolisib (INAVO) is a highly potent PI3K α -selective inhibitor that promotes degradation of mutated p110 α . After first-line treatment (tx) with a CDK4/6i, PIK3CA mutations (mut), which are common, persist and remain a sensitive oncogenic target in these patients. We present a 16-week interim analysis of GIR vs GIR + INAVO in MORPHEUS BC (NCT04802759). **METHODS** Patients whose tumors harbored a PIK3CAmut and who had disease progression on up to two lines of endocrine-based therapy (including at least one prior line of CDK4/6i) for locally advanced (LA)/mBC were randomized 1:6 to receive GIR (30 mg orally daily [PO QD]) or GIR + INAVO (9 mg PO QD) tx until disease progression or unacceptable toxicity. Given the small numbers, the GIR arm is presented for overall safety. Primary endpoints are safety and objective response rate (ORR). Other endpoints include progression-free survival (PFS), disease control rate (DCR), and pharmacokinetics. Genetic alterations were identified centrally in baseline circulating tumor DNA using the FoundationOne Liquid CDx assay. In cases where PIK3CAmut could not be determined centrally, local blood or tissue results are used. **RESULTS** As of April 18, 2023, seven and 15 patients were enrolled in the GIR and GIR + INAVO arms, respectively; 71% (n =

5) and 67% (n = 10) received one prior line of therapy in the LA/mBC setting; 14% (n = 1) and 33% (n = 5) received two prior lines; and one GIR-arm patient received four prior lines. Prior fulvestrant (FUL) was received by 53% of patients in the GIR + INAVO arm (n = 8). For GIR + INAVO, the ORR was 47% (n = 7); the complete response rate was 7% (n = 1); and the partial response (PR) rate was 40% (n = 6). The DCR at 12 weeks was 80% (12/15 patients). The median PFS was 10.3 months (95% confidence interval = 6.5, not evaluable) with 47% of patients (n = 7) having events. In the GIR + INAVO arm, 5/6 patients with an ESR1mut had a PR (83%) and one (17%) had stable disease. No clinically relevant drug–drug interaction was observed. Safety data are presented in the table. Two patients experienced grade 3 hyperglycemia, one of whom had baseline elevated HbA1c and has been on insulin therapy since the event. The other patient received a single day of insulin treatment. In the GIR + INAVO arm, the incidence of rash and stomatitis (all grade 1) was 13% each. **CONCLUSIONS** An encouraging efficacy signal was observed with GIR + INAVO when compared cross-trial with BYLieve arm A (PMID: 33794206). ORRs were 47% in MORPHEUS BC vs 21% in BYLieve for patients with measurable disease (although no prior FUL was allowed in BYLieve). Safety of GIR + INAVO was aligned to the individual safety profiles of each of the drugs, with no new safety signals identified and a favorable tolerability profile for a PI3Kα inhibitor-based combination.

Safety summary

	GIR (n = 7)	GIR + INAVO (n = 15)
All-grade TRAEs	43%	100%
Grade 3 AEs (no Grade 4 or 5)	14%	33%
AE leading to tx discontinuation	0	7% (Grade 2 vomiting)
AEs leading to dose modification/interruption	14%	60%
Most common TRAEs (> 20% incidence rate)	Fatigue: 29%	Diarrhea: 60%; hyperglycemia: 53%; nausea: 47%; fatigue: 33%; decreased appetite: 33%; vomiting: 27%

Data are % of patients.

AE, adverse event; GIR, giredestrant; INAVO, inavolisib; TRAE, treatment-related adverse event; tx, treatment.

PS17-08

A Phase Ib Study to Evaluate the Efficacy and Safety of Afiresertib Plus Fulvestrant in Patients with Locally Advanced or Metastatic HR⁺/HER2⁻ Breast Cancer Who Failed Standard of Care Therapies

Presenting Author(s) and Co-Author(s):

S. Phadke. University of Iowa, Iowa city, Iowa, United States

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

P. Zhang. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

T. Sun. Department of Medical Oncology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Key Laboratory of Liaoning Breast Cancer Research, Shenyang, United States

Y. Wang. 1. Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Guangzhou Regenerative Medicine and Health Guangdong Laboratory, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; 2. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Z. Tong. Tianjin Medical University Cancer Institute & Hospital, United States

T. Feinstein. Piedmont Cancer Institute, P.C., Georgia, United States

P. Guo. Laekna LLC., United States

J. Qu. Laekna LLC., United States

X. Wang. Laekna LLC., United States

Background The combination of an aromatase inhibitor with a CDK4/6 inhibitor is the mainstay of first-line endocrine therapy (ET) for locally advanced or metastatic HR⁺/HER2⁻ breast cancer (LA/mBC). Management of recurrent disease in the post-CDK4/6 inhibitor setting includes additional lines of ET single agent or in combination with a targeted agent. For patients with HR⁺/HER2⁻ LA/mBC tumors, fulvestrant monotherapy as the second- or third-line therapy has limited activity with a median PFS of 1.9-3.6 months. Effective targeted treatments for these patients are needed to maintain quality of life, improve survival, and delay the initiation of cytotoxic chemotherapy. **Methods** This ongoing single arm, open-label global study (NCT04851613) is to evaluate the efficacy and safety of the combination therapy of afuresertib (a pan-AKT inhibitor) plus fulvestrant in patients with HR⁺/HER2⁻ LA/mBC. Eligible patients must have received 1-2 prior lines of ET. Patients may have prior treatment of CDK4/6 inhibitors (up to 1 therapy), and/or up to 1 line of chemotherapy. Patients received afuresertib (125 mg PO, QD) in combination with fulvestrant (500 mg IM; Day 1 and 15 in Cycle 1, and Day 1 in subsequent 28-day cycles). The safety of the initial treatment doses of the combination therapy was evaluated in the first 6 patients during the Cycle 1 safety run-in period. Radiographic assessment per RECIST 1.1 was performed every 8 weeks for the first 6 cycles and every 12 weeks thereafter. The primary endpoint was the investigator-assessed objective response rate (ORR). The secondary endpoints included safety and tolerability of the combination therapy and pharmacokinetic characterization. **Results** Twenty patients (1 male and 19 females, 3 in the US and 17 in China) were enrolled between May 2022 and April 2023. As of the data cut-off date of May 26th, 2023, 10 patients had discontinued the study treatment (9 due to disease progression, 1 due to patient's withdrawal of consent) and 10 patients were

still in treatment. Of the 19 patients who had at least one post-baseline tumor assessment, 4 patients observed confirmed Partial Response (cPR), 12 had best overall response of Stable Disease, and 3 had Progressive Disease (PD). The Disease Control Rate is 84%. Of the 15 patients who had at least 2 tumor assessments or who discontinued treatment early due to PD, the confirmed ORR is 26.7% (4 cPR). No dose modification was required during the safety run-in. The most common treatment-emergent adverse events (TEAEs, > 20% of patients) of all grades were hyperglycemia (50%), diarrhea (45%), ALT/AST increase (40%), nausea (35%), rash (35%), hypercholesterolemia (35%), and anemia (30%), the majority of which were Grade 1. Grade 3 AEs were reported in 4 patients, including diarrhea (1 patient), WBC increase (1 patient), creatine phosphokinase increase (1 patient), and ALT/AST increase and rash (1 patient). No SAE or TEAE \geq Grade 4 were reported. No patient discontinued treatment due to TEAE. Conclusions The preliminary data from the combination therapy of afuresertib plus fulvestrant has shown promising efficacy with a well-tolerated safety profile in patients with HR⁺/HER2⁻ LA/mBC who progressed on 1-2 prior lines of standard of care therapies. These results support further evaluation of this combination therapy in this patient population in an upcoming phase III study.

PS17-09

An FGFR1/2 degrader overcomes antiestrogen resistance in ER+/FGFR1-amplified breast cancer

Presenting Author(s) and Co-Author(s):

Y. Uemoto. UT Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, United States

C. Lin. University of Texas Southwestern Simmons Comprehensive Cancer Center, United States

A. Servetto. Department of Clinical Medicine and Surgery, University of Naples "Federico II", United States

B. Wang. Department of Biochemistry, UT Southwestern Medical Center, United States

D. Ye. UT Southwestern Medical Center, United States

F. Napolitano. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

H. Milan Patel. UT Southwestern Simmons Comprehensive Cancer Center, United States

L. Formisano. Department of Clinical Medicine and Surgery, University of Naples "Federico II", United States

M. Chica-Parrado. University of Texas Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, United States

E. Bikorimana. UT Southwestern Medical Center, United States

S. Mendiratta. UT Southwestern Simmons Comprehensive Cancer Center, United States

C. Chen. Department of Biochemistry, UT Southwestern Medical Center, United States

A. Hanker. UT Southwestern Medical Center, Dallas, Texas, United States

C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

We previously reported that nuclear FGFR1 promotes antiestrogen resistance in ER+/FGFR1-amplified breast cancer. Nuclear FGFR1 activity was not affected by FGFR tyrosine kinase inhibitors (TKIs). Furthermore, pan-FGFR TKIs are not well tolerated. Therefore, new therapeutic strategies that inhibit nuclear FGFR1 while sparing FGFR3 and FGFR4 would be required to overcome antiestrogen resistance and limit toxicity. For this study, we used the proteolysis-targeting chimera (PROTAC) DGY-09-192, consisting of the FGFR TKI BCJ398 linked with a VHL recruiting ligand, to degrade FGFR1 and FGFR2. We aimed to determine whether selective degradation of FGFR1/2 overcomes endocrine resistance. Treatment with 50-100 nM DGY-09-192 strongly induced FGFR1 degradation and suppressed phosphorylation of FGFR1 and its downstream targets FRS2, AKT, and ERK1/2 in ER+/FGFR1-amplified CAMA1 and MDA-MB-134 breast cancer cells. FGFR1 degradation was evident within 4 h and lasted 48-96 h after drug washout. The proteasome inhibitor MG132 (10 μ M) rescued both FGFR degradation and phosphorylation of downstream signaling molecules induced by DGY-09-192, confirming that FGFR1 degradation is dependent on ubiquitination and proteasomal degradation. At equivalent concentrations, DGY-09-192 suppressed phosphorylation of FGFR1 and its downstream targets more potently than BGJ398. Subcellular fractionation showed treatment with DGY-09-192 (100 nM) degraded FGFR1 in membrane, nuclear, and chromatin-bound fractions in both CAMA1 and MDA-MB-134 cells. Treatment of >CAMA1 cells with DGY-09-192 (>100 nM) downregulated nuclear FGFR1 target genes and canonical ER α target

genes, such as CCND1, VEGFA, and CDK12 as measured by qRT-PCR whereas treatment with BGJ398 (100 nM) did not. Treatment with DGY-09-192 (500 nM) reversed resistance to the ER degrader fulvestrant in CAMA1 cells as measured by colony formation assays and using the Incucyte Live-Cell Analysis System. Each drug alone showed a modest effect on cell proliferation whereas the combination completely blocked cell growth ($p < 0.0001$). Finally, treatment of NOD scid gamma (NSG) mice with established ER+/FGFR1-amplified HCI-011 patient-derived xenografts with DGY-09-192 (40 mg/kg daily x2-6) induced FGFR1 degradation and blocked phosphorylation of downstream targets in the tumors. Studies using the combination of DGY-09-192 and fulvestrant in mice bearing established HCI-011 xenografts are in progress. We next investigated the effect of DGY-09-192 on cancer cells harboring FGFR1 and FGFR2 activating mutations. DGY-09-192 treatment induced FGFR2 degradation and blocked downstream signaling in MFE296 endometrial cancer and EFM-19 breast cancer cells that harbor the FGFR2^{N549K} and FGFR2^{K659E} hotspot mutations, respectively. In addition, DGY-09-192 strongly suppressed MFE296 cell proliferation. We are currently investigating whether DGY-09-192 blocks signaling and cell proliferation induced by the N546K and K656E hotspot FGFR1 mutations in ER+ breast cancer cells. Notably, a recent clinical study showed that tumors harboring these FGFR1 activating mutations are refractory to the pan-FGFR TKI pemigatinib. Conclusions: The FGFR1/2 PROTAC DGY-09-192 induced degradation of nuclear and membrane-bound FGFR1 and blocked FGFR1-induced signaling and nuclear activity in ER+/FGFR1-amplified breast cancer cells. The combination of DGY-09-192 and fulvestrant synergistically suppressed proliferation of these cells. Therefore, FGFR1 degradation represents a promising therapeutic strategy to block FGFR1 activity more completely and selectively in ER+ breast cancers harboring activating FGFR1 alterations.

PS17-01

Key drivers of therapeutic response and resistance to giredestrant from GO39932: a Phase Ia/b study in patients with estrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer

Presenting Author(s) and Co-Author(s):

J. Liang. Genentech, Inc., South San Francisco, California, United States

C. Ong. Genentech, Inc., South San Francisco, California, United States

J. Giltane. Genentech, Inc., South San Francisco, California, United States

J. Aimi. Genentech, Inc., South San Francisco, California, United States

C. Chang. Genentech, Inc., South San Francisco, California, United States

M. Gates. Genentech, Inc., South San Francisco, California, United States

J. Eng-Wong. Genentech, Inc., South San Francisco, California, United States

P. Perez-Moreno. Genentech, Inc., South San Francisco, California, United States

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

E. Lim. Garvan Institute of Medical Research, St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

H. Moore. Genentech, Inc., San Francisco, California, United States

BACKGROUND

Several investigational oral selective estrogen receptor antagonists and degraders (SERDs) are under investigation. These were partly developed to benefit patients (pts) with breast cancer (BC) who acquired resistance to standard-of-care (SoC) endocrine therapies (ET); e.g., through gain of ESR1 mutations that enable estrogen-independent ER activity. One such SERD, giredestrant (G), demonstrates activity in pts with ESR1-wild type (WT) or -mutant (m) tumors, and in pts who progressed on other ETs. Results from Phase I/III trials in ER-positive, HER2-negative, locally advanced/metastatic BC (ER+, HER2- LA/mBC) showed that next-generation SERDs had increased activity in ESR1m tumors vs SoC ETs. However, enthusiasm was hindered by heterogeneous responses, driven in part by study design differences. Across aCeLERA BC (NCT04576455), EMERALD (NCT03778931), SERENA-2 (NCT04214288), and AMEERA-3 (NCT04059484), 30–50% of pts progressed rapidly (< 2 months) when treated with SoC ETs or next-generation SERDs, while others benefited for ≥ 1 year. We present an exploratory biomarker analysis aimed at understanding the mechanistic basis for heterogeneous responses to SERDs in ER+, HER2- LA/mBC, by assessing a Phase Ia/b G cohort (NCT03332797) with paired baseline and on-treatment (tx) biopsies.

METHODS

Pts had ≤ 2 prior therapies for LA/mBC; disease recurrence/progression while on adjuvant ET for ≥ 24 months and/or ET for ER+, HER2- LA/mBC; and tumor response/stable disease for ≥ 6 months.

Single-agent dose-escalation stage: 10, 30, 90, or 250 mg G once daily (QD) on Days (D) 1–28 of 28-D cycles (C). Dose-expansion stage: 30, 100, or 250 mg G QD. 100 mg G + 125 mg palbociclib on a 21-D on/7-D off schedule was also explored. Pre-/perimenopausal pts received LHRH agonists.

Paired pre- and on-tx (C2D8) tumor biopsies (n = 29) were immunolabeled for ER, progesterone receptor, and Ki67, and assessed via bulk RNA-sequencing. Pre-tx liquid biopsies (n = 85) were evaluated by FoundationOne Liquid CDx assay. To validate our clinical observations, we generated a SERD-resistant MCF7 cell line and tested its sensitivity to other therapies.

RESULTS

We compared fast-progressing pts (FP; progression-free survival [PFS] < 2 months) with those experiencing long-term benefit (LTB; PFS > 12 months). LTB was significantly associated with high tumor baseline ER pathway activity. Although the benefit of G was of larger magnitude among pts with ESR1m tumors compared with SoC ET in acELERA BC, here pts with predominantly ESR1WT tumors received LTB on G tx. At the molecular level, G acted on LTB tumors by suppressing cell cycle- and ER-associated genes. In contrast, G had no effect on the transcriptome of FP tumors, which had lower baseline ER activity than LTB tumors. FP tumors were instead enriched for multiple cancer-associated pathways, e.g., RAS/MAPK and PI3K, which may drive resistance to G and thus enable fast progression. By liquid biopsy, most FP pts (> 90%) did not harbor a mutation in the associated pathway (e.g., NF1, KRAS), and thus could not be identified by genomic profiling alone. FP tumors were instead enriched for multiple cancer-associated pathways by gene expression. We explored these mechanisms further in the SERD-resistant cell line, which was similarly enriched for EGFR and MAPK activation vs standard MCF7 cells. Although cells became resistant to ER-targeted drugs, they acquired sensitivity to EGFR/MAPK inhibitors e.g., gefitinib, cobimetinib.

CONCLUSIONS

We identified molecular features associated with LTB to G and revealed a set of oncogenic pathways associated with FP pts on tx; demonstrating that these pathways represent acquired dependencies and potential therapeutic targets for SERD-resistant tumors and FP pts.

Disclosure(s):

Jackson Liang, PhD: Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): Genentech-Roche (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Genentech-Roche (Ongoing)

Komal Jhaveri, MD, FACP: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), AstraZeneca (Ongoing), Blueprint Medicines (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Jounce Therapeutics (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Menarini/Stemline (Ongoing), Novartis (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing), Sun Pharma Advanced Research Company Ltd (Ongoing), TAIHO Oncology (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Context Therapeutics (Ongoing), Debio Pharmaceuticals (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck Pharmaceuticals (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Puma Biotechnology, Inc (Ongoing), Zymeworks Inc. (Ongoing)

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the

institution): Guardant Health (Ongoing), Invitae (Ongoing), Natera (Ongoing), Personalis (Ongoing)

Poster Spotlight Session 17: Biomarkers of Response and/or Resistance to Endocrine Based Therapies: Implications for Treatment Approaches

Presenting Author(s) and Co-Author(s):

K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Disclosure(s):

Komal Jhaveri, MD, FACP: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), AstraZeneca (Ongoing), Blueprint Medicines (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Jounce Therapeutics (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Menarini/Stemline (Ongoing), Novartis (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing), Sun Pharma Advanced Research Company Ltd (Ongoing), TAIHO Oncology (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Context Therapeutics (Ongoing), Debio Pharmaceuticals (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck Pharmaceuticals (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Puma Biotechnology, Inc (Ongoing), Zymeworks Inc. (Ongoing)

PS17-02

Elacestrant vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer (mBC) with ESR1 mutation: key biomarkers and clinical subgroup analyses from the phase 3 EMERALD trial

Presenting Author(s) and Co-Author(s):

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

F. Bidard. Institut Curie, Paris, France

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

P. Aftimos. Institut Jules Bordet, Brussels, Belgium

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

J. Lu. Northwestern University Lurie Comprehensive Cancer Center, Chicago, Illinois, United States

G. Tonini. Menarini Group, United States

K. Theall. Stemline Therapeutics, United States

A. Paoli. Menarini Ricerche, Pomezia, Italy

V. Kaklamani. UT Health San Antonio, San Antonio, Texas, United States

Background:

The EMERALD trial reported significantly prolonged progression-free survival (PFS) and a manageable safety profile with elacestrant vs standard of care (SOC) endocrine therapy in patients (pts) with ER+/HER2- ESR1 mutated (ESR1-mut) mBC following progression on prior endocrine therapy (ET). EMERALD is the only pivotal oral SERD clinical trial where prior CDK4/6i usage was mandated. Duration of prior CDK4/6i was shown to be a predictor of efficacy in patients with ESR1 mutations (ESR1-mut) receiving elacestrant, with median PFS (mPFS) for patients with ESR1-mut receiving at least 12 months of CDK4/6i achieved 8.61 months (elacestrant) vs 1.91 months (SOC) (SABCS 2022). This analysis evaluates the clinical benefit of single-agent elacestrant in key clinically relevant subgroups, including biomarkers, usually associated with poorer prognosis.

Methods:

Patients with ER+/HER2- advanced or mBC who previously had 1-2 lines of endocrine therapy, and prior CDK4/6i, were randomized 1:1 to receive elacestrant or SOC (aromatase inhibitor or fulvestrant). A subgroup analysis was performed on patients with ESR1-mut, by prior duration of CDK4/6i plus ET with at least 12 months in the advanced or metastatic setting, with concomitant presence of liver and/or lung metastases, PIK3CA mutations, TP53 mutation, and HER2 low expression.

Results:

Overall, 478 patients were randomized to elacestrant (n=239) or SOC (n=239), 228 pts (47.7%) had ESR1-mut, and 159 pts (71.6%) received at least 12 months of prior CDK4/6i. Out of these

159 pts, 113 pts (71%) had liver and/or lung metastases, 62 pts (39%) had a PIK3CA-mut, 61 pts (38%) had TP53m, and 77 pts (48%) had HER2 low expression. A clinically meaningful improvement in PFS favoring elacestrant compared to SOC was consistent across all relevant subgroups in pts with ESR1-mut.

Conclusions:

Elacestrant showed significantly greater PFS when prior treatment duration with CDK4/6i was at least 12 months, suggesting prior exposure to CDK4/6i is a surrogate marker for endocrine sensitivity. In this population, elacestrant demonstrated superior efficacy, compared to SOC, even in patients with concomitant PIK3CA or TP53 mutations, expression of HER2 low, or presence of liver and/or lung metastases. These results suggest an active ER-driven pathway for this group despite the presence of other resistance mechanisms, where single-agent oral elacestrant could be an attractive option compared to combination therapies or intravenous HER2 low-targeted ADCs.

NCT number: NCT03778931

ER+/HER2-, ESR1-mut patients with ≥ 12 months of prior CDK4/6 inhibitors				
	Patients	Median PFS, months (95% CI)		HR (95% CI)
		Elacestrant	SOC	
All ESR1-mut patients	100% (159)	8.61 (4.14 - 10.84)	1.91 (1.87 - 3.68)	0.410 (0.262 - 0.634)
ESR1-mut and Liver and/or Lung Metastases	71% (113)	7.26 (2.20 - 10.84)	1.87 (1.84 - 1.94)	0.354 (0.209 - 0.589)
ESR1-mut and PIK3CA Mutations ^a	39% (62)	5.45 (2.14 - 10.84)	1.94 (1.84 - 3.94)	0.423 (0.176 - 0.941)
ESR1-mut and TP53 Mutations	38% (61)	8.61 (3.65 - 24.25)	1.87 (1.84 - 3.52)	0.300 (0.132 - 0.643)
ESR1-mut and HER2 Low Expression ^b	48% (77)	9.03 (5.49 - 16.89)	1.87 (1.84 - 3.75)	0.301 (0.142 - 0.604)

a. Includes E545K, H1047R, E542K amongst others

b. HER2 IHC 1+, and 2+ with no ISH amplification

Disclosure(s):

Aditya Bardia, MD, MPH: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Menarini/Stemline (Ongoing)

Joyce O'Shaughnessy, MD: Consulting Fees (e.g., advisory boards): Agendia (Ongoing), Aptitude Health (Ongoing), AstraZeneca (Ongoing), Carrick Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), ELY LILLY (Ongoing), F. Hoffman La Roche Ltd (Ongoing), G1-Therapeutics (Ongoing), Genentech (Ongoing), Loxo@Lilly (Ongoing), Merck Sharp & Dohme, Lda. (Ongoing), Novartis (Ongoing), Ontada (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Samsung Bioepis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing), Synthon (Ongoing)

Javier Cortés, MD, PhD: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), Astrazeneca (Ongoing), Bioasis (Ongoing), BioInvent Pharma (Ongoing), Boehringer Ingelheim (Ongoing), BridgeBio (Ongoing), Clovis Oncology (Ongoing), Daiichi-Sankyo (Ongoing), Ellipses (Ongoing), Expres2ion Biotechnologies (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gemoab (Ongoing), Gilead (Ongoing), HiberCell (Ongoing), Jazz Pharmaceuticals (Ongoing), Leuko (Ongoing), Lilly (Ongoing), Menarini (Ongoing), Merck Sharp&Dhome (Ongoing), Reveal Genomics, S.L. (Ongoing), Scorpion Therapeutics (Ongoing), Seattle genetics (Ongoing), Zymeworks Inc. (Ongoing); honoraria: Lilly (Ongoing), Novartis (Ongoing); honoraria, research funding to the institution, travel and expenses: Astrazeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Europe Ltd. (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Merck Sharp&Dhome (Ongoing), Pfizer, Inc. (Ongoing); honoraria, travel and expenses: Gilead (Ongoing), Steamline Therapeutics (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1 (Ongoing), MAJ3 Capital (Ongoing), Pharmaceutical Combinations of A PI3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. (Ongoing); research funding to the institution: Ariad pharmaceuticals (Ongoing), Baxalta GMBH/Servier Affaires (Ongoing), Bayer Pharmaceuticals (Ongoing), Guardant Health Inc. (Ongoing), IQVIA Inc. (Ongoing), Piquor Therapeutics (Ongoing), Queen Mary University of London (Ongoing); stock (relative): Leuko (Ongoing)

Janice Lu, MD, PhD: Consulting Fees (e.g., advisory boards): AstraZeneca (Terminated, March 30, 2022), Lilly (Terminated, March 30, 2022), Pfizer (Terminated, March 30, 2022), Sanofi (Terminated, March 30, 2022), SeaGen (Terminated, March 30, 2022); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Ambrx (Ongoing)

Virginia Kaklamani, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo |Astrazeneca (Ongoing), Gilead Science (Ongoing), Loxo@Lilly (Ongoing), Menarini/Stemline (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), SeaGen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Daiichi Sankyo |Astrazeneca (Ongoing), Gilead Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Eisai, Inc (Ongoing)

PS17-03

Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR positive/HER2-negative advanced breast cancer: exploratory analysis of PFS by AKT pathway gene from the Phase 3 CAPItello-291 trial

Presenting Author(s) and Co-Author(s):

- S. Howell. The University of Manchester, Manchester, England, United Kingdom
- H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States
- M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain
- F. Dalenc. Oncopole Claudius-Regaud, IUCT, Toulouse, France
- J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US; Department of Medicine, Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Madrid, Spain., Barcelona, Catalonia, Spain
- H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru
- X. Hu. Shanghai Cancer Center, Fudan University, Shanghai, China
- K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States
- P. Krivorotko. N.N. Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russia
- S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany
- S. Morales Murillo. Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Catalonia, Spain
- M. Okera. Adelaide Cancer Centre, Adelaide, Australia
- Y. Park. Samsung Medical Center, Seoul, Republic of Korea
- J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea
- M. Toi. Graduate School of Medicine, Kyoto University, Kyoto, Japan
- E. Tokunaga. National hospital organization Kyushu Cancer Center, Fukuoka, Japan
- L. Zhukova. Loginov Moscow Clinical Scientific Center, Moscow, Russia
- A. Lloyd. Oncology R&D, AstraZeneca, Cambridge, United Kingdom
- E. de Bruin. Oncology R&D, AstraZeneca, Cambridge, United Kingdom
- C. Egile. Oncology R&D, AstraZeneca, Cambridge, United Kingdom
- C. D'Cruz. Oncology R&D, AstraZeneca, Waltham, Massachusetts, United States
- N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

Background:

In the Phase 3 randomized, double-blind CAPItello-291 trial, the addition of capivasertib (a potent, selective pan-AKT inhibitor) to fulvestrant in patients with aromatase inhibitor-resistant, hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative (HER2- defined as immunohistochemistry [IHC] 0, or 1-positive or IHC2-positive/in

situ hybridization-negative) advanced breast cancer (ABC) significantly improved progression-free survival (PFS) versus placebo + fulvestrant (hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.51–0.71; $p < 0.001$). PFS benefit was observed in patients with detectable AKT pathway alterations (HR 0.50, 95% CI 0.38–0.65; $p < 0.001$) and without (0.70; 95% CI; 0.56–0.88). Here, we report PFS by gene within the AKT pathway-altered population.

Methods:

Patients were randomized 1:1 to receive fulvestrant (500 mg intramuscularly on days 1 and 15 of cycle 1, and day 1 of each subsequent 28-day cycle) with either placebo or capivasertib (400 mg twice daily; 4 days on, 3 days off). AKT pathway-alteration status (at least one qualifying alteration in the genes PIK3CA, AKT1, or PTEN) was determined post-randomization, using next-generation sequencing in tumor tissue. HRs were calculated using Cox proportional hazards models. Data cut-off Aug 15, 2022.

Results:

Of the 708 patients randomized to treatment, 289 (41%) had AKT pathway-altered tumors (capivasertib-fulvestrant $n=155$; placebo-fulvestrant $n=134$). In the AKT pathway-altered population, 43% had liver metastases and 40% primary endocrine therapy resistance. Prior therapy for advanced disease included: 89% of patients with ≥ 1 line of prior treatment, 71% with a prior cyclin-dependent kinase 4 and 6 inhibitor, and 18% with prior chemotherapy. Baseline characteristics were broadly balanced between treatment groups.

Most patients with an AKT pathway-altered tumor had only one detectable alteration (272/289, 94%). Thirteen patients (capivasertib-fulvestrant $n=4$; placebo-fulvestrant $n=9$) had co-occurring PIK3CA and PTEN alterations, and four patients (capivasertib-fulvestrant $n=2$; placebo-fulvestrant $n=2$) had co-occurring PIK3CA and AKT1 alterations.

Consistent PFS benefit of capivasertib-fulvestrant over placebo-fulvestrant was observed across all alterations (Table).

The safety profile of capivasertib-fulvestrant in the AKT pathway-altered population was consistent with the overall population.

Conclusions:

Compared with fulvestrant alone, the addition of capivasertib to fulvestrant provided a consistent PFS benefit across alterations in all three key genes within the AKT pathway in patients with HR-positive/HER2-negative ABC.

<https://clinicaltrials.gov/>: NCT04305496

Funding: CAPItello-291 is sponsored by AstraZeneca.

Editorial acknowledgment: AstraZeneca-funded medical writing support was provided by Suzanne Patel, Ph.D., from BOLDSCIENCE Inc.

Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

Alteration	N (%)	HR* for PFS (95% CI)
Any AKT pathway alteration	289 (100)	0.50 (0.38–0.65)
PIK3CA only	202 (69.9)	0.51 (0.37–0.70)
PTEN only	37 (12.8)	0.43 (0.21–0.88)
AKT1 only	33 (11.4)	0.51 (0.22–1.12)
PIK3CA with/without AKT1/PTEN alterations	219 (75.8)	0.51 (0.37–0.69)
*HR<1 favors capivasertib-fulvestrant over placebo-fulvestrant.		

Disclosure(s):

Sacha J. Howell, MD, PhD, FRCP: Consulting Fees (e.g., advisory boards): Pfizer, Inc. (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Eli Lilly and company (Ongoing), Pfizer, Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Eli Lilly and company (Ongoing)

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

Mafalda Oliveira, MD, PhD: Advisory Committee/Board Member: Astra Zeneca (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Daiichi-Sankyo / AstraZeneca (Ongoing), Gilead (Ongoing), iTeos (Ongoing), Lilly (Ongoing), MSD (Ongoing), Pfizer, Inc. (Ongoing), Pierre-Fabre (Ongoing), Relay Therapeutics (Ongoing), Roche (Ongoing), Seagen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Astra Zeneca (Ongoing), Gilead (Ongoing), Lilly (Ongoing), MSD (Ongoing), Novartis (Ongoing), Roche (Ongoing), Seagen (Ongoing); Independent Contractor: Libbs (Ongoing), Pfizer, Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Terminated), Ayala Pharmaceuticals (Terminated), Boehringer-Ingelheim (Terminated), Genentech (Terminated), Gilead (Terminated), Novartis (Terminated), Pfizer, Inc. (Terminated), Roche (Terminated), Seagen (Terminated), Zenith Epigenetics (Terminated); Travel Grant: Gilead (Terminated), Pierre-Fabre (Terminated)

Javier Cortés, MD, PhD: No relevant disclosure to display

Komal Jhaveri, MD, FACP: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), AstraZeneca (Ongoing), Blueprint Medicines (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Jounce Therapeutics (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Menarini/Stemline (Ongoing), Novartis (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing), Sun Pharma Advanced Research Company Ltd (Ongoing), TAIHO Oncology (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Context Therapeutics (Ongoing), Debio Pharmaceuticals (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Merck Pharmaceuticals (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Puma Biotechnology, Inc (Ongoing), Zymeworks Inc. (Ongoing)

Sibylle Loibl, MD, PhD: Advisory Committee/Board Member: GSK, Pfizer, Novartis (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Consulting Fees (e.g., advisory boards): GSK, Pfizer, Novartis (Ongoing), Menarini/Stemline (Ongoing), MSD Co., Ltd. (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Licences for VM Ki67 Quantifier: VM Scope GmbH (Ongoing); patents pending: EP14153692.0 , EP21152186.9 , EP19808852.8 , (Ongoing)

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Guardant Health (Ongoing), Invitae (Ongoing), Natera (Ongoing), Personalis (Ongoing)

PS17-04

Clinical and Genomic Features of ER-Positive/HER2-negative Metastatic Breast Cancer in AURORA Molecular Screening Initiative (BIG 14-01): Mechanisms of Endocrine Therapy Resistance and Implications for Adjuvant Approaches

Presenting Author(s) and Co-Author(s):

A. Guerrero. Fundación Instituto Valenciano de Oncología (FIVO). GEICAM Spanish Breast Cancer Group., Valencia, Comunidad Valenciana, Spain

M. Benelli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

A. Irrthum. Breast International Group, Belgium

D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom

L. Ferrando. IRCCS - Ospedale Policlinico San Martino, Italy

D. Romagnoli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

M. Paoli. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

A. Llinas. Vall d'Hebron Institute of Oncology (VHIO), Spain

M. Dadiani. Sheba Medical Center, Israel

D. Fimereli. Breast Cancer Translational Research Laboratory J.-C. Heuson, Institut Jules Bordet, Belgium

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

C. Caballero. Breast International Group, Brussels, Belgium

T. Crestani. Breast International Group, Belgium

E. Agostinetto. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Bruxelles, Brussels Hoofdstedelijk Gewest, Belgium

D. Martins-Branco. Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Academic Trials Promoting Team (ATPT), Brussels, Belgium

F. Hilbers. NCI, United States

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

M. Balic. Division of Oncology, Department of Internal Medicine, Medical University Graz, Austria

F. Cardoso. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States

C. Sotiriou. Institut Jules Bordet, United States

G. Curigliano. European Institute of Oncology and University of Milano, Milano, Lombardia, Italy

B. Linderholm. Sahlgrenska Academy and University Hospital, Gothenburg, Sweden

E. de Azambuja. Academic Trials Promoting Team and Medical Oncology Department, Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

S. Knox. Europa Donna- The European Breast Cancer Coalition, United States

C. Rotaru. Breast International Group, Belgium

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

N. Davidson. University of Washington, United States

G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy

D. Taylor. Universite catholique de Louvain, CHU UCL Namur—Site Sainte-Elisabeth, Namur, Belgium

J. Canon. Grand Hopital de Charleroi - GHdC site Notre Dame, Belgium

L. Calvo. Oncology Department-Universitary Hospital A Coruña, A Coruña, Galicia, Spain

J. Albanell. Hospital del Mar; IMIM, Barcelona; Pompeu Fabra University, Barcelona; CIBERONC, Spain

M. Colleoni. Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Lombardia, Italy

C. Duhem. Clinique du sein, Centre Hospitalier du Luxembourg, Luxembourg

N. Harbeck. University of Munich, Munich, Bayern, Germany

C. Herremans. , United States

S. Loibl. GBG Forschungs GmbH, Germany

S. Marreaud. EORTC, Belgium

E. Scheepers. Frontier Science Scotland, Kincaig, Kingussie, United Kingdom

A. Raimbault. Breast International Group, Belgium

T. Goulioti. Breast International Group (BIG)-aisbl, Brussels, Belgium

A. Vingiani. Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori, United States

C. Biagioni. Bioinformatics Unit, Hospital of Prato, AUSL Toscana Centro, Prato, Italy

S. Vosberg. Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Austria

G. Zoppoli. Department of Internal Medicine and Medical Specialties DiMI, University of Genoa, Italy

J. Seoane. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

D. Venet. Breast Cancer Translational Research Laboratory J-C Heuson, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

P. Aftimos. Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium

M. Piccart. Institut Jules Bordet, Anderlecht, Brussels Hoofdstedelijk Gewest, Belgium

Background:

Up to 30% of patients (pts) with ER-positive early breast cancers develop metastatic relapse. The molecular differences between endocrine therapy (ET)-sensitive and ET-resistant relapses, as well as the impact of specific adjuvant ET-based therapies, remain unclear.

Methods:

The AURORA program (NCT02102165) analyzed multi-omics data of paired primary (prim) and metastatic (meta) tumor tissue, along with plasma samples, from 1,156 patients with metastatic breast cancer (MBC). Targeted genome sequencing (TGS), RNA sequencing, and circulating tumor DNA analysis were performed. ET-resistance at MBC diagnosis was defined following the 5th ESO-ESMO ABC Guidelines.

Results:

We studied 628 pts with metastatic ER+/HER2- disease. Patient's median age was 56 years, 133 (21%) were premenopausal, 314 (50%) had ET-resistance at recurrence (9% primary, 41% secondary), 132 (21%) had ET-sensitive recurrence, and the rest were ET-naïve recurrences or de novo MBC. Adjuvant treatment was aromatase inhibitor (AI) +/- ovarian function suppression (OFS) in 288 (46%) pts, while 159 (25%) had tamoxifen only (+/- OFS).

Gene expression correlation significantly differed ($p < 0.005$) based on ET-resistance in 92 paired samples. ET-sensitive ($n=11$) and de-novo tumors ($n=41$) showed higher correlation than primary ($n=7$) and secondary ET-resistance ($n=32$), regardless of adjuvant ET type.

Prim and meta showed concordance in 91% of IHC subtypes and 62% of intrinsic subtypes. Intrinsic subtype showed 9% of prim luminal tumors switching to meta non-luminal, with 66% of Luminal A switching to Luminal B. Neither IHC nor intrinsic subtype switching was associated with the type of adjuvant ET or ET resistance. Pts with meta non-luminal intrinsic subtype (18%) had worse PFS on CDK4/6i (HR 4.0, 95% CI 1.9-8.7) and OS (HR 3.6, 95% CI 2.0-5.7) than luminal subtypes.

TGS was performed in 534 meta (365 before 1L, 305 pairs). In meta before 1L, the dN/dS algorithm revealed selection in 17 genes, including TP53, PIK3CA, and ESR1. Mutations (mut) in ESR1, ERBB2, ERBB3, and RB1 among others, were specifically identified in meta. The incidence of ESR1mut was 3% in prim, 12.6% before 1L, 23.4% after 1L, and 4.7% in meta from ET-naïve tumors (Table). Before 1L, ESR1mut was higher after adjuvant AI vs tamoxifen (21% vs. 4%, $p < 0.001$). ESR1mut incidence varied with ET-resistance (16% primary, 19% secondary, 9% sensitive, 4% ET-naïve/de novo, $p < 0.01$). Paired samples showed that ESR1mut were mainly acquired events and associated with higher ER mRNA signaling (hallmark estrogen response) compared to ESR1wt ($p < 0.05$).

The agreement between ESR1mut detected in ctDNA and tissue was high before 1L (90%), and slightly lower after 1L (84%).

In a multivariate model with relevant clinical factors, ESR1mut were associated with worse OS (HR 1.76, 95% CI 1.2-2.5, $p=0.003$), independently of TP53 and PIK3CA mutational status.

Conclusion:

AURORA study sheds light on metastatic tumor alterations acquired under anti-cancer therapy, in ER+/HER2- MBC. We observed a high prevalence of acquired ESR1mut prior to the initiation of first-line therapy, particularly in tumors exposed to adjuvant AI or with primary or secondary ET_resistance. The association of ESR1muts with poorer OS underscores the importance of implementing effective adjuvant ET strategies to prevent the emergence of these mutations.

Frequency of driver gene mutations in primary and metastatic tumors before 1st-line treatment according to adjuvant ET and type of ET resistance

Gene	Metastatic Tumor, before 1 st line						
	Primary Tumor (%)	Adjuvant AI (%)	Adjuvant Tam (%)	Primary ET-Resistance (%)	Secondary ET-Resistance (%)	ET-sensitive (%)	De novo (%)
PIK3CA	40	34	40	37	32	41	42
TP53	26	24	25	39	25	19	29
ESR1 (all)	3	21	5	16	19	9	4
ESR1 (acquired)	NA	21	2	17	15	7	NA

Disclosure(s):

Angel Guerrero, MD, PhD: Advisory Committee/Board Member: Pfizer, Inc. (Ongoing), SeaGen (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Exact Sciences (Genomic Health) (Ongoing), Menarini/Stemline (Ongoing), Novartis Pharma GmbH (Ongoing), PierreFabre (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Astra Zeneca (Ongoing), Novartis Pharma GmbH (Ongoing), Pfizer, Inc. (Ongoing), PierreFabre (Ongoing); Travel to medical congress support: Astra Zeneca (Ongoing), Novartis Pharma GmbH (Ongoing), Pfizer, Inc. (Ongoing)

Mafalda Oliveira, MD, PhD: Advisory Committee/Board Member: Astra Zeneca (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Daiichi-Sankyo / AstraZeneca (Ongoing), Gilead (Ongoing), iTeos (Ongoing), Lilly (Ongoing), MSD (Ongoing), Pfizer, Inc. (Ongoing), Pierre-Fabre (Ongoing), Relay Therapeutics (Ongoing), Roche (Ongoing), Seagen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Astra Zeneca (Ongoing), Gilead (Ongoing), Lilly (Ongoing), MSD (Ongoing), Novartis (Ongoing), Roche (Ongoing), Seagen (Ongoing); Independent Contractor: Libbs (Ongoing), Pfizer, Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Terminated), Ayala Pharmaceuticals (Terminated), Boehringer-Ingelheim (Terminated), Genentech (Terminated), Gilead (Terminated), Novartis (Terminated), Pfizer, Inc. (Terminated), Roche (Terminated), Seagen (Terminated), Zenith Epigenetics (Terminated); Travel Grant: Gilead (Terminated), Pierre-Fabre (Terminated)

Elisa Agostinetti, MD: Honorarium: Sandoz (Terminated); meeting/travel grants: Novartis, Roche, Eli Lilly, Genetic, Istituto Gentili, Daiichi Sankyo, AstraZeneca (Terminated); Research grant to my Institution: Gilead (Terminated); speaking fee: AstraZeneca (Terminated), Eli Lilly (Terminated)

Einav Nili Gal-Yam, MD, PhD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated, November 14, 2023), Eli Lilly & Company (Terminated, November 14, 2023), F. Hoffman La Roche Ltd (Terminated, November 14, 2023), MSD Co., Ltd. (Terminated, November 14, 2023), Novartis Pharmaceuticals (Terminated, November 14, 2023), Pfizer, Inc. (Terminated, November 14, 2023); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): F. Hoffman La Roche Ltd (Ongoing); Honoraria: Astra Zeneca (Terminated, November 14, 2023); Honoraria: Eli Lilly & Company (Terminated, November 14, 2023), MSD Co., Ltd. (Terminated, November 14, 2023),

Novartis Pharmaceuticals (Terminated, November 14, 2023), Pfizer, Inc. (Terminated, November 14, 2023)

Jorge Reis-Filho, MD, PhD: No relevant disclosure to display

Giuseppe Curigliano, Prof, MD, PhD: Advisory Committee/Board Member: Menarini Silicon Biosystems (Terminated); Consulting Fees (e.g., advisory boards): Astra Zeneca, Roche, Novartis, Biocad, R-Pharm, Eisai, Eli Lilly, Pfizer, MSD, BMS (Terminated), Gilead (Terminated), PFS Genomics/Exact Sciences (Terminated)

Nadia Harbeck, MD, PhD: Advisory Committee/Board Member: Roche (Ongoing); Consulting Fees (e.g., advisory boards): Gilead (Ongoing), Sandoz (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Amgen (Ongoing), Astra Zeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Roche (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): West German Study Group (WSG) (Ongoing)

Martine J. Piccart, MD, PhD: Advisory Committee/Board Member: Oncolytics (Ongoing); Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Camel-IDS/Precirix (Ongoing), Gilead (Ongoing), Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Roche-Genentech (Ongoing), Seattle Genetics, Seagen, NBE Therapeutics, Frame Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca PLC (Ongoing), Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Roche-Genentech (Ongoing), Servier, Synthron (Ongoing)

PS17-06

A phase I trial of the PI3K inhibitor (PI3Ki) copanlisib and fulvestrant in combination with continuous or intermittent abemaciclib in patients with estrogen receptor-positive (ER+), HER2-negative (HER2-) metastatic breast cancer

Presenting Author(s) and Co-Author(s):

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

J. Luo. Washington University in St Louis School of Medicine, United States

J. Moss. University of Kentucky, United States

M. Kwa. New York University, United States

R. Parajuli. University of California, Irvine Medical Center, Orange, California, United States

K. Khoury. O'Neal Comprehensive Cancer Center at the University of Alabama, Birmingham, Alabama, United States

E. Douglas. Atrium Health Wake Forest Baptist Health, United States

A. Frith. Washington University in St Louis School of Medicine, United States

C. Rigden. Washington University in St. Louis School of Medicine, United States

F. Ademuyiwa. Washington University in St Louis School of Medicine, United States

S. Thomas. Washington University in St. Louis School of Medicine, Fenton, Missouri, United States

B. Haas. Washington University in St. Louis School of Medicine, United States

G. Wulf. Harvard Medical School, United States

C. Dees. University of North Carolina, Chapel Hill, North Carolina, United States

R. Said. National Cancer Institute Cancer Therapy Evaluation Program, United States

Background:

Activation of the phosphoinositide 3-kinase (PI3K) pathway is a prominent resistance mechanism to endocrine therapy and CDK4/6 inhibition (CDK4/6i) in ER+, HER2- breast cancer. There is reciprocal crosstalk between PI3K and cell cycle regulatory pathways. Triplet therapy that targets ER, CDK4/6, and PI3K prevents or delays disease progression in preclinical models of ER+, HER2- breast cancer. However, the toxicities of triplet therapy hinder its clinical development. Copanlisib (COP) is an intravenous (IV) PI3Ki with potent activity against α and δ isoforms. Intermittent high-dose PI3Ki is expected to be less toxic and more effective than continuous daily dosing. We set out to determine the recommended phase 2 dose (RP2D) for the COP/Fulvestrant (FUL)/Abemaciclib (ABE) combination.

Methods:

Eligible patients (pts) included men or women with ER+, HER2- metastatic breast cancer (MBC), with no more than 1 prior chemotherapy in the metastatic setting, and no limits on prior endocrine or targeted therapy. Prior FUL, CDK4/6i and PI3K/mTORi were allowed. Pts with HbA1c >8.5% were excluded. Pts received FUL 500 mg IM standard dosing and COP/ABE at assigned doses. Premenopausal women also received a GnRH agonist. Dose-limiting toxicity (DLT) was assessed during the first 28-day cycle. Adverse events (AEs) were graded according to NCI-CTCAE v5.0. Dose escalation/de-escalation was based on continual reassessment (CRM) and the RP2D was defined as the dose with the highest probability of the DLT rate within the acceptable 25~35%.

Results:

Between June 2020 and June 2023, 24 pts with ER+, HER2- MBC were enrolled. Table 1 shows the dose levels (DLs) and DLTs. The first 10 pts were enrolled to Part A on two consecutive DLs of COP (DL1: 45 mg IV D1 and D15, n=7; DL2: 45 mg IV D1, D8, and D15, n=3), with ABE fixed at 100 mg PO BID continuously. DL2a exceeded the maximum tolerated dose (MTD). DL1a was tolerable based on Cycle 1 AEs. However, during subsequent cycles, only 1 of the 7 pts in DL1a maintained the intended dose of ABE due to neutropenia, others reduced ABE to 50mg bid (n=5) or discontinued (n=1). This triggered a protocol amendment, adding Part B with ABE administered 5 days on and 2 days off (5-on/2-off) intermittent schedule. 14 pts were enrolled to Part B in 2 consecutive DLs of COP (DL1b: n=7; DL2b: n=7), the same as in Part A. ABE was fixed at 100 mg PO Bid 5-on/2-off. DL2b exceeded the MTD. DL1b was tolerable based on Cycle 1 AEs. In addition, in subsequent cycles, only 1 of 7 pts on DL1b required dose reduction of ABE to 50mg bid. RP2D is therefore defined as DL1b. Grade (G) 4 AEs were rare. The most common all cycle G3 AEs included transient hypertension (45%), rash (30%), anemia (25%), neutropenia (25%), and AST elevation (20%).

As of 6/14/2023, 22 pts, with a median of 1 prior metastatic regimen (range 0-5), prior CDK4/6i in 18 (82%), liver mets in 8 (36%), and PIK3CA mutation in 8 (50%) of 16 pts with known mutation status, were evaluable for response. There were 5 partial responses and 3 stable diseases lasting for ≥24 weeks. Clinical benefit rate was 36.4% (8/22, 95%CI: 17.19% ~ 59.34%). Responses were observed in pts regardless of prior CDK4/6i, FUL, or PIK3CA mutation.

Conclusion:

COP/FUL/intermittent ABE can be safely administered with fair overall tolerability. Preliminary anti-tumor activity was observed, which will be further examined in the randomized phase II trial (NCT 03939897).

Table 1

Table 1	Dose Level	Abemaciclib (PO)	Copanlisib (IV)	No. Enrolled (DLT evaluable)	No. DLT	DLT
Part A	Dose Level 1a (starting dose)	100 mg Bid continuously	45 mg IV D1 and D15	7 (6)	1	Grade 3 ANC, less than 75% abemaciclib dose received
	Dose Level 2a	100 mg Bid continuously	45 mg IV D1, D8 and D15	3 (3)	2	1 Grade 3 rash 1 Grade 3 hypochromemia
Part B	Dose Level 1b (starting dose)	100 mg Bid 5-on/2-off weekly	45 mg IV D1 and D15	7 (6)	1	Grade 3 rash
	Dose Level 2b	100 mg Bid 5-on/2-off weekly	45 mg IV D1, D8 and D15	7 (5)	2	1 Grade 3, new onset atrial fibrillation 1 Grade 3 rash

Dose-limiting Toxicities by Dose Level

Disclosure(s):

Cynthia Ma, MD, PhD: Advisory Committee/Board Member: Puma Biotechnology, Inc (Ongoing); Authorship/Article Publication: Wolters Kluwer/UpToDate (Ongoing); Consulting Fees (e.g., advisory boards): Agendia (Ongoing), AstraZeneca (Ongoing), Athenex (Ongoing), Bayer Healthcare (Ongoing), Biovica (Ongoing), Eisai (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), Inivata (Ongoing), Jacobio (Ongoing), Natera (Ongoing), Novartis (Ongoing), Olaris (Ongoing), OncoSignal (Ongoing), Pfizer (Ongoing), Phillips Electronics (Ongoing), Puma Biotechnology, Inc (Ongoing), Sanofi (Ongoing), Seattle Genetics (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): PlusOne Heath GmbH (Ongoing); Filled out Surveys for Tempus regarding these tests. Did not impact clinical or research activity.: Tempus (Ongoing); Royalty: Wolters Kluwer/UpToDate (Ongoing)

PS17-07

Interim analysis of giredestrant + inavolisib in MORPHEUS Breast Cancer: a Phase Ib/II study of giredestrant treatment combinations in estrogen receptor-positive, HER2-negative, locally advanced/metastatic breast cancer

Presenting Author(s) and Co-Author(s):

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

M. Gion. Ramón y Cajal University Hospital, Madrid, Madrid, Spain

C. Hernando. Hospital Clínico Universitario de Valencia, Valencia, Spain

K. Jung. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Not Applicable, Republic of Korea

M. Oliveira. Department of Medical Oncology, Vall d'Hebron University Hospital; Breast Cancer Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Catalonia, Spain

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

G. Vidal. The West Clinic, Germantown, United States, United States

S. Vatandoust. Flinders Centre for Innovation in Cancer, Flinders University, Bedford Park, South Australia, Australia

J. Zhu. Genentech, Inc., South San Francisco, California, United States

R. Schwab. Genentech, Inc., South San Francisco, California, United States

H. Ngo. Genentech, Inc., South San Francisco, California, United States

E. Ferreira. Roche Products Limited, Welwyn Garden City, United Kingdom

A. Collier. Genentech, Inc., South San Francisco, California, United States

V. Breton. F. Hoffmann-La Roche Ltd, Canada

BACKGROUND

Patients with estrogen receptor-positive metastatic breast cancer (ER+ mBC) almost always progress on first-line endocrine therapy (ET), which is usually combined with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Finding effective ET combinations after progression following CDK4/6is remains a challenge. Giredestrant (GIR) is a highly potent, nonsteroidal, oral, selective ER antagonist and degrader. Inavolisib (INAVO) is a highly potent PI3K α -selective inhibitor that promotes degradation of mutated p110 α . After first-line treatment (tx) with a CDK4/6i, PIK3CA mutations (mut), which are common, persist and remain a sensitive oncogenic target in these patients. We present a 16-week interim analysis of GIR vs GIR + INAVO in MORPHEUS BC (NCT04802759).

METHODS

Patients whose tumors harbored a PIK3CAmut and who had disease progression on up to two lines of endocrine-based therapy (including at least one prior line of CDK4/6i) for locally advanced (LA)/mBC were randomized 1:6 to receive GIR (30 mg orally daily [PO QD]) or GIR + INAVO (9 mg PO QD) tx until disease progression or unacceptable toxicity. Given the small numbers, the GIR arm is presented for overall safety. Primary endpoints are safety and objective response rate (ORR). Other endpoints include progression-free survival (PFS), disease control rate (DCR), and pharmacokinetics. Genetic alterations were identified centrally

in baseline circulating tumor DNA using the FoundationOne Liquid CDx assay. In cases where PIK3CAmut could not be determined centrally, local blood or tissue results are used.

RESULTS

As of April 18, 2023, seven and 15 patients were enrolled in the GIR and GIR + INAVO arms, respectively; 71% (n = 5) and 67% (n = 10) received one prior line of therapy in the LA/mBC setting; 14% (n = 1) and 33% (n = 5) received two prior lines; and one GIR-arm patient received four prior lines. Prior fulvestrant (FUL) was received by 53% of patients in the GIR + INAVO arm (n = 8). For GIR + INAVO, the ORR was 47% (n = 7); the complete response rate was 7% (n = 1); and the partial response (PR) rate was 40% (n = 6). The DCR at 12 weeks was 80% (12/15 patients). The median PFS was 10.3 months (95% confidence interval = 6.5, not evaluable) with 47% of patients (n = 7) having events. In the GIR + INAVO arm, 5/6 patients with an ESR1mut had a PR (83%) and one (17%) had stable disease. No clinically relevant drug–drug interaction was observed. Safety data are presented in the table. Two patients experienced grade 3 hyperglycemia, one of whom had baseline elevated HbA1c and has been on insulin therapy since the event. The other patient received a single day of insulin treatment. In the GIR + INAVO arm, the incidence of rash and stomatitis (all grade 1) was 13% each.

CONCLUSIONS

An encouraging efficacy signal was observed with GIR + INAVO when compared cross-trial with BYLieve arm A (PMID: 33794206). ORRs were 47% in MORPHEUS BC vs 21% in BYLieve for patients with measurable disease (although no prior FUL was allowed in BYLieve). Safety of GIR + INAVO was aligned to the individual safety profiles of each of the drugs, with no new safety signals identified and a favorable tolerability profile for a PI3Kα inhibitor-based combination.

Safety summary

	GIR (n = 7)	GIR + INAVO (n = 15)
All-grade TRAEs	43%	100%
Grade 3 AEs (no Grade 4 or 5)	14%	33%
AE leading to tx discontinuation	0	7% (Grade 2 vomiting)
AEs leading to dose modification/interruption	14%	60%
Most common TRAEs (> 20% incidence rate)	Fatigue: 29%	Diarrhea: 60%; hyperglycemia: 53%; nausea: 47%; fatigue: 33%; decreased appetite: 33%; vomiting: 27%

Data are % of patients.

AE, adverse event; GIR, giredestrant; INAVO, inavolisib; TRAE, treatment-related adverse event; tx, treatment.

Disclosure(s):

Einav Nili Gal-Yam, MD, PhD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated, November 14, 2023), Eli Lilly & Company (Terminated, November 14, 2023), F. Hoffman La Roche Ltd (Terminated, November 14, 2023), MSD Co., Ltd. (Terminated, November 14, 2023), Novartis Pharmaceuticals (Terminated, November 14, 2023), Pfizer, Inc. (Terminated, November 14, 2023); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): F. Hoffman La Roche Ltd (Ongoing); Honoraria: Astra Zeneca (Terminated, November 14, 2023); Honoraria: Eli Lilly & Company (Terminated, November 14, 2023), MSD Co., Ltd. (Terminated, November 14, 2023), Novartis Pharmaceuticals (Terminated, November 14, 2023), Pfizer, Inc. (Terminated, November 14, 2023)

Hope S. Rugo, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo (Ongoing), Mylan (Ongoing), NAPO (Ongoing), Puma (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Daiichi Sankyo, Inc. (Ongoing), F. Hoffmann-La Roche AG/Genentech (Ongoing), Gilead Sciences, Inc. (Ongoing), Lilly; Merck & Co. (Ongoing), Merck & Co., Inc. (Ongoing), Novartis International AG (Ongoing), Novartis Pharmaceuticals Corporation (Ongoing), OBI Pharma (Ongoing), Pfizer (Ongoing), Pionyr Immunotherapeutics (Ongoing), Sermonix Pharmaceuticals Inc. (Ongoing), Stemline Therapeutics (Ongoing)

Maria Gion, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo/Astra Zeneca (Terminated), Gilead Science (Terminated), Novartis (Terminated), Pfizer (Terminated); Travel: F. Hoffman La Roche Ltd (Terminated)

Kyung Hae Jung, MD, MS, PhD: Consulting Fees (e.g., advisory boards): Gilead Science (Terminated, May 26, 2023)

Mafalda Oliveira, MD, PhD: Advisory Committee/Board Member: Astra Zeneca (Ongoing); Consulting Fees (e.g., advisory boards): Astra Zeneca (Ongoing), Daiichi-Sankyo / AstraZeneca (Ongoing), Gilead (Ongoing), iTeos (Ongoing), Lilly (Ongoing), MSD (Ongoing), Pfizer, Inc. (Ongoing), Pierre-Fabre (Ongoing), Relay Therapeutics (Ongoing), Roche (Ongoing), Seagen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Astra Zeneca (Ongoing), Gilead (Ongoing), Lilly (Ongoing), MSD (Ongoing), Novartis (Ongoing), Roche (Ongoing), Seagen (Ongoing); Independent Contractor: Libbs (Ongoing), Pfizer, Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Astra Zeneca (Terminated), Ayala Pharmaceuticals (Terminated), Boehringer-Ingelheim (Terminated), Genentech (Terminated), Gilead (Terminated), Novartis (Terminated), Pfizer, Inc. (Terminated), Roche (Terminated), Seagen (Terminated), Zenith Epigenetics (Terminated); Travel Grant: Gilead (Terminated), Pierre-Fabre (Terminated)

Melinda Telli, MD: Advisory Committee/Board Member: Blueprint Medicine (Terminated, July 20, 2023), Natera, Inc. (Terminated, July 20, 2023), Novartis Pharma GmbH (Terminated, July 20, 2023), Reflexion Medical (Terminated, July 20, 2023), Replicate (Terminated, July 20, 2023), Sanofi Aventis (Terminated, July 20, 2023); Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated, July 20, 2023), Daiichi-Sankyo (Terminated, July 20, 2023), G1 Therapeutics (Terminated, July 20, 2023), Gilead Science (Terminated, July 20, 2023), Guardanth health (Terminated, July 20, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Arvinas (Ongoing), Astra Zeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Genentech-Roche (Ongoing), Hummingbird Biosciences (Ongoing), Merck & Co., Inc. (Ongoing), OncoSec (Ongoing), Pfizer, Inc. (Ongoing)

PS17-08

A Phase Ib Study to Evaluate the Efficacy and Safety of Afiresertib Plus Fulvestrant in Patients with Locally Advanced or Metastatic HR⁺/HER2⁻ Breast Cancer Who Failed Standard of Care Therapies

Presenting Author(s) and Co-Author(s):

S. Phadke. University of Iowa Hospitals and Clinics, Iowa City, Iowa, United States

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

P. Zhang. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, United States

T. Sun. Department of Medical Oncology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Key Laboratory of Liaoning Breast Cancer Research, Shenyang, United States

Y. Wang. 1. Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Guangzhou Regenerative Medicine and Health Guangdong Laboratory, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; 2. Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Z. Tong. Tianjin Medical University Cancer Institute & Hospital, United States

T. Feinstein. Piedmont Cancer Institute, P.C., Georgia, United States

P. Guo. Laekna LLC., United States

J. Qu. Laekna LLC., United States

X. Wang. Laekna LLC., United States

Background

The combination of an aromatase inhibitor with a CDK4/6 inhibitor is the mainstay of first-line endocrine therapy (ET) for locally advanced or metastatic HR⁺/HER2⁻ breast cancer (LA/mBC). Management of recurrent disease in the post-CDK4/6 inhibitor setting includes additional lines of ET single agent or in combination with a targeted agent. For patients with HR⁺/HER2⁻ LA/mBC tumors, fulvestrant monotherapy as the second- or third-line therapy has limited activity with a median PFS of 1.9-3.6 months. Effective targeted treatments for these patients are needed to maintain quality of life, improve survival, and delay the initiation of cytotoxic chemotherapy.

Methods

This ongoing single arm, open-label global study (NCT04851613) is to evaluate the efficacy and safety of the combination therapy of afuresertib (a pan-AKT inhibitor) plus fulvestrant in patients with HR⁺/HER2⁻ LA/mBC. Eligible patients must have received 1-2 prior lines of ET. Patients may have prior treatment of CDK4/6 inhibitors (up to 1 therapy), and/or up to 1 line of chemotherapy. Patients received afuresertib (125 mg PO, QD) in combination with fulvestrant (500 mg IM; Day 1 and 15 in Cycle 1, and Day 1 in subsequent 28-day cycles). The safety of the initial treatment doses of the combination therapy was evaluated in the first 6 patients during the Cycle 1 safety run-in period. Radiographic assessment per RECIST 1.1 was performed every 8 weeks for the first 6 cycles and every 12 weeks thereafter. The primary endpoint was the investigator-assessed objective response rate (ORR). The secondary endpoints included safety and tolerability of the combination therapy and pharmacokinetic

characterization.

Results

Twenty patients (1 male and 19 females, 3 in the US and 17 in China) were enrolled between May 2022 and April 2023. As of the data cut-off date of May 26th, 2023, 10 patients had discontinued the study treatment (9 due to disease progression, 1 due to patient's withdrawal of consent) and 10 patients were still in treatment. Of the 19 patients who had at least one post-baseline tumor assessment, 4 patients observed confirmed Partial Response (cPR), 12 had best overall response of Stable Disease, and 3 had Progressive Disease (PD). The Disease Control Rate is 84%. Of the 15 patients who had at least 2 tumor assessments or who discontinued treatment early due to PD, the confirmed ORR is 26.7% (4 cPR). No dose modification was required during the safety run-in. The most common treatment-emergent adverse events (TEAEs, > 20% of patients) of all grades were hyperglycemia (50%), diarrhea (45%), ALT/AST increase (40%), nausea (35%), rash (35%), hypercholesterolemia (35%), and anemia (30%), the majority of which were Grade 1. Grade 3 AEs were reported in 4 patients, including diarrhea (1 patient), WBC increase (1 patient), creatine phosphokinase increase (1 patient), and ALT/AST increase and rash (1 patient). No SAE or TEAE \geq Grade 4 were reported. No patient discontinued treatment due to TEAE.

Conclusions

The preliminary data from the combination therapy of afuresertib plus fulvestrant has shown promising efficacy with a well-tolerated safety profile in patients with HR⁺/HER2⁻ LA/mBC who progressed on 1-2 prior lines of standard of care therapies. These results support further evaluation of this combination therapy in this patient population in an upcoming phase III study.

Disclosure(s):

Binghe Xu, MD: Advisory Committee/Board Member: Astra Zeneca, Novartis (Ongoing)
Sneha Phadke, DO, MPH: Advisory Committee/Board Member: Starling Pharmaceuticals (Ongoing); Consulting Fees (e.g., advisory boards): Starling Pharmaceuticals (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Arvinas (Ongoing), Astra Zeneca (Ongoing), Hoffmann-La Roche Ltd (Ongoing), Laekna Therapeutics (Ongoing), Olema Oncology (Ongoing)

PS17-09

An FGFR1/2 degrader overcomes antiestrogen resistance in ER+/FGFR1-amplified breast cancer

Presenting Author(s) and Co-Author(s):

Y. Uemoto. UT Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, United States

C. Lin. University of Texas Southwestern Simmons Comprehensive Cancer Center, United States

A. Servetto. Department of Clinical Medicine and Surgery, University of Naples "Federico II", United States

B. Wang. Department of Biochemistry, UT Southwestern Medical Center, United States

D. Ye. UT Southwestern Medical Center, United States

F. Napolitano. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

H. Milan Patel. UT Southwestern Simmons Comprehensive Cancer Center, United States

L. Formisano. Department of Clinical Medicine and Surgery, University of Naples "Federico II", United States

M. Chica-Parrado. University of Texas Southwestern Simmons Comprehensive Cancer Center, Dallas, Texas, United States

E. Bikorimana. UT Southwestern Medical Center, United States

S. Mendiratta. UT Southwestern Simmons Comprehensive Cancer Center, United States

C. Chen. Department of Biochemistry, UT Southwestern Medical Center, United States

A. Hanker. UT Southwestern Medical Center, Dallas, Texas, United States

C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

We previously reported that nuclear FGFR1 promotes antiestrogen resistance in ER+/FGFR1-amplified breast cancer. Nuclear FGFR1 activity was not affected by FGFR tyrosine kinase inhibitors (TKIs). Furthermore, pan-FGFR TKIs are not well tolerated. Therefore, new therapeutic strategies that inhibit nuclear FGFR1 while sparing FGFR3 and FGFR4 would be required to overcome antiestrogen resistance and limit toxicity. For this study, we used the proteolysis-targeting chimera (PROTAC) DGY-09-192, consisting of the FGFR TKI BCJ398 linked with a VHL recruiting ligand, to degrade FGFR1 and FGFR2. We aimed to determine whether selective degradation of FGFR1/2 overcomes endocrine resistance.

Treatment with 50-100 nM DGY-09-192 strongly induced FGFR1 degradation and suppressed phosphorylation of FGFR1 and its downstream targets FRS2, AKT, and ERK1/2 in ER+/FGFR1-amplified CAMA1 and MDA-MB-134 breast cancer cells. FGFR1 degradation was evident within 4 h and lasted 48-96 h after drug washout. The proteasome inhibitor MG132 (10 μ M) rescued both FGFR degradation and phosphorylation of downstream signaling molecules induced by DGY-09-192, confirming that FGFR1 degradation is dependent on ubiquitination and proteasomal degradation. At equivalent concentrations, DGY-09-192 suppressed phosphorylation of FGFR1 and its downstream targets more potently than BGJ398. Subcellular fractionation showed treatment with DGY-09-192 (100 nM) degraded FGFR1 in membrane, nuclear, and chromatin-bound fractions in both CAMA1 and MDA-MB-134 cells. Treatment of

>CAMA1 cells with DGY-09-192 (>100 nM) downregulated nuclear FGFR1 target genes and canonical ER α target genes, such as CCND1, VEGFA, and CDK12 as measured by qRT-PCR whereas treatment with BGJ398 (100 nM) did not. Treatment with DGY-09-192 (500 nM) reversed resistance to the ER degrader fulvestrant in CAMA1 cells as measured by colony formation assays and using the Incucyte Live-Cell Analysis System. Each drug alone showed a modest effect on cell proliferation whereas the combination completely blocked cell growth ($p < 0.0001$). Finally, treatment of NOD scid gamma (NSG) mice with established ER+/FGFR1-amplified HCl-011 patient-derived xenografts with DGY-09-192 (40 mg/kg daily x2-6) induced FGFR1 degradation and blocked phosphorylation of downstream targets in the tumors. Studies using the combination of DGY-09-192 and fulvestrant in mice bearing established HCl-011 xenografts are in progress.

We next investigated the effect of DGY-09-192 on cancer cells harboring FGFR1 and FGFR2 activating mutations. DGY-09-192 treatment induced FGFR2 degradation and blocked downstream signaling in MFE296 endometrial cancer and EFM-19 breast cancer cells that harbor the FGFR2^{N549K} and FGFR2^{K659E} hotspot mutations, respectively. In addition, DGY-09-192 strongly suppressed MFE296 cell proliferation. We are currently investigating whether DGY-09-192 blocks signaling and cell proliferation induced by the N546K and K656E hotspot FGFR1 mutations in ER+ breast cancer cells. Notably, a recent clinical study showed that tumors harboring these FGFR1 activating mutations are refractory to the pan-FGFR TKI pemigatinib.

Conclusions:

The FGFR1/2 PROTAC DGY-09-192 induced degradation of nuclear and membrane-bound FGFR1 and blocked FGFR1-induced signaling and nuclear activity in ER+/FGFR1-amplified breast cancer cells. The combination of DGY-09-192 and fulvestrant synergistically suppressed proliferation of these cells. Therefore, FGFR1 degradation represents a promising therapeutic strategy to block FGFR1 activity more completely and selectively in ER+ breast cancers harboring activating FGFR1 alterations.

Disclosure(s):

Yasuaki Uemoto, MD.PhD: No financial relationships to disclose

Fabiana Napolitano, MD: No financial relationships to disclose

Ariella Hanker, PhD: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Eli Lilly (Ongoing)

PS18-01

Stage Advancement and The Rate of Growth Associated with Preoperative Delay in Patients Having Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Bleicher. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

K. Ruth. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Williams. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

E. Ross. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Porpiglia. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Aggon. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

M. Pronovost. Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, United States

D. Holmes. Adventist Health Glendale, Glendale, California, United States

Introduction:

For every delay interval between breast cancer diagnosis and surgery we have previously found a relative decline in disease-specific survival of 26% (60 d) and overall survival of 9-10% (30 d). There is, however, little explanation for this. In our experience, patients focus on the likelihood of cancer growth between diagnosis and surgery, and whether preoperative delay might lead to upstaging, with nodal status of particular concern when they are clinically node-negative. With little published data about delay-associated upstaging and no large-scale national data determining how fast tumors grow, this study was performed to determine these rates.

Methods:

Patients ≥ 18 years old having stage 0-III breast cancer who received surgery as first treatment between 2010 and 2020 were reviewed in the National Cancer Database (NCDB), the largest national dataset to contain the needed clinical and pathologic staging. Patients were reviewed for correlation between preoperative delay and cancer upstaging, defined as an increase from cT to pT or cN to pN stages, after assessing baseline clinical stage inaccuracy. Accuracy of clinical staging was determined by comparing clinical stages at presentation to pathologic stages at surgeries ≤ 15 days of diagnosis, assuming negligible tumor growth in that period. cN3 and cT3 tumors were excluded as there is no higher size-dependent pathologic stage. Upstaging probabilities and odds ratios (ORs) were estimated with logistic regression, adjusted for age, race, Hispanic ethnicity, gender, histology, grade, phenotype, and clinical T or N stage. For patients with delays > 15 days, adjusted linear regression coefficients of tumor size on preoperative delay were used to estimate primary invasive tumor growth rates.

Results:

Among 1,040,197 patients, the median time between diagnosis and surgery was 34 days (IQR 23-49), with 11.6% having primary tumoral and 14.6% having nodal upstaging. In the 10.2% of patients where surgery was performed ≤ 15 days of diagnosis, 13.9% of DCIS, 11.5% of cT1, and 4.5% of cT2 tumors were upstaged ($p < 0.0001$). For every 30 days of delay between diagnosis and surgery, the ORs for tumor upstaging, adjusted for covariates, were 1.09 for DCIS (95%CI 1.07-1.10, $p < 0.0001$), 1.12 for cT1 (95%CI 1.10-1.14, $p < 0.0001$), and 1.16 for cT2 tumors (95%CI 1.14-1.19, $p < 0.0001$). For invasive tumors, the adjusted 30-d ORs for upstaging in HR+, HER2+, and TN primaries were 1.12 (95%CI 1.11-1.14), 1.11 (95%CI 1.07-

1.15), and 1.19 (95%CI 1.15-1.23), respectively (individual p's < 0.0001). In the 9.8% of clinically N0 (cN0) patients with a diagnosis-to-surgery interval of ≤15 days, 14.2% were upstaged to node-positive. cN0 patients had an adjusted OR for upstaging to node-positive of 1.06 (95%CI 1.05-1.07, p< 0.0001) for every 30 days of delay. The number of 30-d intervals for cT1mi, cT1a, cT1b, cT1c and cT2 invasive primary tumors to grow 1 mm was 7.8, 7.1, 3.9, 2.8, and 2.0, respectively.

Conclusions:

Even when accounting for clinical stage inaccuracy, longer delays are associated with a quantifiable increase in upstaging and likelihood of becoming node-positive at surgery. This may explain the higher disease-specific and overall mortality associated with preoperative delay found in prior studies. With larger tumors having a higher delay-associated likelihood of upstaging and faster growth rates, delays become more problematic as tumor size increases. This information reinforces the need to minimize preoperative delays by demonstrating their consequences. It also provides data to address some of breast cancer patients' most pressing preoperative concerns about how fast breast tumors grow and their upstaging potentials while they await treatment.

Disclosure(s):

Richard J. Bleicher, MD: Consulting Fees (e.g., advisory boards): Elucent Medical (Ongoing)

**Poster Spotlight Session 18: Disparate Care Calls for Desperate Measures:
Understanding Gaps in Quality of Care and Opportunities to Improve it**

Presenting Author(s) and Co-Author(s):

D. Patt. Texas Oncology, Austin, Texas, United States

Disclosure(s):

Debra Patt, MD, PhD, MBA: No financial relationships to disclose

PS18-02

Prevalence of Refusal of Recommended Cancer Treatments and Survival Differences in Breast Cancer Patients: Analysis of the National Cancer Database

Presenting Author(s) and Co-Author(s):

J. Freeman. Department of Public Health Sciences, University of Chicago, Chicago, Illinois, United States

J. Li. Department of Public Health Sciences, University of Chicago, United States

S. Fisher. Northshore University Health System, Evanston, Illinois, United States

K. Yao. Northshore Medical Group, Evanston, Illinois, United States

S. David. NorthShore University HealthSystem, Prizker School of Medicine, The University of Chicago, Chicago, Illinois, United States

D. Huo. Department of Public Health Sciences, The University of Chicago, Chicago, Illinois, United States

Background:

Some breast cancer patients (pts) refused treatment despite their providers' recommendations. Treatment refusals can be detrimental to these pts' short- and long-term health outcomes. Limited research has investigated the national trends in treatment refusals and their impacts on the survival of breast cancer pts.

Methods:

We analyzed data collected from breast cancer pts in the 2004-2020 National Cancer Database (NCDB). Four treatment modalities were assessed: chemotherapy (CT), hormone therapy (HT), radiotherapy (RT), and surgery. The CT cohort included stage I-IV pts. The HT cohort included stage I-IV, hormone receptor-positive pts. The RT or surgery cohort was limited to only stage I-III pts. Refusal status was categorized as "yes/no," and its correlates were assessed using multivariable logistic regression. Estimated rates of overall survival (OS) were calculated using the Kaplan-Meier method. The association between refusal status and OS was examined using log-rank tests, followed by multivariable Cox regression models.

Results:

In the CT cohort, 9.6% of 1,296,488 pts who were offered the treatment refused. In the RT cohort, 6.1% of 1,635,916 pts refused. In the HT cohort, 5.0% of 1,893,339 pts refused. In the surgery cohort, only 0.6% of 2,590,963 pts refused. Significant increasing trends in treatment refusals from 2004-2020 across the four treatment modalities were observed (all p-trends < .001). We found significant differences in age, race, AJCC stage group, molecular subtype, tumor grade, and care access indicators (e.g., insurance, median household income, facility type, and rural/urban area) by refusal status. Black pts were more likely than White pts to refuse surgery (adjusted odds ratio [AOR] 2.01, 95% CI: 1.89-2.14). Asian or Pacific Islander pts were also more likely to refuse surgery (AOR 1.29, 95% CI: 1.15-1.44) and CT (AOR 1.21, 95% CI: 1.16-1.27). Uninsured pts were more likely than privately insured pts to refuse surgery (AOR 4.83, 95% CI: 4.22-5.51), RT (AOR 1.97, 95% CI: 1.83-2.12), CT (AOR 1.61, 95% CI: 1.51-1.72), and HT (AOR 1.61, 95% CI: 1.49-1.73). Compared with pts who did not refuse treatment, those who refused had lower rates of 5-year OS in the cohorts of HT (81.4% vs. 88.4%), CT (74.9% vs. 84.4%), RT (74.4% vs. 90.8%), and surgery (42.0% vs. 88.1%). When stratified by stage, similar patterns of 5-year OS rates were observed across all cohorts. After adjusting for sociodemographic and clinicopathologic factors, pts who refused surgeries had a

higher mortality risk than those who did not (aHR 2.91, 95% CI: 2.82-3.01). Pts who refused RT had a higher risk of dying than those who did not (aHR 1.97, 95% CI: 1.93-2.01). Pts who refused CT had a greater risk of dying than those who did not (aHR 1.86, 95% CI: 1.83-1.90). Pts who refused HT had a greater risk of death than those who did not (aHR 1.56, 95% CI: 1.53-1.59). Black pts had higher mortality risk than their White counterparts across all cohorts (HT: aHR 1.15, 95% CI: 1.13-1.17; CT: aHR 1.14, 95% CI: 1.12-1.16; RT: aHR 1.11, 95% CI: 1.109-1.14; surgery: aHR 1.10, 95% CI: 1.08-1.11).

Conclusions:

In this sample of breast cancer pts, the rate of treatment refusal was highest for CT and lowest for surgery, and there were significantly increased trends in refusals over time. Age, race, stage, molecular subtype, tumor grade, and care access measures were independently associated with treatment refusals, suggesting that differential refusals not only are affected by biological factors but also may reflect disparities in socioeconomic status. Furthermore, pts who refused treatment experienced worse OS, regardless of treatment modality. These findings suggest that stressing the importance of recommended treatment and interventions tailored for this patient population may be needed to improve their survival outcomes.

Disclosure(s):

Jincong Q. Freeman, MPH, MS: No financial relationships to disclose

PS18-03

The Association between Food Deserts, Food Swamps, and Postmenopausal Breast Cancer Mortality in the United States

Presenting Author(s) and Co-Author(s):

M. Bevel. Augusta University, Augusta, Georgia, United States

M. Tsai. Augusta University, United States

A. Parham. Augusta University, United States

S. Andrzejak. Mercer University, United States

S. Jones. Augusta University, United States

J. Moore. University of Kentucky, United States

Purpose:

Breast cancer (BRCA), the 4th leading cause of cancer death in the United States (U.S.), is one of 13 obesity-related cancers. Healthy food consumption is a protective factor shown to decrease obesity risk and postmenopausal BRCA mortality, respectively. However, residing in geographical areas with no access to healthy food options (food deserts) or unhealthy food options (food swamps) reduces access to healthy foods and has been severely understudied. We examined the relationship between residing in food swamps and deserts with postmenopausal BRCA mortality.

Methods:

We conducted an ecological analysis utilizing 2010 – 2020 Center for Disease Control and Prevention postmenopausal BRCA mortality data (restricted to 45+ years old) and aggregated 2012 – 2020 data from the U.S. Department of Agriculture Food Environment Atlas data. Food swamp score (FS) was calculated as the ratio of fast-food and convenience stores to grocery stores and farmer's markets. Food desert score (FD) was calculated as the proportion of residents living more than one mile (urban) or 10 miles (rural) from a grocery store and household income \leq 200% of the federal poverty threshold. We categorized FD and FS to low, moderate, or high; higher scores indicated counties with poorer healthy food resources. Multilevel generalized mixed effects models were used to estimate the mentioned association.

Results:

2,280 counties/county equivalents with high postmenopausal BRCA mortality rates had higher percentage of non-Hispanic (NH)-Black population (5.80 vs. 2.08), poverty rates (17.2 vs. 14.2), and high food swamp scored areas (39.0 vs. 24.5) versus counties/county equivalents with low postmenopausal BRCA mortality rates (p -value < 0.0001). After adjusting for age, percentage of NH-Blacks per county, and poverty rate, we found 42% increased odds of having high postmenopausal BRCA mortality rates among U.S. counties/county equivalents with high food swamp scores (adjusted odds ratio [AOR] = 1.42; 95% CI: 1.14 – 1.78).

Conclusions:

Sampled U.S. counties with the poorest food swamp environment had significantly increased odds of postmenopausal BRCA mortality. We suggest that local policymakers and community stakeholders should employ sustainable approaches at combating obesity and BRCA by increasing healthier accessible food sources (e.g. creating more walkable neighborhoods and community gardens).

Disclosure(s):

Malcolm Bevel, PhD, MSPH: No financial relationships to disclose

PS18-04

Racial disparities in breast cancer and effect of obesity: MammaPrint, Blueprint and whole transcriptome analyses of tumors in Latin American patients in FLEX trial

Presenting Author(s) and Co-Author(s):

M. Mazo-Canola. Mays Cancer Center, San Antonio , Texas, United States

V. Kaklamani. UT Health San Antonio, San Antonio, Texas, United States

P. Advani. Mayo Clinic, United States

S. Kamaraju. Medical College of Wisconsin, Milwaukee, Wisconsin, United States

A. Santillan-Gomez. Texas Oncology – Medical Center, United States

R. Maganini. Ascension Illinois, United States

J. Barone. Vail Health, United States

S. Uygun. Agendia Inc., United States

L. Samraj. Agendia Inc., United States

W. Audeh. Agendia Inc., United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

F. Investigators' Group. Agendia, United States

Background:

Latin Americans are more likely to be diagnosed with aggressive early-stage breast cancer compared to Non-Hispanic White. Multiple factors may contribute to this, including metabolic factors and ancestry. In a previous study, we identified upregulated immune pathway genes in Luminal B tumors from obese Black patients compared to matched White patients. In this study, we report clinical and transcriptomic profiles of breast tumors from Latin and White patients to enhance understanding of factors contributing to aggressive tumor biology in Latin patients.

Methods:

We matched 311 Latin and 311 White breast cancer patients enrolled in FLEX by age, T stage, N stage and clinical subtype (ER/PR and HER2 status). FLEX (NCT03053193) is a prospective, observational trial that includes stage I-III breast cancer patients who receive MammaPrint (with or without Blueprint) as standard of care and consent to whole transcriptome and clinical data collection. MammaPrint is a 70-gene risk of distant recurrence signature that classifies patients as Low Risk or High Risk. Blueprint is an 80-gene molecular subtyping signature, categorizes tumors as Luminal-, HER2- or Basal-Type. MammaPrint further groups Luminal into A (Low Risk) and B (High Risk). ImPrint is a 53-gene signature that has been shown to predict the likelihood of achieving pCR with PD1-PDL1 immune checkpoint inhibitors. Statistical analyses on groups were conducted using arsenal R package and p-value < 0.05 was considered significant. Whole transcriptome comparisons were made, using limma R package, between Latin and White patients stratified by Blueprint subtype Luminal and weight categories normal (body-mass-index (BMI) 18.5 to < 25) and obese (BMI ≥30). Significant differentially expressed genes had an adjusted p-value < 0.05. Gene set enrichment analysis (GSEA) was conducted using fgsea R package.

Results:

Latin patients had significantly higher percentage of type 2 diabetes (23.3% vs 8.5%), BMI obese (49.0% vs 39.4%), Blueprint Basal (14.8% vs 9.3%) and ImPrint Immune Sensitive

(12.0% vs 5.1%) compared to matched White patients. When comparing whole transcriptome of tumors from Latin and White patients, only tumors stratified by Luminal B and obesity resulted in differentially expressed genes: Latin patients had higher expression (>2-fold change) of 42 immunoglobulin genes compared to White, with only IGKV6-21 being statistically significant. Additional immune related genes such as IKZF1 and AGER, as well as UTS2 (gene encoding a vasoconstrictor agent and contributor of angiogenesis) were significantly upregulated in Latin patients. Upregulation of immune related pathways such as inflammatory response, interferon alpha/gamma response and downregulation of adipogenesis, oxidative phosphorylation and MYC targets were identified in Latin patients compared to White using GSEA Hallmarks gene sets.

Conclusion:

There were additional clinical and genomic differences between tumors from Latin and White patients, even when controlling for age, T stage, N stage and clinical subtype. Particularly, there were more type 2 diabetes, BMI obese, BluePrint Basal, and ImPrint Immune Sensitive among Latin patients. In addition, transcriptomic differences between obese Latin and matched White patients were found in Luminal B subgroup that may contribute to the aggressive tumor biology; immunoglobulin genes and immune related pathways were associated with higher expression in Latin patients. This study suggests that biological differences in breast tumors, particularly from obese patients, may result from shared background and reflects the need for inclusion of diverse patient groups in clinical trials.

Disclosure(s):

Marcela Mazo-Canola, MD: No financial relationships to disclose

Virginia Kaklamani, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo |Astrazeneca (Ongoing), Gilead Science (Ongoing), Loxo@Lilly (Ongoing), Menarini/Stemline (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), SeaGen (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Daiichi Sankyo |Astrazeneca (Ongoing), Gilead Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Eisai, Inc (Ongoing)

Joyce O'Shaughnessy, MD: Consulting Fees (e.g., advisory boards): Agendia (Ongoing), Aptitude Health (Ongoing), AstraZeneca (Ongoing), Carrick Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), ELY LILLY (Ongoing), F. Hoffman La Roche Ltd (Ongoing), G1-Therapeutics (Ongoing), Genentech (Ongoing), Loxo@Lilly (Ongoing), Merck Sharp & Dohme, Lda. (Ongoing), Novartis (Ongoing), Ontada (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Samsung Bioepis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing), Synthon (Ongoing)

PS18-07

Trends in Guideline Concordant Care for Inflammatory Breast Cancer: An analysis of the National Cancer Database

Presenting Author(s) and Co-Author(s):

B. Diskin. Memorial Sloan Kettering Cancer Center, New York, New York, United States

A. Tadros. Memorial Sloan Kettering Cancer Center, United States

V. Sevilimedu. Memorial Sloan Kettering Cancer Center, United States

A. Xu. Memorial Sloan Kettering Cancer Center, United States

P. Vingan. Memorial Sloan Kettering Cancer Center, United States

J. Nelson. Memorial Sloan Kettering Cancer Center, United States

Y. Iwai. UNC, United States

M. Morrow. Memorial Sloan Kettering Cancer Center, New York, New York, United States

O. Fayanju. Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background:

Inflammatory breast carcinoma (IBC) is an aggressive form of breast cancer associated with worse survival outcomes compared with other subtypes of breast cancer. Black patients with IBC have worse survival outcomes than White patients. Trimodality treatment (TMT) which includes neoadjuvant chemotherapy (NCT) followed by modified radical mastectomy without immediate reconstruction (MRM), and postmastectomy radiotherapy (PMRT), has been associated with improved survival outcomes for patients with IBC. Whether receipt of TMT varies by race, ethnicity, and insurance status and its impact on survival is largely unknown.

Methods:

Adult female patients with non-metastatic IBC treated from 2010-2018 were identified from the NCDB. Guideline concordant care (GCC) was defined as TMT administered in the correct sequence. In addition, clinical tumor/nodal stage, age, race, ethnicity, facility type, patient location, insurance status, and pathologic complete response (pCR) were examined for each patient. Additional quality metrics of GCC examined included time to initiation of NACT < 60 days (TTNC) and proper surgical care defined as complete axillary lymph node dissection (>6 lymph nodes removed) at the time of MRM without reconstruction. Univariate and multivariate mixed methods were performed to determine association between patient, treatment, and facility-level factors and receipt of GCC, TTNC < 60 days, and proper surgical care. OS was estimated using the Kaplan-Meier method, and the log-rank test was used to compare groups.

Results:

7,374 women with non-metastatic IBC were included. 78% were White, 17% Black, and 2.5% Asian/Pacific Islander patients; 7.7% identified as Hispanic and 92% as non-Hispanic. The majority had private insurance (51%), 29% Medicare, 14% Medicaid, 4.9% uninsured, and 1.3% other government insurance. Only 2,418 patients (32.7%) received GCC with only 29% undergoing MRM without reconstruction. Receipt of GCC was more common among patients age >50 years, patients with higher clinical nodal burden and those treated from 2010-2013 ($p=0.001$). Receipt of GCC did not differ by race, ethnicity, insurance status, or location. 92% (6,005/7,374 patients) received NAC within 60 days of diagnosis. Both Black (OR 0.58, 95% CI 0.46-0.74, $p < 0.001$) and Asian (OR 0.52, 95% CI 0.30-0.90, $p < 0.001$) patients with IBC

were less likely to have TTNC < 60 days when compared to White patients. Non-Hispanic patients (OR 2.24, 95% CI 1.65-3.03, $p < 0.001$) and those with private insurance (OR 1.82, 95% CI 1.23-2.68, $p < 0.001$) were more likely to have TTNC within 60 days of diagnosis. Patients with lower clinical nodal burden (cN0) were less likely to undergo proper surgery compared to patients with higher nodal burden (cN1-3) ($p < 0.001$). In addition, patients treated in a more contemporary cohort (2014-2018) were less likely to undergo proper surgery compared to patients treated earlier (2010-2013) (OR 0.82, 95% CI 0.73-0.92, $p < 0.001$). Among IBC patients receiving GCC, Black patients had significantly worse overall survival compared to White patients ($p < 0.001$)

Conclusions:

The majority of patients with IBC do not receive GCC and GCC has decreased since 2014 with fewer patients undergoing appropriate surgical treatment. The very low level of GCC indicates a need for multidisciplinary education, while improvement in TTNC may improve outcomes among racial/ethnic minorities.

Disclosure(s):

Brian Diskin, MD: No financial relationships to disclose

Monica Morrow, MD: No financial relationships to disclose

PS18-08

Bridging Disparities in Survivorship Care: Leveraging Telehealth for Diverse Patients in Safety Net Hospital

Presenting Author(s) and Co-Author(s):

I. Leung. University of California, San Francisco, San Francisco, California, United States

E. Trejo. University of California, San Francisco, United States

A. Velázquez Mañana. University of California, San Francisco, United States

E. Castillo. San Francisco Department of Public Health, United States

B. Cicerelli. San Francisco Department of Public Health, United States

R. McBride. San Francisco Department of Public Health, United States

P. Wong. San Francisco Department of Public Health, United States

H. Xie. San Francisco Department of Public Health, United States

L. Zhang. San Francisco Department of Public Health, United States

N. Burke. University of California, San Francisco, United States

N. Dixit. University of California, San Francisco, United States

Background

There are 3.8 million breast cancer survivors (BCS) in the United States and 67-88% of them report unmet needs in survivorship care. With advancements in breast cancer treatment and improved survival rates, there is a growing need to expand survivorship care to address the long-term physical, psychosocial, and medical needs of cancer survivors. There is a significant disparity in access to high-quality survivorship care, particularly for diverse patient populations in safety net hospitals. BCS in marginalized communities experience worse health-related quality of life (HRQOL) outcomes following cancer treatment in the management of symptoms, complications of treatment, and overall health-related distress. Thus, new models that leverage complex care management principles and novel care delivery systems, such as telehealth, are needed to provide multidisciplinary care and support for self-management.

Methods

We conducted a single-arm, pilot intervention trial of telehealth group medical visits (tGMV) in a safety net hospital serving low-income and racially and ethnically diverse BCS. The study team included physicians, advanced practitioners, PCPs, clinical psychologists, nurses, dietitians, exercise instructors, Traditional Chinese Medicine practitioners, sexual health counselors, research coordinators, and patient navigators. We enrolled a total of 6 cohorts of 7-10 BCS for the tGMV intervention (2 cohorts each in English, Spanish, and Cantonese). Each cohort had four weekly sessions on the following topics: 1) Reclaiming your health after cancer, 2) Managing emotional health, 3) Sexual health and relationship, and 4) Food is medicine. All participants were trained on the telehealth video conference platform. The curriculum was culturally adapted in the Spanish and Cantonese cohorts. Study staff followed up with participants by phone after each session. We evaluated feasibility and acceptability as primary outcomes with prespecified thresholds for >90 % completion of planned sessions and >70% attendance. Participants' evaluation of the intervention and self-efficacy were secondary outcomes, which are not reported in this abstract.

Results

Fifty-three women with stage I-III breast cancer were enrolled in the study. The age was 37 to

75 (median: 58). There were 14 (26%) English-speaking participants, 19 (36%) Spanish-speaking participants, and 20 (38%) Cantonese-speaking participants. Eight (15%) participants identified as White, three (5.7%) Black A/A, 23 (43%) Asians, and 19 (36%) Hispanic; 43 (81%) participants were foreign-born. Twenty-seven (51%) participants reported food insecurity on the screening survey. The overall attendance rate was 98% (English: 97%, Spanish: 97%, and Cantonese: 100%). Of the 53 participants, 41 (77%) found the telehealth format acceptable, 47 (88%) agreed/strongly agreed that it was easy to log in and stay connected, 53 (100%) agreed/strongly agreed that tGMV were a good use of their time, 52 (98%) understood the purpose of the telehealth format, and 50 (94%) felt the information was easy to understand.

Conclusions

Telehealth-delivered group medical visits are feasible and acceptable in a safety net setting and are a promising intervention that may help in addressing the unmet needs of cancer survivors. We also found that despite the reported low uptake of telehealth in safety net settings, emphasis on training and technical support during sessions can increase the utilization of telehealth.

Disclosure(s):

Ivan C. Leung, MS: No financial relationships to disclose

PS18-09

The DARC side of Breast Cancer - DARC, Duffy-null and African ancestry influence in the Triple Negative Breast Cancer tumor microenvironment

Presenting Author(s) and Co-Author(s):

R. Martini. Morehouse School of Medicine, Atlanta, Georgia, United States

S. Patino. Weill Cornell Medical College, United States

E. Guyonnet. Weill Cornell Medical College, United States

B. Stonaker. Weill Cornell Medical College, United States

I. Elhoussein. Johns Hopkins, United States

J. Sahler. Cornell University, United States

A. August. Cornell University, United States

N. Manley. Arizona State University, Arizona, United States

R. Kittles. Morehouse School of Medicine, United States

C. Yates. Johns Hopkins, United States

L. Newman. Weill Cornell Medicine, New York, New York, United States

M. Davis. Morehouse School of Medicine, United States

Background.

Despite a recent convergence of breast cancer (BC) incidence rates between African American (AA) and European American (EA) women, AA women continue to have ~40% higher mortality rates. BC is a heterogeneous collection of diseases, where African ancestry women are disproportionately burdened with the most aggressive subtype of BC, triple negative BC (TNBC). We have previously reported that the African ancestry-specific Duffy-null allele (FY-) is a risk factor for TNBC diagnoses. FY- is a promoter variant that removes expression of the Duffy Antigen Receptor for Chemokines (DARC/ACKR1), from red blood cells (RBCs). DARC serves as a portal of entry for Plasmodium vivax malaria parasite, and FY- confers immunity, leading to fixation of FY- among Sub-Saharan African populations. DARC is an atypical chemokine receptor that functions to modulate chemokine levels in circulation and tissues to aid immune cell recruitment. DARC is also expressed on breast tumor epithelial cells, however the significance of DARC in the TNBC tumor microenvironment (TME) has not fully been explored. Leveraging our African ancestry enriched International Study for the Center of Breast Cancer Subtypes cohort and in vivo murine models, we employed multi-omics approaches to explore the function of FY- and DARC expression across cell types in the TNBC TME.

Genomics.

Using transcriptomic data from the TCGA BC cohort, we have previously reported that DARC expression is highly correlated with deconvoluted immune cell abundance using CIBERSORT. To build upon this finding among TNBC patients, we have analyzed RNAseq data from two cohorts of African ancestry women to explore correlation of DARC expression status and immune cell abundance. Among TNBC cases, we report that higher DARC expression was significantly associated with increased immune cell abundance, with increases in B cell, T cell and monocyte populations. Using whole genome sequencing data across 86 African ancestry cases, we are currently investigating germline FY- status with mutational signatures.

Circulating biomarkers.

Patient plasma was collected prior to surgery, where Luminex multiplex assays were performed

to quantify levels of >40 circulating chemokines and cytokines. FY- status has been determined for ~550 patients using single-plex or multiplex PCR genotyping methods from germline saliva DNA. Our univariate analyses show several circulating chemokines, including CCL2, CXCL2, CXCL6 and CXCL11, have significant differences between FY- and non-FY- BC patients. Curation of clinicopathological variables for multivariate analysis is ongoing.

Murine models.

We crossed C3(1)Tag BC transgenic mice with a DARC knock-out (KO) line to generate mice lacking DARC expression that spontaneously develop tumors in the mammary fat pads. The C3(1)Tag model is reported to have similar gene expression profiles to basal-like TNBC tumors. Tumors were collected at pre-determined time points of 25 and 30 weeks, where DARC KO mice had increased tumor size and tumor burden at 30 weeks. Initial fluorescent staining revealed an increase in immune cell infiltration in the TME of DARC expressing mice compared to DARC KO mice. To further explore this, we employed multiplex staining across a representative cohort of DARC expressing and KO mice at 25 and 30 weeks to capture the specific immune cell populations infiltrating the TME.

Conclusions.

TNBC tumors have worse prognosis due to lack of targeted therapeutic options. Increased immunogenicity of TNBC tumors, especially among African ancestry women may be driven in part by DARC expression. Characterization of FY- status, in coordination with DARC among other cell types in the TNBC TME could present new opportunities for biomarker and/or therapeutic development to improve prognosis for these underserved populations.

Disclosure(s):

Rachel Martini, PhD: No financial relationships to disclose

PS18-10

Tumor-Infiltrating Lymphocytes and Breast Cancer Mortality in Racially and Ethnically Diverse Participants of the Northern California Breast Cancer Family Registry

Presenting Author(s) and Co-Author(s):

J. Ransohoff. Stanford University School of Medicine, Palo Alto, California, United States

I. Miller. Stanford University School of Medicine, United States

J. Koo. Stanford University School of Medicine, United States

V. Joshi. Stanford University School of Medicine, United States

A. Kurian. Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California, United States

K. Allison. Stanford University School of Medicine, United States

E. John. Stanford University, United States

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

Purpose:

Greater stromal tumor-infiltrating lymphocyte (sTIL) percentage in pre-treatment breast tumor specimens is associated with superior response to neoadjuvant chemotherapy and survival. We hypothesized that sTIL-survival associations vary by race and ethnicity and mediate survival disparities.

Patients and Methods: We evaluated pre-treatment percentages of sTILs in deciles for 284 women enrolled in the Northern California Breast Cancer Family Registry and diagnosed with a first primary invasive breast cancer from 1995-2005. We assessed associations of continuous sTIL scores and lymphocyte-predominant breast cancer (LPBC, defined as $\geq 50\%$ lymphocytic infiltration of tumor stroma or cell nests) with clinical and epidemiologic characteristics using regression analysis and with breast cancer-specific mortality (BCM) and overall mortality (OM) using Cox proportional hazards regression.

Results:

The cohort was diverse (64% from racially and ethnically minoritized populations) with near-complete (98%) germline BRCA1/2 testing and long-term follow-up (average 16.2 years, range: 1.3-26.7). In multivariable analyses, higher sTIL score was associated with reduced BCM [LPBC versus non-LPBC: HR=0.44 (95% confidence interval 0.20-0.98); and per decile increase in sTIL score: HR=0.80 (0.69-0.93)], with the strongest association in the subset of patients with hormone receptor-negative disease [HR=0.71 (0.57-0.88) and HR=0.37 (0.14-0.94), respectively]. While there was no significant difference in sTIL score between racial and ethnic groups, the continuous sTIL-survival association was statistically significant among non-Hispanic White [HR=0.73 (0.57-0.94)] and Asian American [HR=0.56 (0.35-0.89)] women but was not seen among African American and Hispanic women.

Conclusion:

We identified novel sTIL-BCM differences by race and ethnicity, with better survival associated with sTIL enrichment among non-Hispanic White and Asian American but not among African American or Hispanic women. Additional studies are needed to determine whether survival and particularly the response to immunotherapy are differentially mediated by immune factors between racial and ethnic groups.

Multivariable Cox Proportional Hazards Regression Models of Breast Cancer-Specific and Overall Mortality.

Multivariable Cox Proportional Hazards Regression Models of Breast Cancer-Specific and Overall Mortality.

Group	Cases N	Deaths N	Breast Cancer-Specific Mortality HR (95% CI)		Deaths N	Overall Mortality HR (95% CI)	
			sTIL Per decile increase	LPBC vs non- LPBC		sTIL Per decile increase	LPBC vs non- LPBC
Overall^a	284	70	0.80 (0.69-0.93)	0.44 (0.20-0.98)	100	0.88 (0.79-0.99)	0.66 (0.37-1.20)
Breast cancer subtype^a							
ER ⁺ and/or PR ⁺	161	56	0.83 (0.62-1.10)	0.30 (0.04-2.32)	56	0.94 (0.76-1.16)	0.67 (0.20-2.31)
ER ⁺ and PR ⁻	123	30	0.71 (0.57-0.88)	0.37 (0.14-0.94)	44	0.81 (0.69-0.95)	0.57 (0.28-1.20)
TNBC	71	15	0.71 (0.53-0.96)	0.26 (0.06-1.09)	23	0.90 (0.73-1.11)	0.90 (0.34-2.41)
Race and ethnicity^{b,c}							
Non-Hispanic White	102	28	0.73 (0.57-0.94)	0.12 (0.02-0.89)	43	0.87 (0.74-1.03)	0.47 (0.18-1.23)
Asian American	76	15	0.56 (0.35-0.89)	0.19 (0.02-1.49)	19	0.65 (0.46-0.92)	0.30 (0.07-1.34)
African American	38	12	0.99 (0.68-1.42)	2.13 (0.37-12.42)	16	0.95 (0.68-1.32)	1.73 (0.33-9.11)
Hispanic	67	13	0.94 (0.66-1.32)	1.23 (0.29-5.15)	23	0.94 (0.72-1.24)	1.06 (0.33-3.44)

Abbreviations. HR: hazard ratio; CI: confidence interval; LPBC: lymphocyte-predominant breast cancer; sTIL: stromal tumor infiltrating lymphocyte; ER⁺: estrogen receptor-positive; ER⁻: estrogen receptor-negative; PR⁺: progesterone receptor-positive; PR⁻: progesterone receptor-negative; TNBC: triple-negative breast cancer (ER⁻, PR⁻, HER2⁻).

^a Models for breast cancer-specific and overall mortality for the overall cohort and for breast cancer subtypes were adjusted for prognostic variables including age at diagnosis, cancer stage (I vs II vs III/IV/unknown), pre-diagnosis BMI (<25, 25-29.9, >30 kg/m²), and germline *BRCA2* pathogenic variant status.

^b Models for breast cancer-specific and overall mortality by race and ethnicity were adjusted for age at diagnosis, stage (I vs II/III/IV/unknown), pre-diagnosis BMI (<30 vs ≥30 kg/m²), and germline *BRCA2* pathogenic variant status.

^c Excludes 1 Native American patient.

Disclosure(s):

Julia D. Ransohoff, MD: No financial relationships to disclose

Allison W. Kurian, MD, MSc: No financial relationships to disclose

Melinda Telli, MD: Advisory Committee/Board Member: Blueprint Medicine (Terminated, July 20, 2023), Natera, Inc. (Terminated, July 20, 2023), Novartis Pharma GmbH (Terminated, July 20, 2023), Reflexion Medical (Terminated, July 20, 2023), Replicate (Terminated, July 20, 2023), Sanofi Aventis (Terminated, July 20, 2023); Consulting Fees (e.g., advisory boards): Astra Zeneca (Terminated, July 20, 2023), Daiichi-Sankyo (Terminated, July 20, 2023), G1 Therapeutics (Terminated, July 20, 2023), Gilead Science (Terminated, July 20, 2023), Guardanth health (Terminated, July 20, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Arvinas (Ongoing), Astra Zeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Genentech-Roche (Ongoing), Hummingbird Biosciences (Ongoing), Merck & Co., Inc. (Ongoing), OncoSec (Ongoing), Pfizer, Inc. (Ongoing)

PS16-01

Comparison of an Atezolizumab monotherapy window followed by Atezolizumab and chemotherapy vs. Atezolizumab and chemotherapy alone in triple negative breast cancer (TNBC) – final analysis of the neoadjuvant neoMono trial

Presenting Author(s) and Co-Author(s):

H. Kolberg. Department of Gynecology and Obstetrics, Marienhospital Bottrop, Bottrop, Nordrhein-Westfalen, Germany

J. Schumacher. palleos healthcare GmbH, Germany

R. Erber. University Hospital Erlangen, Germany

M. Braun. Rotkreuzklinikum München, Germany

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

E. Grischke. Universitäts-Frauenklinik Tübingen, Eberhard Karls University, Tübingen, Germany

C. Schem. Mammazentrum am Krankenhaus Jerusalem, Hamburg, Germany

M. Lux. St. Vincenz-Kliniken Paderborn, Germany

M. Deryal. CaritasKlinikum Saarbrücken, Germany

O. Hoffmann. University Hospital Essen, Germany

B. Heinrich. HOP - Hämatologisch-onkologische Praxis Augsburg, Germany

G. Kunz. Department of Gynecology and Obstetrics, Johannes-Hospital Dortmund, Germany

K. Lübbe. Diakovere Henriettenstift, Breast Center, Hannover, Germany

P. Krabisch. Department of Gynecology and Obstetrics, Klinikum Chemnitz, Germany

A. Hartmann. University Hospital Erlangen, Germany

P. Raeth. palleos healthcare GmbH, Germany

S. Kasimir-Bauer. University Hospital Essen, Germany

C. Kolberg-Liedtke. University Hospital Essen, Germany

Background: Improvement of systemic therapy of TNBC still is a medical need. Exploratory data from the neoadjuvant GeparNuevo trial suggested a benefit from an immune checkpoint inhibitor (ICI) monotherapy window in TNBC. The neoMono trial prospectively analyzed whether the addition of a preceding Atezolizumab monotherapy window prior to Atezolizumab and chemotherapy (CTX) improves pCR rates among patients (pts) with early TNBC. In an interim analysis after 100 pCR events, patients with unselected TNBC did not show a significant benefit from an Atezolizumab monotherapy window, while an exploratory analysis suggested a highly clinically relevant benefit among pts with PD-L1 positive TNBC. Here we present the final primary endpoint analysis. Methods: NeoMono is a phase 2 randomized multicenter trial that was planned to recruit a maximum of 458 female and male pts with primary TNBC (defined as ER/PR < 10% and HER2 negative) with tumor stages cT1c – cT4d (cN0 and cN+). As the protocol mandated termination of trial recruitment based on the results of the interim analysis, the final ITT population was limited to 359 pts. PD-L1 status had to be identifiable by central pathology by means of the VENTANA PD-L1 (SP142) assay and was defined by PD-L1 expression on immune cells (IC). Neoadjuvant treatment in both study arms consisted of Atezolizumab 1200 mg every 3 weeks in addition to neoadjuvant CTX (12 x Carboplatin/Paclitaxel q1w followed by 4x Epirubicin/Cyclophosphamide q3w). Combination

therapy in arm A was preceded by an Atezolizumab monotherapy window of 840 mg once two weeks prior to initiation of combination therapy, while patients in arm B received no immune monotherapy window. Study goals are to compare the efficacy of neoadjuvant CTX + Atezolizumab with versus without a two-week atezolizumab monotherapy window preceding CTX + ICI (primary endpoint: pCR) and to identify biomarkers for response and resistance through analysis of sequential tissue and liquid biopsies. The neoMono statistical design uses Bayesian posterior probabilities (uniform prior distribution) and logistic regression to analyze the primary endpoint. Results: 180 pts in arm A and 179 in arm B from 34 study sites were included in the final primary endpoint analysis. Demographics and baseline characteristics as well as drug exposure were well-balanced in both arms. Posterior mean pCR rates in the ITT population in study arms A and B were 65.7% (95% high posterior density interval (HPDI): 58.5%, 72.5%) and 69% (62.2%, 75.9%), respectively. In an exploratory analysis stratified by PD-L1 IC status (negative: < 1% versus positive: ≥ 1%), pCR rates in arm A were 91.5% in the PD-L1 IC-positive group and 56.1% in the PD-L1 IC-negative group, the corresponding pCR rates in arm B were 82.2% and 64.5%, respectively. In a multivariate analysis of the ITT population including tumor size, nodal status, tumor grade, age and PD-L1 status, the odds ratio for achieving a pCR was 4.77 ($p < 0.001$) for PD-L1-positive and 2.36 ($p=0.023$) for grade 3 tumors. In an exploratory analysis including HER2 status, odds for achieving a pCR were significantly higher for patients with HER2-negative (IHC 0) vs. HER2-low tumors (OR 1.73, $p=0.036$). No new safety signals were observed. Conclusion: The final primary endpoint analysis of the neoMono trial demonstrated the highest pCR rates ever reported in a phase II/III trial in TNBC. While a significant impact of an ICI monotherapy window on the pCR rate after combination of CTX + ICI in an unselected ITT population could not be demonstrated, neoMono indicates for the first time in a randomized prospective setting that patients with immune active TNBC might derive particular benefit from a preceding ICI monotherapy window. The results of the neoMono trial are mainly justifying the conduction of a confirmative trial in immune active TNBC. However, our results underscore the potential role of pre-therapeutic ICI monotherapy window as part of future therapeutic concepts in TNBC.

PS16-03

Intratumoral dosing of INT230-6 in Early-Stage Breast Cancer Patients Induces Tumor Cell Necrosis and Immunomodulatory Effects: A Phase II Randomized Window-Of-Opportunity Study – the INVINCIBLE Trial

Presenting Author(s) and Co-Author(s):

A. Arnaut. Ottawa Hospital/Ottawa Hospital Research Institute/Ontario Institute of Cancer Research, Ottawa, Ontario, Canada

L. Bender. Intensity Therapeutics, Westport, Connecticut, United States

M. Hopkins. Ontario Institute for Cancer Research, Canada

V. Lopez Ozuna. Ottawa Hospital Research Institute, Canada

L. Liao. Ontario Institute for Cancer Research, Canada

S. Robertson. Ottawa Hospital, Ottawa, Ontario, Canada

V. Talebian. Ontario Institute for Cancer Research, Canada

K. Keyhanian. Ottawa Hospital, Canada

A. Awan. The Ottawa Hospital Cancer Centre, Canada

F. Abbate. Intensity Therapeutics, Inc., United States

I. Walters. Intensity Therapeutics, westport, Connecticut, United States

G. Pond. McMaster University, United States

J. Bartlett. Ontario Institute of Cancer Research, United States

L. Radvanyi. Ontario Institute for Cancer Research, Canada

M. Spears. Diagnostic Development, Ontario Institute for Cancer Research, Toronto, Ontario, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

Background: Larger tumors pose an increased risk for breast cancer (BC) recurrence post-surgery. In addition, most BC outside of the triple negative subtype are considered immunological quiescent and minimally responsive to immunotherapies. One potential method to combat disease recurrence risk and induce immune activation pre-surgery is through a local therapy that could cause cell death to expose tumor antigens, provide adjuvants for anti-tumor immune priming, and thus potentially increase responsiveness to immunotherapies or rates of pathological complete response in combination with chemotherapy. We have conducted a randomized, Phase 2 presurgical Window-Of-Opportunity trial for intratumoral (IT) INT230-6 comprising vinblastine, cisplatin and a diffusion enhancer (SHAO) in patients with early-stage operable BC, the INVINCIBLE trial (NCT04781725). Previous in vivo and clinical studies demonstrated that INT230-6 induces cancer cell death and halts replication while maturing dendritic cells and recruiting T-cells into the tumor. In this trial, IT injections of INT230-6 were conducted to 1) evaluate the safety of regional cytotoxic use on BC, 2) assess the drug's ability to cause necrosis, 3) assess immune response within the tumor, microenvironment and systemically prior to surgical resection, and 4) understand the genetic pathways involved in immune activity. **Methods:** Women awaiting surgery for newly diagnosed early-stage intermediate or high-grade T1-T2 invasive BC were recruited to the trial. The study has two parts. Part I was a randomized (2:1) open label trial comparing 1-3 doses of INT230-6 injected weekly versus no treatment prior to surgery to evaluate safety, feasibility, and optimal drug dosing. Part II was a double-blinded randomized (2:1) trial where patients received one IT dose of INT230-6 vs saline injection IT. **Results:** We successfully recruited 91 patients with age

ranges of 40-77 yrs (mean of 60 yrs) with tumor size ranging from 1.1 - 4.8 cm (mean 2.5 cm; SD 0.9 cm). The most common (>10%) AEs were injection site pain, injection site reaction and nausea/vomiting. Approximately 90% of AEs were grade 1. In the study INT230-6 induced necrosis in 64% of subjects (37 out of 58, range 0 to 100%); whereas saline induced partial necrosis in 25% of patients (5 out of 20, range 0 to 10%). The table below shows the results of necrosis for INT230-6 use in the entire study compared to saline injection for all subjects and those with tumors of size T2. A single injection of INT230-6 caused necrosis in various histologies, including invasive lobular carcinoma. Gene expression analysis showed significant differential gene expression between the baseline biopsy and surgical specimens using INT230-6. Pathway analysis identified genes associated with TCR signaling, B cells and T cell activation that were significantly upregulated in the post INT230-6 treatment samples. There was a relative increase in CD4 and CD8 T cells and B and mast cells. Conclusion: Preliminary evidence shows that a single dose of INT230-6 can cause significant intratumoral necrosis compared to saline especially in tumors >2. cm. INT230-6 stimulates an immune response in breast cancers prior to surgery with minimal adverse effects and good tolerability. Given its immune activation properties, INT230-6 shows promising potential in future breast cancer neoadjuvant studies.

Table 1: INVINCIBLE Study Tumor Necrosis Results

INT230-6 IT injection	(N)	Average tumor size (cm)	% subjects with necrosis	Average % necrosis
All subjects	58	2.5	64%	19.3
Tumors T2 (>2 cm)	39	2.1	74%	25
Saline IT injection				
All subjects	20	2.1	25%	0.86
Tumors T2 (>2 cm)	7	2.4	14%	0.14
p-value for necrosis: INT230-6 compared to saline				
All subjects	0.003			
Tumors T2 (>2 cm)	0.021			

Intratumoral INT230-6 injection compared to IT saline injection

PS16-04

Denosumab as an enhancer of the immune infiltrate in hormone receptor-positive early breast cancer. Subgroup analysis from the D-Biomark window-of-opportunity clinical trial (NCT03691311)

Presenting Author(s) and Co-Author(s):

A. Vethencourt. Institut Català d'Oncologia, Oncology Department, Barcelona, Spain. Insitut d'Investigació Biomèdica Bellvitge IDIBELL, Barcelona, Catalonia, Spain

E. Trinidad. Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, Barcelona, Spain

E. Dorca. University Hospital of Bellvitge and Institut Català d'Oncologia, Pathology Department, Barcelona, Spain

A. Petit. University Hospital of Bellvitge and Institut Català d'Oncologia, Pathology Department, Barcelona, Spain

T. Soler-Monsó. University Hospital of Bellvitge and Institut Català d'Oncologia, Pathology Department, Barcelona, Spain

A. Stradella. Institut Català d'Oncologia, Oncology Department, Barcelona, Spain

C. Capo. Viladecans Hospital. Institut Català d'Oncologia, Gynecology Service and breast unit, Barcelona, Spain

A. Urriticoechea. Oncologikoa, United States

M. Matas. Althaia Xarxa Assistencial Universitària, Oncology Department, Barcelona, Manresa, Spain

G. Pérez-Chacon. Spanish National Cancer Research Center (CNIO), Madrid, Spain

M. Jimenez. Spanish National Cancer Research Center (CNIO), Madrid, Spain

M. Ciscar. Spanish National Cancer Research Center (CNIO), Madrid, Spain

E. Brizzi. Hospital Universitario La Paz, Pathology Department, Madrid, Spain

G. Soria Alcaide. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

G. Gomez. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

E. Piñeiro. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

E. Purqueras. University Hospital of Bellvitge and Institut Català d'Oncologia, Pathology Department, Barcelona, Spain

A. Garcia. Hospital of Bellvitge and Institut Català d'Oncologia , Gynecology Service and breast unit, Barcelona, Spain

A. Iserte. Insitut d'Investigació Biomèdica Bellvitge IDIBELL, Barcelona, Spain

M. Pla. Hospital of Bellvitge and Institut Català d'Oncologia , Gynecology Service and breast unit., Barcelona, Spain

M. Campos. Hospital of Bellvitge and Institut Català d'Oncologia , Gynecology Service and breast unit., Barcelona, Spain

M. Gil-Gil. Institut Català d'Oncología, Insitut d'Investigació Biomèdica Bellvitge. GEICAM Spanish Breast Cancer Group, United States

S. Pernas. SOLTI Cancer Research Group, Barcelona, Spain Institut Catala d'Oncologia; IDIBELL, L'Hospitalet, Barcelona, Spain

E. Gonzalez-Suarez. Spanish National Cancer Research Center (CNIO), Madrid , Spain. IDIBELL, Institut d'Investigacio Biomédica de Bellvitge, Barcelona, Spain

C. Faló. Institut Català d'Oncologia, Oncology Department, Barcelona, Spain

Background: The receptor activator of nuclear factor κ B (RANK) signaling pathway has emerged as a therapeutic target in breast cancer (BC). Recent studies indicate that inhibition of the RANK pathway induces tumor cell differentiation and may enhance the anti-tumor immune response. The D-Biomark clinical trial aims to evaluate the antitumor (antiproliferative and proapoptotic) and immunomodulatory effects of denosumab in HER2-negative early BC. Methods: Patients with early HER2-negative BC scheduled for primary surgery were randomized in a 2:1 ratio to receive two doses of 120 mg denosumab on days 1 and 8 vs no treatment before surgery. Immunohistochemistry (IHC) was used to assess Ki67 (proliferation), cleaved caspase-3 (cell survival), RANK and RANKL. Stromal tumor infiltrating lymphocytes (TILs) and serum markers including free RANKL (sRANKL), tartrate-resistant acid phosphatase 5b (TRACP5b), and osteoprotegerin (OPG) were also analyzed. Paired t-test was used to compare values between core biopsy (biopsy A) and surgical samples (biopsy B). Subgroup analysis by intrinsic subtype was performed on 47 matched cases using PAM50. Results: Between July 2019 and May 2021, we enrolled 60 patients, 58 evaluable, including 10 triple-negative breast cancer (TNBC). The clinicopathologic characteristics of the population at the time of enrollment were well balanced, but the TNBC recruited included 5 out of 10 tumors with a more indolent behavior than the typical tumors of this lineage (apocrine tumors, low cell proliferation). Due to this and the small number of cases, no conclusions can be drawn in this subgroup. RANK expression was detected in 19 tumor cases, while 17 cases expressed RANKL. The treated group showed a decrease in sRANKL ($p < 0.000$), indicating denosumab activity, while the control group showed no change ($p = 1.0$). OPG levels in the experimental group showed a non-significant increase ($p = 0.07$), while TRACP5b remained unchanged. Both groups showed a non-clinically relevant increase in cell proliferation (5 percentage points), control $p = 0.04$, experimental $p = 0.01$. Subgroup analysis of tumors with RANK+ or RANKL+ tumor cells also showed no reduction in Ki67. Cell survival did not decrease in the overall cohort (control $p = 0.05$, experimental $p = 0.24$), nor in subgroups or in tumors with RANK+ or RANKL+ tumor cells. Denosumab treatment increased TILs in the overall population (control $p = 0.06$, experimental $p = 0.0006$) and in the subgroups: RANK+ tumors, RANKL+ tumors, premenopausal and postmenopausal, less so in the TNBC group. The subgroup analysis is shown in Table 1. Analysis by intrinsic subtype showed that in the experimental group there was an increase in cases with a change to luminal A lineage (17%) compared to the control group (6%), suggesting a possible cellular differentiation towards less aggressive tumors. Although the number of patients is small, these changes warrant further investigation and highlight the role of denosumab as an immune activator in these luminal tumors known for their low inflammatory infiltrate. Conclusion: Two doses of denosumab prior to surgery did not reduce proliferation or increase apoptosis. However, this short course of denosumab increased TILs in early BC, particularly in luminal tumors, and may induce tumor cell differentiation into luminal A-like tumors.

Table 1. Analysis by subgroups

RESPONSE VARIABLE	LUMINAL BREAST CANCER N=48				TNBC N=10 *			
	CONTROL	UP/DOWN	EXPERIMENTAL	UP/DOWN	CONTROL	UP/DOWN	EXPERIMENTAL	UP/DOWN
KI 67	0,089	UP	0,081	UP	0,517	UP	0,025	UP
CLEAVED-CASPASE 3	0,114	UP	0,216	DOWN	0,35	UP	0,694	UP
TIL	0,176	UP	0,005	UP	0,237	UP	0,079	UP
			LUMINAL PREMENOPAUSAL N=26				LUMINAL POSTMENOPAUSAL N=22	
KI 67	0,031	UP	0,241	UP	0,314	DOWN	0,146	UP
CLEAVED-CASPASE 3	0,095	UP	0,1687	DOWN	0,899	DOWN	0,689	UP
TILS	0,639	UP	0,048	UP	0,062	UP	0,041	UP
			RANK+ N=19				RANKL+ N=17	
KI 67	0,384	UP	0,060	UP	0,307	DOWN	0,062	UP
CLEAVED-CASPASE 3	0,751	DOWN	0,262	DOWN	0,599	DOWN	0,401	DOWN
TILS	0,120	UP	0,013	UP	0,330	UP	0,048	UP

The results of the P-values of the comparison between biopsy A and biopsy B, together with the direction of the changes (up or down), are indicated for each parameter and each subgroup. * Note that results for TNBC are inconclusive, as 5/10 are "indolent" TNBC and they are not well balanced.

PS16-06

Tumor-infiltrating lymphocytes and pathologic response to neoadjuvant chemotherapy with the addition of platinum and pembrolizumab in TNBC: A single-center real-world study

Presenting Author(s) and Co-Author(s):

M. Kim. Gangnam Severance Hospital, Seoul, Seoul-t'ukpyolsi, Republic of Korea

Y. Kook. Gangnam Severance Hospital, South Korea

S. Baek. Gangnam Severance Hospital, South Korea

J. Kim. Gangnam Severance Hospital, South Korea

S. Moon. Gangnam Severance Hospital, South Korea

S. Lee. Gangnam Severance Hospital, South Korea

J. Kim. Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Background Previous studies have presented compelling evidence suggesting that the inclusion of platinum agents alongside anthracyclines and taxanes could potentially enhance treatment outcomes in high-risk triple-negative breast cancer (TNBC). Moreover, pembrolizumab has been integrated into clinical practice as a part of standard-of-care for non-metastatic TNBC with high risk. In light of these findings, we undertook a real-world study to investigate the impact of incorporating platinum agents and pembrolizumab on achieving pathologic complete response (pCR) in TNBC patients undergoing neoadjuvant chemotherapy (NAC). Furthermore, we specifically examined the influence of tumor-infiltrating lymphocytes (TILs) on the treatment outcomes. **Patients and Methods** In this real-world study conducted at Gangnam Severance Hospital, Seoul, Republic of Korea, we analyzed a cohort of 398 patients with TNBC who underwent surgery following NAC between March 2007 and November 2022. Among them, 247 patients received an anthracycline-taxanes (A-T), 120 received a carboplatin regimen including A-T, and 31 received a pembrolizumab regimen including A-T-carboplatin as part of their neoadjuvant chemotherapy treatment. TIL was evaluated in biopsied samples prior to NAC according to the guideline of TIL international working group. The high TIL was defined with a cutoff of 50%. **Results** Among the 398 patients analyzed, 87 (21.9%) had high TIL tumors. The pCR rates were 32% in the anthracycline-taxane (A-T) regimen group, 57% in the A-T-carboplatin regimen group, and 68% in the pembrolizumab with A-T-carboplatin regimen group. Within the high TIL group, the pCR rate did not increase with the addition of carboplatin (51.8% in the A-T group and 41.7% in the A-T-carboplatin group), but reached 85.7% with the addition of pembrolizumab and carboplatin. Among the low TIL group, the pCR rate increased from 26.7% to 61.1% with the addition of carboplatin, but there was no difference in the pCR rate between the carboplatin and pembrolizumab groups (61.1% and 60.9%, respectively). In clinically node-positive patients, the pCR rate significantly increased with pembrolizumab in the high TIL group (40.9% versus 100%, $p=0.035$). However, in low TIL patients, the addition of carboplatin alone significantly increased the pCR rate to 62.3%, whereas the addition of

pembrolizumab did not show the same effect. Conclusions Our real-world data consistently demonstrates an increased pCR rate with the addition of carboplatin and pembrolizumab. Among patients with high TIL, the addition of carboplatin did not result in an elevated pCR rate. However, the addition of pembrolizumab tended to maximize the pCR rate, surpassing 80%. On the other hand, among patients with low TIL, the addition of carboplatin significantly increased the pCR rate, while the addition of pembrolizumab did not have the same effect. Efforts should be made to improve the response to pembrolizumab-containing regimens for patients with low baseline TIL levels.

PS16-07

Tumor infiltrating lymphocyte stratification refines AJCC TNM staging based outcomes of early-stage triple negative breast cancer treated with neoadjuvant anthracycline-free, docetaxel and carboplatin chemotherapy.

Presenting Author(s) and Co-Author(s):

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

R. Yoder. The University of Kansas Cancer Center, United States

R. Salgado. Department of Pathology, GZA-ZNA-Hospitals, Antwerp, Belgium. Division of Research, Peter Mac Callum Cancer Centre, Melbourne, VIC, Australia

M. del Monte-Millán. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

E. Álvarez. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

I. Echavarría. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

J. Staley. The University of Kansas Cancer Center, United States

C. Bueno-Muiño. Medical Oncology Department, Hospital Infanta Cristina (Parla), Fundación de Investigación Biomédica del H.U. Puerta de Hierro, Majadahonda, Madrid, Spain

Y. Jerez Gilarranz. Hospital General Universitario Gregorio Marañón, Madrid, Spain

A. Godwin. University of Kansas Medical Center; Kansas Institute for Precision Medicine; The University of Kansas Cancer Center, United States

M. Cebollero. Anatomical pathology service. Hospital General Universitario Gregorio Marañón. IISGM, Madrid, Spain

O. Bueno. Radiology Service. Hospital General Universitario Gregorio Marañón. IISGM, Madrid, Spain

J. García-Sáenz. Hospital Clínico San Carlos, Madrid, Spain

F. Moreno Antón. Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISSC), CIBERONC, Madrid, Spain

U. Bohn. Department of Medical Oncology, Hospital Universitario Dr Negrin, Las Palmas de Gran Canaria, Spain

H. Gómez. Departamento de Medicina Oncológica, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Instituto de Investigaciones en Ciencias Biomedicas, Universidad Ricardo Palma, Lima, Peru

T. Massarrah. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

S. López-Tarruella. Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CiberOnc, Madrid, Spain

P. Sharma. University of Kansas Medical Center Westwood, Westwood, Kansas City, Kansas, United States

Background: Stromal tumor-infiltrating lymphocytes (sTILs) quantification is associated with pathological response to neoadjuvant chemotherapy (NAC) and long term outcomes in setting of adjuvant anthracycline based chemotherapy. A previous study in TNBC patients treated with

adjuvant anthracycline chemotherapy shows that at a cut point of 30%, sTILs can up and downstage traditional AJCC stage groups. Additive impact of sTILs on refining outcomes beyond pathological response and TNM stage for patients treated with anthracycline-free chemotherapy is not known. This study aimed to investigate impact of sTILs on outcomes in a large cohort of TNBC patients treated with Docetaxel plus carboplatin NAC. Methods: Patients with stage I (T size > 1cm) to III TNBC scheduled to receive 6 cycles of NAC docetaxel (75 mg/m²) plus carboplatin (AUC 6) (TCb) every 3 weeks from two studies (NCT01560663 and NCT02302742) were combined for this analysis. sTILs were evaluated on pre-treatment H&E slide using standard criteria centrally by one of the investigators (RS). Pathological complete response (pCR) was defined as ypT0/is ypN0. Logistic regression analysis was used to examine the effect of multiple variables on Event free survival (EFS) and overall survival (OS). Results: For 474 patients included in this analysis, median age was 52 years, 8% were Black, 13% had germline BRCA1/2 mutation, 44% had clinical Lymph node (LN) positive disease and 13%, 62% and 25% respectively had TNM stage I, II and III disease. Median sTILs were 5% (range 1-95%) and 25% had >30% sTILs. pCR and RCB 0+1 rates were 50.2% and 60.4% respectively. On multivariable analysis, T stage (OR=0.51, p=0.030), nodal status (OR=0.56, p=0.028), Ki67 (OR=2.74, p< 0.001) and sTILs (OR=2.01, p=0.014) were associated with pCR. pCR rate in those with sTILs< 30 vs sTILs >30 was 45.9% and 63.9% respectively (p=0.0014). At median follow-up of 58 months, 5 years EFS was 81.05% in all patients, 93.94% in those with pCR and 68.67% in those without pCR, 5 year OS was 84.83% in all patients, 96.53% in those with pCR and 74.13% in those with residual disease. On multivariate analysis lower T stage, negative LN status and increasing sTILs were associated with better EFS (T stage: HR =1.98, p=0.018; LN status: HR=2.92, p< 0.001; sTILs: HR:0.46, p=0.04) and OS (T stage: HR=1.89, p=0.040; LN status: HR=3.13, p=0.001; sTILs: HR=0.30, p=0.008). At a cut-point of 30%, sTILs up and downstaged anatomic AJCC TNM stage groups (table 1). Conclusions and Relevance: In patients treated with anthracycline-free TCb chemotherapy, sTILs were independent predictors of EFS and OS beyond clinicopathological features. Notably, 30% sTILs cut-point stratified outcomes beyond anatomical TNM staging. These findings can aid in patient stratification for chemotherapy backbone de-escalation in future trials and have the potential to inform patient selection for adjuvant treatment escalation and de-escalation trials. Tumor infiltrating lymphocyte stratification refines AJCC TNM staging based outcomes of early-stage triple negative breast cancer treated with neoadjuvant anthracycline-free, docetaxel and carboplatin chemotherapy.

TNM (% patients)	sTILs	N	5 years-EFS	Conf. Int.	5 years-OS	Conf. Int.
Stage-I (13%)	<30	22	95.45%	(87.14 - 100%)	100%	(100 - 100%)
	≥30	18	100%	(100 - 100%)	100%	(100 - 100%)
Stage-II (62%)	<30	164	82.24%	(76.33 - 88.61%)	88.69%	(83.73 - 93.95%)
	≥30	74	90.37%	(83.84 - 97.42%)	92.53%	(86.42 - 99.06%)
Stage-III (25%)	<30	67	55.24%	(44.26 - 68.95%)	56.36%	(45.02 - 70.57%)
	≥30	29	82.46%	(69.59 - 97.71%)	85.92%	(74.02 - 99.74%)

Table 1: EFS and overall survival based on combined TNM stage and sTILs

PS16-08

Histologic Pattern and Outcomes in High-Grade Metaplastic Breast Cancer Compared to Triple-Negative Ductal Breast Cancer Counterparts: A Single Institution Retrospective Study

Presenting Author(s) and Co-Author(s):

A. Matusz-Fisher. Karmanos Cancer Institute, McLaren Northern, Charlevoix, Michigan, United States

A. Chen. Atrium Health, United States

E. Donahue. Atrium Health Levine Cancer Institute, United States

C. Schepel. Atrium Health, United States

M. Wallander. Atrium Health, United States

C. Livasy. Atrium Health Levine Cancer Institute, Charlotte, North Carolina, United States

R. White. Atrium Health Levine Cancer Institute, United States

A. Tan. Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, United States

L. Hadzikadic-Gusic. Atrium Health Levine Cancer Institute, United States

Authors Ashley Matusz-Fisher, Annabel Chen, Erin Donahue, Courtney Schepel, Michelle Wallander, Chad Livasy, Richard White, Antoinette R. Tan, Lejla Hadzikadic Gusic
Title Histologic Pattern and Outcomes in High-Grade Metaplastic Breast Cancer Compared to Triple-Negative Ductal Breast Cancer Counterparts: A Single Institution Retrospective Study
Background Metaplastic breast cancer (MpBC) is a rare and aggressive subtype of breast cancer that presents with high tumor stage and a poor prognosis. MpBC tumors tend to have worse outcomes compared to other non-metaplastic triple-negative breast cancers (TNBC). Although MpBC has been described as chemotherapy resistant, chemotherapy remains a mainstay of treatment. MpBC tumors can be further characterized by their specific histologic pattern. The existing literature on outcomes of MpBC by histologic pattern is limited, with varying results regarding response rate and overall survival (OS). Identifying a pattern of MpBC that has better response to treatment could help tailor treatment recommendations.
Methods A retrospective chart review was performed and identified 106 patients with early-stage, high-grade MpBC who were diagnosed at Levine Cancer Institute between January 1, 2010 and September 1, 2021. A matched control cohort (n=106) of patients diagnosed with non-metaplastic TNBC was selected based on propensity score matching on diagnosis date, age at diagnosis, race, pathologic staging, and tumor grade. Patient demographics, tumor characteristics, therapeutic interventions, residual cancer burden (RCB), and outcomes were collected. The associations between the histologic patterns of MpBC and disease characteristics were evaluated using chi-squared tests for categorical variables and Wilcoxon tests for continuous variables. We also examined the differences in RCB scores between the MpBC cohort and the non-metaplastic TNBC cohort who received neoadjuvant chemotherapy. Additionally, Kaplan-Meier and Cox proportional hazard analysis was performed to assess differences in recurrence free survival (RFS) and OS between the spindle cell/sarcomatous pattern versus all other patterns.
Results For the entire group (n=212), median age at diagnosis was 58 years (range, 24-92); all patients were female; 66% White, 29% Black, and 5% unknown race. Most tumors were triple-negative (91%); 19%, 56% and 14% with Clinical Stage I, II, and III disease, respectively. A total of 63% of patients underwent radiation treatment and 76% received chemotherapy (43% neoadjuvant and 57% adjuvant). Recurrence after treatment occurred in 16% of all patients. In the MpBC cohort (n=106), the histologic

patterns included spindle cell/sarcomatous (34%), squamous (17%), heterologous mesenchymal (31%), mixed (17%), and other (1%). Of those with MpBC who received neoadjuvant chemotherapy (n=32), RCB among the different histologic patterns was assessed. When comparing spindle cell/sarcomatous versus the other histologic patterns combined, there was no significant difference in RCB ($p = 0.81$), although more RCB III scores were recorded in the spindle cell/sarcomatous pattern compared to the other MpBC patterns (40% versus 30%). When assessing RFS and OS by histologic pattern in the entire MpBC cohort, spindle cell/sarcomatous tumors had inferior RFS ($p = 0.0194$) and OS ($p = 0.0039$) compared to the other MpBC patterns combined. When comparing RCB values between MpBC and non-metaplastic TNBC, there were numerically more RCB-III classes in the MpBC cohort as compared to the non-metaplastic TNBC. Conclusion MpBC is an aggressive and difficult breast malignancy to treat. Based on our single institution review, no correlation between RCB and the histologic pattern of MpBC was found, however, RFS and OS were worse among the spindle cell/sarcomatous pattern. Furthermore, the MpBC cohort had numerically higher RCB-III scores than the TNBC control cohort, which is in line with historical data.

PS16-09

Analysis of the Radiosensitivity Index/Genomic-Adjusted Radiation Dose (RSI-GARD) in paired pre- and post-treatment TNBC samples: implications for biomarker-guided radiotherapy

Presenting Author(s) and Co-Author(s):

S. Stecklein. University of Kansas Medical Center; Kansas Institute for Precision Medicine, Kansas City, Kansas, United States

J. White. Ohio State University, Columbus, Ohio, United States

R. Yoder. The University of Kansas Cancer Center, United States

J. Staley. The University of Kansas Cancer Center, United States

Z. Schmitt. University of Kansas Medical Center, United States

A. O'Dea. University of Kansas Medical Center, United States

L. Nye. University of Kansas Medical Center, United States

D. Satelli. University of Kansas Medical Center, United States

G. Crane. University of Kansas Medical Center, United States

R. Madan. University of Kansas Cancer Center, United States

M. O'Neil. University of Kansas Cancer Center, United States

A. Godwin. University of Kansas Medical Center; Kansas Institute for Precision Medicine; The University of Kansas Cancer Center, United States

H. Pathak. University of Kansas Cancer Center, United States

Q. Khan. University of Kansas Medical Center, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

P. Sharma. University of Kansas Medical Center Westwood, Westwood, Kansas City, Kansas, United States

Objectives: Adjuvant radiotherapy is an important component of curative treatment for triple-negative breast cancer (TNBC). While there are several accepted variations in nominal dose and fractionation, these regimens are generally felt to be radiobiologically equivalent. Molecular radiosensitivity biomarkers have the potential to allow tailoring of physical radiotherapy dose for individual patients. The Radiosensitivity Index (RSI)/Genomic-Adjusted Radiation Dose (GARD) is a gene expression signature that predicts intrinsic radiosensitivity across multiple malignancies, with initial studies demonstrating clinical utility of RSI-GARD in TNBC. Since most TNBC patients will receive neoadjuvant systemic therapy, we sought to understand how neoadjuvant therapy-induced molecular adaptations could alter intrinsic radiosensitivity and RSI-GARD. **Methods:** Total RNA was isolated from pre-treatment and paired surgical specimens (for patients with residual disease (RD)) from TNBC patients treated with chemotherapy on the NeoSTOP (NCT02413320) or chemoimmunotherapy on the NeoPACT (NCT03639948) neoadjuvant trials and was subjected to RNA exome sequencing. The RSI was calculated according to the published algorithm using normalized expression of the 10 genes in this signature (AR, JUN1, STAT1, PRKCB, RELA, ABL1, SUMO1, PAK2, HDAC1, and IRF1). The resulting RSI score was substituted as the surviving fraction (SF) using the linear quadratic model of radiation-induced cellular lethality assuming a fractional dose of 2.0 Gy and a constant $\beta=0.05 \text{ Gy}^{-2}$ to derive a patient-specific α , which is a coefficient modifying dose-dependent

cellular lethality resulting from binary mis-repair of double-strand breaks (DSBs) arising from a single particle track. Results: Pre-treatment sequencing data were available for N=200 patients and the overall pathologic complete response (pCR) rate was 56.5%. Paired pre- and post-treatment sequencing data were available for N=58 patients (N=27 from NeoSTOP and N=31 from NeoPACT). One NeoPACT patient had a negative RSI, which led to an undefined α . Under the assumptions of the RSI-substituted LQ model, the median α/β ratio (reflecting sensitivity to fractionation) for all pre-treatment samples was 11.7 Gy. TNBC patients who achieved pCR had a significantly higher pre-treatment α (i.e., higher intrinsic radiosensitivity) compared to patients who had residual disease (P=0.04), and this trend was the same for patients treated with chemotherapy (P=0.31) or chemoimmunotherapy (P=0.05). Importantly, α did not change significantly between paired pre- and post-treatment samples (median change post- vs. pre-treatment=0.03 Gy⁻¹ (range -0.25 to +0.24 Gy⁻¹; P=0.26) in patients with RD, with no difference in subgroups treated with chemotherapy (P=0.99) or chemoimmunotherapy (P=0.10). Conclusions: We found that predicted intrinsic radiosensitivity using the RSI-GARD is associated with pathologic response to neoadjuvant systemic therapy, suggesting that this signature also predicts intrinsic chemosensitivity in TNBC patients. The modeled α/β ratio for all pre-treatment samples was 11.7 Gy, which is substantially higher than empirically determined α/β ratios in studies that were enriched for HR+/HER2- breast cancers. Globally, the RSI-GARD score was not impacted by neoadjuvant systemic therapy, with no significant change in the score in paired pre- and post-treatment samples. These results can inform future testing and implementation of RSI-GARD into prospective trials.

PS16-10

SPATIAL IMMUNE CELL DISTRIBUTION CAN REFINE PROGNOSIS IN EARLY-STAGE ER+/HER2-/LN- BREAST CANCER

Presenting Author(s) and Co-Author(s):

Z. Kinsella. Royal College of Surgeons in Ireland, London, England, United Kingdom

H. Nyarko. Royal College of Surgeons, United States

A. Blümel. Royal College of Surgeons in Ireland/School of Pharmacy and Biomolecular Sciences, Ireland

M. Lucas. St Vincent's University Hospital, United States

D. Kalinska-Lysiak. Royal College of Surgeons in Ireland, United States

C. Gonzalez. University College Dublin, United States

A. Rahman. University College Dublin, United States

J. Fay. Royal College of Surgeons in Ireland, United States

T. O'Grady. Royal College of Surgeons in Ireland, United States

V. Murphy. Cancer Trials Ireland, United States

J. Crown. Saint Vincent's University Hospital, United States

C. Kelly. Mater Private Network, United States

W. Gallagher. UCD/Conway Institute, Ireland

D. O'Connor. Royal College of Surgeons in Ireland/ School of Pharmacy and Biomolecular Sciences, Ireland

Lymphocytic infiltrate is a known prognostic biomarker in estrogen receptor(ER)-negative breast cancers (BCs). Comparatively ER+ disease is putatively cold, however, there exists an infiltrate-rich subset of ER+ tumours with significant spatial heterogeneity and unknown clinical impact. Using serial sections taken from early-stage, ER+/HER2- breast tumours of Irish patients enrolled in the TAILORx trial (n=450), we aimed to investigate the prognostic potential of markers encompassing tumour architecture. Immunohistochemistry for Ki67 and CD45 (leukocyte common-antigen), and staining for haematoxylin and eosin was applied to all sections ^[1]. Classifiers for stromal fraction (SF), stromal-infiltrate (sTIL), Ki67-LI, and their spatial relationships within the tumour were generated using QuPath ^[2] and R Studio. Trained marker classifiers were validated against an expert pathologist (R^2 of M-Score to: CD45%: 0.968, Ki67-LI: 0.814, sTIL: 0.864) to define observed lymphocytes as tumour or stromal-infiltrating, retain only tumour Ki67⁺ density, and to investigate SF. Cohort mean SF was 67.69% (range 16.35 – 98.29%), with marginally significant differences in recurrence prediction for cohort high v low SF by mean (c-index = 0.58, $p < 0.032$), and luminal A disease ($p = 0.037$) only. sTILs did not differ significantly between high/low mean SF (Mann-Whitney $p = 0.6201$), though sTIL was prognostic in the OncotypeDx intermediate Recurrence Score (RS) category overall ($p = 0.0076$). This trend appeared strongest in intermediate RS patients receiving chemo-endocrine therapy (HT+CT) ($p < 0.0001$) vs endocrine therapy (HT) alone ($p = 0.86$). Investigating the effects of prescribed therapy on sTIL-derived recurrence risk also revealed significant trends in those patients receiving HT+CT only ($p < 0.00001$) vs HT alone ($p = 0.26$). Spatial analysis of sTILs suggest that tumours become more immune excluded as Oncotype Dx RS increases - particularly from intermediate to high RS (Wilcoxon Intermediate v High: $p = 0.0077$), with significant differences in survival for high/low tumour-immune hotspots

observed in Intermediate RS, HT+CT treated patients ($p=0.0052$). Further spatial analysis suggests that high normalised frequency of infiltrate ^[method adapted from 3] (within 7 μ m of tumour cells) have negative prognostic impact for premenopausal patients ($p=0.017$), and inter-sectional analysis identifies niche tumour environments where high Ki67-LI colocalize with immune infiltrates ^[methods adapted from 4, 5], most notable in Intermediate RS tumours. Overall these data suggest immune-spatial subsets can be used to refine risk stratification of ER+ breast cancer. References: [1] Lucas, M., Kinsella, Z., Gonzalez, C.A. et al. CD45-positive tumour infiltrating lymphocytes in early-stage hormone-positive, HER2-negative (ER+/HER2-) breast cancer: Correlation with proliferation and prognostic signature scores. Meeting Abstract ASCO Annual Meeting I. 2022. [2] Bankhead, P., Loughrey, M.B., Fernandez, J.A. et al. QuPath: Open source software for digital pathology image analysis. Scientific Reports. 2017;7:16878. [3] Yuan. Y. Modelling the spatial heterogeneity and molecular correlates of lymphocytic infiltration in triple-negative breast cancer. Journal of the Royal Society Interface. 2015;12(103):201411532 [4] Maley, C.C., Koelble, K., Natrajan, R. et al. An ecological measure of immune-cancer colocalization as a prognostic factor for breast cancer. Breast Cancer Research. 2022;17(1):131. [5] Ord, J.K., Getis, A. Local spatial autocorrelation statistics: Distributional issues and an application. Geographical Analysis. 1995;27(4):286-306.

PS18-01

Stage Advancement and The Rate of Growth Associated with Preoperative Delay in Patients Having Breast Cancer

Presenting Author(s) and Co-Author(s):

R. Bleicher. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

K. Ruth. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Williams. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

E. Ross. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Porpiglia. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

A. Aggon. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

M. Pronovost. Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, United States

D. Holmes. Adventist Health Glendale, Glendale, California, United States

Introduction: For every delay interval between breast cancer diagnosis and surgery we have previously found a relative decline in disease-specific survival of 26% (60 d) and overall survival of 9-10% (30 d). There is, however, little explanation for this. In our experience, patients focus on the likelihood of cancer growth between diagnosis and surgery, and whether preoperative delay might lead to upstaging, with nodal status of particular concern when they are clinically node-negative. With little published data about delay-associated upstaging and no large-scale national data determining how fast tumors grow, this study was performed to determine these rates. **Methods:** Patients ≥ 18 years old having stage 0-III breast cancer who received surgery as first treatment between 2010 and 2020 were reviewed in the National Cancer Database (NCDB), the largest national dataset to contain the needed clinical and pathologic staging. Patients were reviewed for correlation between preoperative delay and cancer upstaging, defined as an increase from cT to pT or cN to pN stages, after assessing baseline clinical stage inaccuracy. Accuracy of clinical staging was determined by comparing clinical stages at presentation to pathologic stages at surgeries ≤ 15 days of diagnosis, assuming negligible tumor growth in that period. cN3 and cT3 tumors were excluded as there is no higher size-dependent pathologic stage. Upstaging probabilities and odds ratios (ORs) were estimated with logistic regression, adjusted for age, race, Hispanic ethnicity, gender, histology, grade, phenotype, and clinical T or N stage. For patients with delays > 15 days, adjusted linear regression coefficients of tumor size on preoperative delay were used to estimate primary invasive tumor growth rates. **Results:** Among 1,040,197 patients, the median time between diagnosis and surgery was 34 days (IQR 23-49), with 11.6% having primary tumoral and 14.6% having nodal upstaging. In the 10.2% of patients where surgery was performed ≤ 15 days of diagnosis, 13.9% of DCIS, 11.5% of cT1, and 4.5% of cT2 tumors were upstaged ($p < 0.0001$). For every 30 days of delay between diagnosis and surgery, the ORs for tumor upstaging, adjusted for covariates, were 1.09 for DCIS (95%CI 1.07-1.10, $p < 0.0001$), 1.12 for cT1 (95%CI 1.10-1.14, $p < 0.0001$), and 1.16 for cT2 tumors (95%CI 1.14-1.19, $p < 0.0001$). For invasive tumors, the adjusted 30-d ORs for upstaging in HR+, HER2+, and TN primaries were 1.12 (95%CI 1.11-1.14), 1.11 (95%CI 1.07-1.15), and 1.19 (95%CI 1.15-1.23), respectively (individual p 's < 0.0001). In the 9.8% of clinically N0 (cN0) patients with a diagnosis-to-surgery interval of ≤ 15 days, 14.2% were upstaged to node-positive. cN0 patients had an adjusted OR for upstaging to node-positive of 1.06 (95%CI 1.05-1.07, $p < 0.0001$) for every 30 days of delay. The number of 30-d intervals for cT1mi, cT1a, cT1b, cT1c and cT2 invasive primary tumors to grow 1 mm was 7.8, 7.1, 3.9, 2.8, and 2.0, respectively. **Conclusions:** Even when accounting for clinical stage inaccuracy, longer

delays are associated with a quantifiable increase in upstaging and likelihood of becoming node-positive at surgery. This may explain the higher disease-specific and overall mortality associated with preoperative delay found in prior studies. With larger tumors having a higher delay-associated likelihood of upstaging and faster growth rates, delays become more problematic as tumor size increases. This information reinforces the need to minimize preoperative delays by demonstrating their consequences. It also provides data to address some of breast cancer patients' most pressing preoperative concerns about how fast breast tumors grow and their upstaging potentials while they await treatment.

PS18-02

Prevalence of Refusal of Recommended Cancer Treatments and Survival Differences in Breast Cancer Patients: Analysis of the National Cancer Database

Presenting Author(s) and Co-Author(s):

J. Freeman. Department of Public Health Sciences, University of Chicago, Chicago, Illinois, United States

J. Li. Department of Public Health Sciences, University of Chicago, United States

S. Fisher. Northshore University Health System, Evanston, Illinois, United States

K. Yao. Northshore Medical Group, Evanston, Illinois, United States

S. David. NorthShore University HealthSystem, Prizker School of Medicine, The University of Chicago, Chicago, Illinois, United States

D. Huo. Department of Public Health Sciences, The University of Chicago, Chicago, Illinois, United States

Background: Some breast cancer patients (pts) refused treatment despite their providers' recommendations. Treatment refusals can be detrimental to these pts' short- and long-term health outcomes. Limited research has investigated the national trends in treatment refusals and their impacts on the survival of breast cancer pts. Methods: We analyzed data collected from breast cancer pts in the 2004-2020 National Cancer Database (NCDB). Four treatment modalities were assessed: chemotherapy (CT), hormone therapy (HT), radiotherapy (RT), and surgery. The CT cohort included stage I-IV pts. The HT cohort included stage I-IV, hormone receptor-positive pts. The RT or surgery cohort was limited to only stage I-III pts. Refusal status was categorized as "yes/no," and its correlates were assessed using multivariable logistic regression. Estimated rates of overall survival (OS) were calculated using the Kaplan-Meier method. The association between refusal status and OS was examined using log-rank tests, followed by multivariable Cox regression models. Results: In the CT cohort, 9.6% of 1,296,488 pts who were offered the treatment refused. In the RT cohort, 6.1% of 1,635,916 pts refused. In the HT cohort, 5.0% of 1,893,339 pts refused. In the surgery cohort, only 0.6% of 2,590,963 pts refused. Significant increasing trends in treatment refusals from 2004-2020 across the four treatment modalities were observed (all p-trends < .001). We found significant differences in age, race, AJCC stage group, molecular subtype, tumor grade, and care access indicators (e.g., insurance, median household income, facility type, and rural/urban area) by refusal status. Black pts were more likely than White pts to refuse surgery (adjusted odds ratio [AOR] 2.01, 95% CI: 1.89-2.14). Asian or Pacific Islander pts were also more likely to refuse surgery (AOR 1.29, 95% CI: 1.15-1.44) and CT (AOR 1.21, 95% CI: 1.16-1.27). Uninsured pts were more likely than privately insured pts to refuse surgery (AOR 4.83, 95% CI: 4.22-5.51), RT (AOR 1.97, 95% CI: 1.83-2.12), CT (AOR 1.61, 95% CI: 1.51-1.72), and HT (AOR 1.61, 95% CI: 1.49-1.73). Compared with pts who did not refuse treatment, those who refused had lower rates of 5-year OS in the cohorts of HT (81.4% vs. 88.4%), CT (74.9% vs. 84.4%), RT (74.4% vs. 90.8%), and surgery (42.0% vs. 88.1%). When stratified by stage, similar patterns of 5-year OS rates were observed across all cohorts. After adjusting for sociodemographic and clinicopathologic factors, pts who refused surgeries had a higher mortality risk than those who did not (aHR 2.91, 95% CI: 2.82-3.01). Pts who refused RT had a higher risk of dying than those who did not (aHR 1.97, 95% CI: 1.93-2.01). Pts who refused CT had a greater risk of dying than those who did not (aHR 1.86, 95% CI: 1.83-1.90). Pts who refused HT had a greater risk of death than those who did not (aHR 1.56, 95% CI: 1.53-1.59). Black pts had higher mortality risk than their White counterparts across all cohorts (HT: aHR 1.15, 95% CI: 1.13-

1.17; CT: aHR 1.14, 95% CI: 1.12-1.16; RT: aHR 1.11, 95% CI: 1.1.09-1.14; surgery: aHR 1.10, 95% CI: 1.08-1.11). Conclusions: In this sample of breast cancer pts, the rate of treatment refusal was highest for CT and lowest for surgery, and there were significantly increased trends in refusals over time. Age, race, stage, molecular subtype, tumor grade, and care access measures were independently associated with treatment refusals, suggesting that differential refusals not only are affected by biological factors but also may reflect disparities in socioeconomic status. Furthermore, pts who refused treatment experienced worse OS, regardless of treatment modality. These findings suggest that stressing the importance of recommended treatment and interventions tailored for this patient population may be needed to improve their survival outcomes.

PS18-03

The Association between Food Deserts, Food Swamps, and Postmenopausal Breast Cancer Mortality in the United States

Presenting Author(s) and Co-Author(s):

M. Bevel. Augusta University, Augusta, Georgia, United States

M. Tsai. Augusta University, United States

A. Parham. Augusta University, United States

S. Andrzejak. Mercer University, United States

S. Jones. Augusta University, United States

J. Moore. University of Kentucky, United States

Purpose: Breast cancer (BRCA), the 4th leading cause of cancer death in the United States (U.S.), is one of 13 obesity-related cancers. Healthy food consumption is a protective factor shown to decrease obesity risk and postmenopausal BRCA mortality, respectively. However, residing in geographical areas with no access to healthy food options (food deserts) or unhealthy food options (food swamps) reduces access to healthy foods and has been severely understudied. We examined the relationship between residing in food swamps and deserts with postmenopausal BRCA mortality. Methods: We conducted an ecological analysis utilizing 2010 – 2020 Center for Disease Control and Prevention postmenopausal BRCA mortality data (restricted to 45+ years old) and aggregated 2012 – 2020 data from the U.S. Department of Agriculture Food Environment Atlas data. Food swamp score (FS) was calculated as the ratio of fast-food and convenience stores to grocery stores and farmer's markets. Food desert score (FD) was calculated as the proportion of residents living more than one mile (urban) or 10 miles (rural) from a grocery store and household income \leq 200% of the federal poverty threshold. We categorized FD and FS to low, moderate, or high; higher scores indicated counties with poorer healthy food resources. Multilevel generalized mixed effects models were used to estimate the mentioned association. Results: 2,280 counties/county equivalents with high postmenopausal BRCA mortality rates had higher percentage of non-Hispanic (NH)-Black population (5.80 vs. 2.08), poverty rates (17.2 vs. 14.2), and high food swamp scored areas (39.0 vs. 24.5) versus counties/county equivalents with low postmenopausal BRCA mortality rates (p-value < 0.0001). After adjusting for age, percentage of NH-Blacks per county, and poverty rate, we found 42% increased odds of having high postmenopausal BRCA mortality rates among U.S. counties/county equivalents with high food swamp scores (adjusted odds ratio [AOR] = 1.42; 95% CI: 1.14 – 1.78). Conclusions: Sampled U.S. counties with the poorest food swamp environment had significantly increased odds of postmenopausal BRCA mortality. We suggest that local policymakers and community stakeholders should employ sustainable approaches at combating obesity and BRCA by increasing healthier accessible food sources (e.g. creating more walkable neighborhoods and community gardens).

PS18-04

Racial disparities in breast cancer and effect of obesity: MammaPrint, Blueprint and whole transcriptome analyses of tumors in Latin American patients in FLEX trial

Presenting Author(s) and Co-Author(s):

M. Mazo-Canola. Mays Cancer Center, San Antonio , Texas, United States

V. Kaklamani. UT Health San Antonio, San Antonio, Texas, United States

P. Advani. Mayo Clinic, United States

S. Kamaraju. Medical College of Wisconsin, Milwaukee, Wisconsin, United States

A. Santillan-Gomez. Texas Oncology – Medical Center, United States

R. Maganini. Ascension Illinois, United States

J. Barone. Vail Health, United States

S. Uygun. Agendia Inc., United States

L. Samraj. Agendia Inc., United States

W. Audeh. Agendia Inc., United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

F. Investigators' Group. Agendia, United States

Background: Latin Americans are more likely to be diagnosed with aggressive early-stage breast cancer compared to Non-Hispanic White. Multiple factors may contribute to this, including metabolic factors and ancestry. In a previous study, we identified upregulated immune pathway genes in Luminal B tumors from obese Black patients compared to matched White patients. In this study, we report clinical and transcriptomic profiles of breast tumors from Latin and White patients to enhance understanding of factors contributing to aggressive tumor biology in Latin patients. Methods: We matched 311 Latin and 311 White breast cancer patients enrolled in FLEX by age, T stage, N stage and clinical subtype (ER/PR and HER2 status). FLEX (NCT03053193) is a prospective, observational trial that includes stage I-III breast cancer patients who receive MammaPrint (with or without Blueprint) as standard of care and consent to whole transcriptome and clinical data collection. MammaPrint is a 70-gene risk of distant recurrence signature that classifies patients as Low Risk or High Risk. Blueprint is an 80-gene molecular subtyping signature, categorizes tumors as Luminal-, HER2- or Basal-Type. MammaPrint further groups Luminal into A (Low Risk) and B (High Risk). ImPrint is a 53-gene signature that has been shown to predict the likelihood of achieving pCR with PD1-PDL1 immune checkpoint inhibitors. Statistical analyses on groups were conducted using arsenal R package and p-value < 0.05 was considered significant. Whole transcriptome comparisons were made, using limma R package, between Latin and White patients stratified by Blueprint subtype Luminal and weight categories normal (body-mass-index (BMI) 18.5 to < 25) and obese (BMI ≥30). Significant differentially expressed genes had an adjusted p-value < 0.05. Gene set enrichment analysis (GSEA) was conducted using fgsea R package. Results: Latin patients had significantly higher percentage of type 2 diabetes (23.3% vs 8.5%), BMI obese (49.0% vs 39.4%), Blueprint Basal (14.8% vs 9.3%) and ImPrint Immune Sensitive (12.0% vs 5.1%) compared to matched White patients. When comparing whole transcriptome of tumors from Latin and White patients, only tumors stratified by Luminal B and obesity resulted in differentially expressed genes: Latin patients had higher expression (>2-fold change) of 42 immunoglobulin genes compared to White, with only IGKV6-21 being statistically significant. Additional immune related genes such as IKZF1 and AGER, as well as UTS2 (gene encoding a

vasoconstrictor agent and contributor of angiogenesis) were significantly upregulated in Latin patients. Upregulation of immune related pathways such as inflammatory response, interferon alpha/gamma response and downregulation of adipogenesis, oxidative phosphorylation and MYC targets were identified in Latin patients compared to White using GSEA Hallmarks gene sets. Conclusion: There were additional clinical and genomic differences between tumors from Latin and White patients, even when controlling for age, T stage, N stage and clinical subtype. Particularly, there were more type 2 diabetes, BMI obese, Blueprint Basal, and ImPrint Immune Sensitive among Latin patients. In addition, transcriptomic differences between obese Latin and matched White patients were found in Luminal B subgroup that may contribute to the aggressive tumor biology; immunoglobulin genes and immune related pathways were associated with higher expression in Latin patients. This study suggests that biological differences in breast tumors, particularly from obese patients, may result from shared background and reflects the need for inclusion of diverse patient groups in clinical trials.

PS18-07

Trends in Guideline Concordant Care for Inflammatory Breast Cancer: An analysis of the National Cancer Database

Presenting Author(s) and Co-Author(s):

B. Diskin. Memorial Sloan Kettering Cancer Center, New York, New York, United States

A. Tadros. Memorial Sloan Kettering Cancer Center, United States

V. Sevilimedu. Memorial Sloan Kettering Cancer Center, United States

A. Xu. Memorial Sloan Kettering Cancer Center, United States

P. Vingan. Memorial Sloan Kettering Cancer Center, United States

J. Nelson. Memorial Sloan Kettering Cancer Center, United States

Y. Iwai. UNC, United States

M. Morrow. Memorial Sloan Kettering Cancer Center, New York, New York, United States

O. Fayanju. Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Inflammatory breast carcinoma (IBC) is an aggressive form of breast cancer associated with worse survival outcomes compared with other subtypes of breast cancer. Black patients with IBC have worse survival outcomes than White patients. Trimodality treatment (TMT) which includes neoadjuvant chemotherapy (NCT) followed by modified radical mastectomy without immediate reconstruction (MRM), and postmastectomy radiotherapy (PMRT), has been associated with improved survival outcomes for patients with IBC. Whether receipt of TMT varies by race, ethnicity, and insurance status and its impact on survival is largely unknown. Methods: Adult female patients with non-metastatic IBC treated from 2010-2018 were identified from the NCDB. Guideline concordant care (GCC) was defined as TMT administered in the correct sequence. In addition, clinical tumor/nodal stage, age, race, ethnicity, facility type, patient location, insurance status, and pathologic complete response (pCR) were examined for each patient. Additional quality metrics of GCC examined included time to initiation of NACT < 60 days (TTNC) and proper surgical care defined as complete axillary lymph node dissection (>6 lymph nodes removed) at the time of MRM without reconstruction. Univariate and multivariate mixed methods were performed to determine association between patient, treatment, and facility-level factors and receipt of GCC, TTNC < 60 days, and proper surgical care. OS was estimated using the Kaplan-Meier method, and the log-rank test was used to compare groups. Results: 7,374 women with non-metastatic IBC were included. 78% were White, 17% Black, and 2.5% Asian/Pacific Islander patients; 7.7% identified as Hispanic and 92% as non-Hispanic. The majority had private insurance (51%), 29% Medicare, 14% Medicaid, 4.9% uninsured, and 1.3% other government insurance. Only 2,418 patients (32.7%) received GCC with only 29% undergoing MRM without reconstruction. Receipt of GCC was more common among patients age >50 years, patients with higher clinical nodal burden and those treated from 2010-2013 (p=0.001). Receipt of GCC did not differ by race, ethnicity, insurance status, or location. 92% (6,005/7,374 patients) received NAC within 60 days of diagnosis. Both Black (OR 0.58, 95% CI 0.46-0.74, p< 0.001) and Asian (OR 0.52, 95% CI 0.30-0.90, p< 0.001) patients with IBC were less likely to have TTNC < 60 days when compared to White patients. Non-Hispanic patients (OR 2.24, 95% CI 1.65-3.03, p< 0.001) and those with private insurance (OR 1.82, 95% CI 1.23-2.68, p< 0.001) were more likely to have TTNC within 60 days of diagnosis. Patients with lower clinical nodal burden (cN0) were less likely to undergo proper surgery compared to patients with higher nodal

burden(cN1-3) ($p < 0.001$). In addition, patients treated in a more contemporary cohort (2014-2018) were less likely to undergo proper surgery compared to patients treated earlier (2010-2013) (OR 0.82, 95% CI 0.73-0.92, $p < 0.001$). Among IBC patients receiving GCC, Black patients had significantly worse overall survival compared to White patients ($p < 0.001$)

Conclusions: The majority of patients with IBC do not receive GCC and GCC has decreased since 2014 with fewer patients undergoing appropriate surgical treatment. The very low level of GCC indicates a need for multidisciplinary education, while improvement in TTNC may improve outcomes among racial/ethnic minorities.

PS18-08

Bridging Disparities in Survivorship Care: Leveraging Telehealth for Diverse Patients in Safety Net Hospital

Presenting Author(s) and Co-Author(s):

I. Leung. University of California, San Francisco, San Francisco, California, United States

E. Trejo. University of California, San Francisco, United States

A. Velázquez Mañana. University of California, San Francisco, United States

E. Castillo. San Francisco Department of Public Health, United States

B. Cicerelli. San Francisco Department of Public Health, United States

R. McBride. San Francisco Department of Public Health, United States

P. Wong. San Francisco Department of Public Health, United States

H. Xie. San Francisco Department of Public Health, United States

L. Zhang. San Francisco Department of Public Health, United States

N. Burke. University of California, San Francisco, United States

N. Dixit. University of California, San Francisco, United States

Background There are 3.8 million breast cancer survivors (BCS) in the United States and 67-88% of them report unmet needs in survivorship care. With advancements in breast cancer treatment and improved survival rates, there is a growing need to expand survivorship care to address the long-term physical, psychosocial, and medical needs of cancer survivors. There is a significant disparity in access to high-quality survivorship care, particularly for diverse patient populations in safety net hospitals. BCS in marginalized communities experience worse health-related quality of life (HRQOL) outcomes following cancer treatment in the management of symptoms, complications of treatment, and overall health-related distress. Thus, new models that leverage complex care management principles and novel care delivery systems, such as telehealth, are needed to provide multidisciplinary care and support for self-management.

Methods We conducted a single-arm, pilot intervention trial of telehealth group medical visits (tGMV) in a safety net hospital serving low-income and racially and ethnically diverse BCS. The study team included physicians, advanced practitioners, PCPs, clinical psychologists, nurses, dietitians, exercise instructors, Traditional Chinese Medicine practitioners, sexual health counselors, research coordinators, and patient navigators. We enrolled a total of 6 cohorts of 7-10 BCS for the tGMV intervention (2 cohorts each in English, Spanish, and Cantonese). Each cohort had four weekly sessions on the following topics: 1) Reclaiming your health after cancer, 2) Managing emotional health, 3) Sexual health and relationship, and 4) Food is medicine. All participants were trained on the telehealth video conference platform. The curriculum was culturally adapted in the Spanish and Cantonese cohorts. Study staff followed up with participants by phone after each session. We evaluated feasibility and acceptability as primary outcomes with prespecified thresholds for >90 % completion of planned sessions and >70% attendance. Participants' evaluation of the intervention and self-efficacy were secondary outcomes, which are not reported in this abstract.

Results Fifty-three women with stage I-III breast cancer were enrolled in the study. The age was 37 to 75 (median: 58). There were 14 (26%) English-speaking participants, 19 (36%) Spanish-speaking participants, and 20 (38%) Cantonese-speaking participants. Eight (15%) participants identified as White, three (5.7%) Black A/A, 23 (43%) Asians, and 19 (36%) Hispanic; 43 (81%) participants were foreign-born. Twenty-seven (51%) participants reported food insecurity on the screening survey. The overall attendance rate was 98% (English: 97%, Spanish: 97%, and Cantonese: 100%). Of the 53

participants, 41 (77%) found the telehealth format acceptable, 47 (88%) agreed/strongly agreed that it was easy to log in and stay connected, 53 (100%) agreed/strongly agreed that tGMV were a good use of their time, 52 (98%) understood the purpose of the telehealth format, and 50 (94%) felt the information was easy to understand. Conclusions Telehealth-delivered group medical visits are feasible and acceptable in a safety net setting and are a promising intervention that may help in addressing the unmet needs of cancer survivors. We also found that despite the reported low uptake of telehealth in safety net settings, emphasis on training and technical support during sessions can increase the utilization of telehealth.

PS18-09

The DARC side of Breast Cancer - DARC, Duffy-null and African ancestry influence in the Triple Negative Breast Cancer tumor microenvironment

Presenting Author(s) and Co-Author(s):

R. Martini. Morehouse School of Medicine, Atlanta, Georgia, United States

S. Patino. Weill Cornell Medical College, United States

E. Guyonnet. Weill Cornell Medical College, United States

B. Stonaker. Weill Cornell Medical College, United States

I. Elhussein. Johns Hopkins, United States

J. Sahler. Cornell University, United States

A. August. Cornell University, United States

N. Manley. Arizona State University, Arizona, United States

R. Kittles. Morehouse School of Medicine, United States

C. Yates. Johns Hopkins, United States

L. Newman. Weill Cornell Medicine, New York, New York, United States

M. Davis. Morehouse School of Medicine, United States

Background. Despite a recent convergence of breast cancer (BC) incidence rates between African American (AA) and European American (EA) women, AA women continue to have ~40% higher mortality rates. BC is a heterogeneous collection of diseases, where African ancestry women are disproportionately burdened with the most aggressive subtype of BC, triple negative BC (TNBC). We have previously reported that the African ancestry-specific Duffy-null allele (FY-) is a risk factor for TNBC diagnoses. FY- is a promoter variant that removes expression of the Duffy Antigen Receptor for Chemokines (DARC/ACKR1), from red blood cells (RBCs). DARC serves as a portal of entry for *Plasmodium vivax* malaria parasite, and FY- confers immunity, leading to fixation of FY- among Sub-Saharan African populations. DARC is an atypical chemokine receptor that functions to modulate chemokine levels in circulation and tissues to aid immune cell recruitment. DARC is also expressed on breast tumor epithelial cells, however the significance of DARC in the TNBC tumor microenvironment (TME) has not fully been explored. Leveraging our African ancestry enriched International Study for the Center of Breast Cancer Subtypes cohort and in vivo murine models, we employed multi-omics approaches to explore the function of FY- and DARC expression across cell types in the TNBC TME. **Genomics.** Using transcriptomic data from the TCGA BC cohort, we have previously reported that DARC expression is highly correlated with deconvoluted immune cell abundance using CIBERSORT. To build upon this finding among TNBC patients, we have analyzed RNAseq data from two cohorts of African ancestry women to explore correlation of DARC expression status and immune cell abundance. Among TNBC cases, we report that higher DARC expression was significantly associated with increased immune cell abundance, with increases in B cell, T cell and monocyte populations. Using whole genome sequencing data across 86 African ancestry cases, we are currently investigating germline FY- status with mutational signatures. **Circulating biomarkers.** Patient plasma was collected prior to surgery, where Luminex multiplex assays were performed to quantify levels of >40 circulating chemokines and cytokines. FY- status has been determined for ~550 patients using single-plex or multiplex PCR genotyping methods from germline saliva DNA. Our univariate analyses show several circulating chemokines, including CCL2, CXCL2, CXCL6 and CXCL11, have significant differences between FY- and non-FY- BC patients. Curation of clinicopathological variables for

multivariate analysis is ongoing. Murine models. We crossed C3(1)Tag BC transgenic mice with a DARC knock-out (KO) line to generate mice lacking DARC expression that spontaneously develop tumors in the mammary fat pads. The C3(1)Tag model is reported to have similar gene expression profiles to basal-like TNBC tumors. Tumors were collected at pre-determined time points of 25 and 30 weeks, where DARC KO mice had increased tumor size and tumor burden at 30 weeks. Initial fluorescent staining revealed an increase in immune cell infiltration in the TME of DARC expressing mice compared to DARC KO mice. To further explore this, we employed multiplex staining across a representative cohort of DARC expressing and KO mice at 25 and 30 weeks to capture the specific immune cell populations infiltrating the TME. Conclusions. TNBC tumors have worse prognosis due to lack of targeted therapeutic options. Increased immunogenicity of TNBC tumors, especially among African ancestry women may be driven in part by DARC expression. Characterization of FY- status, in coordination with DARC among other cell types in the TNBC TME could present new opportunities for biomarker and/or therapeutic development to improve prognosis for these underserved populations.

PS18-10

Tumor-Infiltrating Lymphocytes and Breast Cancer Mortality in Racially and Ethnically Diverse Participants of the Northern California Breast Cancer Family Registry

Presenting Author(s) and Co-Author(s):

J. Ransohoff. Stanford University School of Medicine, Palo Alto, California, United States

I. Miller. Stanford University School of Medicine, United States

J. Koo. Stanford University School of Medicine, United States

V. Joshi. Stanford University School of Medicine, United States

A. Kurian. Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California, United States

K. Allison. Stanford University School of Medicine, United States

E. John. Stanford University, United States

M. Telli. Stanford University School of Medicine, San Francisco, California, United States

Purpose: Greater stromal tumor-infiltrating lymphocyte (sTIL) percentage in pre-treatment breast tumor specimens is associated with superior response to neoadjuvant chemotherapy and survival. We hypothesized that sTIL-survival associations vary by race and ethnicity and mediate survival disparities.

Patients and Methods: We evaluated pre-treatment percentages of sTILs in deciles for 284 women enrolled in the Northern California Breast Cancer Family Registry and diagnosed with a first primary invasive breast cancer from 1995-2005. We assessed associations of continuous sTIL scores and lymphocyte-predominant breast cancer (LPBC, defined as $\geq 50\%$ lymphocytic infiltration of tumor stroma or cell nests) with clinical and epidemiologic characteristics using regression analysis and with breast cancer-specific mortality (BCM) and overall mortality (OM) using Cox proportional hazards regression. **Results:** The cohort was diverse (64% from racially and ethnically minoritized populations) with near-complete (98%) germline BRCA1/2 testing and long-term follow-up (average 16.2 years, range: 1.3-26.7). In multivariable analyses, higher sTIL score was associated with reduced BCM [LPBC versus non-LPBC: HR=0.44 (95% confidence interval 0.20-0.98); and per decile increase in sTIL score: HR=0.80 (0.69-0.93)], with the strongest association in the subset of patients with hormone receptor-negative disease [HR=0.71 (0.57-0.88) and HR=0.37 (0.14-0.94), respectively]. While there was no significant difference in sTIL score between racial and ethnic groups, the continuous sTIL-survival association was statistically significant among non-Hispanic White [HR=0.73 (0.57-0.94)] and Asian American [HR=0.56 (0.35-0.89)] women but was not seen among African American and Hispanic women. **Conclusion:** We identified novel sTIL-BCM differences by race and ethnicity, with better survival associated with sTIL enrichment among non-Hispanic White and Asian American but not among African American or Hispanic women. Additional studies are needed to determine whether survival and particularly the response to immunotherapy are differentially mediated by immune factors between racial and ethnic groups.

Multivariable Cox Proportional Hazards Regression Models of Breast Cancer-Specific and Overall Mortality.

Multivariable Cox Proportional Hazards Regression Models of Breast Cancer-Specific and Overall Mortality.

Group	Cases N	Deaths N	Breast Cancer-Specific Mortality HR (95% CI)		Deaths N	Overall Mortality HR (95% CI)	
			sTIL Per decile increase	LPBC vs non- LPBC		sTIL Per decile increase	LPBC vs non- LPBC
Overall^a	284	70	0.80 (0.69-0.93)	0.44 (0.20-0.98)	100	0.88 (0.79-0.99)	0.66 (0.37-1.20)
Breast cancer subtype^a							
ER ⁺ and/or PR ⁺	161	56	0.83 (0.62-1.10)	0.30 (0.04-2.32)	56	0.94 (0.76-1.16)	0.67 (0.20-2.31)
ER ⁻ and PR ⁻	123	30	0.71 (0.57-0.88)	0.37 (0.14-0.94)	44	0.81 (0.69-0.95)	0.57 (0.28-1.20)
TNBC	71	15	0.71 (0.53-0.96)	0.26 (0.06-1.09)	23	0.90 (0.73-1.11)	0.90 (0.34-2.41)
Race and ethnicity^{b,c}							
Non-Hispanic White	102	28	0.73 (0.57-0.94)	0.12 (0.02-0.89)	43	0.87 (0.74-1.03)	0.47 (0.18-1.23)
Asian American	76	15	0.56 (0.35-0.89)	0.19 (0.02-1.49)	19	0.65 (0.46-0.92)	0.30 (0.07-1.34)
African American	38	12	0.99 (0.68-1.42)	2.13 (0.37-12.42)	16	0.95 (0.68-1.32)	1.73 (0.33-9.11)
Hispanic	67	13	0.94 (0.66-1.32)	1.23 (0.29-5.15)	23	0.94 (0.72-1.24)	1.06 (0.33-3.44)

Abbreviations. HR: hazard ratio; CI: confidence interval; LPBC: lymphocyte-predominant breast cancer; sTIL: stromal tumor infiltrating lymphocyte; ER⁺: estrogen receptor-positive; ER⁻: estrogen receptor-negative; PR⁺: progesterone receptor-positive; PR⁻: progesterone receptor-negative; TNBC: triple-negative breast cancer (ER⁻, PR⁻, HER2⁻).

^a Models for breast cancer-specific and overall mortality for the overall cohort and for breast cancer subtypes were adjusted for prognostic variables including age at diagnosis, cancer stage (I vs II vs III/IV/unknown), pre-diagnosis BMI (<25, 25-29.9, >30 kg/m²), and germline *BRCA2* pathogenic variant status.

^b Models for breast cancer-specific and overall mortality by race and ethnicity were adjusted for age at diagnosis, stage (I vs II/III/IV/unknown), pre-diagnosis BMI (<30 vs ≥30 kg/m²), and germline *BRCA2* pathogenic variant status.

^c Excludes 1 Native American patient.

GS03-01

Magnetic Resonance Imaging and a 12-Gene Expression Assay to Optimize Local Therapy for Ductal Carcinoma In Situ: 5-year clinical outcomes of E4112

Presenting Author(s) and Co-Author(s):

S. Khan. Northwestern University, Chicago, Illinois, United States

J. Romanoff. Brown University - ECOG-ACRIN Biostatistics Center, Providence, Rhode Island, United States

C. Gatsonis. Dept of Biostatistics, Brown University School of Public Health, United States

H. Rahbar. University of Washington, United States

R. Carlos. University of Michigan, United States

S. Badve. Indiana University, United States

J. Wright. Johns Hopkins, United States

C. Lehman. Massachusetts General Hospital, United States

W. McCaskill-Stevens. National Cancer Institute, United States

R. Corsetti. Ochsner Medical Center, United States

D. Spell. Gulf South NCORP, United States

K. Blankstein. Hunterdon Medical Center, United States

L. Han. Indiana University, United States

J. Sabol. LMC, United States

J. Bumberry. Mercy Hospital, United States

I. Gareen. Brown University, United States

B. Snyder. Brown University, United States

L. Wagner. Wake Forest University School of Medicine, United States

K. Miller. Indiana University, United States

J. Sparano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

C. Comstock. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Disclosure(s):

Seema Khan, MD: No financial relationships to disclose

General Session 3

Presenting Author(s) and Co-Author(s):

M. Torres. Winship Cancer Institute of Emory University, Atlanta, Georgia, United States

M. Rimawi. Baylor College of Medicine, Houston, Texas, United States

Disclosure(s):

Mylin A. Torres, MD: Consulting Fees (e.g., advisory boards): Genentech-Roche (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Genentech-Roche (Ongoing)

Mothaffar F. Rimawi, MD: Consulting Fees (e.g., advisory boards): AstraZeneca (Terminated, September 1, 2021), Novartis Pharmaceuticals Corporation (Terminated, September 1, 2021)

GS03-02

Mammographic surveillance in early breast cancer patients aged 50 years or over: results of the Mammo-50 non-inferiority trial of annual versus less frequent mammography

Presenting Author(s) and Co-Author(s):

- J. Dunn. University of Warwick, Coventry, England, United Kingdom
- P. Donnelly. Torbay and South Devon NHS Foundation Trust, United States
- N. Elbeltagi. Warwick clinical Trials Unit, University of Warwick, United Kingdom
- A. Marshall. Warwick Clinical Trials Unit, University of Warwick, Coventry, England, United Kingdom
- A. Thompson. Baylor College of Medicine, Houston, Texas, United States
- R. Audisio. Department of Surgery, Institute of Clinical Sciences, University of Göteborg, Sweden
- S. Pinder. School of Cancer and Pharmaceutical Sciences, King's College London Faculty of Life Sciences and Medicine, London, England, United Kingdom
- D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom
- A. Campbell. Warwick Clinical Trials Unit, University of Warwick, United States
- S. Hartup. Leeds Teaching Hospitals NHS Trust, Leeds, England, United Kingdom
- L. Turner. Independent Cancer Patients' Voice, United States
- A. Young. Emerita Professor of Nursing, United States
- H. Higgins. University of Warwick, United States
- E. Watson. Oxford Institute of Applied Health Research, Oxford Brookes University, United States
- S. Gasson. Warwick Clinical Trials Unit, University of Warwick, United States
- P. Barrett-Lee. Velindre University NHS Trust, Cardiff University, United States
- C. Hulme. University of Exeter Medical School, United States
- B. Shinkins. Warwick Medical School, University of Warwick / Leeds Institute for Health Sciences, University of Leeds, United States
- P. Hall. University of Edinburgh, Edinburgh, United Kingdom
- A. Evans. University of Dundee and NHS Tayside, United States

Disclosure(s):

Janet A. Dunn, PhD: No financial relationships to disclose

Alastair M. Thompson, MD: Spouse employed by Eli Lilly: Eli Lilly, (Ongoing)

GS03-03

Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2- early breast cancer: final invasive disease-free survival (iDFS) analysis from the NATALEE trial

Presenting Author(s) and Co-Author(s):

G. Hortobagyi. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Stroyakovskiy. City Clinical Oncology Hospital 62, Moscow, Russia

D. Yardley. Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, United States

C. Huang. National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, Taipei, United States

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

J. Crown. St Vincent's University Hospital, Dublin 4, Dublin, Ireland

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

S. Chia. British Columbia Cancer Agency, Vancouver, British Columbia, Canada

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

B. Xu. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China (People's Republic)

S. Hurvitz. Fred Hutchinson Cancer Center/University of Washington, Los Angeles, California, United States

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

M. Untch. AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany, Berlin, United States

R. Moroos. UF Health Cancer Center – Orlando Health, Orlando, FL, United States

F. Visco. National Breast Cancer Coalition (NBCC), Washington DC, District of Columbia, United States

F. Parnizari. TRIO - Translational Research in Oncology, Montevideo, Uruguay

F. Ghaznawi. Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

Z. Li. Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

S. Waters. Novartis Ireland, Dublin, Ireland

A. Chakravarty. Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

D. Slamon. UCLA David Geffen School of Medicine, Los Angeles, California, United States

Background: Interim results from the phase 3 NATALEE trial demonstrated that adding RIB to standard-of-care adjuvant NSAI had a statistically significant iDFS benefit in patients with stage II and III HR+/HER2- early breast cancer at risk of recurrence, including those with node-

negative disease (Slamon et al, ASCO 2023). We present the final protocol-specified analysis of the primary endpoint of iDFS.

Methods: A total of 5101 pre-/postmenopausal women and men underwent 1:1 randomization to receive RIB (400 mg/day; 3 weeks on/1 week off for 36 months) + NSAI (letrozole 2.5 mg/day or anastrozole 1 mg/day for ≥ 60 months) or NSAI alone. Men and premenopausal women received goserelin (3.6 mg once every 28 days). Patients were required to have anatomic stage IIA (either N0 with additional risk factors or N1), IIB, or III breast cancer per the AJCC (8th edition). Patients remained on trial as long as they were continuing on NSAI (≤ 5 years), regardless of RIB discontinuation. The primary endpoint was iDFS according to STEEP v1.0 criteria, and the secondary efficacy endpoints were recurrence-free survival (RFS), distant disease-free survival (DDFS), and overall survival (OS). This final analysis was planned after approximately 500 iDFS events. iDFS was evaluated by the Kaplan-Meier method, and statistical comparison was made by a stratified log-rank test. P values were not corrected for multiple comparisons.

Results: At the data cutoff (July 21, 2023), among the 2549 patients in the RIB + NSAI arm, 1091 (42.8%) completed 3 years of RIB treatment, and 905 (35.5%) discontinued RIB or RIB + NSAI early and 528 patients (20.7%) remained on RIB. 1748 patients (68.5%) remain on treatment in the NSAI arm.

Median follow-up for iDFS was 33.3 months, an additional 5.6 months from the previous interim analysis. A total of 509 iDFS events were observed, 226 (8.9%) in the RIB + NSAI arm and 283 (11.1%) in the NSAI alone arm. RIB + NSAI demonstrated a significant iDFS benefit over NSAI alone (HR, 0.749; 95% CI, 0.628-0.892; $P = .0006$). The 3-year iDFS rates were 90.7% (95% CI, 89.3%-91.8%) vs 87.6% (95% CI, 86.1%-88.9%). A consistent benefit was observed across patient subgroups, including those with node-negative, stage II, or stage III disease (Table). Secondary endpoints of DDFS and RFS favored RIB + NSAI over NSAI alone (Table). OS data were immature, with 84 (3.3%) and 88 (3.4%) total events in the RIB + NSAI and NSAI alone arms, respectively. No new safety signals were observed since the prior interim analysis. Discontinuation of RIB due to adverse events was observed in 19.5% of patients (a $< 1\%$ increase from the prior interim analysis).

Conclusions: With a substantial proportion of patients completing 3 years of RIB treatment, NATALEE continues to demonstrate a significant iDFS improvement with RIB + NSAI over NSAI alone. Efficacy results confirm continued improvement in benefit across subgroups, including stage II disease. Safety findings support the manageable toxicity profile of RIB at the 400-mg starting dose in early breast cancer.

Table

	RIB + NSAI n = 2549	NSAI alone n = 2552
iDFS in ITT population		
HR (95% CI)	0.749 (0.628-0.892)	
P value ^a	.0006	
3-Year iDFS rate, %	90.7	87.6
iDFS in clinically relevant subgroups		
Node negative		
HR (95% CI)	0.723 (0.412-1.268)	
3-Year iDFS rate, %	93.2	90.6
Stage II		
HR (95% CI)	0.700 (0.496-0.986)	
3-Year iDFS rate, %	94.2	92.6
Stage III		
HR (95% CI)	0.755 (0.616-0.926)	
3-Year iDFS rate, %	88.1	83.8
Secondary efficacy endpoints in ITT population		
RFS		
HR (95% CI)	0.727 (0.602-0.877)	
3-Year RFS, %	92.1	89.1
DDFS		
HR (95% CI)	0.749 (0.623-0.900)	
3-Year DDFS, %	92.9	90.2
OS		
HR (95% CI)	0.892 (0.661-1.203)	
3-Year OS, %	97.0	96.1

ITT, intent to treat.

^a One-sided P value.

Disclosure(s):

Gabriel N. Hortobagyi, MD, MACP, FASCO: Advisory Committee/Board Member: Novartis Pharma GmbH (Ongoing)

Aditya Bardia, MD, MPH: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Menarini/Stemline (Ongoing)

Miguel Martín, MD, PhD: Advisory Committee/Board Member: Eli Lilly, Exelixis, Faron Pharmaceuticals Ltd, Forma Therapeutics, Gamamabs, Genentech, Glaxosmithkline, H3 Biomedicine (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Novartis Pharma GmbH (Ongoing); Consulting Fees (e.g., advisory boards): daichii-Sankyo (Ongoing), Gilead (Ongoing), Pfizer, Inc. (Ongoing), Seagen Inc (Ongoing)

Sherene Loi, MD, PhD: Advisory Committee/Board Member: Bristol-Myers Squibb Company (Ongoing), MSD Co., Ltd. (Ongoing); Consulting Fees (e.g., advisory boards): Aduro Biotech (Ongoing), Amunix (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if

received/managed by the institution): Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), MSD Co., Ltd. (Ongoing), Nektar Therapeutics (Ongoing), Novartis International AG (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics (Ongoing); Uncompensated consultant: Aduro Biotech (Ongoing), Amunix (Ongoing), Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing)

Binghe Xu, MD: Advisory Committee/Board Member: Astra Zeneca, Novartis (Ongoing)

Sara Hurvitz, MD, FACP: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Ambrx, Inc (Terminated), Arvinas (Terminated), Astra Zeneca (Terminated), Celcuity Inc. (Terminated), CytomX Therapeutics (Terminated), Daiichi-Sankyo (Terminated), Dantari, Inc. (Terminated), Eli Lilly (Terminated), F. Hoffman La Roche Ltd (Terminated), G1-Therapeutics (Terminated), Genentech (Terminated), Gilead (Terminated), Greenwich Lifesciences (Terminated), Novartis (Terminated), Orinove (Terminated), Orum Therapeutics (Terminated), Phoenix Molecular Designs, Ltd. (Terminated), Pieris Pharmaceuticals (Terminated), Puma Biotechnology, Inc (Terminated), Radius Health (Terminated), Sanofi (Inst) (Terminated), Seagen Inc (Terminated), Zymeworks Inc./Jazz (Terminated)

Carlos H. Barrios, MD: Consulting Fees (e.g., advisory boards): AstraZenca (Ongoing), BMS (Ongoing), Daiichi-Sankyo (Ongoing), Eisai, Inc (Ongoing), Gilead Science (Ongoing), Loxo@Lilly (Ongoing), MSD Pharma (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche/GNE (Ongoing), Zodiac (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Amgen Inc. (Ongoing), AstraZenca (Ongoing), Aveo (Ongoing), Bayer Pharmaceuticals (Ongoing), BMS (Ongoing), Celgene (Ongoing), Daiichi-Sankyo (Ongoing), Exelixis, Inc. (Ongoing), Gilead Science (Ongoing), GSK (Ongoing), ICON (Ongoing), IQVIA Inc. (Ongoing), Janssen Biotech (Ongoing), Labcorp (Ongoing), Loxo@Lilly (Ongoing), MerkSerono (Ongoing), MSD Pharma (Ongoing), Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncopeptides, Orion Pharma, Ose Pharma, (Ongoing), Novartis International AG (Ongoing), Novocure (Ongoing), Nuvisan (Ongoing), OBI Pharma Inc. (Ongoing), Parexel International (Ongoing), Pfizer, Inc. (Ongoing), PharmaMar (Ongoing), Polyphor (Ongoing), PPD Global (Ongoing), PsiOxus (Ongoing), Regeneron Pharmaceuticals Inc. (Ongoing), Roche/GNE (Ongoing), Sanofi Aventis (Ongoing), SeaGen (Ongoing), Servier (Ongoing), Syneos Health (Ongoing), Takeda Pharmaceuticals, Ltd. (Ongoing), TRIO (Ongoing), Worldwide (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): MedSIR (Ongoing), Thummi (Ongoing)

GS03-04

Novel Mechanisms of CDH1 Inactivation in Breast Invasive Lobular Carcinoma Unveiled by the Integration of Artificial Intelligence and Genomics

Presenting Author(s) and Co-Author(s):

F. Pareja. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, United States

H. Dopeso. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Y. Wang. Paige AI, United States

A. Gazzo. Memorial Sloan Kettering Cancer Center, New York, New York, United States

D. Brown. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, United States

P. Selenica. Memorial Sloan Kettering Cancer Center, United States

J. Bernhard. Paige AI, United States

F. Derakhshan. Memorial Sloan Kettering Cancer Center, New York, NY, United States

E. da Silva. Memorial Sloan Kettering Cancer Center, New York, New York, United States

L. Colon-Cartagena. Department of Pathology, Yale School of Medicine, United States

T. Basili. Memorial Sloan Kettering Cancer Center, New York, NY, United States

A. Marra. IEO Istituto Europeo di Oncologia, United States

J. Sue. Paige AI, United States

Q. Ye. Memorial Sloan Kettering Cancer Center, New York, NY, United States

A. Da Cruz Paula. Department of Surgery, Memorial Sloan Kettering Cancer Center, United States

S. Yeni. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, United States

X. Pei. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

H. Green. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, United States

K. Gill. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, United States

Y. Zhu. Memorial Sloan Kettering Cancer Center, New York, New York, United States

M. Lee. Paige AI, United States

R. Godrich. Paige AI, United States

A. Casson. Paige AI, United States

B. Weigelt. Memorial Sloan Kettering Cancer Center, New York, New York, United States

N. Riaz. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States

H. Wen. Memorial Sloan Kettering Cancer Center, United States

E. Brogi. Memorial Sloan Kettering Cancer Center, United States

M. Hanna. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, United States

D. Mandelker. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, United States

J. Kunz. Paige AI, United States

B. Rothrock. Paige AI, United States

S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

C. Kanan. University of Rochester, Rochester, NY, United States

G. Oakley III. Paige, United States

D. Klimstra. Paige, Middletown, NY, United States

T. Fuchs. Paige AI, United States

J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States

Background: Invasive lobular carcinoma (ILC) of the breast is the second most common histologic subtype of breast cancer (BC), following invasive ductal carcinoma of no special type (IDC-NST). The hallmark histologic feature of ILC is cellular discohesiveness, the result of bi-allelic inactivation of CDH1, and represents an important genotypic-phenotypic correlation in BC. Although most ILCs harbor CDH1 loss-of function mutations associated to loss-of-heterozygosity (LOH) of the wild type-allele, a subset of ILCs lack these alterations despite displaying a typical lobular phenotype. Here, we sought to identify alternative molecular mechanisms converging on CDH1 inactivation by employing an integrative artificial intelligence (AI) and genomics approach. Materials and Methods: A genomics-driven AI-based algorithm using hematoxylin and eosin (H&E) whole slide images (WSIs) as input, previously developed to detect bi-allelic CDH1 mutations (inactivating mutation associated to LOH) in BC was employed. WSIs of 1,057 BCs including ILCs (n=187) and non-lobular BCs (n=870) previously subjected to FDA-cleared tumor/normal targeted sequencing were subjected to analysis with the AI-based algorithm. Cases predicted to harbor CDH1 bi-allelic mutations by the AI-model but lacking CDH1 bi-allelic mutations by targeted sequencing were assessed through targeted sequencing data re-analysis, CDH1 gene promoter methylation evaluation and/or whole genome sequencing analysis. Results: AI-based analysis WSIs corresponding to 1,057 BCs resulted in the identification of 34 cases found to lack CDH1 bi-allelic mutations by targeted sequencing but predicted to harbor these genetic alterations by the AI-based model. CDH1 gene promoter methylation assessment revealed CDH1 promoter methylation in 18 cases. Targeted sequencing data reanalysis revealed other genetic mechanisms of CDH1 inactivation including CDH1 homozygous deletions (n=3), intragenic deletion with LOH (n=1), and likely pathogenic non-coding CDH1 alterations associated with LOH (n=2). WGS analysis of an ILC revealed a novel deleterious CDH1 fusion stemming from translocation t(13;16), resulting in loss of the 5'UTR, transcription start site and exons 1 and 2 of CDH1, associated with complete loss of E-cadherin protein expression. Taken together, we identified alternative/novel mechanisms of bi-allelic CDH1 inactivation in 74% (25/34) cases analyzed. Conclusions: By applying an AI-based algorithm trained to detect a genetic alteration (i.e., CDH1 bi-allelic mutations), we were able to identify alternative epigenetic and genetic molecular mechanisms of CDH1 inactivation in ILCs, including novel non-coding CDH1 genetic alterations and a new inactivating CDH1 fusion gene. These findings indicate that molecular mechanisms affecting a single gene or process converging on the same phenotype can be unveiled by the integration of AI and genomics, highlighting the robustness of this approach for the discovery of novel biology.

Disclosure(s):

Fresia Pareja, MD PhD: Advisory Committee/Board Member: MultiplexDx (Ongoing); Consulting Fees (e.g., advisory boards): MultiplexDx (Ongoing)

Jorge Reis-Filho, MD, PhD: Advisory Committee/Board Member: Bain Capital (Terminated, July 23, 2023), Grupo Oncoclinicas (Terminated, July 23, 2023), Paige.ai (Terminated, July 23, 2023), REPARE Therapeutics (Terminated, July 23, 2023); Consulting Fees (e.g., advisory boards): Bain Capital (Terminated, July 23, 2023), Goldman Sachs (Terminated, July 23, 2023), Grupo Oncoclinicas (Terminated, July 23, 2023), Paige.ai (Terminated, July 23, 2023), REPARE Therapeutics (Terminated, July 23, 2023), SAGA Diagnostics (Terminated, July 23, 2023); Employee (Ineligible company: whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by/on patients): AstraZeneca PLC (Ongoing); Independent Contractor: Goldman Sachs (Terminated); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Grupo Oncoclinicas (Terminated, July 23, 2023), Paige.ai (Terminated, July 23, 2023), REPARE Therapeutics (Terminated, July 23, 2023)

GS03-06**Genomic and transcriptomic profiling of primary tumors from patients with HR+, HER2-, node-positive, high-risk early breast cancer in the monarchE trial**

Presenting Author(s) and Co-Author(s):

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

H. Sasano. Department of Pathology, Tohoku University Hospital, Sendai, Japan.

C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

S. Graff. Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, United States

D. Liu. Eli Lilly and Company, Indianapolis, Indiana, United States

V. Rodrik-Outmezguine. Eli Lilly and Company, Indianapolis, Indiana, United States

A. Sireci. Eli Lilly and Company, Indianapolis, Indiana, United States

C. Sandoval Rubenstein. Eli Lilly and Company, Indianapolis, Indiana, United States

H. Won. Eli Lilly and Company, Indianapolis, Indiana, United States

L. M. Litchfield. Eli Lilly and Company, Indianapolis, Indiana, United States

M. Munoz. Eli Lilly and Company, United States

S. Johnston. The Royal Marsden Hospital, London, United Kingdom

Background Two years of adjuvant abemaciclib combined with endocrine therapy (ET) resulted in significant and clinically meaningful improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) in patients (pts) with HR+, HER2-, node-positive, high-risk early breast cancer in the monarchE trial (NCT03155997). Abemaciclib benefit was sustained beyond the completion of treatment (tx) with deepening magnitude of absolute benefit in IDFS and DRFS at 5 years. Here, we evaluate comprehensive molecular profiling of archived primary tumor tissue and association with clinical outcomes. **Methods** For biomarker analysis, a proportionally stratified random sampling case-cohort design was utilized to include all patients who experienced an IDFS event at a pre-specified interim analysis with a median follow up of 54 months. A cohort of 895 pts (189 with IDFS event) in the abemaciclib + ET arm was matched 1:1 with 903 pts (270 with IDFS event) in the ET arm. Baseline primary tumor samples underwent exome-capture RNA sequencing (RNAseq; n=1324, 23% intent-to-treat (ITT) population) and paired tumor-normal (germline blood samples) whole-exome sequencing (WES; n=1234, 22% ITT population). Expression-based intrinsic subtypes (i.e., luminal A (LumA), luminal B (LumB), HER2-enriched (HER2E), basal- and normal-like) were characterized using the Absolute Intrinsic Molecular Subtyping model. The 21-gene expression signature score (Oncotype DX test) was inferred from RNAseq; samples were categorized into lower (0-25) and high (26-100) risk groups. To investigate associations of biomarkers with

abemaciclib benefit, WES genomic events including oncogenic and hotspot mutations by OncoKB, and copy number events, of incidence >9% were pre-selected. **Results** The biomarker subset of monarchE was reflective of the ITT population. A total of 1190 tumors (abemaciclib+ET n= 605; ET alone n=585) yielded adequate RNAseq results. Intrinsic subtype distribution was consistent across tx arms (Table A). Low tumor purity limited assessment of the normal-like subtype. The 4-year IDFS benefit of abemaciclib was consistent across all subtypes. LumA cancers had the lowest risk of recurrence while HER2E and basal-like subtypes had the highest. Inferred 21-gene expression signature score showed similar benefits from abemaciclib in both lower and high-risk groups (Table B). A total of 1173 tumors yielded adequate WES results (abemaciclib+ET n=580; ET alone n=593). Consistent abemaciclib benefit was observed across the most frequently altered genes (Table C). In exploratory analysis, lower benefit from abemaciclib was seen in the subset of focal-high level MYC amplified tumors (n=176, HR 1.30, 95% CI, 0.77, 2.20) compared to MYC non-amplified tumors (n=997, HR 0.62, 95% CI, 0.47, 0.80, nominal interaction p=0.014). The treatment benefit of abemaciclib was observed across all subpopulations of altered genes based on gene expression data. **Conclusions** Adjuvant abemaciclib+ET maintained IDFS benefit compared to ET alone across all molecular subtypes as measured by RNAseq. Benefit was consistent across most altered genes assessed by WES, except for the subset of tumors with MYC amplification. Additional research is necessary to confirm these findings.

Table. RNA signatures, most frequent genomic alterations and IDFS.

	Abemaciclib + ET			ET			HR (95% CI)	Interaction p-value
	Event/ N	4-year IDFS rate (95% CI)	Incidence (%)	Event/ N	4-year IDFS rate (95% CI)	Incidence (%)		
A. RNA Molecular subtypes								
All pts	138/ 605	77.4 (74.1-80.9)	NA	182/ 585	69.8 (66.1-73.7)	NA	0.703 (0.563, 0.877)	NA
Luminal A	28/230	87.4 (83.1-92.0)	38%	45/228	81.4 (76.3-86.8)	39%	0.594 (0.371, 0.952)	0.602
Luminal B	65/265	76.0 (70.9-81.5)	44%	88/262	66.6 (61.1-72.7)	45%	0.701 (0.509, 0.966)	
HER2E	32/69	53.4 (42.5-67.2)*	11%	34/59	42.5 (31.4-57.5)*	10%	0.74 (0.456, 1.20)*	
Basal-like	9/21	59.1 (41.7-83.7)*	4%	8/15	46.7 (27.2-80.2)*	3%	0.748 (0.288, 1.94)*	
Normal-like (Low purity)	4/20	85 (70.7-100)*	3%	7/21	79.2 (62.9-99.6)*	4%	0.492 (0.144, 1.68)*	
B. Inferred 21-gene expression signature score								
All pts	138/ 605	77.4 (74.1-80.9)	NA	182/ 585	69.8 (66.1-73.7)	NA	0.7 (0.56, 0.88)	NA
Lower risk (0-25)	18/ 173	90.2 (85.8-94.9)	26%	28/ 165	84.2 (78.7-90.1)	27%	0.59 (0.33, 1.1)	0.532
High-risk (26-100)	120/ 432	72.3 (68.1-76.8)	74%	154/ 420	64.1 (59.6-69.0)	73%	0.73 (0.57, 0.92)	
C. Genomic alterations								
PIK3CA mutation	55/ 217	76 (70.5-82.1)	37%	73/ 229	68.5 (62.6-75)	39%	0.75 (0.528, 1.06)	0.758
TP53 mutation/deep deletion	55/ 189	72.1 (65.8-78.9)	33%	82/ 184	56.6 (48.8-63.4)	31%	0.597 (0.424, 0.841)	0.184
CCND1 amplification	36/ 113	72.9 (65.1-81.7)	19%	42/ 129	67.6 (59.9-76.2)	22%	0.938 (0.601, 1.46)	0.177
ZNF703 amplification	28/ 96	72.5 (63.9-82.3)	17%	37/ 100	64.8 (55.9-75.1)	17%	0.768 (0.47, 1.26)	0.776*
MYC amplification	34/ 92	66.7 (57.6-77.2)	16%	25/ 84	69.4 (60-80.1)	14%	1.29 (0.767, 2.16)	0.014*
FGFR1 mutation/ amplification	26/ 88	72.4 (63.4-82.7)	15%	35/ 98	66.4 (57.6-76.6)	17%	0.803 (0.483, 1.33)	0.641*
GATA3 mutation	13/ 73	84.3 (76.1-93.3)	13%	17/88	81.1 (73.2-89.9)	15%	0.861 (0.417, 1.78)	0.513*

NA, not applicable; NE, not estimated due to low numbers. *Limited sample size

Disclosure(s):

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide

GS03-07

Protocol-defined biomarker analysis in the PALLAS (AFT-05) adjuvant trial: Genomic subtype derived from RNA sequencing of HR+/HER2- early breast cancer.

Presenting Author(s) and Co-Author(s):

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

D. Hlauschek. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria

E. Mayer. Associate Professor in Medicine, Harvard Medical School, Boston, Massachusetts, United States

W. Symmans. UT MD Anderson Cancer Center, United States

M. Watson. Washington University School of Medicine, United States

I. Barozzi. Medical University of Vienna, United States

M. Filipits. Center for Cancer Research, Medical University of Vienna, Vienna, Austria

K. Ballman. Mayo Clinic, United States

M. Bellet- Ezquerra. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain

J. Balko. Vanderbilt University Medical Center, Nashville, Tennessee, United States

G. Rubovszky. National Institute of Oncology, Budapest, Hungary

N. Zdenkowski. Breast Cancer Trials, Newcastle, New South Wales, Australia

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

G. Steger. Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria, Wien, Austria

C. Isaacs. Georgetown University, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

F. Henao. Medical Oncology Hospital Virgen de la Macarena, Sevilla, United States

M. Regan. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Y. Liu. Pfizer Inc, San Diego, California, United States

C. Fesl. Austrian Breast Cancer and Colorectal Study Group, Vienna, Austria

P. O'Brien. Mayo Clinic, United States

A. DeMichele. University of Pennsylvania, Philadelphia, Pennsylvania, United States

M. Gnant. Medical University of Vienna, Wien, Austria

O. Metzger. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background. The phase 3 PALLAS trial (NCT02513394) compared two years of the CDK4/6 inhibitor palbociclib with endocrine therapy of provider choice, versus endocrine therapy alone, as adjuvant treatment for patients with Stage II-III hormone receptor-positive HER2-negative (HR+/HER2-) breast cancer. Genomic subtype (PAM50 intrinsic subtype) measured from whole-transcriptome RNA sequencing data was defined in the protocol of the PALLAS trial as the primary biomarker for analysis of prediction and prognosis. Clinical data have been previously presented (Gnant et al, JCO 2022), and the trial now has 5-year median follow-

up. **Methods.** As part of trial eligibility, all participants in PALLAS provided a tumor tissue block prior to randomization (surgical if primary resection, core biopsy if neoadjuvant treatment) for translational analyses (TRANS-PALLAS). The biorepository and laboratory were blinded to identity and processed samples in random order, to minimize bias. Nucleic acids were extracted from samples with sufficient tumor tissue and cellularity ($>25 \text{ mm}^2$ with $\geq 20\%$ cancer nuclei). The Genome Sequencing Center at Washington University St. Louis performed whole-transcriptome RNA sequencing. Libraries were prepared from $1 \mu\text{g}$ DNase-1 treated total RNA, if total RNA DV200 >28 (Agilent Bioanalyzer), using an unbiased library protocol of RNA HyperPrep kit with RiboErase (HMR) (Kapa Biosystems, Wilmington, MA). 100 bp paired-end sequencing was performed on NovaSeq 6000 using S4 Reagent Kit (Illumina, San Diego, CA), with 48 libraries pooled per lane. Intrinsic subtype was determined using Bioclassifier package (Research PAM50 script, Parker et al.) only for the analysis population of primary breast cancer samples that had not been exposed to prior neoadjuvant therapy. Invasive disease-free survival (IDFS) will be visualized using Kaplan-Meier plots, with log-rank test between groups. Cox models of proportional hazards will be developed to evaluate prognosis adjusted for known clinical covariates, or for predictive interactions. The pre-defined level of significance is a two-sided 0.05. **Results.** From the total study population of 5796 enrolled patients, 4655 tissue blocks had sufficient tumor content to process for RNA, with 3931 yielding sufficient RNA for sequencing, and 2669/4655 (57.3%) submitted tissue blocks had DV200 ≥ 28 and were successfully sequenced. Clinical unblinding revealed 2370 unique patients (1182 in the palbociclib treatment arm and 1188 in the control arm) with intrinsic subtype defined from their untreated primary tumor: 1555 (65.6%) luminal A, 287 (12.1%) luminal B, 167 (7.0%) HER2-enriched, 310 (13.1%) basal-like, 51 (2.2%) normal-like. We will report the results for association of molecular subtype, proliferation score, and Risk of Recurrence (ROR) scores with invasive disease-free survival (IDFS) by treatment arm at the meeting. **Conclusions.** The TRANS-PALLAS cohort represents one of the largest biorepositories of HR+/HER2- early breast cancer reflecting contemporary systemic management in the framework of a prospectively randomized global trial. Required tumor block submission in this phase 3 trial yielded data from unbiased whole-transcriptome RNA sequencing of the primary tumor prior to treatment from 41% of the PALLAS participants. The proportion of luminal A cancers was unexpectedly high (66%), indicating a lower-risk distribution of cancers in this population. The planned analyses of prediction and prognosis are ongoing and those results will be presented at the time of the meeting. **Support:** AFT, ABCSG, Pfizer, ECOG-ACRIN, NSABP Foundation, GBG, BIG; Clinicaltrials.gov Identifier: NCT02513394; <https://acknowledgments.alliancefound.org>

Disclosure(s):

Daniel Stover, MD: Consulting Fees (e.g., advisory boards): Novartis Pharma GmbH (Terminated, November 30, 2021)

Erica L. Mayer, MD, MPH: Consulting Fees (e.g., advisory boards): AstraZeneca PLC (Ongoing), Lilly Pharmaceuticals/Loxo Oncology (Ongoing), Novartis Pharma GmbH (Ongoing)

Justin Balko, PharmD, PhD: Consulting Fees (e.g., advisory boards): Astra Zeneca (Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus)) (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Genentech-Roche (Ongoing), Incyte (Ongoing)

Nicholas Zdenkowski, B Med, FRACP, PhD: Advisory Committee/Board Member: Novartis Pharmaceuticals (Terminated, June 5, 2023); Consulting Fees (e.g., advisory boards): AstraZenca (Terminated, June 13, 2023), Lilly Australia Pty Ltd (Terminated, June 13, 2023), MSD Co., Ltd. (Terminated, June 13, 2023), Pfizer, Inc. (Terminated, June 13, 2023); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Eisai Co.Ltd (Terminated, August 18, 2023), Gilead (Terminated, August 18, 2023);

Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): BMS (Terminated, October 14, 2022), Roche/Genentech (Terminated, October 14, 2022)

Sibylle Loibl, MD, PhD: Advisory Committee/Board Member: GSK, Pfizer, Novartis (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Consulting Fees (e.g., advisory boards): GSK, Pfizer, Novartis (Ongoing), Menarini/Stemline (Ongoing), MSD Co., Ltd. (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Licences for VM Ki67 Quantifier: VM Scope GmbH (Ongoing); patents pending: EP14153692.0 ,EP21152186.9 , EP19808852.8 , (Ongoing)

Otto Metzger, MD: Consulting Fees (e.g., advisory boards): Alliance for Clinical Trials in Oncology (Terminated, September 19, 2023), Astra Zeneca (Terminated, September 19, 2023), Merck & Co., Inc. (Terminated, September 19, 2023); Independent Contractor: Alliance for Clinical Trials in Oncology (Ongoing), Grupo Oncoclinicas (Ongoing)

GS03-09**Characterization and proposed therapeutic exploitation of fusion RNAs in metastatic breast cancers**

Presenting Author(s) and Co-Author(s):

N. Priedigkeit. Dana-Farber Cancer Institute / Broad Institute of MIT and Harvard, Boston, Massachusetts, United States

A. Lebrón-Torres. Broad Institute of MIT and Harvard / Davidson College, United States

J. Liao. Broad Institute of MIT and Harvard / Harvard College, United States

J. Alberge. Dana-Farber Cancer Institute, United States

S. Morganti. Dana-Farber Cancer Institute; Harvard Medical School; Broad Institute of MIT and Harvard, United States

J. Weiss. Dana-Farber Cancer Institute / Broad Institute of MIT and Harvard, United States

J. Gomez Tejada Zanudo. Dana-Farber Cancer Institute, United States

A. Grinshpun. Dana-Farber Cancer Institute, and Harvard Medical School, United States

M. Hughes. Dana Farber Cancer Institute, United States

K. Helvie. Dana-Farber Cancer Institute, United States

K. Sendrick. Dana-Farber Cancer Institute, United States

K. Nguyen. Dana Farber Cancer Institute, United States

S. Strauss. Dana-Farber Cancer Institute, United States

J. Files. Dana-Farber Cancer Institute, United States

M. Lloyd. Beth Israel Deaconess Medical Center, United States

N. Wagle. Dana-Farber Cancer Institute, United States

C. Stewart. Broad Institute of MIT and Harvard, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

B. Johnson. Medical Oncology, Dana-Farber Cancer Institute; Harvard Medical School, United States

Y. Li. Medical Oncology, Dana-Farber Cancer Institute, United States

R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

S. Tolaney. Dana-Farber Cancer Institute, Boston, MA, United States

D. Abravanel. Dana-Farber Cancer Institute, United States

N. Lin. Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts, United States

H. Parsons. Dana Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

G. Getz. Harvard Medical School / Broad Institute of MIT and Harvard, United States

S. Oesterreich. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

A. LEE. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

T. Golub. Harvard Medical School / Broad Institute of MIT and Harvard, United States

Disclosure(s):

Nolan Priedigkeit, MD, PhD: No financial relationships to disclose

Eric Winer, MD: No financial relationships to disclose

Sara Tolaney, MD, MPH: Consulting Fees (e.g., advisory boards): Aadi Biopharma (Ongoing), ARC Therapeutics (Ongoing), Artios (Ongoing), AstraZeneca (Ongoing), Bayer Pharmaceuticals (Ongoing), Blueprint Medicine (Ongoing), Bristol Myers Squibb (Ongoing), CytomX Therapeutics (Ongoing), CytomX Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), eFFECTOR Therapeutics (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Incyte Corp. (Ongoing), Infinity Therapeutics (Ongoing), Jazz Pharmaceuticals (Ongoing), Luzsana (Ongoing), Menarini/Stemline (Ongoing), Merck & Co., Inc. (Ongoing), Natera, Inc. (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), Reveal Genomics, S.L. (Ongoing), Sanofi Genzyme (Ongoing), Seattle Genetics (Ongoing), Sumitovant Biopharma (Ongoing), Systimmune (Ongoing), Tango (Ongoing), Umoja Biopharma (Ongoing), Zetagen (Ongoing), Zymeworks Inc. (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Bristol Myers Squibb (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Co., Ltd, (Ongoing), Eli Lilly (Ongoing), Exelixis, Inc. (Ongoing), Genentech/Roche (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), NanoString Technologies (Ongoing), Novartis (Ongoing), OncoPep (Ongoing), Pfizer (Ongoing), Seattle Genetics (Ongoing)

Nancy U. Lin, MD: Consulting Fees (e.g., advisory boards): Affinia Therapeutics (Ongoing), Aleta Biopharma (Ongoing), AstraZeneca (Ongoing), Blueprint Medicine (Ongoing), Daiichi-Sankyo (Ongoing), Genetech / Roche (Ongoing), Janssen (Ongoing), Menarini/Stemline (Ongoing), Olema Pharmaceuticals (Ongoing), Prelude Therapeutics (Ongoing), Reverie Labs (Ongoing), SeaGen (Ongoing), Voyager Therapeutics (Ongoing); Independent Contractor: Artera (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): AstraZeneca (Ongoing), Genetech / Roche (Ongoing), Menarini/Stemline (Ongoing), Merck (Ongoing), Olema Pharmaceuticals (Ongoing), Pfizer, Inc. (Ongoing), SeaGen (Ongoing), Zion Pharmaceuticals (Ongoing)

Heather A. Parsons, MD, MPH: Advisory Committee/Board Member: AstraZenca (Terminated, December 9, 2022), Caris (Terminated, December 9, 2022); Consulting Fees (e.g., advisory boards): Daiichi-Sankyo (Terminated, June 3, 2023)

Steffi Oesterreich, PhD: No financial relationships to disclose

GS03-10

Allosteric PI3K-alpha inhibition overcomes on-target resistance to orthosteric inhibitors mediated by secondary PIK3CA mutations

Presenting Author(s) and Co-Author(s):

- A. Varkaris. Massachusetts General Hospital, Boston, Massachusetts, United States
- F. Fece de la Cruz. Massachusetts General Cancer Center, United States
- E. Martin. Broad Institute of MIT, United States
- B. Nordern. Massachusetts General Cancer Center, United States
- N. Chevalier. Mass General Cancer Center, United States
- I. Leshchiner. Boston University, United States
- A. Stavridi. Beth Israel Deaconess Medical Center, United States
- J. Kim. Massachusetts General Hospital, Boston, Massachusetts, United States
- A. Papatheodoridi. Department of Therapeutics, University of Athens, United States
- H. Gunaydin. Relay Therapeutics, United States
- B. Danysh. Broad institute of MIT, United States
- L. Parida. IBM, United States
- I. Sanidas. Mass General Cancer Center, United States
- Y. Ji. Emerson Hospital, United States
- K. Lau. Massachusetts General Cancer Center, United States
- G. Wulf. Harvard Medical School, United States
- A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States
- L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States
- S. Isakoff. Cancer Center, Massachusetts General Hospital, United States
- J. Lennerz. Mass General Cancer Center, United States
- L. Pierce. Relay Therapeutics, United States
- E. Pazolli. Relay Therapeutics, United States
- G. Getz. Broad Institute of MIT, Mass General Cancer Center, United States
- R. Corcoran. Massachusetts General Cancer Center, United States
- D. Juric. Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

Background: PIK3CA mutations occur in ~40% of HR-positive breast cancers, where alpelisib, an orthosteric PI3K α inhibitor, is FDA-approved in combination with fulvestrant. Although prior studies have identified potential resistance mechanisms, such as PTEN loss, clinical acquired resistance to orthosteric PI3K α inhibitors and the role of next-generation allosteric PI3K α inhibitors remain poorly understood. Methods: To identify on-target and off-target alterations potentially mediating resistance to PI3K α inhibitors, we used a targeted next-generation sequencing assay (Guardant360; Guardant Health) to analyze ctDNA in serially collected plasma samples from 32 patients with PIK3CA-mutated advanced HR-positive, HER2-negative breast cancer treated with alpelisib and inavolisib. In addition, we performed whole exome

sequencing (WES) of 100 tissue samples collected from 8 autopsy series from patients with metastatic, PIK3CA-mutant HR-positive, HER2-negative breast cancer previously treated with PI3K α inhibitors. Acquired alterations were prioritized through a combination of structural modeling and free-energy perturbation simulation and validated in genomically engineered PIK3CA mutant breast cancer cell lines T47D (PIK3CA H1047R-mutant) or MCF7 (PIK3CA E545K-mutant). Results: We observed that 50% of patients acquire genomic alterations within the PI3K-pathway, including PTEN loss and activating AKT1 mutations. Notably, while secondary PIK3CA mutations were previously reported to increase sensitivity to PI3K α -inhibitors, we identified emergent secondary resistance mutations in PIK3CA that alter the inhibitor binding pocket including PIK3CA Q859K and PIK3CA W780R. Some mutations had differential effects on PI3K α -selective vs. pan-PI3K inhibitors, but resistance induced by all mutations could be overcome by the novel allosteric pan-mutant-selective PI3K α -inhibitor RLY-2608. Conclusion: In one of the largest patient cohorts analyzed to date, this study defines the clinical landscape of acquired resistance to PI3K α inhibitors. Genomic alterations within the PI3K pathway represent a major mode of resistance and identify a novel class of secondary PIK3CA resistance mutations that can be overcome by an allosteric PI3K α inhibitor. Together, these findings provide insights to guide strategies to overcome resistance in PIK3CA-mutated cancers.

Disclosure(s):

Andreas Varkaris, MD, PhD: No financial relationships to disclose

Aditya Bardia, MD, MPH: Consulting Fees (e.g., advisory boards): Menarini/Stemline (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Menarini/Stemline (Ongoing)

GS03-11

Germline-mediated immunoediting sculpts breast cancer subtypes and metastatic proclivity

Presenting Author(s) and Co-Author(s):

K. Houlihan. Stanford University, CA, United States

A. Khan. Stanford, United States

N. Greenwald. Stanford, United States

R. West. Stanford University Medical Center, Stanford, California, United States

M. Angelo. Stanford, United States

C. Curtis. Stanford University, Stanford, California, United States

Background: Somatic genomic aberrations are acquired within the context of germline genomes which differ across individuals at millions of polymorphic sites. However, the role of germline variation in somatic evolution remains poorly understood. The most compelling example is that deleterious germline variants in BRCA1 and, to a lesser extent, BRCA2 are preferentially associated with the development of triple-negative breast cancer (BC). The variable frequency of BC subtypes across ancestral populations further suggests a role for germline contributions. On the other hand, various lines of evidence indicate that avoidance of the adaptive immune system is a strong determinant of which somatic mutations persist within a tumor. Whether and how germline differences influence immunoediting has not been studied. Building on these observations, we sought to investigate whether germline variation mediates somatic evolution through immunoediting. Specifically, we hypothesize inherited variation in oncogenes would be subject to varied immunoediting pressures during malignant transformation and progression. A high burden of germline-derived epitopes in recurrently amplified oncogenes is predicted to select against amplification of the cognate gene during malignant transformation because this would increase epitope availability, the likelihood of epitope presentation, and immune-mediated cell death. Instead, immune pressures may select for amplification of an alternate driver gene with a lower germline-mediated epitope burden. We evaluated this hypothesis in a collection of 3,855 BC, spanning ductal carcinoma in situ (DCIS) to invasive BC, and metastatic lesions. Methods: We analyzed paired tumor and normal sequencing data from 1,087 primary and 702 metastatic breast cancer patients as well as somatic genomic profiles from 341 patients with DCIS using a novel algorithm to estimate germline-derived epitope burden (GEB) based on an individual's genotype and class 1 HLA alleles. The relationship between GEB and subtype commitment, defined by the acquisition of focal oncogenic amplifications in five prognostic subgroups of BC: HER2+ disease and four high-risk of relapse ER+/HER2 integrative subgroups/clusters (ICs) which we previously described (IC1: 17q23, IC2: 11q13, IC6: 8p12, and IC9: 8q24) was evaluated. Specifically, we evaluated the association between the GEB per gene and whether an individual developed the corresponding subtype via logistic regression, correcting for the first six genetic principal components and somatic mutation burden. Outcome associations were evaluated via Cox Proportional Hazards Models. Results: Interrogating 3,855 breast cancer lesions, we demonstrate that germline-derived epitopes in recurrently amplified genes influence somatic evolution by mediating immunoediting. Individuals with a high GEB in ERBB2/HER2 are significantly less likely to develop HER2-positive breast cancer compared to other subtypes. The same holds true for recurrent amplicons that define four aggressive, high-risk of relapse, ER-positive integrative subgroups. Thus, GEB selects against cognate oncogene amplification. Tumors that overcome such immune-mediated negative selection are more aggressive and exhibited microenvironments depleted of

lymphocytes, consistent with “immune cold” tumors. Conclusions: We demonstrate that inherited variation sculpts breast cancer subtypes, aggressivity, and immune landscapes by mediating anti-tumor immune responses. The implications of these findings are several-fold. First, GEB is prognostic, complementing other molecular measurements. Second, immunoediting pressures differ across the disease course, with implications for the timing of therapeutic interventions. Third, these data illuminate a broad source of currently under-appreciated immunogenic antigens.

Disclosure(s):

Christina Curtis, PhD, MS: Advisory Committee/Board Member: 3T Biosciences (Ongoing), DeepCell (Ongoing), Genentech (Ongoing); Consulting Fees (e.g., advisory boards): 3T Biosciences (Ongoing), AstraZeneca (Ongoing), Bristol Meyer Squibb (Ongoing), Genentech (Ongoing), Resistance Bio (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): DeepCell (Ongoing), Grail/Illumina (Ongoing), Ravel (Ongoing)

GS03-12

Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final DFS and updated OS analysis

Presenting Author(s) and Co-Author(s):

- S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany
- M. Mano. Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil, Brazil
- M. Untch. AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany, Berlin, United States
- C. Huang. National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, Taipei, United States
- E. Mamounas. NSABP Foundation and Orlando Health Cancer Institute, Orlando, FL, USA, Windermere, Florida, United States
- N. Wolmark. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States
- A. Knott. Roche Products Limited, Welwyn Garden City, UK, United States
- A. Siddiqui. Roche Products Limited, Welwyn Garden City, UK, United States
- T. Boulet. F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States
- B. Nyawira. F. Hoffmann-La Roche Ltd, Basel, Switzerland, United States
- E. Restuccia. F. Hoffmann-La Roche Ltd, Basel, Switzerland, Basel-Stadt, Switzerland
- C. Geyer. NSABP Foundation and University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA, USA, Pittsburgh, Pennsylvania, United States

Disclosure(s):

Sibylle Loibl, MD, PhD: Advisory Committee/Board Member: GSK, Pfizer, Novartis (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Consulting Fees (e.g., advisory boards): GSK, Pfizer, Novartis (Ongoing), Menarini/Stemline (Ongoing), MSD Co., Ltd. (Ongoing), Novartis, Ascentage, Genentech/Roche, Lilly, Seattle Genetics, AstraZeneca, Daiichi Sankyo (Ongoing); Licences for VM Ki67 Quantifier: VM Scope GmbH (Ongoing); patents pending: EP14153692.0 ,EP21152186.9 , EP19808852.8 , (Ongoing)

Eleftherios P. Mamounas, MD: Consulting Fees (e.g., advisory boards): TerSera (Terminated, October 8, 2022); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Olaris, Novartis, Gilead, AstraZeneca, Sanofi-Genzyme, Biovica, Jacobio, Natera, Inivata, Athenex, Bayer, OncoSignal (Terminated, October 13, 2022)

LBO1-01

Neoadjuvant pembrolizumab or placebo plus chemotherapy followed by adjuvant pembrolizumab or placebo for early-stage triple-negative breast cancer: Updated event-free survival results from the phase 3 KEYNOTE-522 study

Presenting Author(s) and Co-Author(s):

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

R. Dent. National Cancer Centre Singapore, Singapore

L. Pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

H. McArthur. UT Southwestern, Dallas, Texas, United States

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

C. Denkert. Institut für Pathologie, Philipps Universität Marburg und Universitätsklinikum Marburg (UKGM), Germany

Y. Park. Samsung Medical Center, Seoul, Republic of Korea

R. Hui. Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia

N. Harbeck. University of Munich, Munich, Bayern, Germany

M. Takahashi. Hokkaido University, Sapporo, Japan

T. Foukakis. Karolinska Institutet, Solna, Stockholms Lan, Sweden

M. Mouret-Reynier. Centre Jean-Perrin, Clermont-Ferrand, France

M. Ferreira. Instituto Português de Oncologia do Porto Francisco Gentil (IPO-Porto), Medical Oncology Department, Porto, Portugal, United States

S. Im. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

F. Cardoso. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

Y. Ding. Merck & Co., Inc., Rahway, NJ, United States

W. Pan. Merck & Co., Inc., Rahway, New Jersey, United States

K. Tryfonidis. Merck & Co., Inc., Rahway, New Jersey, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

Background: In KEYNOTE-522 (NCT03036488), neoadjuvant pembrolizumab (pembro) plus chemotherapy (chemo) followed by adjuvant pembro showed statistically significant and clinically meaningful improvements in pathological complete response (pCR) and event-free survival (EFS) compared with neoadjuvant placebo (pbo) plus chemo followed by adjuvant pbo in patients (pts) with early-stage triple-negative breast cancer (TNBC). Here, we present updated EFS results after a median follow-up of ~5 y. **Methods:** Eligible pts with previously untreated, non-metastatic, centrally confirmed TNBC (stage T1c N1-2 or T2-4 N0-2 per American Joint Committee on Cancer) were randomized 2:1 to neoadjuvant pembro 200 mg Q3W or placebo (pbo), both given with 4 cycles of paclitaxel + carboplatin, then with 4 cycles of

doxorubicin or epirubicin + cyclophosphamide. After definitive surgery, pts received adjuvant pembro or pbo for 9 cycles or until recurrence or unacceptable toxicity. Dual primary endpoints are pCR (ypT0/Tis ypN0) and EFS (time from randomization to disease progression that precluded definitive surgery, local/distant recurrence, second primary cancer, or death from any cause). Results: 1174 pts were randomized to pembro (n=784) or pbo (n=390) group. At data cutoff (March 23, 2023), median follow-up was 63.1 mo. 145 pts (18.5%) in the pembro group and 108 pts (27.7%) in the pbo group had an EFS event (hazard ratio [HR] 0.63 [95% CI, 0.49-0.81]). The 60-mo EFS rate (95% CI) was 81.3% (78.4-83.9) vs 72.3% (67.5-76.5), respectively; the median was not reached in either group. The benefit of neoadjuvant pembro + chemo followed by adjuvant pembro versus neoadjuvant chemo alone was consistent with the primary EFS results in all 5 sensitivity analyses, showing durable and robust EFS benefit in the pembro arm. The EFS benefit with pembro was consistent across prespecified subgroups, including PD-L1 expression, nodal status, disease stage, menopausal status, HER2 status, and lactate dehydrogenase (LDH) level (table). In a prespecified, non-randomized, exploratory analysis, 5-yr EFS rates in the pembro and pbo groups were 92.2% vs 88.2% in pts with a pCR, and 62.6% vs 52.3% in pts without a pCR. Additional analyses will be included in the presentation. Follow-up for OS is ongoing Conclusions: Neoadjuvant pembro + chemo followed by adjuvant pembro continues to show a clinically meaningful improvement in EFS compared with neoadjuvant chemo alone in pts with early-stage TNBC. This is seen across subgroups and regardless of the pCR outcome.

Table. EFS results in overall population and by subgroup

Table. EFS results in overall population and by subgroup

	Pembro + Chemo No. of Events/N (%)	Pbo + Chemo No. of Events/N (%)	HR (95% CI)^a
Overall population	145/784 (18.5)	108/390 (27.7)	0.63 (0.49-0.81)
PD-L1 CPS 1 cutoff			
≥1	115/656 (17.5)	83/317 (26.2)	0.64 (0.48-0.85)
<1	30/128 (23.4)	25/69 (36.2)	0.57 (0.33-0.98)
PD-L1 CPS 10 cutoff			
≥10	46/393 (11.7)	36/177 (20.3)	0.54 (0.35-0.83)
<10	99/391 (25.3)	72/209 (34.4)	0.71 (0.52-0.96)
Nodal status			
Positive	94/408 (23.0)	64/196 (32.7)	0.67 (0.49-0.93)
Negative	51/376 (13.6)	44/194 (22.7)	0.56 (0.38-0.84)
Overall disease stage			
II	84/590 (14.2)	66/291 (22.7)	0.59 (0.43-0.82)
III	61/194 (31.4)	42/98 (42.9)	0.71 (0.48-1.05)
Menopausal status			
Pre-menopausal	70/438 (16.0)	54/221 (24.4)	0.63 (0.44-0.89)
Post-menopausal	75/345 (21.7)	54/169 (32.0)	0.64 (0.45-0.91)
HER2 status			
2+ by IHC (but FISH-)	35/188 (18.6)	29/104 (27.9)	0.65 (0.40-1.07)
0-1+ by IHC	110/595 (18.5)	79/286 (27.6)	0.63 (0.47-0.84)
LDH			
>ULN	31/149 (20.8)	28/80 (35.0)	0.56 (0.34-0.93)
≤ULN	113/631 (17.9)	79/309 (25.6)	0.67 (0.50-0.89)

^aAnalysis in the overall population and PD-L1 subgroups is based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by nodal status, tumor size, and choice of carboplatin; for other subgroups, analysis is based on the unstratified Cox model.

Disclosure(s):

Peter Schmid, MD, PhD: Consulting Fees (e.g., advisory boards): Eli Lilly & Company (Ongoing), Gilead Science (Ongoing)

Javier Cortés, MD, PhD: Consulting Fees (e.g., advisory boards): AbbVie Inc (Ongoing), Astrazeneca (Ongoing), Bioasis (Ongoing), BioInvent Pharma (Ongoing), Boehringer Ingelheim (Ongoing), BridgeBio (Ongoing), Clovis Oncology (Ongoing), Daiichi-Sankyo (Ongoing), Ellipses (Ongoing), Expres2ion Biotechnologies (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gemoab (Ongoing), Gilead (Ongoing), HiberCell (Ongoing), Jazz Pharmaceuticals (Ongoing), Leuko (Ongoing), Lilly (Ongoing), Menarini (Ongoing), Merck Sharp&Dhome (Ongoing), Reveal Genomics, S.L. (Ongoing), Scorpion Therapeutics (Ongoing), Seattle genetics (Ongoing), Zymeworks Inc. (Ongoing); honoraria: Lilly (Ongoing), Novartis (Ongoing); honoraria, research funding to the institution, travel and expenses: Astrazeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eisai Europe Ltd. (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Merck Sharp&Dhome (Ongoing), Pfizer, Inc. (Ongoing); honoraria, travel and expenses: Gilead (Ongoing), Steamline Therapeutics (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1 (Ongoing), MAJ3 Capital (Ongoing), Pharmaceutical Combinations of A PI3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. (Ongoing); research funding to the institution: Ariad pharmaceuticals (Ongoing), Baxalta GMBH/Servier Affaires (Ongoing), Bayer Pharmaceuticals (Ongoing), Guardant Health Inc. (Ongoing), IQVIA Inc. (Ongoing), Piquar Therapeutics (Ongoing), Queen Mary University of London (Ongoing); stock (relative): Leuko (Ongoing)

Lajos pusztai, MD, DPhil: Consulting Fees (e.g., advisory boards): Natera Inc (Ongoing)

Heather McArthur, MD, MPH: Consulting Fees (e.g., advisory boards): Crown Bioscience (Ongoing), Daiichi Sankyo |Astrazeneca (Ongoing), Gilead (Ongoing), Merck & Co., Inc. (Ongoing), Pfizer (Ongoing), Seattle Genetics/Seagen (Ongoing)

Nadia Harbeck, MD, PhD: Advisory Committee/Board Member: Roche (Ongoing); Consulting Fees (e.g., advisory boards): Gilead (Ongoing), Sandoz (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Amgen (Ongoing), Astra Zeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Roche (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): West German Study Group (WSG) (Ongoing)

Joyce O'Shaughnessy, MD: Consulting Fees (e.g., advisory boards): Agendia (Ongoing), Aptitude Health (Ongoing), AstraZeneca (Ongoing), Carrick Therapeutics (Ongoing), Daiichi-Sankyo (Ongoing), Eisai (Ongoing), ELY LILLY (Ongoing), F. Hoffman La Roche Ltd (Ongoing), G1-Therapeutics (Ongoing), Genentech (Ongoing), Loxo@Lilly (Ongoing), Merck Sharp & Dohme, Lda. (Ongoing), Novartis (Ongoing), Ontada (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Samsung Bioepis (Ongoing), SeaGen (Ongoing), Stemline Therapeutics (Ongoing), Synthron (Ongoing)

Late Breaking Abstracts

Presenting Author(s) and Co-Author(s):

N. Turner. Royal Marsden Hospital, Institute of Cancer Research, London, England, United Kingdom

E. Roussos Torres. University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, United States

Disclosure(s):

Nicholas C. Turner, MD, PhD: Advisory Committee/Board Member: Exact Sciences Corporation (Ongoing), Gilead Science (Ongoing), Relay Therapeutics (Ongoing), REPARE Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Guardant Health (Ongoing), Invitae (Ongoing), Natera (Ongoing), Personalis (Ongoing)

Evanthia T. Roussos Torres, MD, PhD: Consulting Fees (e.g., advisory boards): Synaptical Inc (Ongoing)

LBO1-02

Pathologic complete response (pCR) of neoadjuvant therapy with or without atezolizumab in HER2-positive, early high-risk and locally advanced breast cancer: APTneo Michelangelo randomized trial

Presenting Author(s) and Co-Author(s):

- L. Gianni. Fondazione Michelangelo, Milano, Lombardia, Italy
- E. Munzone. European Institute of Oncology, IRCCS, Milano, Italy
- M. Mansutti. Department of Medical Oncology, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC) Udine, Italy
- G. Bianchini. IRCCS Ospedale San Raffaele, Milan, Lombardia, Italy
- Y. Izarzuzaga. Fundación Jimenez Díaz, Madrid, Spain
- E. Rota Caremoli. UO Oncologia Medica, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy
- L. Dirix. Translational Cancer Research Unit, GZA Hospitals & CORE, MIPRO, University of Antwerp, Antwerp, Belgium, United States
- L. Del Mastro. University of Genova - IRCCS Ospedale Policlinico San Martino, United States
- S. González-Santiago. Hospital Universitario San Pedro de Alcántara, Cáceres, Spain
- A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany
- J. Ponce. Hospital General Universitario Dr. Balmis, ISABIAL, Alicante, Comunidad Valenciana, Spain
- C. Huang. National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, Taipei, United States
- P. Wimberger. Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Sachsen, Germany
- S. Altintas. Antwerp University Hospital, Edegem, Belgium, United States
- M. Martín. Hospital General Universitario Gregorio Marañón, Madrid, Spain
- N. Antone. Cancer Institute Ion Chiricuta, Department of Breast Tumors, Cluj-Napoca, Romania
- C. Singer. Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Austria
- U. De Giorgi. Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Italy
- A. Godoy Ortiz. UGCI Oncología Medica, Hospitales Universitarios Regional y Virgen de la Victoria de Málaga, Spain. Universidad de Málaga (UMA). Centro de Investigación Biomédica en Red de Oncología, CIBERONC-ISCIII. GEICAM Breast Cancer Group, Spain
- H. Lueck. Gynäkologisch-Onkologische Praxis, Hannover, Germany
- R. Spezia. Fondazione Michelangelo, Milano, Italy
- A. Fasolo. Fondazione Michelangelo, Milano, Italy
- G. Viale. European Institute of Oncology IRCCS, and University of Milan, Milan, Italy
- P. Valagussa. Fondazione Michelangelo, Milano, Italy

Background: Neoadjuvant dual targeting of HER2 with trastuzumab (H) and pertuzumab (P) plus chemotherapy is the standard of care for high-risk HER2-positive (HER2+) breast cancer

(BC). Compelling data show the contribution of the immune system in prognosis and response/resistance to HER2 directed therapies, supporting combination of immune checkpoint inhibitors with anti HER2 antibodies. We designed APTneo to test the role of adding atezolizumab to neoadjuvant dual targeting of HER2 with chemotherapy, and the value of also using anthracyclines in this setting. Methods: In this multicenter open label phase III trial (NCT03595592), 661 patients (pts) with high-risk early and locally advanced (LA) centrally confirmed HER2+ BC were randomized to neoadjuvant HPCT (H and P d1, carboplatin and paclitaxel iv d1 and 8) given q3 wks for 6 cycles w/o (n=223, ARM A) or with atezolizumab 1200 mg iv d1 (n=438, ARM B). In Arm B pts were randomized to Arm B1 (n=218) to receive anthracycline and cyclophosphamide (AC) + atezolizumab iv d1 q3 wks for 3 cycles followed by HPCT + atezolizumab for 3 cycles, or to arm B2 (n=220) to receive HPCT + atezolizumab for 6 cycles. After surgery pts continued adjuvant HER2 directed therapies w/wo atezolizumab until completion of 1 year. Among intent-to-treat (ITT) pts, 44.8% were LABC, 35% hormonal receptor (HR) negative and 30.4% PD-L1 positive.

Primary endpoint is event-free survival (EFS) of Arm B vs A. A key secondary endpoint is the rate of pCR (ypT0/Tis, ypN0) w/wo atezolizumab. Primary population for all efficacy endpoints is ITT. We also assessed baseline PD-L1 status (Ventana SP142) and stromal Tumor Infiltrating Lymphocytes (sTILs). Results: pCR rate in Arm B (57.8%) vs Arm A (52.0%) was not significantly increased (adjHR 1.33, 95% CI 0.95-1.86; p=0.091). Also, the difference in pCR rate in Arm B1 (61.9%) vs Arm B2 (53.6%) was not significant (adjHR 1.402, 95% CI 0.95-2.07; p=0.089). Compared to Arm A, Arm B1 had a 9.9% significantly higher pCR rate (multivariate analysis in Table).

The different pCR rate in arms B1 and A was similar regardless of HR and PD-L1 status. High sTILs ($\geq 30\%$) and PD-L1 positive tumors had a higher likelihood of pCR in all arms.

Serious adverse events (SAE) after start of therapy occurred in 6.8% pts in Arm A and 14.1% in Arm B (p=0.0064). SAE were numerically more frequent in Arm B1 than Arm B2 (16.7% and 11.6%, respectively), due to hematological toxicity with AC. Immune-related SAE were quite infrequent and similar in B1 (4.7%) and B2 (7.8%), respectively. No grade 5 AE did occur. Conclusions: Addition of atezolizumab to chemotherapy and HP did not significantly increase the rate of pCR in women with HER2+ BC. An exploratory analysis showed that adding atezolizumab to neoadjuvant AC followed by HPCT led to higher pCR rate compared to HPCT and atezolizumab. This could be because of anthracyclines themselves or to drug-drug enhancement of anthracyclines and immune modulation. Atezolizumab did not cause major tolerability issues. Molecular studies of collected biospecimens are ongoing. Patients will continue to be followed up for EFS and overall survival analyses.

Supported in part by unrestricted grant from Hoffman-La Roche, Ltd, Switzerland

Variable	Effect	OR (95% CI)	P value
Treatment	B1 vs A	1.58 (1.07-2.33)	0.022
	B2 vs A	1.13 (0.77-1.66)	0.526
PD-L1	Pos vs neg	1.57 (1.10-2.23)	0.012
Disease stage	Early vs locally advanced	0.85 (0.62-1.17)	0.332
HR status	Neg vs pos	2.16 (1.53-3.06)	< 0.0001
Age	<= 50 vs > 50	1.18 (0.86-1.63)	0.311

Disclosure(s):

Luca Gianni, MD: Consulting Fees (e.g., advisory boards): AMGEN (Ongoing), ARTEMIDA PHARMA (Ongoing), ASTRAZENECA (Ongoing), BIOMEDICAL INSIGHTS (Ongoing), Daiichi-Sankyo (Ongoing), Denali Therapeutics (Ongoing), F. Hoffman La Roche (Ongoing), Menarini Recherche (Ongoing), PFIZER (Ongoing), Revolution Medicines, Inc. (Ongoing), SYNAFFIX (Ongoing), Zymeworks Inc. (Ongoing); Patent: No compensation provided. Co-inventor of European Patent Application 12195182.6 + 12196177.5 "PDL-1 expression in anti-HER2 Therapy-Roche: ROCHE (Ongoing)

Giampaolo Bianchini, MD: Advisory Committee/Board Member: Eisai Europe Ltd. (Ongoing), Pfizer, Inc. (Ongoing); Consulting Fees (e.g., advisory boards): Agendia (Ongoing), AstraZeneca (Ongoing), Daiichi-Sankyo (Ongoing), Exact Sciences (Genomic Health) (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gilead (Ongoing), Lilly/Loxo (Ongoing), Menarini/Stemline (Ongoing), Merck MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), SeaGen, Inc. (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Daiichi-Sankyo (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Gilead (Ongoing), Lilly/Loxo (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Gilead (Ongoing)

Miguel Martín, MD, PhD: Advisory Committee/Board Member: Eli Lilly, Exelixis, Faron Pharmaceuticals Ltd, Forma Therapeutics, Gamamabs, Genentech, Glaxosmithkline, H3 Biomedicine (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Novartis Pharma GmbH (Ongoing); Consulting Fees (e.g., advisory boards): daiichii-Sankyo (Ongoing), Gilead (Ongoing), Pfizer, Inc. (Ongoing), Seagen Inc (Ongoing)

LBO1-03

Randomized Phase II Study of Neoadjuvant Nivolumab (N) 2 week lead-in followed by 12 weeks of concurrent N+carboplatin plus paclitaxel (CbP) vs concurrent N+CbP in Triple Negative Breast Cancer (TNBC): (BCT1902/IBCSG 61-20 Neo-N)

Presenting Author(s) and Co-Author(s):

N. Zdenkowski. Breast Cancer Trials, Newcastle, New South Wales, Australia

S. Loi. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

S. Niman. Dana Farber Cancer Institute, United States

P. Francis. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

S. Baron Hay. Royal North Shore Hospital, North Shore Private Hospital, United States

W. Fox. Coffs Harbour Hospital, United States

K. Punie. Leuven Cancer Institute, University Hospitals Leuven, United States

A. Menzies. Royal North Shore Hospital, The University of Sydney, United States

R. Angus. Breast Cancer Trials, United States

C. Mavin. Breast Cancer Trials, United States

L. Rennie. Breast Cancer Trials, United States

I. Stoodley. Breast Cancer Trials, United States

B. Mann. The Royal Melbourne Hospital, Parkville, Victoria, Australia

M. Kuper-Hommel. Waikato Hospital, United States

M. Regan. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: A previous clinical study suggested that a priming dose of programmed cell death ligand 1 (PD-L1) inhibitor monotherapy 2 weeks prior to addition of chemotherapy could be more efficacious than starting all agents concurrently. Furthermore, the addition of checkpoint therapy may allow shorter chemotherapy duration in selected patients. The aim of this study was to investigate the strategies of lead-in Nivolumab (N) monotherapy and starting concurrent N with 12 weeks of carboplatin and paclitaxel in TNBC. Methods: In this multicenter Phase II study, eligible patients with stage I (cT1c)-II TNBC were randomized to receive either Arm A (lead-in): N 240 mg monotherapy, followed 2 weeks later by N 360mg + carboplatin (AUC 5) every 21 days x 4 cycles + weekly paclitaxel (80 mg/m²) for 12 weeks; or Arm B (concurrent): same agents initiated concurrently given over 12 weeks, followed 2 weeks later by N 240mg monotherapy, prior to surgery. The primary endpoint was pathological complete response (pCR ypT0/Tis ypN0). Secondary endpoints are residual cancer burden (RCB), safety, response according to baseline stromal tumor infiltrating lymphocytes (sTILs) quantity and PD-L1 expression and event-free survival (EFS). sTIL high was defined as ≥30% and PD-L1 positive as ≥1% (SP142 assay). A non-comparative Simon two-stage design was used to test the null hypothesis, in each Arm separately, of a pCR rate ≤40% vs an alternative pCR rate of ≥60% with 90% Confidence Intervals (CI). No adjuvant N was given, and adjuvant chemotherapy was at the discretion of the investigator in case of non-pCR. Results: 110 patients were randomized from July 2020 to April 2022; 108 patients who initiated treatment were analyzed. Baseline characteristics: median age was 49yrs (IQR 43-60yrs), 16.7% had node-positive disease, 34.3/64.8% had stage I/II disease, 33.3% were sTIL high and 47.2% were PD-L1 positive. For Arms A and B respectively, pCR rates were 50.9% (90% CI:39.0-63.2) and 54.5% (90% CI:42.7-66.2) with an overall pCR rate of 52.8% (90% CI:44.4-61.0). The RCB 0+1 rates were

overall 68.5% (90% CI: 60.4-75.9); with 64.2% (90% CI: 52.0-75.1) and 72.7% (90% CI: 61.2-82.4) for Arms A and B respectively. Overall, in the sTIL high vs low subgroups, pCR was 66.7% (CI: 51.7-79.5) vs 45.7% (CI: 35.5-56.2%), and in the PD-L1 positive vs negative subgroups, pCR was 70.6% (CI: 58.4-80.9) vs 33.3% (CI: 21.8-46.6) respectively. pCR was 48.6% in stage I and 54.9% in stage II. Treatment-related adverse events were similar in both arms, with grade 3-4 adverse events in 64.8% patients. Early discontinuation of N occurred in 17 patients (15.7%). Immune related endocrine dysfunction (any grade) was observed in 22 patients (20.4%). Conclusion: The pCR rates exceeding 50% support that 12 weeks of a neoadjuvant non-anthracycline chemotherapy regimen with nivolumab is efficacious for Stage I/II TNBC with either concurrent or lead-in N. This study did not support the hypothesis that lead-in N was associated with a pCR advantage. The regimen was well tolerated, with no new safety signals. Patients with immune enriched tumors, identified by high sTILs or PD-L1 positivity, had very high pCR rates, identifying a subpopulation for whom a 12 week anthracycline-free chemotherapy regimen with N may be appropriate. EFS results are still maturing.

Disclosure(s):

Sherene Loi, MD, PhD: Advisory Committee/Board Member: Bristol-Myers Squibb Company (Ongoing), MSD Co., Ltd. (Ongoing); Consulting Fees (e.g., advisory boards): Aduro Biotech (Ongoing), Amunix (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Puma Biotechnology, Inc (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), MSD Co., Ltd. (Ongoing), Nektar Therapeutics (Ongoing), Novartis International AG (Ongoing), Puma Biotechnology, Inc (Ongoing), Seattle Genetics (Ongoing); Uncompensated consultant: Aduro Biotech (Ongoing), Amunix (Ongoing), Bristol-Myers Squibb Company (Ongoing), Daiichi Sankyo/Astra Zeneca (Ongoing), Eli Lilly & Company (Ongoing), G1 Therapeutics (Ongoing), Gilead Therapeutics (Ongoing), GlaxoSmithKline (Inst) (Ongoing), MSD Co., Ltd. (Ongoing), Novartis International AG (Ongoing), Pfizer, Inc. (Ongoing), Roche-Genentech (Ongoing), Seattle Genetics (Ongoing), Silverback Therapeutics (Ongoing), Tallac Therapeutics (Ongoing)

Nicholas Zdenkowski, B Med, FRACP, PhD: Advisory Committee/Board Member: Novartis Pharmaceuticals (Terminated, June 5, 2023); Consulting Fees (e.g., advisory boards): AstraZenca (Terminated, June 13, 2023), Lilly Australia Pty Ltd (Terminated, June 13, 2023), MSD Co., Ltd. (Terminated, June 13, 2023), Pfizer, Inc. (Terminated, June 13, 2023); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Eisai Co.Ltd (Terminated, August 18, 2023), Gilead (Terminated, August 18, 2023); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): BMS (Terminated, October 14, 2022), Roche/Genentech (Terminated, October 14, 2022)

Bruce Mann, MBBS, PhD, FRACS: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Prelude corporation (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): Prelude corporation (Ongoing)

LBO1-04

Primary results from a phase 2a study of zanidatamab (zani) + palbociclib (palbo) + fulvestrant (fulv) in HER2+/HR+ metastatic breast cancer (mBC)

Presenting Author(s) and Co-Author(s):

S. Escrivá-de-Romaní. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

J. Cejalvo. Hospital Clínico Universitario de Valencia, Valencia, Spain

E. Alba. Hospital Regional Universitario y Virgen de la Victoria, Málaga, Andalucía, Spain

J. Friedmann. Jewish General Hospital, Montréal, QC, Canada

□. Rodríguez -Lescure. Hospital General Universitario de Elche, Elche, Alicante, Spain

M. Savard. The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada, United States

R. Pezo. Sunnybrook Health Sciences Centre, Toronto, ON, Canada

M. Gion. Ramón y Cajal University Hospital, Madrid, Madrid, Spain

M. Ruíz - Borrego. Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain

E. Hamilton. Sarah Cannon Research Institute (SCRI), Nashville, Tennessee, United States

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

M. Webster. Tom Baker Cancer Centre, Calgary, AB, Canada

M. Beeram. The START Center, United States

H. Linden. University of Washington, Fred Hutchison Cancer Center, Seattle, Washington, United States

C. Saura. Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain

D. Shpektor. Zymeworks Inc, Vancouver, BC, Canada, United States

B. Salim. Jazz Pharmaceuticals, Palo Alto, CA, USA, United States

P. Harvey. Jazz Pharmaceuticals, Palo Alto, CA, USA, United States

S. Hurvitz. Fred Hutchinson Cancer Center/University of Washington, Los Angeles, California, United States

Background: HER2+ mBC remains incurable, thus novel HER2-directed therapies including chemotherapy-free options are needed. Approximately 50% of HER2+ mBC is also HR+, making the estrogen pathway an additional therapeutic target. The CDK4/6 inhibitor palbo + endocrine therapy fulv is approved for HER2-/HR+ mBC. Targeting all 3 pathways may further improve outcomes in pts with HER2+/HR+ mBC. Zani is a bispecific HER2-targeted antibody that binds HER2 in a unique trans configuration, driving multiple mechanisms of action. A prior analysis of the current single-arm, phase 2a study (NCT04224272) demonstrated antitumor activity and a tolerable safety profile for zani + palbo + fulv in heavily pretreated pts with HER2+/HR+ mBC. Enrollment has been completed; here we report the primary endpoint of PFS at 6 mo (PFS6) and other endpoints. Methods: Eligible pts had HER2+ (by local HER2 testing) and HR+, unresectable, locally advanced or mBC; ECOG PS \leq 1; prior treatment with at least trastuzumab, pertuzumab, and T-DM1; and no prior CDK4/6 inhibitor. Pts received zani (20 mg/kg Q2W) + palbo + fulv (standard doses)—recommended doses determined in Part 1 assessment. The Part 2 primary endpoint was PFS6. Other endpoints included median PFS

(mPFS), confirmed objective response rate (RECIST v1.1), disease control rate, and duration of response. PAM50 analysis was exploratory. A centrally confirmed HER2+ (ccHER2) subset was analyzed post hoc. Results: As of August 3, 2023, 51 pts (median age [range] 54 yr [36-77]) received zani + palbo + fulv treatment with a median follow-up time of 16.1 mo. Of the 51 pts, 32 (63%) were ccHER2+. Nine pts (18%) remained on treatment; median (range) duration of zani treatment was 8.4 (1.0-29.5) mo. In the metastatic setting, pts received a median (range) of 4 (1-12) prior systemic regimens, 3 (1-10) prior different HER2-targeted therapies, and 1 (0-5) prior endocrine therapy; 12 (24%) pts had prior T-DXd and 11 (22%) had prior fulv.

The primary endpoint of PFS6 was 67% (69% in ccHER2+ subset). The mPFS was 11.7 mo (14.9 mo in ccHER2+ subset). See Table 1 for other efficacy endpoints. PAM50 subtyping was available for 29 pts (57%; 1 basal like; 16 HER2 enriched; 12 luminal B). Compared with HER2 enriched, luminal B was associated with numerically, but not statistically, longer mPFS (11.7 vs 9.3 mo; P=0.74) and similar PFS6 (66.7% vs 62.5%).

The most common (>20%) treatment (zani, palbo, and/or fulv)-related adverse events (TRAEs) were diarrhea (80%), neutrophil count decrease/neutropenia (59%), nausea (39%), stomatitis (37%), anemia (29%), vomiting (25%) and asthenia (24%). Grade ≥3 TRAEs in ≥2 pts were neutrophil count decrease/neutropenia (53%), diarrhea (14%), anemia (10%), thrombocytopenia (6%), hypokalemia (4%), and hypomagnesemia (4%). One serious TRAE (transaminases increased) was reported. AEs of special interest: 6 pts with cardiac events (all LVEF decrease; 5 pts with grade 1 or 2 events, 1 pt with a grade 3 event) and 2 pts with infusion-related reactions (both grade 1). Three pts discontinued palbo due to an AE; 1 pt discontinued zani and fulv due to an AE. No treatment-related deaths were reported. Conclusions: Zani + palbo + fulv showed a promising PFS6 and mPFS with durable responses. The safety profile was manageable. These results support further development of a novel chemotherapy-free treatment regimen for heavily pretreated pts with HER2+/HR+ mBC.

Table 1. Efficacy of Triplet Regimen (Zani + Palbo + Fulv) for HER2+/HR+ mBC

Efficacy	All pts (N=51)	ccHER2+ subset (n=32)
PFS6, n (%) (95% CI)	34 (66.7) (52.1-79.2)	22 (68.8) (50.0-83.9)
Median PFS, mo (95% CI)	11.7 (8.4-14.9)	14.9 (9.0-16.8)
cORR ^a , n (%) (95% CI)	16 (34.8) (21.4-50.2)	14 (48.3) (29.4-67.5)
cBOR ^a , n (%)		
CR	3 (6.5)	3 (10.3)
PR	13 (28.3)	11 (37.9)
SD	26 (56.5)	13 (44.8)
PD	4 (8.7)	2 (6.9)
DCR ^b , n (%) (95% CI)	42 (91.3) (79.2-97.6)	27 (93.1) (77.2-99.2)
Median DOR ^b , mo (95% CI)	14.8 (11.6-24.7)	14.1 (11.1-24.7)

a Patients with measurable disease (n=46 all pts; n=29 ccHER2+ subset).

b Defined as best response of CR, PR, non-CR/non-PD (for patients who have only non-target

lesions) or SD per RECIST 1.1.

c Patients with DOR (n=16 all pts; n=14 ccHER2+ subset).

cBOR, confirmed best overall response; ccHER2+, centrally confirmed HER2+; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; HER2+, human epidermal growth factor receptor 2 positive; HR+, hormone receptor positive; mBC, metastatic breast cancer; mo, month; PD, progressive disease; PFS, progression-free survival; PFS6, progression-free survival at 6 months; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Disclosure(s):

Santiago Escrivá-de-Romaní, MD: Consulting Fees (e.g., advisory boards): COR2ED (Ongoing), Daiichi Sankyo |Astrazeneca (Ongoing), PierreFabre (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): COR2ED (Ongoing), Daiichi Sankyo |Astrazeneca (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Novartis (Ongoing), Pfizer (Ongoing), PierreFabre (Ongoing), Seagen Inc (Ongoing), SOLTI Breast Cancer Research Group (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Byondis B.V. (Ongoing), Daiichi Sankyo |Astrazeneca (Ongoing), F. Hoffman La Roche Ltd (Ongoing), MedSIR (Ongoing), Synthon (Ongoing), Zymeworks Inc./Jazz (Ongoing); Travel expenses: Daiichi Sankyo |Astrazeneca (Ongoing), F. Hoffman La Roche Ltd (Ongoing), Kern (Ongoing), Pfizer (Ongoing), Seagen Inc (Ongoing), SOLTI Breast Cancer Research Group (Ongoing)

Maria Gion, MD: Consulting Fees (e.g., advisory boards): Daiichi Sankyo/Astra Zeneca (Terminated), Gilead Science (Terminated), Novartis (Terminated), Pfizer (Terminated); Travel: F. Hoffman La Roche Ltd (Terminated)

Erika P. Hamilton, MD: Consulting Fees (e.g., advisory boards): Arcus, Arvinas, AstraZeneca, Daiichi Sankyo, Deciphera Pharmaceuticals, Ellipses Pharma, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo, Mersana, Novartis, Orum Therapeutics, Pfizer, Relay Therapeutics, Roche/Genentech, SeaGen, Verascity Science (Ongoing); Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Abbvie, Acerta Pharma, Accutar Biotechnology ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, (Ongoing)

Sara Hurvitz, MD, FACP: Industry Grant Support (Principal Investigators must provide information on research funding from ineligible companies, even if received/managed by the institution): Ambrx, Inc (Terminated), Arvinas (Terminated), Astra Zeneca (Terminated), Celcuity Inc. (Terminated), CytomX Therapeutics (Terminated), Daiichi-Sankyo (Terminated), Dantari, Inc. (Terminated), Eli Lilly (Terminated), F. Hoffman La Roche Ltd (Terminated), G1-Therapeutics (Terminated), Genentech (Terminated), Gilead (Terminated), Greenwich Lifesciences (Terminated), Novartis (Terminated), Orinove (Terminated), Orum Therapeutics (Terminated), Phoenix Molecular Designs, Ltd. (Terminated), Pieris Pharmaceuticals (Terminated), Puma Biotechnology, Inc (Terminated), Radius Health (Terminated), Sanofi (Inst) (Terminated), Seagen Inc (Terminated), Zymeworks Inc./Jazz (Terminated)

LBO1-05

Impact of age and ovarian function suppression (OFS) on endocrine response to short preoperative endocrine therapy (ET): Results from the multicenter ADAPTcycle trial (n=4,334)

Presenting Author(s) and Co-Author(s):

O. Gluz. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; University Clinics Cologne, Moenchengladbach, Nordrhein-Westfalen, Germany

M. Christgen. Medizinische Hochschule Hannover, Hannover, Niedersachsen, Germany

U. Nitz. West German Study Group and Breast Center Niederrhein, United States

S. Küemmel. Breast Unit, Kliniken Essen-Mitte, Essen, Germany

M. Braun. Rotkreuzklinikum München, Germany

M. Thill. Agaplesion Markus Krankenhaus Frankfurt, Frankfurt, Hessen, Germany

R. Wuerstlein. Breast Center, Dept. OB&GYN and CCC Munich, LMU University Hospital, Munich, Germany

P. Wimberger. Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Sachsen, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

C. Schem. Mammazentrum am Krankenhaus Jerusalem, Hamburg, Germany

M. Zaiss. Clinic for Interdisciplinary Oncology & Hematology GbR, Freiburg, Baden-Wuerttemberg, Germany

V. Bjelic-Radusic. Breast Unit, Helios University Clinic, University Witten/Herdecke, Germany

M. Just. Onkologische Schwerpunktpraxis Bielefeld, Bielefeld, Germany

K. Veselinovic. Breast Center, University Hospital Ulm, Department of Women's Health, Ulm, Baden-Wuerttemberg, Germany

M. Vincent. Breast Center, Municipal Hospital Holweide. Cologne, Cologne, Nordrhein-Westfalen, Germany

M. Graeser. West German Study Group, Moenchengladbach, Germany; Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Germany; Department of Gynecology, University Medical Center Hamburg, Moenchengladbach, Nordrhein-Westfalen, Germany

K. Krauss. Breast Center Niederrhein, Ev. Hospital Bethesda, Moenchengladbach, Moenchengladbach, Nordrhein-Westfalen, Germany

O. Hoffmann. University Hospital Essen, Germany

K. Lüdtko-Heckenkamp. Department of Oncology and Hematology, Niels-Stensen-Kliniken, Georgsmarienhütte, Germany

R. Kates. West German Study Group GmbH, Moenchengladbach, Moenchengladbach, Nordrhein-Westfalen, Germany

C. zu Eulenburg. West German Study Group, Moenchengladbach, Germany; Department of Medical Biometry and Epidemiology, University Medical Center Hamburg, Hamburg, Germany

K. Jozwiak. Institute of Biostatistics and Registry Research, Brandenburg Medical School Theodor Fontane, Neuruppin, Neu-Ruppin, Germany

S. Burmeister. MHB Campus Neuruppin, Neu-Ruppin, Germany

R. Baehner. Precision Oncology, Exact Sciences, Redwood City, California, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

H. Kreipe. Medical School Hannover, Institute of Pathology, Hannover, Germany; Institute of Neuropathology, United States

N. Harbeck. University of Munich, Munich, Bayern, Germany

Background: In HR+/HER2- early breast cancer (EBC), short preoperative endocrine therapy (ET) is a promising tool for ET-efficacy assessment based on Ki67-decrease after 2-4 weeks of ET. Low post-endocrine Ki67 (Ki67post) is associated with good prognosis in large prospective trials. WSG-ADAPT demonstrated that ET-response is a valid criterion for decisions in uncertain adjuvant chemotherapy indications, e.g., in premenopausal patients (pts) with N0 and Recurrence Score (RS, Oncotype DX®) RS 16-25 or with N1 and RS ≤25. Preliminary results from the phase III ADAPTcycle trial indicated higher efficacy of preoperative ET in premenopausal pts. if ovarian function suppression (OFS) was used together with tamoxifen (TAM) or aromatase inhibitors (AI). In the final screening population, we are now able to confirm these results and investigate the influence of age subgroups, RS, individual biological markers, and OFS on ET-response. **Methods:** In ADAPTcycle (n=5,290 screened, 1,670 randomized by 06/23; 84 sites in Germany), N0-1 pts with RS >25 or N2-3 pts with RS ≤25 and ET-response were randomized to (neo)adjuvant chemotherapy (CT) followed by ET vs. ribociclib + AI (premenopausal: +GnRH). In premenopausal pts, participation with N1-disease and RS ≤25 or N0 and RS 16-25 was allowed irrespective of ET-response, but randomization recommended only for ET-responders; in the preoperative phase, OFS+TAM or AI for ET-response assessment was protocol-recommended. **Results:** This analysis includes all pts with complete baseline characteristics (including RS) and ET-response data (n=4,334); ET-response was defined as Ki67post ≤10% (central pathology) after 2-4 weeks (if OFS: 4 weeks) of therapy. ER, PR, and HER2-levels were analyzed by IHC and mRNA. Median age was 56 years (22-87y). 55% had cT2-4 tumors; 28% had cN+ disease; 42% were G3 (central lab). Median RS was 20, median baseline Ki67 25%. n=1,368 were ≤50y and premenopausal ("≤50y"): n=314 (23.0%) and 255 (18.6%) were treated by AI+OFS and TAM+OFS, respectively. 2,966 were >50y or postmenopausal (">50y"), of whom 2,565 received AI (86.5%). ET-response occurred in 48.2% of "≤50y" vs. 72.7% in ">50y" pts (p< 0.001). We observed significant differences in ET-response rates between "≤50y" vs. ">50y" with TAM alone (34.7% vs. 46.4%); In "≤50y" pts, 55.7% ET-response occurred with TAM+OFS vs. 76.4% with AI+OFS, comparable to 76.8% in ">50y" patients with AI. Moreover, OFS led to higher ET-response rates (by uni- and multivariable analysis) even in the small (n=78) group of premenopausal pts >50y. Remarkably, even in pts with RS >25, substantial ET-response rates were observed with AI: 66.7% ("≤50y", AI+OFS), 55.6% (">50y", AI) vs. lower rates with TAM alone (>50y: 18.2%; < 50y: 15.8%). ET-response rate in "≤50y" pts was associated with ET type, RS, and baseline Ki67 in both uni- and multivariable analysis, but not age subgroup (≤40 vs. 41-50y). ER, PR, and HER2 expression by IHC or RT-PCR were associated with ET-response by univariable (but not multivariable) analysis. In ">50y" pts, by uni- and multivariable analysis, again ET-type, RS, and baseline Ki67, as well as ER-expression (by IHC) and ESR1, PR, and HER2-expression (by RT-PCR) were associated with higher ET-response rates. **Conclusions:** With about 10,000 pre- and postmenopausal pts, ADAPT and ADAPTcycle provide the largest international database regarding ET-response. ADAPTcycle confirms ADAPT ET-response rates in pts receiving TAM or AI; adding OFS to either improves ET-response, irrespective of RS. ET-response measurement adds value in therapy decisions, particularly in ≤50y N0-1 pts. ET-response might provide key information even in pts with high RS; outcome data of ADAPTcycle will reveal potential clinical consequences. Optimal preoperative ET, especially in premenopausal pts, might even enable sparing chemotherapy in additional pts.

Disclosure(s):

Oleg Gluz, MD: Consulting Fees (e.g., advisory boards): Roche, Novartis, Lilly, MSD, Gilead, ExactScience, Agendia, Seagen, DaiichiSankyo, Pfizer, Astra Zeneca (Ongoing)

Monika Graeser, PD Dr. med.: Consulting Fees (e.g., advisory boards): AstraZeneca (Terminated); Travel support: Daiichi Sankyo (Terminated, November 1, 2023)

Peter Schmid, MD, PhD: Consulting Fees (e.g., advisory boards): Eli Lilly & Company (Ongoing), Gilead Science (Ongoing)

Nadia Harbeck, MD, PhD: Advisory Committee/Board Member: Roche (Ongoing); Consulting Fees (e.g., advisory boards): Gilead (Ongoing), Sandoz (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus): Amgen (Ongoing), Astra Zeneca (Ongoing), Daiichi-Sankyo (Ongoing), Eli Lilly (Ongoing), Gilead (Ongoing), MSD (Ongoing), Novartis (Ongoing), Pfizer, Inc. (Ongoing), Pierre Fabre (Ongoing), Roche (Ongoing), sanofi (Ongoing), Seagen Inc (Ongoing); Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds): West German Study Group (WSG) (Ongoing)

PO5-01-01

The comparison of HER2 low and HER2 0 in ductal carcinoma in situ (DCIS) for breast cancer

Presenting Author(s) and Co-Author(s):

N. Kureyama. Department of Breast Oncology, Aichi Cancer Center Hospital, United States

M. Kusudo. Aichi Cancer Center Hospital, United States

A. nakakami. Aichi Cancer Center Hospital, United States

R. Komaki. Aichi Cancer Center Hospital, United States

Y. Endo. Aichi Cancer Center Hospital, United States

K. Nozawa. Aichi Cancer Center Hospital/Department of Breast Oncology, Nagoya, Aichi, Japan

A. Kataoka. Aichi Cancer Center Hospital, United States

H. Kotani. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

A. Yoshimura. Aichi Cancer Center Hospital, United States

M. Hattori. Aichi Cancer Center, United States

M. Sawaki. Aichi Cancer Center Hospital, United States

H. Iwata. Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Background: Trastuzumab deruxtecan is a standard of care after prior chemotherapy for metastatic breast cancer with HER2 low. HER2 low recognized as a new category of breast cancer. The definition of HER2 low is IHC 1+ or IHC 2+/ISH- in invasive ductal components. We have already reported the frequency and prognosis of HER2 positive and low in invasive cancer (Breast Cancer. 2022;29:234-241), but the distribution and characteristics of HER2 low in ductal carcinoma in situ (DCIS) is unknown. It is also well known that HER2 expression is higher in DCIS than in invasive cancer. We focused on the frequency of HER2 low in DCIS, performed an analysis of its frequency and characteristics, and compared to DCIS with HER2 0.

Methods: We retrospectively examined breast cancer patients with DCIS and invasive ductal carcinoma (IDC) who underwent surgery at our institution between 2005 and 2015. Regarding the expression status of HER2, we classified cases into three groups: HER2 0, HER2-low (defined as IHC 1+ or IHC 2+/ISH-), and HER2-positive (IHC 2+/ISH+ or IHC 3+), and investigated their frequency. We analyzed the relationship between HER2 expression and Van Nuys classification, as well as the relationship between HER2 expression and ER expression, using the chi-square test.

Results: A total of 726 DCIS patients were included in this analysis. The patient demographics showed a median age of 52 years (range: 20-84), with 413 patients (56.9%) undergoing total mastectomy and 311 patients (42.8%) undergoing breast-conserving surgery (two cases had unknown surgical procedures). The expression of HER2 in DCIS patients was observed as HER2-0, low and positive in 100 (13.8%), 474 (65.3%) and 152 patients (20.9%), respectively. The expression of HER2 in IDC was observed as HER2 0, low and positive in 838 (17.1%), 3169 patients (64.4%) and 911 patients (18.5%) (Table1). DCIS tended to have higher HER2 expression(P=0.048). Then we compared the characteristics of HER2 0 and HER2 low in DCIS. Table 2 shows the relation between Van Nuys classification and HER2 expression. Van Nuys

classification was evaluated in 346 cases. Van Nuy grade 3 accounted for 4.8% of the HER2 0 cases and 15.8% of the HER2 low cases. HER2 low cases tend to have higher grades ($P < 0.01$). Table 3 shows the relation between ER expression and HER2 expression. ER negative accounted for 5% of HER2 0 cases and 8.4% of HER2 low cases. ER negatives tended to be more common in Her2 low cases ($P < 0.01$).

Conclusion: HER2 low is not considered a molecular biological classification, but rather a classification of the target of treatment for Trastuzumab deruxtecan. In our study, comparing HER2 0 and HER2 low, HER2 low tended to have higher grade and lower ER expression. Further investigation including basic research is needed to clarify the biological meaning of her2 low.

Table1: The frequency of HER2 expression in DCIS and IDC

	HER2 0	HER2-low	HER2-positive	total	P
					0.048
DCIS	100(13.8%)	474(65.3%)	152(20.9%)	726(100%)	
IDC	838(17.1%)	3169(64.4%)	911(18.5%)	4918(100%)	

Table2: The relationship between Van Nuys classification and HER2 expression

	HER2 0	HER2-low	P
VanNuys			<.001
Grade1	49 (79%)	124(57.7%)	
Grade2	10 (16.1%)	57(26.5%)	
Grade3	3 (4.8%)	34 (15.8%)	
Total	62(100%)	215 (100%)	

Table3: The relationship between ER status and HER2 expression

	HER2 0	HER2-low	P
ER status			<.001
negative	5(5%)	40(8.4%)	
positive	95(95%)	434(91.6%)	
Total	100(100%)	474(100%)	

PO5-01-02

A retrospective review of pathological complete response and toxicity rates to a modified version of TCHP (Paclitaxel, Trastuzumab, Pertuzumab, Carboplatin) for HER2 positive breast cancer stage II and III

Presenting Author(s) and Co-Author(s):

- C. Moloney. Beaumont Hospital, United States
- M. O'Connor. Beaumont Hospital, United States
- C. O'Leary. Beaumont Hospital, United States
- A. Reilly. Beaumont Hospital, United States
- S. Barry. Beaumont Hospital, United States
- D. O'Reilly. Beaumont Hospital, United States
- P. Bredin. Beaumont Hospital, United States
- H. Paryani. Bons Hospital, United States
- D. Solaligue. Our Lady of Lourdes Hospital, Drogheda, Ireland, United States
- B. Hennessy. Beaumont Hospital, United States
- M. Greally. Beaumont Hospital, United States
- P. G. Morris. Cancer Trials Ireland, Ireland; Beaumont RCSI Cancer Centre, Dublin, Ireland, United States

Background In 2018 the TRAIN-2 clinical trial demonstrated that in stage II–III HER2-positive breast cancer, the use of a neoadjuvant non-anthracycline chemotherapy regimen of 9 cycles of TCHP [paclitaxel and carboplatin (AUC 6 mg/mL/min) with trastuzumab and pertuzumab resulted in lower toxicity and comparable pathological complete responses to an anthracycline based regimen. A pathological complete response was recorded in 141 (67%) of 212 patients in the anthracycline group and in 140 (68%) of 206 in the non-anthracycline group. Our primary aim was to identify rates of pathological complete response and rates of toxicity with a less intensive regimen of 6 cycles of TCHP where carboplatin was dose adjusted to AUC5. **Methods** In this single center cohort study, we reviewed patients with stage II-III Her2-positive breast cancer who received a modified chemotherapy regimen of 6 cycles of neoadjuvant paclitaxel (80 mg/m² days 1 and 8) and reduced dose of carboplatin (AUC= 5 mg/mL/min) with trastuzumab (6 mg/kg; loading dose 8 mg/kg) and pertuzumab (420 mg intravenously; loading dose 840 mg) every 3 weeks from 2021- June 2023. Clinicopathologic data, the number and length of treatment delays, treatment related toxicities of all grades, and pCR rate were extracted from the electronic medical record. **Results** 32 patients were included in the analysis. The median age of the cohort was 51 years (30-65). No patient had a BRCA mutation. 20 (62.5%) had T1-2 disease and 12 (37.5%) had T3-4 disease. 14(43.75%) patients had N0 disease and 20 (62.5%) had N1-3 disease. ECOG Performance status was 0, 1 and 2 in 26 patients (81.25%), 4 (12.5%) patients and 2(6.25%) patients respectively. At the time of analysis, 2 patients (6.25%) were continuing active treatment, while 30 (93.75%) had completed planned neoadjuvant therapy and underwent surgery. Of patients who completed planned neoadjuvant therapy, 6 patients (18.75%) had 1 or more hospitalisations due to toxicity. 10 patients (31.25%) required dose reductions and 3(9.38%) had early treatment discontinuation. Rates of adverse events will be presented. pCR rate was 60 % (N=18/30). 19 (63%) of 30 patients underwent mastectomy and 11 (36.7%) underwent breast-conserving surgery. Updated analysis will be included at time of presentation. **Conclusion** In this single-

center retrospective study of patients receiving a modified version of TCHP we found a 60% pCR rate. The rate of dose reductions and treatment discontinuations appears favorable with use of this modified regimen. This was in a heterogeneous population of patients treated in routine clinical practice where there was a high rate of patients with locally advanced disease. Limitations of our study include immaturity of data and small sample size; however, these data warrant further exploration through longer-term follow-up and multi-center validation.

PO5-01-03

Neoadjuvant HER2-targeted regimens with or without anthracyclines for HER2-positive inflammatory breast cancer (IBC): a multicenter retrospective study

Presenting Author(s) and Co-Author(s):

T. Iwase. Translational Cancer Research, University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

S. Nithya. Baylor College of Medicine, United States

M. Kai. MD Anderson Cancer Center, United States

J. Willey. The University of Texas MD Anderson Cancer Center, United States

W. Dong. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Y. Shen. UT MD Anderson Cancer Center, United States

S. Krishnamurthy. MD Anderson cancer center, United States

A. Lucci. MD Anderson Cancer Center, Houston, Texas, United States

H. Le-Petross. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Nasrazadani. Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Saleem. MD Anderson Cancer Institute, United States

R. Layman. The University of Texas MD Anderson Cancer Center, United States

V. Valero. Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Bellaire, Texas, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

W. Woodward. UT MD Anderson Cancer Center, Houston, Texas, United States

Y. Cheng. Medical College of Wisconsin, United States

F. Nakhliis. Dana-Farber Cancer Institute, United States

J. Bellon. DFCI/BWH, Boston, Massachusetts, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

N. Ueno. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

Background Previous randomized clinical trials have shown no significant benefit with the addition of anthracyclines to neoadjuvant treatment for HER2-positive breast cancer. However, these studies did not focus on inflammatory breast cancer (IBC), or a small minority of patients on these trials. The study aims to compare pathologic complete response rates with and without anthracyclines in HER2-positive IBC. **Methods** We reviewed patients diagnosed with Stage III HER2-positive IBC who underwent neoadjuvant therapy and modified radical mastectomy at MD Anderson Cancer Center and Dana-Farber Cancer Institute between 2014 and 2021. Patients received either docetaxel/trastuzumab/pertuzumab-doxorubicin/cyclophosphamide (THP-AC) or docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP). The primary outcome was pathologic complete response (pCR) rate, defined as ypTisT0/N0. Secondary outcomes included 2-year event-free survival (EFS) and overall survival (OS). Univariate and multivariable analyses were performed with adjustments for clinically relevant covariates. **Results** Ninety-nine patients were included in the analysis. Thirty-

nine patients received TCHP and 60 received THP-AC. The median follow-up time was 3.02 years. Three patients had disease progression during neoadjuvant therapy. pCR rates did not differ between the two regimens (48.7% TCHP vs. 51.7% THP-AC; $p = 0.774$). Patient's baseline characteristics did not significantly affect the pCR rate, except for age. A multivariable logistic regression model adjusted for age and estrogen receptor (ER) status did not show a significant association between pCR and regimen (odds ratio 1.232, 95% CI 0.537–2.829 for THP-AC vs. TCHP, $p = 0.623$). The 2-year EFS rates for TCHP and THP-AC were 57% and 74%, respectively. In univariate analysis, patients who received THP-AC had better EFS than patients who received TCHP (hazard ratio [HR] 0.423, 95% CI 0.214–0.835, $p = 0.013$). The EFS benefit of THP-AC remained statistically significant after adjusting for age and type of adjuvant therapy in the final reduced multivariable Cox model (HR 0.441, 95% CI 0.220–0.882, $p = 0.021$). Univariate analysis did not show a significant association between EFS and other baseline covariates (body mass index, race, N and M category, nuclear grade, ER status, and HER2-targeted therapy). OS did not differ between the THP-AC and TCHP groups (HR 0.419, 95% CI 0.122–1.440, $p = 0.167$). Conclusions The present analysis revealed that a non-anthracycline-containing regimen in HER2-positive IBC patients had no significant difference in pCR rates but was associated with lower 2-year EFS when compared to an anthracycline-containing regimen. However, OS was similar. Limitations of the study include a small sample size, lack of temporal analysis, and retrospective design with its possible selection bias. Further investigation of the optimal neoadjuvant regimen for patients with HER2-positive IBC is warranted.

PO5-01-04

HER2 Amplification Level and Focal/Broad Region Size as Predictors of Treatment Response in Neoadjuvant Chemotherapy and Anti-HER2 Therapy for HER2-Positive Breast Cancer.

Presenting Author(s) and Co-Author(s):

N. Liao. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

G. Zhang. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

X. Lv. Burning Rock Biotech, Guangzhou, China, United States

K. Li. Department of Breast Cancer, the General Surgical Department, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China., United States

T. Hou. Burning Rock Biotech, United States

Z. Zhang. Burning Rock Biotech, United States

Background: Neoadjuvant chemotherapy combined with anti-HER2 therapy has become the standard treatment approach for HER2-positive breast cancer. However, not all HER2-positive patients can achieve pathological complete response after neoadjuvant therapy. This raises the question of which subset of HER2+ patients derive the greatest benefit from pre-operative HER2-targeted treatment. Therefore, this study aims to determine whether the level and amplification region size of HER2 amplification are associated with the efficacy of neoadjuvant chemotherapy combined with anti-HER2 therapy. Methods: A total of 523 breast cancer samples were collected from 2017 to 2018, among which 202 cases were HER2-positive patients. Among these, 55 HER2-positive patients received neoadjuvant chemotherapy combined with anti-HER2 targeted therapy. The amplification status of HER2 was assessed using immunohistochemistry/fluorescence in situ hybridization (IHC/FISH) and next-generation sequencing (NGS). The HER2/CEP17 ratio, determined by FISH, was used to represent the amplification level of HER2. The size of the amplification region was calculated using NGS and neighboring genes located in chr17q. Amplification regions smaller than 1 Mb were classified as focal amplification, while those larger than 1 Mb were classified as broad amplification. Results: We compared the HER2/ERBB2 status of 523 breast cancer patients using different detection methods and found a high concordance between ERBB2 amplification detected by NGS and HER2-positivity detected by IHC and FISH, with a sensitivity of 96.0%, specificity of 97.8%, and overall concordance of 97.1%. Based on the HER2/CEP17 ratio determined by FISH, we observed that using a threshold of 6 for classification, the high amplification group had a significantly higher pCR rate compared to the low amplification group (86.7% vs. 41.7%; $p=0.037$, odds ratio [OR]=0.121, 95% confidence interval [CI]: 0.009-0.919). Moreover, the focal amplification group showed a higher pCR rate compared to the broad amplification group (65.9% vs. 30.8%, $p=0.051$, OR=0.237, 95% CI: 0.045-1.035). Additionally, within the low amplification group (HER2/CEP17 < 6), the pCR rate was 66.7% for focal amplification and 20% for broad amplification, suggesting that focal amplification of ERBB2 may further guide clinical benefit in the low HER2/CEP17 ratio group. Conclusion: This study demonstrates a high concordance between ERBB2 amplification determined by NGS and HER2-positivity determined by IHC/FISH. High HER2/CEP17 ratio and focal amplification of ERBB2 are

associated with a higher pCR rate in neoadjuvant chemotherapy combined with anti-HER2 targeted therapy.

PO5-01-05

An Open-label, Single-center Study Assessing the Efficacy of PH-based Regimen as Neoadjuvant Therapy for HER2-positive Early-stage Breast Cancer: Integrating Genomic Features and Functional Imaging

Presenting Author(s) and Co-Author(s):

M. Chen. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, 200032 China, United States

B. Yang. Fudan University Shanghai Cancer Center, Shanghai, China, Shanghai, China (People's Republic)

s. yuyun. fudan university shanghai cancer center, United States

L. Ma. Fudan University Shanghai Cancer Center, Shanghai, China, United States

s. shaoli. fudan university shanghai cancer center, United States

M. He. Fudan University Shanghai Cancer Center, United States

Z. Shao. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, Shanghai, China (People's Republic)

B. Xiu. Fudan University Shanghai Cancer Center, Boston, Massachusetts, United States

J. Wu. Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Fudan University Shanghai Cancer Center, Shanghai, 200032 China Department of Oncology, Fudan University Shanghai Medical College, Shanghai, Shanghai, China (People's Republic)

Background: Pathological complete response (pCR) has been demonstrated as a surrogate endpoint for disease-free and overall survival in HER2-positive early-stage breast cancer (EBC). Trastuzumab (H) plus pertuzumab (P) improved pCR rates in patients with HER2-positive early-stage breast cancer. Nevertheless, biomarkers to assess the effectiveness of this treatment in the neoadjuvant setting are still unclear. This study aims to evaluate the effectiveness of fluorodeoxyglucose positron emission tomography (18F-FDG-PET) and 68 Ga-Affibody HER2 Imaging PET (HER2-PET) in HER2 EBC neoadjuvant therapy, and to identify novel biomarkers for this regimen. Methods : HER2-positive EBC patients were prospectively recruited at Fudan University Shanghai Cancer Center between April 2020 and March 2022. All patients received the 1 dose of HP, followed by 6 cycles of docetaxel (T), carboplatin (Cb), and HP. We use FoundationOne to evaluate the genomic alterations before treatment. In addition, 18F-FDG-PET and HER2 PET were performed at baseline, after 1 cycle of HP, and after 6 cycles of TCbHP, to assess the effectiveness of these examinations in the prediction of pCR and correlation to disease burden. All patients were received surgery and completed 1 year of HP-based regimen in the adjuvant setting. Results: A total of 61 patients with a median age of 49 years were included. Among them, 93.5% of patients are node positive. 75.8% of the patients reported adverse events (AEs), primarily grade 1 and 2. The incidence of serious AEs was 6.6%. Patients exhibiting a greater than 40% reduction in SUVmax of 18-FDG-PET or HER2-PET scans from baseline to the fifth day after the initial HP treatment were classified as the treatment-sensitive group. The pCR rate for the 18-FDG-PET-sensitive group was 79.3%, while for the insensitive group was 48.1%. For HER2-PET scans, the pCR rate was 70.0% in the sensitive group and 59.3% in the non-sensitive group. To evaluate the potential biomarkers, 25 patients (13 pCR and 12 non-pCR) were evaluated with FoundationOne, with the identification of 1,321 somatic alterations. The most frequently altered genes were ERBB2

(100%), TP53 (96%), CDK12 (76%), MYC (56%), CCND1 (44%), PIK3CA (40%), and SRSF2 (36%). In the pCR group, we found PPM1D (38.5%) and RAD21 (38.5%) were altered more frequently than the non-pCR group. PIK3CA alterations were significantly reduced in pCR group, only 23% of cases are affected compared to 58.3% in non-pCR group. Patients were non-pCR had more MDM4 (41.7%) and ZNF217 (41.7%) alterations than pCR patients. Conclusion: The SUVmax value of 18-FDG-PET and HER2-PET scans are correlated well with the tumor burden and the residual disease in the HER2 EBCs. The reduction of SUVmax could predict pCR but need further exploration. Patients with alterations in PPM1D and RAD21 have a favorable response to the TCbHP regimen. Conversely, alterations in PIK3CA, MDM4, and ZNF217 are associated with treatment resistance. These results indicate the significance of 18-FDG-PET and HER2-PET in monitoring treatment effectiveness. The biomarker analysis in this study will help us understand the mechanism of HER2 positive breast cancer treatment resistance and assisting in tailoring personalized therapy. Clinical trial information: NCT04281641.

PO5-01-08

The impact of Human Epidermal growth factor Receptor 2 (HER2) expression by RT-PCR on tumor characteristics and outcome in estrogen receptor (ER) positive, HER2 negative early-stage breast cancer

Presenting Author(s) and Co-Author(s):

H. Goldvaser. Shaare Zedek Medical Center, United States

R. Mutai. Rabin Medical Center, Beilinson Hospital, Davidoff Center, United States

S. Stemmer. Institute of Oncology, Davidoff Center, Rabin Medical Center, Petach Tiqwa, and the Sackler Faculty of Medicine, Tel-Aviv University, Israel

I. Kuchuk. Meir Medical Center, United States

M. Tokar. Soroka University Medical Center, United States

S. Paluch-Shimon. Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, and Faculty of Medicine, Hebrew University, Jerusalem, Israel

R. Yerushalmi. Rabin Medical Center-Beilinson Campus, Petah Tikva, Israel

K. Drumea. Lin Medical Center, Clalit, United States

E. Evron. Kaplan Medical Center, United States

A. Sonnenblick. Oncology Division, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

G. Bar Sela. Ha'emek Medical Center, United States

A. Shai. Rambam Medical Center, United States

R. Merose. Shamir (Assaf Harofeh) Medical Center, United States

A. Bareket-Samish. BioInsight, Israel

L. Soussan-Gutman. Oncotest, Rhenium, Modi'in, Israel

Background: The role of HER2 expression in HER2 negative breast cancer is evolving. Whether HER2 expression has an impact on ER positive, HER2 negative early-stage breast cancer is unclear. Oncotype DX assay Recurrence Score comprises of standardized quantitative HER2 mRNA expression levels by RT-PCR. The objective of this study was to investigate the impact of Oncotype HER2 score on tumor characteristics and outcome.

Methods: All women assigned to the Clalit Health Services registry between 2006 to 2011 with ER positive, HER2 negative early-stage breast cancer whose tumor were sent for oncotype were identified. Patients in which HER2 score was reported in the oncotype results were included. Differences in age, tumor characteristics and chemotherapy administration between lower HER2 score (H1), i.e. HER2 score ≤ 9.1 , to higher HER2 score (H2), i.e. 9.2-10.7, were analyzed. 5-year Kaplan–Meier for distant recurrence free survival (DRFS) and overall survival (OS) were estimated and differences between H1 and H2 were evaluated. Analyses were repeated separately for node negative and for node positive (N mic and 1-3 lymph nodes) disease.

Results: A total of 1535 patients were included, 948 patients with node negative disease and 587 with node positive disease. Of these, 814 and 721 patients were categorized to the H1 and

H2 groups, respectively. Median follow-up was 5.4 years. The distribution of oncotype RS was different, with significantly lower proportion of patients with RS between 0-10 and higher proportion of RS above 25 in the H1 group compared to the H2 groups. This difference was identified both for patients with node negative and node positive disease (Table). The distributions of age, tumor size and histological subtype were comparable between the H1 and the H2 groups, both for node negative and node positive disease. Within each RS group, administration of chemotherapy was comparable between H1 and H2 groups, regardless of nodal involvement. DRFS and OS were not associated with HER2 score. For RS 0-25, node negative disease, 5-year DRFS was 96.2% in H1 and 96.4% in H2 groups (p=0.92) and 5-year OS was 97.2% in H1 and 98.1% in H2 groups (p=0.39). For RS >25, node negative disease, 5-years DRFS was 89% in H1 and 90.8% in H2 groups (p=0.33) and 5-year OS was 90.6% in H1 and 90.8% in H2 groups (p=0.7). Similarly, for node positive disease, DRFS and OS were comparable between H1 and H2 group in all subgroups.

Conclusions: Low HER2 mRNA expression by Oncotype RT-PCR assay was associated with significantly high Oncotype RS. Patients' outcome was not directly affected by HER2 score and was determined by RS. Further study is desired to clarify the role of HER2 expression in early stage, luminal breast cancer.

	H1, %	H2, %	P
N negative			
Age ≤ 50	20.1	20	0.95
T ≤ 1cm	22.9	22.6	0.5
1<T≤ 2 cm	53.4	56.7	
T> 2 cm	23.7	20.7	
IDC	80.1	77.6	0.6
ILC	13.2	15.4	
Other	6.7	7	
Oncotype RS			<0.001
0-10	13.1	25	
11-25	61.3	61.7	
26-100	25.6	13.3	
N positive			
Age ≤ 50	18.5	13.7	
T ≤ 1cm	16.7	16.7	0.41
1<T≤ 2 cm	55.2	50.3	
T> 2 cm	28.1	33	
IDC	85.5	80.8	0.19
ILC	11.5	16.7	
Other	3	2.5	
Oncotype RS			0.02
0-10	12.2	20	
11-25	65.9	63.2	
26-100	21.9	16.8	

Comparison of age and tumor characteristics between low (H1) and high (H2) HER2 score

PO5-01-09

Exploring cellular heterogeneity of localised breast cancers

Presenting Author(s) and Co-Author(s):

B. Kiedik. Cancer Ecosystems Program, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia; St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, NSW 2052, Australia, United States

D. Roden. Cancer Ecosystems Program, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia; St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, NSW 2052, Australia, United States

K. Harvey. Cancer Ecosystems Program, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia, United States

G. Al-Eryani. Broad Institute of MIT and Harvard, United States

S. Wu. Genentech, United States

M. Hui. Cancer Ecosystems Program, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia; Chris O'Brien Lifehouse, Camperdown NSW, Australia, United States

S. O'Toole. (1) Cancer Ecosystems Program, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia; Department of Tissue Pathology and Diagnostic Pathology, New South Wales Health Pathology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia; Faculty of Medicine & Health Sciences, Western Sydney University, Campbelltown, New South Wales, Australia; Sydney Medical School, Sydney University, Sydney, New South Wales, Australia, United States

E. Lim. Garvan Institute of Medical Research, St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia

C. Perou. University of North Carolina, Chapel Hill, North Carolina, United States

A. Swarbrick. Garvan Institute of Medical Research, Darlinghurst, Australia

Breast cancer is a heterogeneous disease at multiple levels, ranging from subtype differences between patients (inter-patient heterogeneity) to the diverse composition of malignant cells, heterogeneity of hormone receptor (HR) expression and cellular makeup within single breast cancer samples (intra-tumour heterogeneity). Despite an increase in the number of effective therapies available, many patients will experience an incomplete treatment response and subsequent relapse. These adverse treatment outcomes may be attributed to the often overlooked but critical factor of cellular heterogeneity.

In order to gain deeper insights into intra-tumour heterogeneity, we have applied single-cell technologies on a cohort comprising 250 primary, untreated breast cancers. We have optimized methods for tissue cryopreservation, eliminating the need for fresh sample processing, and multiplex tissue profiling. Together, these are cost-efficient processes that allow for improved handling of small tissue sizes, such as biopsies, and reduce batch effect. To ensure accurate and reliable data processing, we have developed a scalable computational workflow that includes benchmarked methods for sample SNP-demultiplexing, doublet detection, high-resolution cell annotation and cellular integration. Finally, we are extending our existing methods¹ to study the cellular heterogeneity of breast cancers. Our method, scSubtyper, explores the phenotypic differences between malignant cells within tumours, by comparing each single cell to distinct features associated with different molecular subtypes and assigning each cell to one of these subtypes. Our previous study¹ and preliminary results of this project

revealed that over 90% of the samples exhibit a mix of malignant cells of different subtypes, and 50% of samples contain cells that have characteristics of all subtypes, demonstrating cellular heterogeneity exists not only between malignant cells, but also within malignant cells of a tumour. Our second approach, known as ecotyping, assesses patterns of cell type frequencies across samples and groups them based on similarity of these co-occurrences. Our preliminary results have revealed the existence of 5 ecotypes that lack significant associations with samples clinical subtypes. Applying the same approach exclusively within the HR-positive samples identified 4 ecotypes characterized by distinct abundances of immune and stromal cells. This analysis revealed that ecotypes are not a simple surrogate for clinical and molecular subtypes, but their presence could drive different response to treatment.

Together, our high-throughput tissue processing and computational approaches to studying intra-tumour heterogeneity are now being applied to our large, well annotated, clinical cohort. Supported by the preliminary results, we hypothesize that this study will play a vital role in optimizing breast cancer patient stratification to improve treatment management and outcome.

1. Wu, Sunny Z., et al. "A single-cell and spatially resolved atlas of human breast cancers." *Nature genetics* 53.9 (2021): 1334-1347.

PO5-01-10

Evaluating a computer-aided platform for predicting recurrence and survival in an Oncotype Dx tested breast cancer cohort

Presenting Author(s) and Co-Author(s):

S. Mukhopadhyay. 4D Path Inc., Newton, Massachusetts, United States

E. Walsh. NHS, United States

R. Millican-Slater. NHS, United States

A. hanby. St James's University Hospital, Leeds, United States

J. Stephenson. NHS, United States

T. Dasgupta. 4D path Inc., United States

N. Orsi. St James's University Hospital, Leeds, United States

Background: Oncotype DX Breast Recurrence Score[®] (ODXRS) is a widely used predictive measure of breast cancer recurrence risk and chemotherapy benefit for patients with estrogen receptor positive (ER+), human epidermal growth factor receptor-2 negative (HER2-) breast cancers. ODXRS testing incurs additional costs and delays. These drawbacks could be obviated by innovative computer-aided technologies within digital pathology workflows. Such technologies could be developed to perform a wide variety of diagnostic and prognostic tests on digital whole slide images (WSIs) of hematoxylin and eosin (H&E)-stained tissue alone. This would save time, cost, and sample tissue whilst still providing critical prognostic information for patient management. Q-Plasia OncoReader Breast (QPORB) is a computer-aided solution which extracts information from H&E WSIs to provide diagnostic and prognostic information for breast cancer specimens.

Aims: The aim of this study was to identify whether the computer aided QPROB platform could successfully predict breast cancer recurrence from H&E WSIs alone in line with recurrence predicted by ODXRS.

Methods: H&E slides corresponding to tissue blocks sent for ODXRS testing from primary breast cancer resection/excision specimens from St James's University Hospital, Leeds, UK (n=137 cases, 1 slide per case) were collected, anonymized, and scanned at x20 magnification on an Aperio AT2 scanner. Relevant pathological and clinical data were collected from electronic pathology reports and patient records. These data included ODXRS and recurrence events. QPORB analyzed each case/slide and generated a digital biomarker profile from the H&E images alone, combining statistical physics and tumor biology to quantify malignant cell cycle deformation. QPORB's biomarker profile and ODXRS for each case was compared to disease-free survival (DFS) and overall survival (OS). Kaplan-Meier survival analyses were performed. Confounding factors (age, tumor grade, invasive tumor size and Charlson Comorbidity Index) were accounted for.

Results: Results of three QPORB-generated indices - two putatively associated with overall cell cycle signature and one with G1 deformation, and their combined overall biomarker profile did not predict DFS in this cohort. However, with regards to OS, all three indices and the combined biomarker profile predicted OS over a median follow-up period of 5 years (P=0.044). 5% of WSIs (7/137) did not meet the criteria to be analyzed by QPORB and 4% (6/137) could not be analyzed by QPORB (attrition). While ODXRS similarly predicted OS but not DFS, the follow-up duration was suboptimal.

Conclusion: While QPORB indices evaluated in this work, putatively associated with overall cell cycle signature and G1 deformation, did not predict breast cancer recurrence on a par with ODXRS, it has shown promising results as potential adjunct device to provide an estimate of OS for breast cancer patients eligible for ODXRS testing. Future work will expand on this observational cohort, blindly validate these findings, and extend the work to encompass all breast cancer molecular subtypes.

PO5-01-11

Breast Cancer Index and comparative analysis of late distant recurrence risk with results from the TEAM trial

Presenting Author(s) and Co-Author(s):

J. MS Bartlett. University of Edinburgh, Scotland, United Kingdom, United Kingdom

Y. Zhang. Biotheranostics, A Hologic Company, United States

G. Pond. McMaster University, United States

J. Wong. Biotheranostics, A Hologic Company, San Diego, United States

K. Xu. Diagnostic Development, Ontario Institute for Cancer Research, Toronto. Ontario, Canada, United States

M. Spears. Diagnostic Development, Ontario Institute for Cancer Research, Toronto. Ontario, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

E. Mallon. Department of Pathology, University of Glasgow, Glasgow, United Kingdom, United States

K. Taylor. Cancer Research UK Scotland Centre, University of Edinburgh, Edinburgh, United Kingdom., United States

A. Hasenburg. University Medical Center Mainz, Johannes Gutenberg University, Mainz, Germany, United States

C. Markopoulos. National and Kapodistrian University of Athens, Medical School, Athens, Greece, United States

L. Dirix. St. Augustinus Hospital, Antwerp, Belgium, United States

C. Seynaeve. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

C. J.H. van de Velde. Department of Surgery, Leiden University Medical Center, United States

D. Rea. University of Birmingham, Cancer Research UK Clinical Trials Unit (CRCTU), England, United Kingdom

A. Brufsky. UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, United States

O. Stål. Department of Biomedical and Clinical Sciences and Department of Oncology, Linköping University, Linköping, Sweden, United States

D. Sgroi. Massachusetts General Hospital, United States

C. Schnabel. Biotheranostics, A Hologic Company, San Diego, California, United States

K. Treuner. Biotheranostics, A Hologic Company, United States

J. Bayani. Diagnostic Development, Ontario Institute for Cancer Research Toronto, Ontario, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto. Toronto, Ontario, Canada, United States

Background: Individualized risk assessment of distant recurrence (DR) is critical for early-stage HR+ breast cancer patients, as prolonged risk of recurrence continues even after completing 5 years of adjuvant endocrine therapy. The Breast Cancer Index (BCI) is a guideline-endorsed, validated gene expression assay that provides an individualized risk of overall (0-10y) and late (5-10y) DR and predicts the likelihood of benefit from extended endocrine therapy. The current BCI assay reports prognostic risk estimates based on tamoxifen-treated patients from the

Stockholm (STO-3) cohort for node-negative (N0) patients, enrolled between 1976 through 1990 and a retrospective cohort from Massachusetts General Hospital (MGH) for patients with 1 to 3 positive nodes (N1), diagnosed between 1993 and 2007, of which approximately 50% were tamoxifen-treated. More recently, additional validation was completed in the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial, in which patients were enrolled between 2001 and 2006. Here, individualized DR risk estimates from the TEAM trial were compared with those from Stockholm and MGH cohorts.

Methods: For the TEAM translational study, BCI testing was performed blinded to clinical outcome and BCI and BCIN+ risk scores were calculated as previously described. A total of 2910 postmenopausal patients with HR+ breast cancer, including 1285 N0 and 1625 N1 patients, who remained DR-free for five years were analyzed to determine the risk of late DR. Cox proportional hazard models using Breslow estimates were used to calculate the risk of late DR as a function of continuous BCI risk scores.

Results: Late DR risk estimates from both the TEAM trial and the Stockholm/MGH cohorts are summarized in the table below. In N0 patients, comparison of 5-10y risk estimates of late DR observed in TEAM patients were higher than those in the Stockholm cohort for BCI scores less than 8.0, but reduced for BCI scores greater than 8.0. Risk estimates differed by 1.5% for a BCI score of 0 and -4.3% for a BCI score of 10. A similar pattern was observed for N1 patients between the TEAM and MGH cohorts, with risk estimates from TEAM trial being higher for BCI scores less than 8.0 but reduced for BCI scores greater than 8.0 compared to those from the MGH cohort.

Conclusions: BCI prognostic validation in the TEAM trial enabled the characterization of DR risk that is more compatible with the current standard of care in the US, as postmenopausal patients were all treated with at least 2-3 years or 5 years of primary adjuvant endocrine therapy with an aromatase inhibitor. Results from the TEAM study provide a more representative assessment of late DR risk to guide individualized treatment decision-making for HR+ early-stage breast cancer patients.

Cohort	N	Adj Endocrine Regimen	Risk of Late DR (%)				
			BCI=0	BCI=2.5	BCI=5	BCI=7.5	BCI=10
N0 Stockholm	285	100% tamoxifen	1.0	2.2	4.7	10.3	21.5
N0 TEAM	1285	50% AI, 50% tam-AI	2.5	4.1	6.7	10.8	17.2
Difference in risk			1.5	2.0	2.0	0.6	-4.3
N1 MGH	223	48% tam, 17% AI, 35% tam-AI	0.8	1.9	4.5	10.4	23.2
N1 TEAM	1625	50% AI, 50% tam-AI	2.3	3.9	6.7	11.3	18.9
Difference in risk			1.5	2.0	2.2	0.9	-4.3

PO5-01-12

Factors Influencing Late Recurrence in Breast Cancer: A Comprehensive Analysis of the Impact of Hormone Therapy Regimens

Presenting Author(s) and Co-Author(s):

M. Mendoza. Korea University Anam Hospital / Bicol Medical Center, Seoul, Republic of Korea

E. Lee. Korea University Anam Hospital, United States

Late recurrence of breast cancer remains a significant challenge in patient management. Despite the established efficacy of hormone therapy, factors influencing late recurrence and the impact of different hormone therapy regimens on this outcome are not yet fully understood. This study aims to investigate the key determinants contributing to late recurrence within the context of different hormone therapy regimens.

This study is a retrospective analysis of medical records from two institutions between 1988 and 2018, specifically examining patients who had HR-receptor positive breast cancer who underwent surgery and completed a 5-year course of standard hormone therapy. Primary endpoint is to identify the demographic, clinical and pathologic factors as associated with late recurrence.

Out of 1929 eligible patients, 49.6% (956) received Tamoxifen (TMX), 37.6% (726) received Aromatase inhibitors (AI), and 12.8% (247) switched between regimens (TMX to AI or AI to TMX).

Median follow-up was 12.1 years (3.75 - 21.41 years). During this period, all-type recurrence (ATR) occurred in 9.3% of all patients, with higher rates in the TMX recipients (12.2%). Locoregional and contralateral recurrence were identified in 10.6% of TMX recipients, 6.5% of patients who switched regimens, and 5% of AI recipients. In all patients, 5.4% were diagnosed with distant metastasis, with slightly higher rates in the TMX recipients (6.4%). Multiple sites in the bone, lung, liver and brain (34.3%) was the most prevalent location of distant metastasis (DM), followed by soft tissue (20%), liver (16.2%), bone (10.5%), lung (8.6%), and other locations.

Significant differences in recurrence-free survival (RFS) were observed between hormone therapy groups ($p=0.004$, log-rank test). Mean overall RFS was 20.4 years (95% C.I. 20.1-20.9 years). TMX recipients had a mean RFS of 19.8 years, AI recipients had a mean RFS of 18.3 years and those who switched regimens had a mean RFS of 21.9 years. Further analysis showed premenopausal patients who switched regimens had higher RFS ($p=0.014$). No significant difference in RFS was seen between premenopausal patients receiving AI or Tamoxifen, or amongst post-menopausal patients with different hormone therapy regimens. No significant difference in distant metastasis-free survival (DMFS) was observed between hormone therapy groups ($p=0.442$). Mean overall DMFS was 21.5 years (95% C.I. 21.2 - 21.8 years), with TMX patients 21.1 years, AI patients at 18.6 years, and those who switched regimens at 21.4 years. Sub-analyses of DMFS in pre and postmenopausal patients with different hormone therapy regimens showed no significant differences.

Multivariate analysis showed tumor size $\leq 2\text{cm}$ ($p= 0.0001$) and negative axillary node involvement ($p= 0.0001$) significantly decreased odds of developing late all-type recurrence (ATR) in TMX recipients. In patients who switched regimens, Her2 positivity ($p=0.04$) significantly decreased the odds of late ATR. In AI recipients, not undergoing axillary operation

(p = 0.008) significantly increased the odds of late ATR. For TMX recipients, negative axillary node involvement (p=0.004), tumor size ≤ 2cm (p=0.03), and undergoing mastectomy (p=0.02) significantly decreased odds of distant metastasis (DM). Among patients who switched regimens, adjuvant anti-Her2 therapy (p=0.02) significantly decreased odds of DM. For AI recipients, high PR score (p=0.02) and undergoing sentinel lymph node biopsy significantly decreased odds of DM, while age < 50 years significantly increased odds of developing DM.

These findings emphasize the significance of the relationship between hormone therapy regimens and factors affecting late recurrence, thereby providing valuable insights for clinical decision-making. Risk stratification based on identified factors can help in identifying patients at higher risk of late recurrence allowing for more intensive surveillance and potentially early intervention.

Univariate (Chi-square, Logistic Regression) and Multivariate Analysis (Logistic Regression) for Clinicopathologic factors associated with all-type recurrence and distant metastasis after surgery and completion of 5-years endocrine therapy

Variables	All-type Recurrence												Distant Metastasis																			
	Tamoxifen				Switch				Aromatase Inhibitor				Tamoxifen				Switch				Aromatase Inhibitor											
	UV		MV		UV		MV		UV		MV		UV		MV		UV		MV		UV		MV									
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI								
Age, years <50 vs ≥ 50	5.46	0.89-33.1	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Menopausal status pre op	1.65	0.58-4.63	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Tumor size ≤ 2cm vs > 2cm	0.84	0.34-2.08	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Axillary LN metastasis negative vs positive	0.38	0.16-0.92	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Histologic Grade high vs low to intermediate	0.84	0.34-2.08	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Estrogen receptor high vs low	0.74	0.32-1.75	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Progesterone receptor high vs low	0.85	0.37-1.95	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Her2 status positive vs negative	0.63	0.28-1.46	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Ki67 high vs low	0.76	0.33-1.87	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Breast operation mastectomy vs BCS	0.54	0.23-1.28	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Axilla operation none vs SLNB vs ALND	0.54	0.23-1.28	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Radiation Therapy yes vs no	0.41	0.17-1.01	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Chemotherapy yes vs no	0.41	0.17-1.01	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35
Anti-Her2 therapy yes vs no	0.41	0.17-1.01	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35	1.00	0.20-5.07	0.20	0.07-0.57	0.75	0.30-1.86	0.80	0.39-1.69	0.89	0.59-1.35

- a. LN lymph node
- b. SLNB, Sentinel lymph node biopsy
- c. ALND, Axillary lymph node dissection
- d. Cutoff values of Ki67 14% in KUAH and 10% in SNUH
- e. ER and PR cutoff value is 10%
- f. UV, Univariate analysis, MV multivariate analysis, O.R. Odds Ratio, C.I. Confidence Interval

PO5-01-14

Genomic risk analyses in patients with clinical low risk ER-positive HER2-negative early breast cancer developing an early metastatic event

Presenting Author(s) and Co-Author(s):

J. Van Cauwenberge. KU Leuven, United States

H. Izci. KU Leuven, United States

H. Wildiers. University Hospitals Leuven, United States

S. Han. University Hospitals Leuven, Leuven, Vlaams-Brabant, Belgium

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

G. Floris. University Hospitals Leuven, United States

S. Vander Borgh. Department of Pathology, University Hospitals Leuven, Leuven, Belgium, United States

A. Smeets. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, United States

I. Nevelsteen. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, Leuven, Belgium

I. Vanden Bempt. University Hospitals Leuven, United States

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

Background:

Over the past decade, there have been notable changes in the definition of risk estimation in patients with early-stage breast cancer (EBC). Specifically, within the timeframe of 2000 to 2017, following Estrogen Receptor (ER) positive and HER2-negative EBC cases were classified as low risk according to the University Hospitals of Leuven (UHL) criteria of that time: if ER H-score was >200: all patients with tumors N0 and Grade (G) 1, \leq pT2; or G2-3 pT1a-b; in patients \geq 40 years with tumors N0 and G2 pT1c-2 or G3 pT1c; in patients \geq 55 years with tumors N0 G3 pT2 or N1 any Grade, pT \leq 2. For lower H-scores, other criteria applied. However, despite undergoing endocrine therapy, a subset of these patients with clinically low-risk tumors unexpectedly experienced metastasis within five years of initial diagnosis. This unforeseen outcome may indicate potential undertreatment, as these patients did not receive adjuvant chemotherapy.

We have conducted a case-cohort study of those patients with early relapse and performed the current clinical risk assessment methods and genomic risk analyses.

Methods:

In this study, we included patients with ER-pos, HER2-neg early-stage breast cancer diagnosed between 1-1-2000 and 31-12-2017, who were classified as low-risk tumors by UHL guidelines at that time, who were older than 35 but younger than 71 years, had an unilateral, unifocal breast tumor with tumor size up to 5 cm. These patients did not receive adjuvant chemotherapy. We selected the patients that experienced early distant recurrence, defined as distant recurrence (DR) within 5 years after the initial diagnosis. To ensure comparability for the analyses they were matched to controls for grade, menopausal status, tumor size, lymphovascular invasion, progesterone receptor status, and the year of diagnosis. For each patient, we have calculated the clinical risk score according to the criteria outlined by

MyMammprint.com, based on the modified Adjuvant Online tool used in the MINDACT trial. For the analysis, formalin-fixed paraffin-embedded (FFPE) breast tumor tissue samples were subjected to in-house validated targeted RNA-based Mammprint(MP) analysis by NGS (MP Agendia).

Results:

Of the 3190 patients with EBC at UHL during the study period, 2476 patients were considered for this analysis and fitted the clinical low-risk criteria defined low-risk at UHL. Among those, only 42 or 1.7% of the eligible cohort had developed metastasis within 5 years. Tissue for MP analysis was available for 35 of these cases and for their matched control. Due to technical failure, the 1:1 matching was lost and MP results were known for 28 cases and 27 controls. The patient and tumor characteristics of both groups were comparable. In this UHL clinical low-risk group, 21/28 (75%) cases would be identified as clinical high-risk by MyMammprint.com and 18/27 (67%) controls. We identified 13 patients (46.43%) with high genomic risk within the group with DR and 9 (33.33%) within the control group. There was no statistically significant difference (p=0.412) in the proportion of genomically high-risk patients within the group with DR compared to the control group.

Conclusions:

In a database of patients with EBC of whom 98% did not develop metastasis within 5 years, we observed in a small series of chemotherapy naïve patients with early DR and UHL-defined clinical low-risk tumors, that nearly half had a genomically high risk of distant metastasis. Albeit numerically higher than the matched-control group, this observation was not significant and would warrant a larger sample size and power to confirm these results.

Genomic versus Clinical Risk by MyMammprint.com

	Clinical High risk by myMP.com		Clinical Low risk by myMP.com	
	Cases	Controls	Cases	Controls
MP Genomic risk by NGS: high	10	7	3	2
MP Genomic risk by NGS: low	11	11	4	7

PO5-02-01

Concerning Discrepancies in Estradiol Levels in Premenopausal Women Receiving Abemaciclib and Ovarian Function Suppression

Presenting Author(s) and Co-Author(s):

A. Kessler. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

R. Patel. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

E. Gallagher. Icahn School of Medicine at Mount Sinai, United States

T. Sheng. Icahn School of Medicine at Mount Sinai, United States

D. Rao Mendu. Icahn School of Medicine at Mount Sinai, United States

A. Tiersten. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New, New York, United States

P. Klein. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

A. Bhardwaj. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

A. Goel. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

J. Sparano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, United States

T. Shao. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

J. Fasano. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

Background: Adjuvant abemaciclib in combination with endocrine therapy improves outcomes for patients with high-risk, hormone receptor-positive (HR+), HER2-negative early-stage breast cancer. In premenopausal women, the use of an aromatase inhibitor (AI) requires chemical or surgical ovarian function suppression (OFS). Our published case report of a premenopausal woman receiving adjuvant abemaciclib with elevated estradiol levels measured by the Abbott Alinity chemiluminescent microparticle immunoassay (CMIA) despite bilateral salpingo-oophorectomy (BSO) but low estradiol levels using liquid chromatography-mass spectrometry (LC-MS/MS) suggested an interference of abemaciclib with the immunoassay (PMID: 37124155). The aim of this study was to determine discrepancies in estradiol levels using CMIA compared to LC-MS/MS and subsequent treatment changes in a larger patient population.

Methods: We conducted an IRB-approved retrospective review of premenopausal women with early-stage HR+ breast cancer treated with adjuvant OFS and abemaciclib at our institution from October 2021 to April 2023 who had at least 1 CMIA estradiol level drawn during abemaciclib therapy. Pathology, treatment plans, and lab data were abstracted from medical records. Postmenopausal estradiol levels were based on reference ranges of < 41 pg/mL using CMIA or < 15 pg/mL using LC-MS/MS. We utilized descriptive statistics to describe the population and management.

Results: We identified 22 patients who met criteria for our review. The average age was 42.3 years, all had positive axillary nodes, 6 (27%) received neoadjuvant chemotherapy, and 15 (68%) received adjuvant chemotherapy. There were 14 (64%) patients who received leuprolide and 8 (36%) received goserelin, whereas 19 (86%) received AI and 3 (14%) received tamoxifen as their initial oral antiestrogen therapy. The majority of patients did not have baseline estradiol levels when starting OFS though after starting abemaciclib, 20 patients had CMIA estradiol levels in the premenopausal range, 9 of which had estradiol monitored by both CMIA and LC-MS/MS (Table 1). The average length of time from starting OFS to starting abemaciclib was

144.6 days with 1 patient switching from tamoxifen to OFS and AI after starting abemaciclib. Due to elevated CMIA estradiol, treatment changes included increased OFS dosage (5 patients), change of OFS (2 patients), and change to tamoxifen (3 patients). There were 6 patients who underwent BSO, 3 due to persistently elevated CMIA estradiol levels, 2 due to patient preference, and 1 due to a BRCA mutation. Following surgery, 2 patients had persistently elevated CMIA estradiol but low LC-MS/MS estradiol. The remainder of these patients did not have estradiol levels measured by CMIA.

Conclusions: Our retrospective review demonstrated the likely interference of abemaciclib with the Abbott Alinity immunoassay as shown by 9 patients treated with OFS and abemaciclib with simultaneous premenopausal range CMIA estradiol levels and postmenopausal range LC-MS/MS estradiol levels. As up to 91% of patients in our study may have had a false positive estradiol level erroneously suggesting inadequate OFS, monitoring of estradiol levels using the CMIA assay in patients receiving adjuvant abemaciclib in addition to OFS could lead to changes in therapy that may be unnecessary. It is recommended that the LC-MS/MS assay be used when monitoring of estradiol levels is indicated in patients receiving abemaciclib concurrently with OFS.

Table 1: Estradiol levels in patients receiving OFS and abemaciclib who had both CMIA and LC-MS/MS assays

Patient	CMIA estradiol level (pg/mL)	LC-MS/MS estradiol level (pg/mL)	Time between starting OFS and abemaciclib (days)
1	128.0	<1.0	70
2	48.0	<1.0	508
3	57.0	<1.0	152
4	96.0	<1.0	71
5	57.0	<1.0	53
6	100.0	<1.0	56
7	84.0	<1.0	173
8	41.0	<1.0	74
9	101.0	4.1	N/A

PO5-02-02

LyKi1: a highly predictive immune-based score of pathological response to chemotherapy in luminal breast cancer.

Presenting Author(s) and Co-Author(s):

M. Debled. Institut Bergonié, Bordeaux, France

H. Deboissy. Department of Pathology, Institute Bergonié, Bordeaux, France, United States

C. Cantarel. Clinical and Epidemiological Research Unit, INSERM CIC1401, Institut Bergonié, Bordeaux, France, United States

C. Delfour. Department of Pathology, Institute Bergonié, Bordeaux, France, United States

L. Alran. Department of Pathology, Institute Bergonié, Bordeaux, France, United States

M. Fournier. Institut Bergonié, Bordeaux, France

N. Quenel-Tueux. Department of Medical Oncology, Institute Bergonié, Bordeaux, France, United States

V. Velasco. Department of Pathology, Institute Bergonié, Bordeaux, France, United States

F. Chammings. department of breast radiology, Institut Bergonié, Bordeaux, United States

V. Brouste. Clinical and Epidemiological Research Unit, INSERM CIC1401, Institut Bergonié, Bordeaux, France, United States

M. Arnedos. Department of Medical Oncology, Institute Bergonié, Bordeaux, France, United States

G. MacGrogan. Department of Pathology, Institute Bergonié, Bordeaux, France, United States

Background: Identifying which luminal breast cancer (BC) patients will benefit from (neo)adjuvant chemotherapy still remains a challenge. Efficient predictive tests and genomic signatures are still lacking. Because neoadjuvant chemotherapy (NACT) constitutes an in vivo chemotherapy-sensitivity test, we used the pre-treatment core biopsies to identify predictive factors of pathological response in luminal HR+/Her2- BC. Analyses on sTILs and TIL subtypes (CD3, CD4, CD8, CD20) are rare in luminal BC while a predictive value has been reported in TNBC and Her-2 positive BC.

Patients and Methods: We performed a retrospective analysis of 211 patients treated with NACT followed by surgery for a T0-T4 luminal (HR+/Her2-) breast cancer. Association of anthracyclin and taxane was used in 99% of cases. Median age was 48.4 yo (28 – 76). Initial clinical stage was: I: 0.5%, II: 67%; III: 33%. Biopsy analyses were the followings: NST carcinomas: 90%; luminal B: 82%; E&E grade I/II/III: 10%/57%/32%; KI-67 > 20%: 74%.

After NACT, RCB 0-1 was observed in 32 cases (15.2%) and pCR in 19 (9.0 %) cases.

All pre-therapeutic biopsies were reviewed for pathological factors, blinded to the patients' outcomes. Clinico-pathological analyses were performed using standard methods. sTILs were estimated on H&E slides. Intratumoral CD3, CD4, CD8 and CD20 infiltrates were carried out by an independent laboratory using a machine learning model for automated and quantitative evaluation based on digital IHC stains.

Correlation between sTILs and TIL subtypes were assessed by Spearman's coefficient. Predictive factors of RCB 0/1 were explored using unconditional logistic regression analysis. After selection on univariate analysis ($p < 0.05$), multivariate prognostic models were developed

using stepwise backward variable elimination process and compared using area under the curve (AUC).

Results: sTILs levels $\geq 10\%$ were observed in 15.2% of biopsies. 42 % of tumors had $\geq 10\%$ CD3-positive cells, 46% for CD4, 38% for CD8, and 8% for CD20. A high level of correlation was observed between these different markers (Spearman's coefficient ≥ 0.73 for each comparison).

By univariate analysis, significant factors ($p < 0.05$) associated with RCB 0-1 were: age, mitotic index (1 vs 2 vs 3), aneuploidy (1-2 vs 3), differentiation (1-2 vs 3), E&E grade (1-2 vs 3), mitotic count, Ki-67, Magee equation 3, phenotypic group (luminal A vs B), ER, sTILs and each TIL subtype. Age, E&E grade, Ki-67, Magee equation 3, sTILs and all TIL subtypes were selected for multivariate analysis.

As TIL subtypes were highly correlated, different predictive models could be performed. The model we selected (called LyKi1) was constructed based on CD8 [OR 2.24 (95%CI 1.55-3.25; $p < 10^{-4}$)], E&E grade [OR 3.00 (95%CI 1.22-7.42; $p = 0.017$)] and Ki-67 [OR 1.74 (95%CI 1.09-2.76; $p = 0.019$)]. It was highly significantly associated with RCB 0-1, with an AUC value of 0.856 (95%CI 0.756-0.916). For instance, LyKi1 could isolate a group of 30% of patients that achieved RCB 0-1 in 39.7% of cases vs 4.7% for the 70% of patients with lowest LyKi1 scores. pCR rates were 25% and 2%, respectively.

Importantly, prediction value of LyKi1 remained very high if restricted to luminal B tumors (AUC 0.817; 95% CI: 0.741-0.894). Ability to predict pCR was also very high (AUC 0.837 (95%CI: 0.750-0.924) in this phenotype).

Conclusion: This retrospective analysis clearly highlights the important predictive role of sTILs and TIL subpopulations for the response to an anthracyclin-taxane based regimen in a neoadjuvant setting for luminal breast cancer. Within this cohort, LyKi1 score (combining CD8, grade and Ki-67) has a very high value to predict pathological response to NACT in luminal breast cancer. Importantly, such score has to be validated in a multicentric prospective cohort and investigated in adjuvant setting.

PO5-02-03

Does the recommendation of adjuvant CDK4/6 inhibitors implicate more ovarian suppression in premenopausal patients? A real-world study of a public and a private Argentinean institution.

Presenting Author(s) and Co-Author(s):

V. Lopez. Instituto de Oncología Ángel H. Roffo, Ciudad Autonoma de Buenos Aires, Argentina

D. Narvaez. Instituto Alexander Fleming, Ciudad Autonoma de Buenos Aires, Argentina

J. Nadal. Instituto Alexander Fleming, Ciudad Autonoma de Buenos Aires, Argentina

F. Waisberg. Medical Oncologist, Caba, Buenos Aires, Argentina

A. Nervo. Instituto Alexander Fleming, Ciudad Autonoma de Buenos Aires, Argentina

V. Costanzo. Instituto Alexander Fleming, Buenos Aires, Argentina, United States

C. Paletta. Instituto Alexander Fleming, Ciudad Autonoma de Buenos Aires, Argentina

F. Petracci. Instituto Alexander Fleming, United States

S. Rivero. Instituto Alexander Fleming, Buenos Aires, Argentina, United States

A. Ostinelli. Instituto Alexander Fleming, United States

M. Chacón. Instituto Alexander Fleming, Ciudad Autonoma de Buenos Aires, Argentina

A. Aguilar. Instituto de Oncología Ángel H. Roffo, United States

A. Kuzminin. Instituto de Oncología Ángel H. Roffo, United States

A. Nico. Instituto de Oncología Ángel H. Roffo, United States

E. Rovera. Instituto de Oncología Ángel H. Roffo, United States

N. Kassis. Instituto Roffo, United States

M. Zapata Camaño. Instituto de Oncología Ángel H. Roffo, United States

C. Almada. Instituto Roffo, United States

M. Savignano. Instituto de Oncología Ángel H. Roffo, United States

G. Roganovich. Instituto de Oncología Ángel H. Roffo, United States

M. Azar. Instituto de Oncología Ángel H. Roffo, United States

V. Caceres. Roffo Institute, United States

Introduction

The recently published NATALEE trial has reported an increase of invasive disease free survival with the addition of ribociclib to hormone therapy during 3 years. Given the fact that aromatase inhibitors are required as the endocrine therapy backbone, premenopausal patients require ovarian function suppression (OFS) during CDKi treatment

In the era of CDKi in the adjuvant setting, we hypothesize that the recommendation of GnRh analogs administration in addition to aromatase inhibitors will increase for premenopausal patients, given the inclusion criteria of this pivotal trial.

For this reason, we explored in a retrospective cohort of a public and a private Argentinean institution to define whether the application of these criteria would imply an increase of the recommendation of OFS as part of the adjuvant endocrine treatment.

Methods

This was a multicentric retrospective cohort comprising premenopausal patients with early breast cancer diagnosis. Descriptive statistics were used to summarize data. The criteria for defining ribociclib recommendations were based on the phase III NATALEE clinical trial. Univariate analysis, including t and chi-square tests were used to determine differences between the populations that received and did not receive OFS, and between both participating institutions. $p < 0,05$ was considered to evaluate statistical significance.

Results

191 premenopausal patients were incorporated in our analysis, and 48 (25.1%) received OFS. In this subgroup, mean age was lower (38.1 vs 44.2 years; $p < 0.001$) and the incidence of T3 (23.9 vs 6.5%; $p = 0.002$), node-positive tumors (57.4 vs 28.9%; $p = 0.005$), and prior chemotherapy treatment (75.5 vs 58.8%; $p < 0.001$) was higher. Among the 143 patients that did not receive OFS, 121 (84.6%) would have fulfilled clinical trial criteria for receiving ribociclib. No differences were observed according to the treating institution: 80.3 vs 87.8%; ($p = 0.22$). The patient subgroup that would have met NATALEE criteria and did not receive OFS, had median age of 44.19 (SD 4.18), and had prior chemotherapy in 63.8% of the cases. Considering these characteristics, we observed that chemotherapy-induced amenorrhea and local institutional guidelines were the main explanations to understand why these moderate and high-risk patients did not receive OFS.

Conclusion

We observed that in premenopausal patients, the application of NATALEE criteria would result in an increase of the recommendation of GnRh analogues in around 80% of patients that had not received OFS in a retrospective cohort. This scenario may result in new challenges in treatment adherence and quality of life. In addition, this information is of special importance to carefully analyze the financial toxicity of a modern adjuvant approach that will be applied in a high proportion of eBC patients, especially in low and middle-income countries.

PO5-02-04

Irish National Analysis of the Clinical and Economic impact of 21-gene Oncotype DX® testing in Early-Stage, 1-3 lymph node positive, Hormone Receptor positive (HR+), HER2-Negative (HER2-), Breast Cancer (BC).

Presenting Author(s) and Co-Author(s):

I. Browne. Department of Medical Oncology, St Vincent's University Hospital, Dublin, Ireland, United States

R. McLaughlin. Department of Medical Oncology, Beaumont Hospital, Dublin, Ireland, United States

C. Weadick. Department of Medical Oncology, Cork University Hospital, Cork Ireland, Ireland

S. O'Sullivan. Department of Medical Oncology, Mater Misericordiae University Hospital, Dublin, Ireland, United States

S. Millen. Exact Sciences UK Ltd, London, UK, United States

D. Hadi. Department of Medical Oncology, St James's Hospital, Dublin, Ireland, United States

S. Bilal-Shah. Department of Medical Oncology, St James's Hospital, Dublin, Ireland, United States

M. Al Sendhi. Salmaniya Medical Complex, Bahrain, United States

M. Higgins. Department of Medical Oncology, St Vincent's University Hospital, Dublin, Ireland, United States

J. Crown. St Vincent's University Hospital, Dublin 4, Dublin, Ireland

R. Prichard. Department of Surgery, St Vincent's University Hospital, Dublin, Ireland, United States

D. McCartan. Department of Surgery, St Vincent's University Hospital, Dublin, Ireland, United States

A. Hill. Department of Surgery, Beaumont Hospital, Dublin, Ireland, United States

R. Connolly. Cancer Research, College of Medicine and Health, University College Cork, Ireland and Department of Medical Oncology, Cork University Hospital, Cork, Ireland, United States

S. Noonan. Department of Medical Oncology, Cork University Hospital, Cork, Ireland, United States

D. O'Mahony. Medical Oncology Department, Bon Secours Hospital, Cork, Ireland, United States

C. O'Hanlon-Brown. Department of Medical Oncology, St James's Hospital, Dublin, Ireland, United States

B. Hennessy. Department of Medical Oncology, ICORG/Cancer Trials Ireland, Beaumont Hospital, Royal College of Surgeons in Ireland, Dublin, Ireland, Ireland

C. Quinn. St. Vincent's University Hospital, Dublin, Ireland, United States

C. Kelly. Cancer Trials Ireland, Dublin, Ireland

S. O'Reilly. Department of Medical Oncology, Cork University Hospital, Cork, Ireland, Cork, Ireland

P. G. Morris. Cancer Trials Ireland, Ireland; Beaumont RCSI Cancer Centre, Dublin, Ireland, United States

J. Walshe. Department of Medical Oncology, St Vincent's University Hospital, Dublin, Ireland, United States

Background:

The treatment landscape of HR+ BC is evolving, with a reduction in chemotherapy (CT) use because of Oncotype DX Recurrence Score® testing. Results from the RxPONDER trial suggest that adjuvant CT may benefit some premenopausal women with HR+, HER2- disease with 1-3 positive LN (N1), and a Recurrence Score® (RS) result of ≤ 25 . Postmenopausal women with similar characteristics did not benefit from adjuvant CT. A previous analysis of the impact of Oncotype DX® testing in a N1 BC population from 2 Irish cancer centres identified a 55% reduction in CT use with savings of over €1 million. In this study, we have extended the analysis to 5 Irish cancer centres. The objectives of this study were to examine the clinical and economic impact of Oncotype DX testing on treatment (tx) decisions in N1 patients at a national level with a larger patient (pt) population, and to examine changes in the ordering of Oncotype DX tests pre and post RxPONDER data.

Methods:

From November 2012 to October 2022, a retrospective, cross-sectional observational study was performed of HR+, HER2-, N1 pts who had Oncotype DX testing across five of Ireland's BC centres. All pts with N1 disease were assumed to be recommended adjuvant CT pre-Oncotype DX testing. Using RxPONDER risk groupings, pts were classified into low risk (RS 0-13), intermediate risk (RS 14-25) and high risk (RS >25). Data was collected via electronic pt records and clinical chart review. Information regarding costing was provided by the National Healthcare Pricing Regulatory Authority and the economic analysis was adjusted for changing costs over the study time-period. RxPONDER was presented at SABCS December 2020. We compared the changes in the demographics of Oncotype DX test ordering and CT prescribing from 2019 – 2020 and 2021 – 2022.

Results:

828 pts were included in this study. Mean age was 58 years (range 22-81). Median tumour size was 2.28cm (range 0.3-12.5cm), and 92 (11%), 530 (64%) and 206 (25%) had grade 1, grade 2, and grade 3 disease, respectively. 319 (38%) had RS 0-13, 396 (48%) RS 14-25 and 113 (14%) RS >25. 378 pts (46%) had 1 LN+, 126 (15%) 2 LN+ and 47 (6%) 3 LN+. 277 pts (33%) had micro-metastatic disease only. No association between the numbers of nodes affected and RS result was identified. 171 pts (21%) were < 50 years at diagnosis; 54 (32%) had RS 0-13, 89 (52%) RS 14-25 and 28 (16%) RS >25.

Post Oncotype DX -testing, 480 pts (58%) had a change in tx decision; 446 (54%) were prescribed hormone therapy (HT) alone and 34 (4%) prescribed HT and ovarian function suppression. In total 348 pts (42%) were recommended adjuvant CT; 48 (14%) RS 0-13, 191 (55%) RS 14-25 and 109 (31%) RS >25. Of 171 pts age < 50, 60 (35%) avoided CT. Use of the RS assay was associated with a 58% reduction in CT administration overall. This resulted in savings of over €6 million in tx costs. Deducting the assay cost, net savings of over €3.3 million euro was achieved.

Changes in the ordering demographics of RS tests were identified after RxPONDER data was presented. Between 2019 and 2020, 150 tests were ordered, 50 (33%) for pts < 50. Between 2021 and 2022, 271 tests were ordered, 47 (17%) for pts < 50, corresponding to a 48% reduction in the proportion of Oncotype DX tests ordered for pts < 50. We also observed a change in CT recommendation for pts < 50; a 40% reduction in CT administration in the pre-RxPONDER time-period fell to 21% post RxPONDER. Conversely, in pts ≥ 50 , we identified less CT administration; whereas 60% of pts avoided CT pre RxPONDER, 71% of pts avoided

CT post RxPONDER. This indicates increasing confidence in this genomic test for postmenopausal women with N1 disease.

Conclusions:

Ireland was one of the first public healthcare systems to approve reimbursement for Oncotype DX testing in both N0, and N1 pts. Between 2012-2022, assay use resulted in a 58% reduction in CT administration and net savings of over €3 million. The presentation of RxPONDER has led to reduced Oncotype DX testing in premenopausal patients and increased testing in postmenopausal women.

PO5-02-05

Assessing Vaccine-Mediated Cellular Immune Responses in Patients Receiving Combined Vaccine and Chemotherapy Treatment

Presenting Author(s) and Co-Author(s):

D. Johann. University of Arkansas for Medical Sciences, United States

F. Jousheghany. University of Arkansas for Medical Sciences, United States

E. Blitz. University of Arkansas for Medical Sciences, United States

B. Nounamo. University of Arkansas for Medical Sciences, United States

S. Makhoul. CARTI, United States

E. Siegel. University of Arkansas for Medical Sciences, United States

T. Kieber-Emmons. University of Arkansas for Medical Sciences, United States

B. Monzavi-Karbassi. University of Arkansas for Medical Sciences, United States

Background: We showed recently that immunizing breast cancer patients with the P10s-PADRE vaccine in combination with chemotherapy activates both humoral and cellular immune responses. Induction of specific antibody response was easily determined by measuring anti-P10s antibodies, however, we observed increase in serum interferon-gamma (IFN γ) and tumor necrosis factor-alpha (TNF α) as well as activation of Natural Killer (NK) and T-cells, accurate assessing of which proved complicated due to the non-specific impact of chemotherapy. This study was undertaken to further distinguish the vaccine-induced cellular immune responses from the immune effects induced by chemotherapy, and to evaluate their potential contributions to anti-tumor activity. Methods: Peripheral blood mononuclear cells (PBMCs) from twenty-five subjects who received a combination of P10s-PADRE and standard-of-care chemotherapy were utilized for gene expression analysis and various immune assays. PBMC samples collected before and after treatment were subjected to flow cytometry and ELISpot assays, as well as bulk and single-cell RNA sequencing analyses. For functional assays PBMCs were stimulated with P10s, P10s-PADRE, anti-CD3/CD28, and tumor cell lysates. Differential gene expression analysis, gene set analysis, Hierarchical Clustering, and principal component analysis were performed. Results: Non-specific (anti-CD3/CD28) and specific (peptide, cancer cells) stimulation of PBMCs significantly activated immune cells in post-immune samples compared to pre-immune samples as measured by cytokine secretion, with IFN γ being the dominant cytokine secreted. Flow cytometry showed activation of both natural killer and CD8+ cells measured by a significant increase in CD69 expression. These data plus detection of Ab response suggests induction of both humoral and cellular immune responses. However, bulk RNA-seq performed on 24 patients indicate a dramatic reduction of B, T, and NK cells in the post-immune samples. Deconvolution reanalysis of the bulk sequencing data together with complementary scRNA-seq analysis of PBMCs of select subjects supports vaccine-mediated activation of both CD8+ and NK cells and suggests NK cells as a source of detected serum increase in IFN γ and TNF α . Conclusions: The P10s-PADRE vaccine elicits substantial and quantifiable cellular and humoral immune responses, despite the deleterious effects of chemotherapy on effector immune cells involved. The evidence indicates that the activation of both CD8+ and NK cells is facilitated by the vaccine. It is probable that the NK cells are the primary contributors of IFN γ and TNF α . These findings carry considerable implications for the structuring of advanced phase trials and the potential application of the vaccine in treating other forms of malignancies.

PO5-02-07

Multifocal breast cancer: tumor biology and prognostic importance

Presenting Author(s) and Co-Author(s):

E. Söderberg. Department of surgery, Sundsvall Hospital. Umeå University, Sundsvall, Sweden

M. Sund. Umeå University, United States

F. Wärnberg. Gothenburg University, Gothenburg, Sweden

H. Garmo. Regional cancer centre, Uppsala, Sweden

A. Wennstig. Region of Västernorrland, Department of oncology, Sundsvall, Sweden

L. Holmberg. Uppsala University, Sweden

G. Nilsson. Department of oncology Gävle hospital, Sweden

C. Wadsten. Dept of Surgery, Sundsvall Hospital, Sundsvall, Sweden

>Multifocal breast cancer: tumor biology and prognostic importance
Background The incidence of multifocal breast cancer (MBC) varies widely in the literature and recent reports indicate that the incidence of MBC is increasing. Several studies have shown similar tumor biology in the different foci of multifocal tumors, and it has been suggested that multifocal tumors may in fact be intramammary metastases and thus be a sign of a more aggressive cancer type than unifocal tumors. Knowledge regarding outcome and optimal treatment of MBC compared to unifocal breast cancer (UBC) is still limited. The aim of the present study was to explore if multifocal breast cancers have less favorable characteristics and prognosis compared to unifocal breast cancers. Method Patient and tumor characteristics were obtained from Breast Cancer database Sweden (BcBaSe3) including women with invasive breast cancer 2008-2019 who had undergone primary surgery. Women with distant metastases at time of diagnosis, women receiving neoadjuvant systemic therapy, and men were excluded. Overall- and breast cancer specific survival were calculated with Kaplan-Meier and Cox-regression analyses. Results A total of 71607 women met our inclusion criteria, 11961 (16.7%) with MBC and 59512 (83.3%) with UBC. Among women with MBC, 64.1% underwent mastectomy compared to 32.4% of women with UBC and 40.1% with MBC underwent complete axillary lymph node dissection compared to 23.5% of the women with UBC. MBC was associated with higher T-stage (T2 31.9% vs. 25.8% and T3 4.6% vs. 2.6%. $p < 0.001$) and higher N-stage (N+ 13.7% vs. 8.4%, $P < 0.001$), compared to UBC. MBC were more often of lobular type (18.8% vs. 12.4%, $P < 0.001$), of higher grade (grade 3 29.3% vs. 27.3%, $p < 0.001$), with positive hormone receptor status (88.4% vs. 86.7%, $p < 0.001$), and Her2 positivity (13.3% vs. 10.9%, $p < 0.001$). Adjuvant systemic treatment was more frequently administered to women with MBC, adjuvant chemotherapy (45.3% vs. 33.3%, $p < 0.001$) and endocrine treatment (82.9% vs. 75.3%, $p < 0.001$). Breast cancer specific 10- year survival was 86.4% and 88.5% for MBC and UBC respectively, hazard ratio for breast cancer death 1.19 (95 % confidence interval, 1.11- 1.28). Overall survival did not differ between the two groups (10-year survival 76.0%, $p = 0.35$) Conclusion MBC appears to have a more aggressive tumor biology than UBC, with the exception of hormone receptor status and MBC is associated with decreased breast cancer specific survival. Further analysis of possible interactions with different treatment methods will be conducted.

PO5-02-08

Prognostic value of serum lipid levels in breast cancer patients who received neoadjuvant chemotherapy: A retrospective exploratory analysis of the prospective cohort

Presenting Author(s) and Co-Author(s):

X. Chen. Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China, China (People's Republic)

W. Yin. Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China, United States

Y. Zhao. Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China, China (People's Republic)

J. Lu. Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China, United States

【Background】 Lipid metabolism is one of the most conspicuous metabolic changes in malignant tumors. Previous studies confirmed that higher levels of “adverse lipids” might lead to poor outcomes and lipid-lowering drugs could act as a protective role in improving the prognosis of breast cancer patients. Nevertheless, few studies have clarified the impact of serum lipid levels and their changes on the tumor prognosis. Particularly for breast cancer patients treated with neoadjuvant chemotherapy, little has been studied whether their lipid levels or changes during neoadjuvant chemotherapy can serve as a valid prognostic factor.

【Methods】 This study enrolled patients who received surgical treatment after neoadjuvant chemotherapy in Renji Hospital from March 2016 to December 2020. Patients were included if they were female aged 18 years or older; had pathologically confirmed unilateral invasive breast cancer; had tumor of at least 2cm in size without distant metastasis (T1-4, N0-3, M0); and underwent radical surgery for breast cancer successfully after neoadjuvant chemotherapy. We retrospectively gathered the baseline clinicopathological information and lipid metabolism-related biomarkers from electronic medical records. The study endpoints were disease free survival (DFS), overall survival (OS), relapse free survival (RFS), distance recurrence free survival (DRFS), and local recurrence free survival (LRFS). The prognostic value of each lipid levels and their variation levels were systematically evaluated and the importance of lipid biomarkers were ranked by Random Forest.

【Results】 The baseline clinicopathological information and lipid metabolism biomarkers were available from 200 eligible patients. As of the last follow-up in March 2023, 11 patients died, 24 experienced DFS events and 20 underwent RFS events. It showed no significant correlations of lipid levels before (baseline) and after (preoperative) neoadjuvant chemotherapy with any survival outcome. However, we found that the relative increase of low-density lipoprotein (LDL) led to poorer DFS ($P=0.003$), RFS ($P=0.01$), DRFS ($P=0.01$), and LRFS ($P=0.0039$), meanwhile the relative increase of total cholesterol (TC) and non-high-density lipoprotein (NHDL) during neoadjuvant period was significantly related to the worse prognosis (TC, DFS $P=0.0084$; NHDL, DFS $P=0.031$, RFS $P=0.009$) as well. After adjusted by multiple factors, the adverse impacts of increasing TC (DFS $P=0.005$; RFS $P=0.026$), LDL (DFS $P=0.004$; RFS $P=0.006$) and NHDL (DFS $P=0.032$; RFS $P=0.014$) on DFS or RFS were still maintained.

The results of Random Forest revealed that LDL changes and Body Mass Index (BMI) ranked

higher in terms of predicting survival outcomes. Based on these data, BMI >25.4 kg/m² or LDL elevation >0.54 mmol/L were defined as High-risk Lipid Metabolism (HLM), while BMI ≤ 25.4 kg/m² and LDL elevation ≤ 0.54 mmol/L were regarded as Low-risk Lipid Metabolism (LLM). Compared to LLM, HLM had a worse OS (P=0.026), DFS (P=0.0011) and RFS (P=0.0011).

【Conclusion】 Our study demonstrated that the relative elevation of LDL, TC and NHDL levels during neoadjuvant chemotherapy is an independent prognostic risk factor for breast cancer patients. It was also the first time to propose the concept of high-risk lipid metabolism (HLM).

【keywords】 Breast cancer, Lipid metabolism, Low-density lipoprotein (LDL), Body Mass Index (BMI), Prognosis.

PO5-02-09

Discordance of the PAM50 intrinsic subtypes with the immunohistochemistry-based subtypes in HER2-negative early breast cancer treated with neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

J. Kim. Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, United States

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

J. Lim. Institute for Breast Cancer Precision Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; , United States

M. Kim. Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, United States

G. Kim. Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, United States

J. Sohn. Yonsei Cancer Center, Seoul, Republic of Korea

J. Jeong. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Background

The PAM50 (Prosigna Breast Cancer Gene Signature Assay) can be used to assess the expression levels of 50 genes in early breast cancer biopsies, including formalin-fixed paraffin-embedded (FFPE) tissue from human epidermal growth factor receptor 2 (HER2)-negative patients. However, there is currently no practical molecular assay for intrinsic subtype in real-world practice that addresses the problems of cost and run-time.

Methods

In the phase 2 HER2E-PAM/PAMILIA study (NCT04817540), we prospectively analyzed molecular subtyping through the PAM50 test in low HER2 (HER2 IHC 1+ or 2+ SISH-) breast cancer patients. PAM50 intrinsic subtypes were determined according to 50 cancer genes using the NanoString nCounter Analysis System. This study was originally designed to determine whether adding HER2-targeted treatment in HER2 enriched molecular subtype increases the pathologic complete rate (pCR). We aimed to analyze the discordance between immunohistochemistry (IHC)-based surrogate subtyping of pre- & post-operative tissues and PAM50 intrinsic subtypes, and to assess the pCR according to the discordance.

Results

In a total 82 patients, the proportions of HR+/HER2- and triple negative breast cancer (TNBC) in the preoperative tissue were 85.4% (n=70) and 14.6% (n=12), respectively. According to PAM50 intrinsic subtypes, 11.0% (n=9) were basal, 8.5% (n=7) were HER2-enriched, 34.1% (n=28) were luminal A, 36.6% (n=30) were luminal B, and 3.7% (n=3) were normal-like type. In total, 32 patients (41.5%) were discordant between IHC-based preoperative subtype and PAM50 intrinsic subtype. Among the 70 patients with HR+/HER2-, non-luminal A, B type was found in 12.9% with basal-like, 8.6% with HER2-enriched, and 4.3% with normal-like type, respectively. Of 12 TNBC patients, 83.3% were luminal A, B type, and 8.3% were HER2-enriched. In the other hands, 6 patients (13.0%) were discordant between IHC-based post-

operative subtype and PAM50 intrinsic subtype. Among the 40 patients with HR+/HER2- postoperative subtype, non-luminal A, B type was found in 2.5% with basal-like, 2.5% with HER2-enriched, and 5.0% with normal-like type, respectively. Of 6 TNBC postoperative patients, 16.7% were normal-like. Most received anthracycline- and taxane-based neoadjuvant chemotherapy. During data analysis (June 2023), 54 cases underwent surgery after neoadjuvant chemotherapy. 4 of 54 patients (7.4%) achieved a pCR, of which one was HER2-enriched, one was luminal B-like, and two were basal-like PAM50 intrinsic subtype. However, discordance of IHC based subtype with intrinsic subtype was not considerable and was not correlated with pCR.

Conclusion

A substantial portion of patients showed discrepancy between preoperative and postoperative IHC subtype and PAM50 intrinsic subtype in our study.

PO5-02-10

Favorable effect of HER2-low expression on prognosis for breast cancers after neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

Y. Zhao. Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China, Shanghai, China (People's Republic)

W. Yin. Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China, Shanghai, China (People's Republic)

X. Chen. Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China, China (People's Republic)

J. Lu. Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China, Shanghai, China (People's Republic)

[Background] The clinicopathological characteristics, pathological complete response and survival outcomes of HER2-low, HER2-zero and HER2-positive breast cancers are yet to be elucidated in Chinese patients especially those administered neoadjuvant chemotherapy.

[Methods] We retrospectively identified 259 patients with different HER2 statuses (zero, low and positive) who underwent surgery as planned after neoadjuvant chemotherapy from a prospectively maintained institutional cohort database in Renji Hospital, School of Medicine, Shanghai Jiao Tong University between 2014 and 2019. Overall survival (OS) denoted the time from surgery to death, irrespective of cause. Locoregional relapse-free survival (LRFS) was estimated from surgery to first occurrence of locoregional, ipsilateral relapse, or death, irrespective of cause. We defined pathologic complete response (pCR) as ypT0 ypN0 (absence of cancer in the breast and axillary nodes). The definition of ypT0/is ypN0 (absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ) was evaluated as an additional endpoint.

[Results] A total of 89 (34.36%), 66 (25.48%) and 104 (40.16%) HER2-low, HER2-zero and HER2-positive breast cancers were enrolled in this analysis, respectively. The median follow-up interval was 5.74 years. Hormone receptor(HR) expression was numerically more common in HER2-low breast cancers than the other two subgroups (83.15% in HER2-low vs 72.73% in HER2-zero vs 77.88% in HER2-positive, $P > 0.05$). The level of Ki-67 index was significantly lower in the HER2-low tumors than that of HER2-zero tumors ($P=0.023$). HER2-positive tumors had the highest proportion of histological grade III ($P=0.005$). The HER2-low breast cancers showed significantly better OS ($P=0.0056$) and LRFS ($P=0.002$) than HER2-zero counterparts. Subgroup analysis revealed the similar benefit in LRFS ($P=0.018$) rather than OS ($P=0.055$) for patients with HR positive/HER2-negative tumors. When the HER2-positive tumors was combined together for comparison, the OS ($P=0.016$) and LRFS ($P=0.0062$) also significantly differed among patients with HER2-low, HER2-zero, and HER2-positive tumors. Additionally, the HR negative patients had analogous OS outcome to the entire population according to different HER2 status ($P=0.041$). Multivariable Cox-regression analysis and external validation in the TCGA database as well as Kaplan-Meier plotter database supported that HER2-low tumors and HER2-positive tumors treated with HER2-directed therapy may have similar survival outcomes, while HER2-zero peers may have the worst outcome compared with the above two groups. There were no remarkable differences in pCR rates between HER2-low and HER2-zero tumors after neoadjuvant chemotherapy (ypT0ypN0 and ypT0/isypN0, $P=0.452$ and $P=0.777$, respectively). HER2-positive tumors had a significantly higher pCR rate, especially

compared to HER2-low tumors in the entire population (both $P < 0.001$) as well as in the HR positive subgroup (both $P < 0.0001$). The pCR status affected survival outcomes for breast cancers with different HER2 status. As for those without pCR, the HER2-low subgroup showed a remarkably better performance compared with HER2-zero patients in terms of OS ($P=0.018$) and LRFS ($P=0.005$), while little difference was found for patients who achieved pCR.

[Conclusion] Our study demonstrated that HER2-low breast cancer may be a different entity from HER2-zero or HER2-positive tumors, which provide illuminating evidence in view of patients receiving neoadjuvant treatment.

[Keywords] neoadjuvant chemotherapy, HER2-low, HER2-zero, HER2-positive

PO5-02-11

Is There A Survival Benefit With Adjuvant Chemotherapy Use In Elderly Breast Cancer Patients? A Retrospective Study Using The National Cancer Database.

Presenting Author(s) and Co-Author(s):

P. Ashok Kumar. SUNY Upstate Medical University, Syracuse, New York, United States

M. Sravanthi. SUNY Upstate Medical University, United States

D. Wang. SUNY Upstate Medical University, United States

D. Huang. SUNY Upstate Medical University, United States

A. Sivapiragasam. Upstate Medical University, United States

Background

Geriatric patients (Age ≥ 65 years) with Breast Cancer (BC) face a unique challenge due to the relatively lower functional status, as well as co-existing comorbidities. Studies like the recently published meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) group provide irrefutable evidence for the recurrence free survival benefit of anthracycline and taxane based adjuvant chemotherapy (ACT) regimes in early-stage BC patients. However, the age range of the trials analyzed ranged between 46-55 years, with underrepresentation of the geriatric group. The question on whether ACT results in an overall survival (OS) benefit for the elderly remains at large, which we hope to answer through our study.

Methods

The 2019 National Cancer Database (NCDB) was used to extract patients aged ≥ 65 years with breast cancer. We included stage 1-3 patients and stratified them into those who received ACT (ACT+) and those who did not (ACT-). Patients who received ACT were identified from the columns that specified the times of events from diagnosis or from the column for systemic therapy-surgery sequence. Patients should have had definitive surgery for their BC management to be included. Odds Ratio (OR) from logistic regression was used to analyze the utility of ACT based on various factors. Kaplan Meier (KM) survival curves and Hazard Ratio (HR) estimates from multivariate cox model was used to compare OS outcomes.

Results

Our cohort had 866,071 (ACT+: 642721, ACT-:223350) patients. The age distribution showed that ACT+ had 86.45% in the 65-80 years group and 13.55% in the >80 years group. ACT- had 68.32% aged 65-80 and 31.68% >80 years. The distribution of various demographic, pathologic and clinical factors by ACT use are shown in Table 1. Factors associated with ACT use based on OR estimates are shown in Table 2. ACT use is more likely in younger age group (65-80), lower comorbidity score, poorly differentiated and undifferentiated tumors, ER/PR negativity, T2 and lymph node positivity, those who underwent partial mastectomy and regional lymph node surgery, and HER2 positivity. Both 5-year (86.3 vs 74.2%) and 10-year (66 vs 50.8) OS were better with ACT+ (Table 2). The HR using propensity score (PS) weighted cox model revealed a higher hazard rate on omitting ACT [1.436, 95% Confidence Interval (CI) 1.417,1.456, $p < .0001$] (Table 2). HR estimates between ACT- vs ACT+, stratified by subgroups [Age (65-80, >80), T stage, grade (G), HER2] favored ACT use in all groups except G1 tumors (Table 3).

Discussion

Our study using a large national database, supports the use of ACT in the geriatric BC population by showing a clear OS advantage of 15.2% at 10 years. This benefit was observed even in BC patients aged more than 80 years with a HR of 1.683 when compared to ACT-, as

represented in Table 3. While the existing literature provides robust evidence for ACT use in situations such as a high oncotype recurrence score, our study provides real-world evidence from a population-based dataset to supports its use in the elderly, including those above 80 years. The geriatric assessment recommended by the American Society of Clinical Oncology guideline for geriatric oncology should be followed in this setting. Utilization of geriatric assessment tools among oncologists has been poor with a survey revealing that 60% of providers did not utilize these tools in making treatment decisions. Limitations of our study include the potential for missing confounding factors and the retrospective nature of the study using a large database.

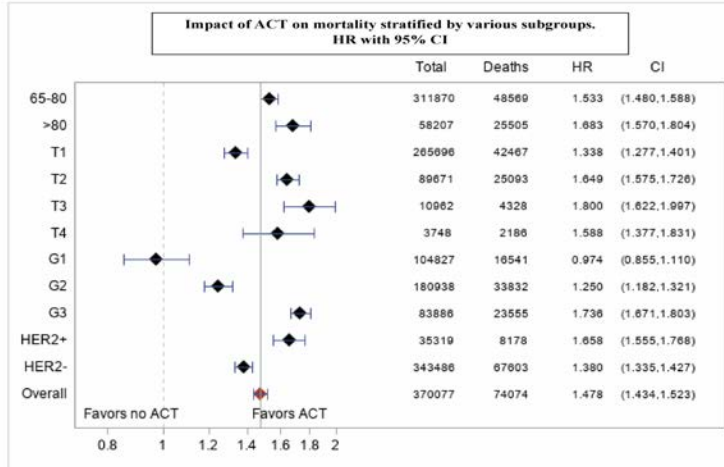
Table 1 Demographic, pathological, and clinical characteristics of the study population and their distribution based on ACT use.

Demographic, pathological, and clinical characteristics of the study population and their distribution based on ACT use.			
	ACT+	ACT-	P-value
Age			<.001
65-80	555643 (86.45)	152596 (68.32)	
>80	87078 (13.55)	70754 (31.68)	
Race			0.042
White	564956 (87.90)	196675 (88.06)	
Black	52602 (8.18)	18185 (8.14)	
Others	25163 (3.92)	8490 (3.80)	
Charlson Deyo Score (CDS)			<.001
0	498724 (77.60)	171730 (76.89)	
1	107018 (16.65)	36771 (16.46)	
2	25425 (3.96)	10048 (4.50)	
≥3	11554 (1.80)	4801 (2.15)	
ER, PR			<.001
ER Positive, PR Positive	298898 (80.13)	70427 (65.36)	
ER Positive, PR Negative	42664 (11.44)	10368 (9.62)	
ER Negative, PR Positive	2079 (0.56)	1062 (0.99)	
ER Negative, PR Negative	29365 (7.87)	25895 (24.03)	
Regional Lymph Node Surgery			<.001
No regional lymph node surgery	47517 (7.39)	37762 (16.91)	
Regional lymph node surgery	594785 (92.54)	185308 (82.97)	
Unknown if there was any regional lymph node surgery	419 (0.07)	280 (0.13)	
Type of facility			<.001
Community Cancer Program	338082 (52.60)	121092 (54.22)	
Academic/Research Program	165417 (25.74)	52331 (23.43)	
Integrated Network Cancer Program	139222 (21.66)	49927 (22.35)	
Grade			<.001
Well differentiated, differentiated	140594 (27.79)	55299 (30.13)	
Moderately differentiated	250652 (49.54)	79892 (43.53)	
Poorly differentiated	113846 (22.50)	47680 (25.98)	
Undifferentiated, anaplastic	863 (0.17)	660 (0.36)	
HER2			<.001
Positive	41724 (8.66)	11081 (8.42)	
Negative	430643 (89.36)	117126 (88.97)	
Unknown	9553 (1.98)	3445 (2.62)	
Income in 2012			0.106
<\$48,000	208141 (36.54)	74560 (36.74)	
≥\$48,000	361493 (63.46)	128377 (63.26)	
Insurance			<.001
Not Insured	2396 (0.37)	801 (0.36)	
Private Insurance	8790 (13.65)	2721 (12.18)	
Government	545777 (84.92)	192105 (86.64)	
Unknown	6848 (1.07)	3229 (1.45)	
Type of Surgery			<.001
Partial mastectomy	437357 (68.06)	141586 (63.40)	
Mastectomy	205010 (31.90)	81570 (36.53)	
Surgery, NOS	282 (0.04)	167 (0.07)	
Pathological N			<.001
N0	456258 (76.13)	167576 (86.43)	
N1	106678 (17.80)	19487 (10.05)	
N2	24445 (4.08)	4575 (2.36)	
N3	11965 (2.00)	2255 (1.16)	
Pathological T			<.001
T1	455778 (70.91)	167977 (78.21)	
T2	160903 (25.03)	45491 (20.37)	
T3	19488 (3.03)	6113 (2.74)	
T4	6552 (1.02)	3769 (1.69)	

Table 2 Odds Ratio for ACT use, KM survival curves and HR estimates of ACT use

OR and 95% CI of receiving ACT from multivariate logistic regression.			
	Point Estimate	95% CI	
Age >80 vs 65-80	0.128	0.122	0.135
CDS 1 vs 0	0.933	0.893	0.975
CDS 2 vs 0	0.769	0.710	0.833
CDS >=3 vs 0	0.566	0.503	0.638
Grade Moderately differentiated vs Well differentiated	2.040	1.920	2.168
Grade Poorly differentiated vs Well differentiated	3.816	3.578	4.069
ER Negative, PR Negative vs ER Positive, PR Positive	7.811	7.470	8.167
T2 vs T1	1.537	1.477	1.599
T3 vs T1	1.081	0.984	1.188
T4 vs T1	0.565	0.491	0.650
N1 vs N0	2.522	2.403	2.647
N2 vs N0	3.599	3.303	3.922
N3 vs N0	3.995	3.558	4.486
Mastectomy vs Partial mastectomy	0.820	0.791	0.850
Regional lymph node surgery vs No regional lymph node surgery	1.753	1.590	1.934
HER2 Negative vs Positive	0.408	0.391	0.427
KM Survival estimates in %			
Time frame	ACT+	ACT-	All subjects
5 years	86.3(86.2,86.4)	74.2(74.0,74.4)	82.4(82.3,82.5)
10 years	66.0(65.8,66.2)	50.8(50.6,51.1)	61.0(60.8,61.1)
HR (ACT-vs ACT+)			
	HR	95% Wald CI	P value
Multivariate Cox model with backward selection procedure	1.478	1.434, 1.523	<.0001
PS weighted cox model	1.436	1.417,1.456	<.0001

Table 3 HR estimates of mortality for ACT- vs ACT+ stratified by various subgroups



PO5-02-12

Comparison of survival outcomes according to axillary ultrasonography findings and cytology results in early-stage breast cancer patients

Presenting Author(s) and Co-Author(s):

S. Lee. Yonsei University college of Medicine, United States

Purpose: Axillary lymph node dissection and sentinel lymph node biopsy are associated with increased risk of post-surgical complications including lymphedema and recent trials have raised questions about the therapeutic benefit of axillary operation in early-stage breast cancer patients. While treatment options for lymph nodes with negative findings on axillary ultrasonography (AUS) or positive findings on fine needle aspiration biopsy (FNAB) are evident, data regarding lymph nodes that are suspicious on AUS but negative by FNAB are limited. Thus, we aimed to compare clinicopathological characteristics of AUS positive and FNAB negative patients with those of AUS negative or FNAB positive patients.

Materials and Methods: Medical records of patients who underwent breast cancer surgery between January 2010 and December 2017 were reviewed. Patients were grouped into the following three groups: (a) negative findings on AUS, (b) suspicious findings on AUS but negative on FNAB, (c) and FNAB positive. A total of 4,506 patients were included for analysis, with 3,771 patients with no suspicious lymph nodes on AUS, 557 patients who had suspicious AUS findings but were negative on FNAB, and 178 patients with positive findings on both AUS and FNAB. Primary endpoints were disease free survival (DFS) and recurrence free survival (RFS), and secondary endpoint was overall survival (OS).

Results: At a median follow-up period of 92 months, DFS and RFS was significantly higher in the AUS negative group compared to the other two groups (10-year-DFS: 91.6% vs 87.5% vs 75.7%, 10-year-RFS: 95.0% vs 89.9% vs 77.1%, $p < 0.001$). In terms of OS, AUS negative group and the AUS positive and FNAB negative group did not show statistically significant survival difference (10-year-OS: 94.5% vs 92.8%, $p = 0.061$), while the FNAB positive group showed significantly lower survival rates (10-year-OS: 81.8%, $p < 0.001$). Multivariable analysis revealed that not AUS positive and FANB negative but positive FNAB was significantly associated with poor RFS. Moreover, hormone receptor (HR) positive and HER2 negative subtype showed poor DFS and RFS in subgroup analysis.

Conclusion: Early breast cancer patients with suspicious findings on AUS but negative FNAB results had similar OS but inferior DFS and RFS compared to those with negative features on AUS, especially in HR(+)HER2(-) subtype. While further prospective trials are warranted to determine whether additional treatment is necessary, close surveillance is recommended for this subgroup of patients.

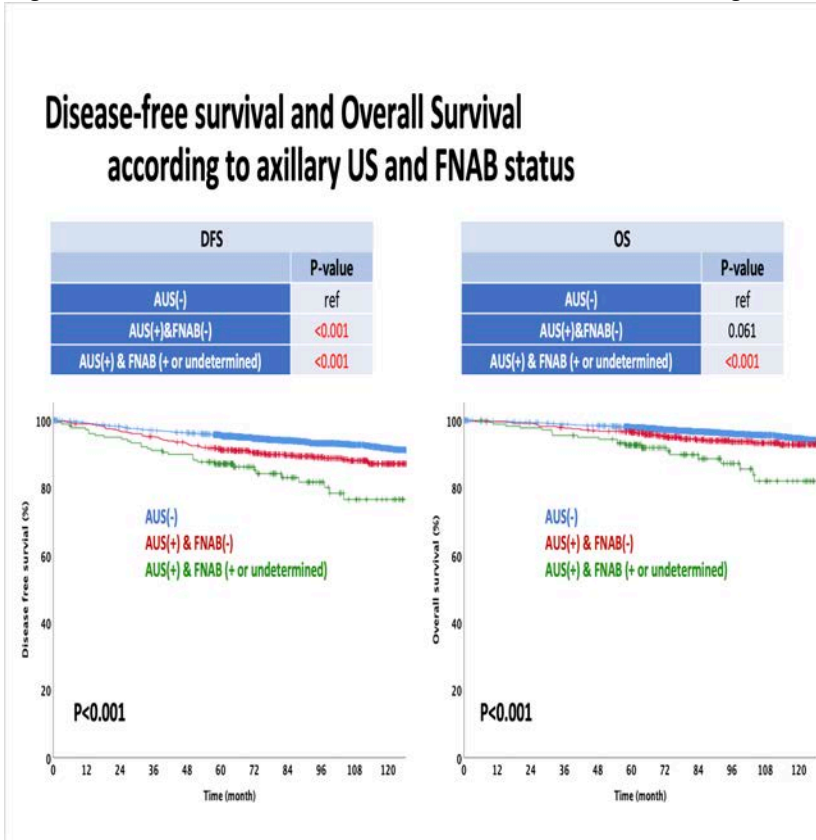
Table1. patients' characteristics

	AUS(-)		AUS(-) & FNAB(-)		AUS(+) & FNAB (positive / cellular paucity / not done)		P
	N	%	N	%	N	%	
Age							0.001
<50	1733	46.0	297	53.3	71	39.9	
≥50	2038	54.0	260	46.7	107	60.1	
T stage							<0.001
1	3036	80.5	348	62.5	92	51.7	
2	735	19.5	209	37.5	86	48.3	
N stage							<0.001
N0	3163	83.9	402	72.2	38	21.3	
N1mi	167	4.4	35	6.3	9	5.1	
N1	368	9.8	89	16	69	38.8	
N2	58	1.5	23	4.1	33	18.5	
N3	15	0.4	8	1.4	29	16.3	
Histologic Grade							<0.001
1	1094	29.0	73	13.1	20	11.2	
2	1965	52.1	270	48.5	89	50.0	
3	712	18.9	214	38.4	69	38.8	
Nuclear Grade							<0.001
1	363	9.8	26	4.7	8	4.5	
2	2359	63.4	255	46.5	90	50.9	
3	998	26.8	267	48.7	79	44.6	
Unknown	51		9		1		
LVI							<0.001
negative	3507	93.0	492	88.3	138	77.5	
positive	264	7.0	65	11.7	40	22.5	
Estrogen receptor							<0.001
negative	695	18.4	210	37.7	38	21.3	
positive	3076	81.6	347	62.3	140	78.7	
Progesterone receptor							<0.001
negative	1389	36.8	305	54.8	70	39.3	
positive	2382	63.2	252	45.2	108	60.7	
HER2							<0.001
negative	3184	84.4	411	73.8	143	80.3	
positive	587	15.6	146	26.2	35	19.7	
Ki-67							<0.001
<20%	2689	72.8	291	53.2	102	56.6	
≥20%	1005	27.2	256	46.8	72	41.4	
unknown	7		10		4		
Subtypes							<0.001
Luminal A	2332	61.8	214	38.4	85	47.8	
Luminal B	756	20.0	134	24.1	56	31.5	
HER2 (+)	250	6.6	85	15.3	15	8.4	
TNBC	493	11.5	124	22.3	22	12.4	
Endocrine therapy							<0.001
No	759	20.1	213	38.2	52	29.2	
Yes	3012	79.9	344	61.8	126	70.8	
Herceptin treatment							<0.001
No	3375	89.5	445	79.9	146	82.0	
Yes	396	10.5	112	20.1	32	18.0	
Adjuvant Chemotherapy							<0.001
No	1931	51.2	131	23.5	45	25.3	
Yes	1840	48.8	426	76.5	133	74.7	
Radiotherapy							<0.001
No	1131	30.0	228	40.9	45	25.3	
Yes	2640	70.0	329	59.1	133	74.7	
Breast operation							<0.001
PM	2501	66.3	264	47.4	71	39.9	
TM	1270	33.7	293	52.6	107	60.1	
Axillary operation							<0.001
SNB	3240	85.9	411	73.8	34	19.1	
SNB+ALND	531	14.1	146	26.2	144	80.9	

Table 2. prognostic factors for overall survival and disease free survival related to axillary US and FNAB status

		Disease Free Survival						Overall Survival									
		Univariate			Multivariate			Univariate			Multivariate						
		HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p				
Age	≥50 vs <50	1.286	1.042	1.587	0.019	1.155	0.932	1.447	0.010	1.596	1.437	2.575	<0.001	1.754	1.293	2.378	<0.001
T stage	2 vs 1	2.237	1.811	2.765	<0.001	1.613	1.269	2.050	<0.001	2.234	1.794	2.900	<0.001	1.619	1.190	2.203	0.002
N stage	0	ref			ref			ref				ref					
	1	1.629	1.264	2.099	<0.001	1.412	1.044	1.906	0.024	1.598	1.416	2.053	<0.001	1.912	1.319	2.774	0.001
	2-3	3.574	2.519	5.072	<0.001	2.317	1.388	3.868	0.001	4.123	2.674	6.358	<0.001	2.869	1.480	5.456	0.002
Histologic Grade	1	ref			ref			ref				ref					
	2	1.798	1.354	2.423	<0.001	1.408	1.021	1.943	0.037	1.791	1.214	2.641	0.003	1.571	1.035	2.386	0.034
	3	2.657	1.868	3.819	<0.001	1.515	1.081	2.201	0.040	2.326	1.800	4.109	<0.001	2.106	1.207	3.719	0.003
LVI	Yes vs No	2.546	1.945	3.336	<0.001	1.889	1.371	2.621	<0.001	2.747	1.982	3.847	<0.001	2.021	1.390	2.938	<0.001
Estrogen receptor	Yes vs No	0.620	0.495	0.778	<0.001	0.854	0.483	1.533	0.958	0.685	0.496	0.885	0.007	0.812	0.375	1.760	0.690
Progesterone receptor	Yes vs No	0.655	0.517	0.797	<0.001	0.909	0.669	1.079	0.748	0.678	0.520	0.884	0.004	0.938	0.644	1.390	0.089
HER2	Yes vs No	0.860	0.753	1.307	0.085	0.676	0.480	1.120	0.128	0.709	0.477	1.054	0.080	0.365	0.153	0.700	0.011
Ki67	≥20% vs <20%	1.746	1.400	2.165	<0.001	1.352	1.032	1.773	0.029	1.534	1.157	2.034	0.003	1.164	0.800	1.636	0.440
Endocrine therapy	Yes vs No	0.624	0.489	0.780	<0.001	0.949	0.545	1.722	0.015	0.656	0.482	0.876	0.004	0.804	0.461	1.304	0.054
Herceptin treatment	Yes vs No	1.855	0.772	1.441	0.070	0.974	0.515	1.623	0.010	0.860	0.543	1.337	0.021	1.520	0.620	3.727	0.040
Adjuvant Chemotherapy	Yes vs No	1.510	1.216	1.874	<0.001	0.940	0.681	1.188	0.456	1.242	0.646	1.632	0.119	0.698	0.491	0.902	0.045
Radiotherapy	Yes vs No	0.574	0.466	0.707	<0.001	0.588	0.384	0.877	0.009	0.582	0.446	0.760	<0.001	0.637	0.326	0.882	0.014
Breast surgery	TM vs PM	2.160	1.755	2.659	<0.001	1.219	0.803	1.812	0.028	2.183	1.671	2.853	<0.001	1.119	0.682	1.837	0.037
FNAB group	AUS(-)	ref			ref			ref				ref					
	AUS(+) & FNAB(-)	1.622	1.224	2.157	0.001	1.116	0.815	1.493	0.458	1.412	0.980	2.035	0.004	1.008	0.692	1.491	0.017
	AUS(+) & FNAB (+)/cell paucity	2.078	2.052	4.290	<0.001	1.461	0.918	2.275	0.094	3.255	2.065	5.131	<0.001	1.306	0.744	2.252	0.032

Figure1. Overall survival and Disease free survival according to axillary US and FNAB status



PO5-02-13

Distinct differences in the prognostic implication of tumor size for invasive lobular carcinoma of breast when compared to invasive ductal carcinoma

Presenting Author(s) and Co-Author(s):

I. Shin. Department of Surgery, Seoul National University Hospital, United States

E. Kang. Seoul National Univ. Hospital, Surgery, Republic of Korea

J. Jung. Seoul National Univ. Hospital, Surgery, Korea, United States

H. Lee. Department of Surgery, Seoul National University Hospital, United States

J. Byeon. Department of Surgery, Seoul National University Hospital, United States

Y. Choi. Medical Research Collaborating Center, Seoul National University Hospital, United States

C. Lim. Seoul National Univ. Hospital, Surgery, Korea, United States

J. Cheun. Seoul Metropolitan Government Seoul National University Boramae Medical Center, United States

H. Kim. Seoul National Univ. Hospital, Surgery, Korea, United States

H. Lee. Seoul National University Hospital, United States

W. Han. Seoul National University Hospital, Seoul, Republic of Korea

H. Moon. Seoul National University, Republic of Korea

Distinct differences in the prognostic implication of tumor size for invasive lobular carcinoma of breast when compared to invasive ductal carcinoma

Ik Beom Shin, Eunhye Kang, Ji-Jung Jung, Hawjeong Lee, Jin Young Byeon, Yunhee Choi, Changjin Lim, Jong-Ho Cheun, Hong-Kyu Kim, Han-Byoel Lee, Wonshik Han, Hyeong-Gon Moon

Purpose

Invasive lobular carcinoma (ILC) is the second common types of breast cancer and its clinicopathological feature and outcomes differ from invasive ductal carcinoma (IDC). However, in terms of survival outcomes, there are conflicting data on the prognostic implication of the ILC when compared to that of IDC. This study aims to evaluate the survival outcomes of patients diagnosed with ILC at single center and compared them with those of IDC.

Methods

We reviewed the data of the 13,034 IDC patients and 935 ILC patients who were treated between January 2005 and December 2022 at Seoul National University Hospital. We investigated the overall treatment outcomes of two histologic types with a special focus on the tumor size and lymph nodes.

Result

ILC exhibited distinct characteristics compared to IDC, including a larger tumor size (2.6 ± 1.8 vs. 1.9 ± 1.1 cm, $p < 0.001$) and a higher hormone receptor positivity (97.4% vs. 79.3%, $p < 0.001$). Additionally, the presence of lymphovascular emboli was lower in ILC (8.0% vs. 24.6%, $p < 0.001$). While IDC patients showed slightly better overall survival (OS) than ILC (10-year OS, ILC 89.9% vs. IDC 91.1%, the difference was not statistically significant ($p = 0.85$)). However, distant metastasis-free survival (DMFS) was significantly higher in ILC (10-year

DMFS, ILC 93.2% vs. IDC 89.9%, $p = 0.001$). Age at diagnosis, tumor size, presence of lymphovascular emboli, high expression of Ki-67, and higher pathologic N stage were poor prognostic markers for ILC. Multivariate analysis for DMFS showed that age, high expression of Ki-67 and higher pathologic N stage were poor prognostic markers for ILC. Tumor size was not an independent prognostic factor for DMFS (HR: 0.92, 95% CI: 0.72-1.17, $p = 0.491$) and for OS (HR: 1.18, 95% CI: 0.99-1.41, $p = 0.060$) in ILC.

Conclusion

Our data suggest that the tumor size, which is a well-known prognostic factor in IDC, carries distinctly different prognostic implication in ILC. These observation indicate that adjuvant treatment decisions based on tumor size can be tailored to different histologic subtypes of breast cancer.

PO5-02-14

Clinical-pathological determinant factors to choose between four or six cycles of adjuvant chemotherapy with docetaxel/cyclophosphamide (TC) in a retrospective real-world cohort of HER2-negative breast cancer patients.

Presenting Author(s) and Co-Author(s):

M. Kraychete. AC CAMARGO CANCER CENTER, Sao Paulo, Sao Paulo, Brazil

M. Cesca. AC Camargo Cancer Center, São Paulo, Brazil, Brazil

G. Almeida. AC CAMARGO CANCER CENTER, United States

L. Santana. AC CAMARGO CANCER CENTER, United States

L. Leite. AC CAMARGO CANCER CENTER, United States

S. Sanches. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil

V. Cordeiro de Lima. AC CAMARGO CANCER CENTER, Sao Paulo, Brazil

R. Pirolli. INSTITUTO DO CÂNCER DE LONDRINA, United States

R. Manea. INSTITUTO DO CÂNCER DE LONDRINA, United States

F. Kaneta. INSTITUTO DO CÂNCER DE LONDRINA, United States

J. Coutinho. INSTITUTO DO CÂNCER DE LONDRINA, United States

L. Vian. Grupo OncoVitta Campo Grande -MS, United States

W. Zeviani. Grupo OncoVitta Campo Grande -MS, United States

M. Reis. Grupo OncoVitta Campo Grande -MS, United States

L. Landeiro. Grupo Oncoclínicas Bahia, United States

C. Mathias. Grupo Oncoclínicas Bahia, United States

G. Nunez. Grupo Oncoclínicas Bahia, United States

T. Santana. Grupo Oncoclínicas Bahia, United States

M. Tavares. AC CAMARGO CANCER CENTER, United States

Introduction: The long-term severe adverse events associated with anthracyclines, including irreversible cardiotoxicity, myelodysplastic syndromes, and therapy-related leukemias, led researchers to question the risk-benefit of anthracycline-based chemotherapy regimens, especially for patients without axillary lymph node involvement, leading to an increasing trend to omit anthracyclines in adjuvant treatment. Docetaxel plus cyclophosphamide (TC) has replaced doxorubicin plus cyclophosphamide (AC) for lower-risk patients that need adjuvant chemotherapy. However, the optimal number of cycles of adjuvant in patients with node-positive or node-negative breast cancer is currently unknown.

Methods: We performed a retrospective cohort study of patients with HER2-negative breast cancer, stage I to III, that received adjuvant docetaxel and cyclophosphamide (TC) for four or six cycles, treated from January 2010 to December 2021. Patients were included from four cancer institutions, both private and public, located in the South, Southeast, and Northeast of Brazil.

Objectives: To investigate the clinical-pathological characteristics and survival of earlystage HER2-negative breast cancer patients who received four (TC4) or six cycles (TC6) of adjuvant docetaxel and cyclophosphamide (TC).

Results: We collected data from six hundred and ninety-eight patients, 98.7% were female with an average age of 52 years, 51.9% were postmenopausal, 14.6% BRCA gene mutation, 66% had some comorbidity, and only 8.4% were not candidates for anthracyclines. Two hundred and twenty-five patients had public and 473 private health insurance. About 13.2% of the patients were hormone receptor negative (HR-) and 86.8% hormone receptor positive (HR+), 57.4% breast-conserving surgery and 77.7% sentinel lymph node (SL). Five hundred sixty-four (80.8%) patients received TC4 and 134 (19.2%) TC6. We observed that patients who received TC 6 had unfavorable prognostic factors such as: (TC4 vs TC6) previous breast cancer (8.7% vs 16.3%) ($p=0.002$), invasive ductal carcinoma (IDC) (73.4 vs 86.7%) ($p=0.009$), histological grade 3 (HG3) (34.9 vs 42.9%) ($p=0.085$) conservative surgery (59.4% vs 53%) ($p=0.144$), SL (80.9% vs 62.2%) ($p=0.001$), Lymph node positive (15% vs 42.3%) ($p=0.001$), pathological stage II (37.5% vs 50%) ($p=0.001$). Treatment completion rates were 96.5% and 84.3% for TC4 and TC6, respectively ($p=0.02$). The incidence of grade 3 or higher toxicity with TC6 (14% vs 21.1%; $p=0.043$). Febrile neutropenia was observed in 6.7% of both groups. Grade 3 or higher neuropathy was most common with TC6 (2.2% vs 10.3%; $p=0.163$). Permanent treatment discontinuation was more frequent in the TC6 group (3.4% vs. 9.8%; $p=0.004$), as well as late toxicity (3.4% vs. 9.2%; $p=0.004$). Ninety-four percent of the patients completed the proposed cycles of chemotherapy, 72% received adjuvant radiotherapy and 85.4% received adjuvant hormone therapy, with 42% of these receiving an aromatase inhibitor for 5 years. The median follow-up of the entire cohort was 61 months. There was no difference in the 5-year DFS (77.5% vs. 64.7%; $p=0.159$) or the 5-year OS (89.5% vs. 70.5%; $p=0.06$) between patients treated with TC4 and TC6.

Conclusion: TC6 was commonly used for patients with unfavorable prognostic factors as history of previous breast cancer, (IDC), HG III, lymph node positive and stage II. Patients who received TC6 had less chance of completing the treatment and more severe toxicity, especially late peripheral neuropathy. There was no difference in DFS or OS.

PO5-03-01

Clinical outcomes of breast-conserving surgery under local anesthesia versus general anesthesia for breast malignancies

Presenting Author(s) and Co-Author(s):

H. Lee. Department of Surgery, Seoul National University Hospital, United States

H. Jo. 1. Department of Surgery, Seoul National University Hospital and College of Medicine, Seoul, Korea, United States

E. Kang. Seoul National Univ. Hospital, Surgery, Republic of Korea

J. Jung. Seoul National Univ. Hospital, Surgery, Korea, United States

I. Shin. Department of Surgery, Seoul National University Hospital, United States

J. Byeon. Department of Surgery, Seoul National University Hospital, United States

C. Lim. 1. Department of Surgery, Seoul National University Hospital and College of Medicine, Seoul, Korea, United States

H. Kim. Seoul National Univ. Hospital, Surgery, Korea, United States

H. Moon. Seoul National University, Republic of Korea

W. Han. Seoul National University Hospital, Seoul, Republic of Korea

H. Lee. Seoul National University Hospital, United States

Clinical outcomes of breast-conserving surgery under local anesthesia versus general anesthesia for breast malignancies Hwajeong Lee, Hyunjong Jo, Eunhye Kang, Ji-Jung Jung, Ik Beom Shin, Jin Young Byeon, Changjin Lim, Hong-Kyu Kim, Hyeong-Gon Moon, Wonshik Han, Han-Byoel Lee Purpose With the increase in the incidence and proportion of stage I and in situ breast cancer, there is a growing trend for de-escalation of surgery. Several ongoing trials are evaluating the omission of sentinel lymph node biopsy (SLNB), including the SOUND trial, which showed no difference in disease-free survival. Breast-conserving surgery (BCS) under local anesthesia (LA) could be performed when no axillary surgery is necessary and could potentially reduce the physical and psychological burden on patients caused by surgery compared to BCS under general anesthesia (GA). We aim to compare the clinical outcomes between BCS under LA versus GA in patients who did not require SLNB. Methods We retrospectively collected and analyzed data from 116 patients who received BCS under LA from January 2021 to June 2023 and 260 patients who received BCS under GA in 2022. Clinical tumor size, pathologic tumor size (both including in situ carcinoma), surgical specimen volume, resection margin (RM) positivity, re-excision rate, operation time, and length of hospital stay were compared. Result There was no difference between LA and GA in terms of age, BMI, and proportion of in situ cancer. The LA group had a higher proportion of tumors with clinical tumor size ≤ 2 cm. The LA group had a higher RM positive rate (11.2 vs. 5.4%, $p=0.043$) and re-excision rate (12.9 vs 3.5%, $p < 0.001$). According to tumor size, the higher RM positivity was only observed in clinical tumor size >1 cm & ≤ 2 cm group ($p=0.039$). In patients whose clinical tumor size ≤ 2 cm was upgraded to pathologic tumor size > 2 cm, there was no difference in RM positivity between the two groups (5/18 [27.8%] vs. 4/34 [11.8%], $p=0.247$). A smaller surgical specimen volume was excised under LA (22.01 ± 14.11 vs 65.67 ± 48.43 cm³, $p < 0.001$). The overall operation time (64 ± 16 vs 73 ± 22 min, $p < 0.001$) and hospital stay (1 ± 0 vs 4 ± 1 days, $p < 0.001$) was shorter in the LA group Conclusion Breast-conserving surgery under LA showed a higher RM positive rate, of which most were in patients with discordance in clinical and pathologic tumor size. Although this resulted in a higher re-excision rate, the smaller surgical specimen volume, shorter operation time, and hospital stay for BCS under LA could positively

impact patient recovery and quality of life. The benefits of LA should be considered when evaluating the de-escalation of surgery for breast malignancies.

PO5-03-02

Ductal carcinoma in situ: An excess regard of the axilla?

Presenting Author(s) and Co-Author(s):

A. Amorim. Perola Byington Hospital, United States

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

M. Ramos. Perola Byington Hospital, United States

R. COELHO LOPES. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

L. Damous. Hospital do Servidor Público Estadual – Francisco Morato de Oliveira, São Paulo, Brazil., United States

L. Gebrim. Perola Byington Hospital, United States

Abstract: Ductal Carcinoma in Situ (DCIS) is a malignant proliferation of the epithelial inside the breast duct, which does not invade the myoepithelial layer and, therefore, does not have the capacity to generate metastases. [1]. However, an upstaging after surgery is possible, since there may be a concomitant invasive lesion that was not diagnosed in the pathological examination from biopsy, being discovered only after the surgical procedure [1]. In the pre-screening mammography era, DCIS was diagnosed more commonly in symptomatic women presenting with a palpable nodule, papillary flow, or through an incidental finding on a breast biopsy [2], accounting for 1-2% of cancer cases. [3]. After the advent of mammographic screening, the incidence has considerably increased among asymptomatic women with mammographic changes such as calcifications. [4]. Nowadays the diagnosis of DCIS corresponds to 20-25% of biopsies secondary to screening mammographic changes. [1]. As we do know that the chance of axillary metastasis is potentially null, old series where axillary dissection (AD) was performed ipsilateral to the index tumor, axillary involvement was observed in less than 1% of cases [9]. **Objectives:** Our objective in this study was to describe in a single breast cancer reference center the surgical treatment of patients diagnosed with DCIS (mastectomy or breast conservative surgery – BCS). **Methods:** A retrospective analysis was made using the Pérola Byington Hospital's database, from January 2011 to December 2019. During this period, 11,373 cases of breast cancer were treated in the institution and 812 (7.4%) were DCIS. Data was available and we could analyze 494 patients who underwent vacuum-guided biopsy guided by mammography or ultrasound and were diagnosed with DCIS and underwent surgical treatment at the Hospital. We grouped the patients into 3 age groups: under 40, 40-49, and 50 and over. In all groups, we had patients who underwent SNB using the patent blue technique or AD and were evaluated using the H&E method. It is not part of the Institutional protocol to perform IHC in axillary lymph nodes. We had also evaluated the type of surgery (BCS or mastectomy) in each age group. **Results:** DCIS was diagnosed through mammographic alterations in 62% of all cases and nuclear grade 2 was the most common, with 47%, followed by grade 3 and 1, 46% and 4%, respectively. In 2% of cases the data was missing. Comedoconecrosis was present in 78% of our specimens. BCS was the most frequently surgery performed (73% of cases), with the axillary approach being performed in 35% of these patients (32% for SNB and 3% for AD). While 27% of patients underwent radical surgery and in this group 92% were submitted to axillary approach (70% SNB and 22% AD). In the group of patients younger than 40 years, 74% of patients (17 out of 23 in total) underwent an axillary approach regardless of the type of surgery. When evaluating the predetermined age groups, we saw that most of our patients were 50 years or more (69%), followed by patients between 40-49 years (26%) and 5% in patients under 40 years. In 3% of cases (16 in 494) we reclassified the lesion as invasive carcinoma. None of them had a lymph node involved by

malignant cells after surgery and that's include the cases reclassified as invasive carcinoma. Conclusion: The results obtained in this analysis showing no axillary involvement will make us rethink the indications for the concomitant surgical approach of the breast and the axilla in cases with a diagnosis of DCIS as a way to reduce the axillary surgical overtreatment. It was not our goal to compare the costs and complications of each method of diagnosis and the prognostic factors after the treatment of DCIS.

PO5-03-03

Nomogram for predicting brain metastasis in early-stage breast cancer patients

Presenting Author(s) and Co-Author(s):

A. Singareeka Raghavendra. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

N. Kotecki. Jules Bordet Institut, United States

K. Jennings. University of Texas MD Anderson Cancer Center, United States

O. Amato. Jules Bordet Cancer Institute, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

A. Awada. Jules Bordet Cancer Institute, United States

N. Ibrahim. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Nomogram for predicting brain metastasis in early-stage breast cancer patients Background: Brain metastasis is a significant concern for patients with early-stage breast cancer, as it can have a detrimental impact on survival and quality of life. Clinical and pathological characteristics of the primary tumor may be modeled into a nomogram that can predict the risk of brain metastasis. The goal is to create a nomogram and clinical calculator to assist in selection of patients with high risk of brain metastasis to enrich patient population for accrual on clinical trials for the purpose of preventing or delaying emergence of brain metastasis, at an early stage of their disease. Methods: We reviewed all early-stage breast cancer patients (stages I to III) N=40290 from the University of Texas MD Anderson Cancer Center, Houston, TX, from 1/1/1997 to 5/8/2020. We utilized multiple predictive statistical models to identify the most relevant variables and optimal predictive criteria. Variables for the model included patient age, tumor characteristics (such as grade, hormone receptor and HER2 status) and medical treatment (such as chemotherapy and endocrine therapy). The Receiver Operating Characteristic (ROC), and its AUC (area under the curve) was used to demonstrate the performance of the multivariate model to predict the occurrence of brain metastasis at different time points (1 year, 2 years, and 5 years), distinguishing between patients who develop brain metastasis in a time-dependent manner and those who do not. Results: The results showed the following clinical variables to be statistically significant in predicting brain metastasis: younger age, high estrogen and progesterone receptor percentage, higher tumor size; use of aromatase inhibitor therapy, and use of selective estrogen receptor modulator therapy were associated with a decreased risk of brain metastasis. Higher grade, Ki-67 levels, HER2-positive status, lymphovascular invasion and the use of chemotherapy was associated with an increased risk. The AUC values for the prediction of brain metastasis at different time points are as follows: 0.85 at 1 year, 0.83 at 2 years, and 0.82 at 5 years. These values indicate that the multivariate model has good discriminative ability, with higher values indicating a better predictive performance. An AUC of 0.85 suggests that the model has a high probability of correctly distinguishing between patients who will develop brain metastasis and those who will not at 1 year. Conclusions: Our predictive tool holds promise in assisting clinicians when making informed, personalized care decisions for patients at risk of developing brain metastasis. The model will be validated using independent patient cohorts from Institut Jules Bordet, Brussel, Belgium, to assess their accuracy and reproducibility. Continued research and validation will further refine these models, increasing their reliability and their clinical/clinical research applicability.

PO5-03-05

Rethinking the value of pathologic complete response rate for the survival outcomes of early triple-negative breast cancer treated with neoadjuvant chemotherapy: a systematic review and network meta-analysis

Presenting Author(s) and Co-Author(s):

X. Qiao. Peking University People's Hospital, Beijing, China (People's Republic)

T. Hu. Breast Center - Peking University People's Hospital, United States

B. Liang. School of Public Health, Peking University, United States

S. Wang. Breast Center - Peking University People's Hospital, Beijing, United States

Background: Neoadjuvant chemotherapy (NACT) has been more frequently used in breast cancer, but it's controversial whether NACT or adjuvant chemotherapy (ACT) is more effective in improving survival outcomes for triple-negative breast cancer (TNBC) patients. Recent studies also proposed pathologic complete response (pCR) could not be a robust surrogate for survival outcomes in certain types of breast cancer. To address these questions, a general meta-analysis and a network meta-analysis (NMA) were conducted to compare the survival outcomes of patients with pCR, non-pCR after NACT and ACT. The cut-off pCR rate was also declared to indicate when NACT produces equivalent survival outcomes to ACT (Registration: PROSPERO CRD42022336732).

Methods: Databases including PubMed, Embase, Web of science and Cochrane library were searched up to June 2023 to investigate studies comparing NACT and ACT, as well as randomized controlled trials (RCTs) comparing different regimens in NACT or ACT settings in early operable TNBC patients. Heterogeneity was assessed using χ^2 based Q-test and I^2 , combined with hazard ratios (HRs) with 95% confidence intervals (CI) computed for overall survival (OS), and disease-free survival (DFS, or event-free survival). The NMA with a Bayesian framework was conducted using both random and fixed effect model. The Weighted Least Square method and the Least Absolutely Deviation method were used to determine the cut-off pCR rates of OS and DFS.

Results: A total of 35 studies involving 21 RCTs and 34143 TNBC patients were included. The general meta-analysis comprised 14 cohort studies. Eight high-quality cohort studies with propensity score matching and 21 RCTs were included in NMA. The pooled pCR rate for NACT was 42.2% (95% CI 37.8%-46.8%). Overall, the NACT cohort showed significantly worse OS and DFS than ACT cohort (HR=1.67, 95% CI 1.22-2.31; HR=1.37, 95% CI 1.14-1.64). However, patients with pCR after NACT showed improved OS than ACT (HR=0.58, 95% CI 0.50-0.66), while the patients without pCR after NACT had poorer OS than ACT (HR=2.03, 95% CI 1.88-2.19). As for DFS, there was no statistically difference between pCR after NACT and ACT groups (HR=1.04, 95% CI 0.63-1.73), while patients without pCR after NACT had significantly worse DFS than ACT (HR=2.65, 95% CI 1.98-3.55). From the NMA, the OS and DFS were better when combining modern target therapy such as Bevacizumab, PARPi, and PD-1/PD-L1 inhibitor, but not achieving pCR completely negated the benefits of newer drugs. Adding adjuvant capecitabine to patients not achieving pCR seemed to favor the OS. It was predicted that when the pCR rates were 64.7% and 44.6%, respectively, the OS and DFS of patients treated with NACT would be the same as those of patients treated with ACT.

Conclusions: Higher pCR rate after NACT was associated with improved OS compared with ACT in TNBC patients. However, failure to achieve pCR after NACT resulted in worse survival

outcomes than ACT. NACT had similar survival outcomes with ACT only when the pCR rate was at least 44.6%. The development of effective NACT regimens is beneficial for breast cancer patients.

PO5-03-06

Optimizing therapeutic regimens via digital twins to improve triple negative breast cancer response to neoadjuvant therapy

Presenting Author(s) and Co-Author(s):

C. Wu. UT Austin, Texas, United States

E. Lima. UT Austin, Texas, United States

C. Stowers. UT Austin, United States

Z. Xu. MD Anderson Cancer Center, Texas, United States

C. Yam. Breast Medical Oncology Department, The University of Texas MD Anderson Cancer Center, United States

J. Son. University of Texas MD Anderson Cancer Center, United States

J. Ma. University of Texas MD Anderson Cancer Center, United States

G. Rauch. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Yankeelov. UT Austin, United States

Introduction:

Neoadjuvant systemic therapy (NAT) has been the standard-of-care of stage II-III, locally advanced triple-negative breast cancer (TNBC). However, about 50% of TNBC patients achieve a pathological complete response (pCR) to conventional neoadjuvant chemotherapy (NAC)¹. Recently approved combination of NAC with the immunotherapy pembrolizumab, has improved the pCR rate by 7.5%², although with a 44% risk of immune-related adverse reaction³. Aside from the need to develop new therapies with higher efficacy and lower toxicity, a critical barrier to improving TNBC response is the lack of rigorous ways to personally tailor therapeutic regimens. We seek to address this challenge by employing digital twins (i.e., mathematical models that provide virtual representation of individual patients and predict the changes at future time points) to systematically evaluate individual TNBC patient's response to different NAT regimens, thereby patient-specifically optimizing treatments.

Methods:

A TNBC cohort (n = 139) from the ARTEMIS trial (NCT02276433)⁴ was used for this study. All patients received 4 cycles of Adriamycin/Cytoxan (A/C) every 2 weeks, followed by 12 cycles of weekly Taxol or experimental therapy in Phase II trials. All patients had surgery after NAT and post-surgical pathology to assess response status. For each patient, longitudinal MRIs were collected before, during, and after A/C.

We have developed digital twins to integrate the longitudinal MRIs with a mechanism-based model to accurately predict TNBC response⁵. The model was based on a reaction-diffusion equation that describes the change in tumor cellularity due to migration, proliferation, and drug-induced death. With parameters personalized using MRIs, the patient-specific model (i.e., digital twin) significantly improved the accuracy to predict pCR⁵.

We investigated patient-specific treatment optimization on 37 (19 pCR, 18 non-pCR) chemo-sensitive patients ($\geq 70\%$ volume decrease after A/C) who received only NAC. We evaluated the effect of altering the A/C/Taxol schedules on patient response. Specifically, each patient's

digital twin was used to predict the patient's response to 128 clinically reasonable schedules of A/C/Taxol; i.e., 8 candidate A/C schedules combining with 16 candidate Taxol schedules (Table 1). The predicted response (pCR or non-pCR) from each alternative schedule was compared to the patient response from the actual treatment.

Results:

Without changing the total dose, shortening the duration of A/C/Taxol administration increased the treatment efficacy. The effectiveness of altering the schedules varied substantially in different patients. In particular, 8 patients who had non-pCR responses to their actual treatment were predicted to achieve pCR with the dense-dose Taxol (i.e., 4 cycles Taxol, 2 weeks per cycle), indicating a 21.62% improvement of pCR rate in the cohort.

Discussion and conclusion:

The preliminary results with our digital twin approach provided a unique opportunity of improving TNBC response to NAT through patient-specific optimization of therapeutic schedules. The ongoing effort focuses on accounting for toxicity and investigating the effects of altering therapy types and doses in combination with the schedules on the patient response.

[1] Spring et al., Clin Cancer Res, 2020.

[2] Schmid et al., NEJM, 2022.

[3] Shah et al., Clin Cancer Res, 2022.

[4] Yam et al., Clin Cancer Res, 2021.

[5] Wu et al., Cancer Res, 2022.

Table 1. Candidate therapeutic schedules

Treatment	Schedule strategy	
	No. of cycles	Duration of therapy (days) [†]
A/C	4	56, 60, 64, 68, 72, 76, 80, 84
Taxol	12	56, 60, 64, 68, 72, 76, 80, 84
	4	56, 60, 64, 68, 72, 76, 80, 84

[†]NAT cycles are evenly separated during a given duration. For example, a therapeutic schedule of “No. of cycles = 4, duration of therapy = 84 days” is the same as “4 cycles, 3 weeks per cycle”.

PO5-03-07

Impact of age and stage on pathologic complete response rates in Black vs White patients with triple negative breast cancer

Presenting Author(s) and Co-Author(s):

M. Sheen. Ochsner Clinic Foundation, New Orleans, Louisiana, United States

C. Taylor. Ochsner Health, United States

R. Cattie. Ochsner Health, United States

M. Bratton. Ochsner Health, United States

M. Lakey. Ochsner Health, United States

V. Chung. Ochsner Health, New Orleans, Louisiana, United States

E. Biggs. Ochsner Health, United States

Background

Triple-negative breast cancer (TNBC) accounts for approximately 10-15% of breast cancers. Women with TNBC have worse survival outcomes, increased rates of relapse, and distant metastasis as compared to women with non-TNBC. Regardless of subtype, Black women have worse breast cancer outcomes than White women. Early stage treatment of TNBC has focused on neoadjuvant therapy (NACT) with a goal of achieving a pathologic complete response (pCR), which is associated with longer event-free survival and overall survival in TNBC patients. NACT with pembrolizumab was presented at the San Antonio Breast Cancer Symposium in December 2019 and FDA approved in July 2021. The Keynote-522 Trial found that patients who received NACT + pembrolizumab were more likely to achieve pCR than women who received NACT + placebo, regardless of stage. The KEYNOTE-522 trial did not examine race or age differences in treatment efficacy. Since TNBC disproportionately affects younger women and Black women, optimizing pCR rates in these groups is essential. Our objective is to examine racial differences in pCR rates by cancer stage and age among patients with TNBC who completed NACT/pembrolizumab.

Methods

Patient records from Ochsner Health, a regional network, were reviewed for those with early stage TNBC who had completed treatment with NACT/ pembrolizumab from January 2020 to January 2022. Exclusion criteria included no surgical treatment for TNBC, unknown receptor status, and age < 18 years-old. Chi-square and Fisher's Exact tests were used to examine the relationship between race and pCR stratified by stage at diagnosis and age. Risk ratios and 95% confidence intervals were also estimated to examine the strength of these relationships.

Results

We identified 92 patients with TNBC who completed treatment with NACT/ pembrolizumab and underwent surgery. 52 patients (56%) were Black and 40 patients (43%) were White. 53.85% of Black patients had pCR and 67.50% of White patients experienced pCR ($p=0.19$). Among patients with stage III disease, only 37.50% of Black patients experienced pCR compared to 69.23% of White patients ($p=0.09$). Notably, Black patients were 46% less likely to experience pCR than = White patients (RR: 0.54, 95% CI: 0.28-1.02) in the stage III group. Among patients less than 50 years of age, 41.18% of Black patients experienced pCR compared to 84.21% of White patients ($p=0.01$), where younger Black patients were 51% less likely to experience pCR than younger White patients (RR: 0.49, 95% CI: 0.27-0.89) There were no observed racial differences in pCR rates for stage I/II patients ($p=1.00$) or patients aged 50 years or older

(p=0.64).

Discussion

These data demonstrate that Black women are at a pCR rate disadvantage receiving NACT/pembrolizumab. This is primarily driven by advanced stage and young age. Black patients with stage III cancers had significantly lower pCR rates than their White counterparts after having received the same treatment. Additionally, young patients who are Black have significantly lower pCR rates. For older patients and those with stage I/II disease, there was no statistically significant difference in pCR rates between Black vs White race.

Conclusion

While NACT/pembrolizumab offers overall increased rates of pCR, Black women, especially those who are young or with more advanced disease at presentation, still have worse outcomes. Further research is needed to determine underlying predictors or alternative treatments to benefit these populations.

Table 1

	Pathological Complete Response		P-value
	Yes n (%)	No n (%)	
Stage I/Stage II			1.00
Black	18 (66.67)	9 (33.33)	
White	18 (66.67)	9 (33.33)	
Stage III			0.09*
Black	9 (37.50)	15 (62.50)	
White	9 (69.23)	4 (30.77)	
<50 years old			0.01*
Black	7 (41.18)	10 (58.82)	
White	16 (84.21)	3 (15.79)	
50+ years old			0.64
Black	20 (58.02)	14 (41.18)	
White	11 (51.38)	10 (47.62)	

Distribution of Pathological Complete Response Following NACT/pembrolizumab treatment (Nf91)

Table 2

	Crude Risk Ratio	95% CI
Age		
<50 years old		
Black vs. White	0.49	0.27-0.89
50+ years old		
Black vs. White	1.12	0.68-1.84
Stage		
Stage I/Stage II		
Black vs. White	1.00	0.32-3.10
Stage III		
Black vs. White	0.54	0.28-1.02

Crude Risk Ratios for the Relationship between Race and Pathological Complete Response by Age and Stage (Nf92)

PO5-03-08

Detection and quantification of triple-negative breast cancer (TNBC) across ethnicities through analysis of cell-free DNA (cfDNA) methylation

Presenting Author(s) and Co-Author(s):

W. Cance. GRAIL, LLC, Menlo Park, CA, USA, United States

E. Liu. The Jackson Laboratory for Genomic Medicine, United States

M. Antonio. GRAIL, LLC, Menlo Park, CA, USA, United States

T. Shaver. GRAIL, LLC, Menlo Park, CA, USA, United States

S. Shih. GRAIL, LLC, Menlo Park, CA, USA, United States

B. Chu. GRAIL, LLC, Menlo Park, CA, USA, United States

K. Kurtzman. GRAIL, LLC, Menlo Park, CA, USA, United States

L. Newman. Weill Cornell Medicine, New York, New York, United States

Introduction: Triple-negative breast cancer (TNBC) is an aggressive subtype contributing to race-related outcome disparities in breast cancer. These disparities are partly explained by the higher burden of TNBC in Black women, less access to new mammography technologies, and further compounded by limited efficacy of screening mammography in early detection of TNBC (Newman L & Mitchell E, J Natl Med Assoc 2023). To better understand these disparities, we compared results from the Galleri® multi-cancer early detection (MCED) test and the tumor methylated fraction (TMeF) tumor quantification algorithm in a population of TNBC patients across different stages and self-reported ethnicities (SRE).

Methods: Within the case-control Circulating Cell-free Genome Atlas third substudy, we performed MCED testing and TMeF estimation in 507 women with breast cancer, 84 of whom had TNBC. The MCED test detects methylation patterns associated with circulating tumor DNA (ctDNA) to identify a common cancer signal and predict a cancer signal of origin. Tumor methylated fraction (TMeF) is an estimate of ctDNA abundance using machine learning models trained on whole-genome bisulfite sequencing of tumor biopsy tissue. We used SRE to compare results between non-Hispanic Black and White participants and those of other (Hispanic, Asian, Pacific Islander) or unreported ethnicities for both cancer detection by MCED test and ctDNA abundance estimation by TMeF.

Results: In Black women, 19 (49%) of 39 diagnosed breast cancers were TNBC, compared to 58 (15%) of 396 breast cancers in White women and 7 (13%) of 52 breast cancers in women of other or unreported ethnicities. The MCED test did not detect Stage I TNBC (Table 1). In patients with Stage II-IV TNBC, the MCED test successfully detected a cancer signal in 16 (94%) of 17 Black women, 31 (72%) of 43 White women, and 6 (100%) of 6 women of other or unreported ethnicities (Table 1). When we examined the TMeF in these patients using a two-way ANOVA, we found a significant difference in mean TMeF by cancer stage ($p < 0.001$) but no significant difference in mean TMeF between SRE groups ($p = 0.09$) with the distribution of TMeF (Table 2). The ANOVA additionally found a significant interaction between cancer stage and SRE ($p < 0.001$) that could represent an impact of stage on TMeF that varied by SRE or differences in cancer stage distribution by SRE.

Conclusions: In this pilot study, we observed that MCED testing was effective in detecting Stage II, III, and IV TNBC across SRE. These findings, in combination with the association of estimated ctDNA abundance with cancer stage but not patient SRE, provide hypothesis-

generating evidence that analysis of methylation signals from across the genome can provide meaningful TNBC screening/detection information, independent of self-reported race/ethnicity.

Table 1. MCED cancer detection rate by stage and SRE among TNBC patients.

Stage	Black, non-Hispanic (n = 19)		White, non-Hispanic (n = 58)		Other/Unreported (n = 7)	
	Detected/ Total	% (95% CI)	Detected/ Total	% (95% CI)	Detected/ Total	% (95% CI)
I	0/2	0% (0-80)	0/15	0% (0-25)	0/1	0% (0-95)
II	10/11	91% (57-100)	22/33	67% (48-81)	4/4	100% (40-100)
III	3/3	100% (31-100)	8/9	89% (51-99)	1/1	100% (5.5-100)
IV	3/3	100% (31-100)	1/1	100% (5.5-100)	1/1	100% (5.5-100)

Table 2. Tumor methylated fraction (TMeF) by stage and SRE among TNBC patients.

Stage	Black, non-Hispanic	White, non-Hispanic
I	5.60 ± 2.11	21.8 ± 45.6
II	7,240 ± 10,200	2,760 ± 5,950
III	5,980 ± 8,260	13,000 ± 19,200
IV	65,800 ± 37,200	3,900 ± 0
<i>Mean TMeF ± Standard Deviation in parts per million (ppm) reported</i>		

PO5-03-09

Concurrent versus sequential use of adjuvant capecitabine and radiation in patients with triple-negative breast cancer with residual disease: A retrospective review

Presenting Author(s) and Co-Author(s):

C. Yu. Icahn School of Medicine at Mount Sinai, United States

A. Kessler. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

T. Shao. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

S. Cate. Department of Surgery, Icahn School of Medicine at Mount Sinai, United States

P. Klein. Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, United States

M. Chadha. Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, United States

Background:

The CREATE-X trial demonstrated benefit of adjuvant capecitabine for patients with triple-negative breast cancer (TNBC) with residual disease after neoadjuvant chemotherapy and surgery. In clinical practice however, physician discretion determines the sequence of capecitabine relative to radiation therapy (RT), as well as the treatment dose. Therefore, our study aimed to assess the treatment patterns and tolerance of capecitabine and RT in patients with residual TNBC at our institution after publication of the CREATE-X study.

Methods:

This was a retrospective IRB-approved study that included patients with TNBC who had residual disease following neoadjuvant chemotherapy and surgery and received both adjuvant loco-regional RT and capecitabine at our institution between July 1, 2017 and June 30, 2021. Patient characteristics and treatment regimens were abstracted from medical charts. For this study, we defined optimally-delivered capecitabine to be a starting dose of 1250 mg/m² twice per day on days 1-14 every 3 weeks as per the CREATE-X trial, and all planned cycles completed without dose reductions or discontinuation. RT was defined as optimally delivered when patients completed the prescribed dose without a treatment break of > 1 week or discontinuation of planned RT. We used descriptive statistics to report our observations.

Results:

Thirty-four patients met our eligibility criteria. The median age at diagnosis was 56 years (range: 30-77 years) and the median follow up time was 48 months. Of the 27 patients who received sequential RT and capecitabine, the median starting dose of capecitabine was 1000 mg/m². Of the 7 patients who received concomitant RT and capecitabine, the median starting dose during RT was 800 mg/m²; after completion of RT, patients completed 6 additional cycles of capecitabine at a median dose of 1000 mg/m². We observed a greater residual breast tumor burden in patients prescribed concomitant RT and capecitabine; 71.4% were ypT2/T3 compared to only 18.5% ypT2/T3 in sequentially treated patients (OR 11.0; 95% CI, 1.64 to 73.97; p=0.05). There was no significant difference in the positive lymph node status between the 2 groups (42.9% and 40.7%, respectively).

A median RT dose of 50 Gy in 25 fractions was delivered in both schedules. No patients discontinued RT due to intolerance. In the 27 sequentially treated patients, the majority (73%) received RT before capecitabine. Among these, 14 patients (51.9%) required a dose reduction

and 6 patients (22.2%) discontinued capecitabine due to intolerance. Of the 7 patients receiving concomitant RT and capecitabine, 2 patients (28.5%) discontinued capecitabine due to intolerance (one during RT and one following completion of RT). The concomitant RT and capecitabine regimen was not associated with higher odds of prematurely discontinuing capecitabine compared to the sequential schedule (OR 1.15; 95% CI, 0.18 to 7.34).

Conclusion:

In this study, most patients received a sequential schedule and those with a higher residual disease burden were more likely to be prescribed concomitant RT and capecitabine. The starting dose of capecitabine in both schedules was lower than the starting dose in the CREATE X trial but consistent with the practice standard in the US. Our early experience did not demonstrate any signal to suggest a difference in the tolerance of capecitabine administered sequentially or concurrently. Further studies are needed to evaluate the optimal sequence of RT and capecitabine in the adjuvant setting.

PO5-03-10

The prognostic role of androgen receptor status in patients with triple negative breast cancer with an associated ductal carcinoma in situ.

Presenting Author(s) and Co-Author(s):

M. Merckx. Kuleuven, ANTWERPEN (2018), Belgium

Micaëlle Merckx¹, Hava Izci^{2,3}, Annouschka Laenen⁴, Kristien Borremans^{1,3}, Christine Desmedt³, Hans Wildiers^{2,5}, Giuseppe Floris^{2,6}, Patrick Neven¹ ¹Department of Gynaecology and Obstetrics, University Hospitals Leuven, Leuven, Belgium ²Department of Oncology, University Hospitals Leuven, Leuven, Belgium ³Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium ⁴Leuven Biostatistics and Statistical Bioinformatics Centre, KU Leuven, Leuven, Belgium ⁵Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium ⁶Department of Pathology, University Hospitals Leuven, Leuven, Belgium

Abstract Background Triple negative breast cancer (TNBC) is defined by the lack of expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. Prognostic immunohistochemical biomarkers in TNBC have been studied in recent years such as the androgen receptor (AR) which is expressed in 10-40% of TNBC. However the prognostic value of AR expression is not clear. Here, we studied the prognostic significance of AR expression in combination with the presence of a ductal carcinoma in situ (DCIS). Considering DCIS is a precursor of invasive ductal carcinoma, we hypothesize that TNBC with co-existing DCIS and presence of AR expression is less aggressive and patients are older at diagnosis. **Methods** We analyzed data retrospectively from all patients with stage 1-3 TNBC who underwent primary surgery and adjuvant chemotherapy in the University hospitals Leuven, between 01-01-2000 and 31-12-2017. Patient and tumor related characteristics were compared between two subgroups, one with co-existing DCIS and one with pure invasive carcinoma, without co-existing DCIS. AR expression was assessed by immunohistochemistry (IHC). We used AR expression in $\geq 1\%$ and $\geq 10\%$ of cells as cut-off scores. The prognostic role of the expression of AR in combination with a co-existing DCIS was analyzed, using the distant metastasis rate as primary endpoint. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Secondary endpoints were associations of AR expression with clinical-pathological characteristics, time between diagnosis and metastasis, and disease specific mortality. **Results** In the 426 included patients with TNBC, co-existing DCIS was present in 66.7%; AR expression was expressed $\geq 1\%$ in 29.3% and $\geq 10\%$ in 21.4% of cases. Median age at diagnosis was 51 years (range: 22-85y). Age at diagnosis was independent of DCIS, dependent of AR expression; in DCIS positive cases, median age was 49 years if AR negative (IHC $< 1\%$), 53 years if AR positive (IHC $\geq 1\%$), and 56 years if AR positive (IHC $\geq 10\%$) ($p=0.006$). In contrast in DCIS negative cases, median age was 51 years if AR negative (IHC $< 1\%$), 51 if AR positive (IHC $\geq 1\%$), and 51 years if AR positive (IHC $\geq 10\%$) ($p=0.895$). AR expression was DCIS dependent and was $\geq 1\%$ in 34.9% and $\geq 10\%$ in 25.0% of patients in the DCIS group compared to 18.3% and 14.1% in the non-DCIS group ($p=0.001$ and $p< 0.001$ respectively). In both subgroups there was no significant difference for AR positive versus AR negative cases in lymph node involvement, tumor grade, tumor size and Nottingham Prognostic Index. Patients with a coexisting DCIS and AR expression did not have a different incidence of distant relapse compared to AR negative cases (AR $\geq 1\%$: $p=0.2803$ and AR $\geq 10\%$: $p=0.5527$). Of patients with coexisting DCIS, 12.0% (95% CI: 7.8; 17.1) in the AR negative group, 8.2% (95% CI: 3.8; 14.6) in the AR $\geq 1\%$ group and 7.1% (95% CI: 2.6; 14.7) in the AR $\geq 10\%$ group, had distant relapse within 2 years. **Conclusion**

In patients with TNBC, AR expression is associated with older age in case of co-existing DCIS and patients with co-existing DCIS are more frequently AR positive. In patients with co-existing DCIS, there was no significant difference in distant relapse between AR negative and AR positive cases.

PO5-03-11

Ultra-low dose nivolumab added to dose-dense, cisplatin-based neoadjuvant chemotherapy in locally advanced, borderline operable triple negative breast cancer: A matched case-control study.

Presenting Author(s) and Co-Author(s):

Z. Thomas. Christian Medical College Vellore, Tamil Nadu, India
J. Georgy. Christian Medical College Vellore, Tamil Nadu, India
A. Singh. Christian Medical College Vellore, Tamil Nadu, India
A. Joel. Christian Medical College Vellore, Tamil Nadu, India
D. Thumaty. Christian Medical College Vellore, Tamil Nadu, India
A. John. Christian Medical College Vellore, Tamil Nadu, India
J. Wisely. Christian Medical College Vellore, Tamil Nadu, India
G. Rebekah. Christian Medical College Vellore, Tamil Nadu, India
E. Sigamani. Christian Medical College Vellore, Tamil Nadu, India
A. Cherian. Christian Medical College Vellore, Tamil Nadu, India
D. Abraham. Christian Medical College Vellore, Tamil Nadu, India
P. Jacob. Christian Medical College Vellore, Tamil Nadu, India
R. Balakrishnan. Christian Medical College Vellore, Tamil Nadu, India
P. Solomon. Christian Medical College Vellore, Tamil Nadu, India
S. Backianathan. Christian Medical College Vellore, Tamil Nadu, India
R. Chacko. Christian Medical College Vellore, Tamil Nadu, India

Background In India, the majority of patients with triple negative breast cancer(TNBC) present with locally advanced and often inoperable disease due to lack of screening, awareness, and social stigma. This makes pathological complete response(pCR) after neoadjuvant chemotherapy(NAC) less likely, leading to early recurrence and poor survival outcomes. Immune checkpoint inhibitors(ICI) in addition to platinum agents have improved both pCR and disease-free survival(DFS). However, these are accessible only to a very small proportion(< 3%) of patients in LMICs due to exorbitant costs. The activity and cost-effectiveness of low dose ICI has been demonstrated in head and neck. The efficacy of low dose ICI in the neoadjuvant setting for TNBC has not been studied. We examined our outcomes with ultra-low dose nivolumab(< 0.6 mg/kg every 2 weeks) added to NAC for locally advanced and borderline operable TNBC. **Methods** A retrospective analysis of 132 patients with TNBC who received NAC with the ddDCEP regimen(Docetaxel 75mg/m² and Cyclophosphamide 600 mg/m² alternating with Epirubicin 90mg/m² and Cisplatin 60mg/m² every 2 weeks for 8 cycles) or ddDCEP plus low dose nivolumab(< 0.6mg/kg/2 weeks) and underwent mastectomy at our centre between 2018-2023 was carried out. 105 and 27 patients received ddDCEP alone and ddDCEP + low dose nivolumab respectively. Using rigorous exact matching, 26 matched pairs(52 patients) were obtained based on tumour grade and AJCC TNM stage. pCR in the surgical specimen was the principal outcome assessed. Survival data, adverse events and cost were also analysed. **Results** The median age of cases and controls was 42 and 40 years respectively. Tumour histology was ductal carcinoma most patients. Across both groups the stage distribution was the same with nearly 85% stage III(IA 3.8%;IIB 7.7%; IIIA 23.1%;IIIB 43.2%;IIIC 19.2%). 92% of cases and 85% of controls had node positive disease. 62% of cases

and 46% of controls had T4 disease. At a median follow up of 9 months, there were no recurrences or deaths among the cases. The most common immune mediated adverse event was hypothyroidism seen in 11.5% of cases. The rates of grade 3/4 anaemia, thrombocytopenia and febrile neutropenia were approximately 38%, 10% and 3.8% across cases and controls respectively. The median dose of nivolumab was 0.27mg/kg/2weeks as opposed to the approved dose of 3mg/kg/2weeks for most indications. The range of doses varied from 0.07 to 0.58mg/kg/2weeks. In the overall cohort, the addition of nivolumab did not have any apparent effect on the pCR rates which were identical at 42.3% in both cases and controls. However, there was a positive correlation between the total dose of nivolumab/kg(body weight) and the likelihood of pCR(coefficient 0.34; p-value 0.046). Patients who received higher than the median dose of nivolumab had a significantly higher likelihood of attaining pCR than those who received lower doses (69.2% pCR vs. 15.4%;p-value 0.015). The cost of nivolumab at 0.6 mg/kg for 4 doses is approximately USD2000 compared to USD34400 for 8 doses of pembrolizumab in the neoadjuvant component of the KEYNOTE-522 regimen. Conclusion In this cohort with locally advanced/inoperable TNBC, the addition of ultra-low dose nivolumab did not improve pCR overall compared to a matched control set who did not receive ICI. However, in the subset of patients who received between 0.27-0.58 mg/kg/2weeks, the pCR rates were significantly higher at 69%. This presents a promising and cost-effective approach for TNBC management in LMICs. This effect needs verification in larger phase II/III trials.

	Entire cohort		At various dose levels (mg/kg/2weeks)				
	DCEP alone	DCEP + low dose nivolumab	≤0.27	>0.27	≤0.19	0.19 to 0.38	>0.38
pCR(yoT0/TisN0) %	42.3	42.3%	18.2%	69.2%	20%	54.5%	60%

PO5-03-12

Genomic differences of primary triple negative breast cancer in patients younger than 45 years vs. patients older than 45 years of age

Presenting Author(s) and Co-Author(s):

N. Vidula. Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, United States

L. Ellisen. Massachusetts General Hospital, Boston, Massachusetts, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

C. Yau. University of California, San Francisco and Buck Institute for Research on Aging, Novato, California, United States

Background:

Triple negative breast cancer (TNBC) is often associated with an aggressive clinical course, especially in younger women. We previously demonstrated that there are differences in the genomic spectrum of metastatic TNBC in patients who are ≤ 45 years and those who are > 45 years of age (Vidula et al, SABCs, 2020). Here we explore genomic differences of primary TNBC in patients ≤ 45 years and patients > 45 years to understand variations in the overall number of non-silent mutations and proportion of patients with specific gene mutations.

Methods:

We obtained filtered mutation calls generated by the Multi-Center Mutation Calling in Multiple Cancers (MC3) working group (Ellrott et al, Cell Syst, 2018), from whole exome sequencing data of 9079 The Cancer Genome Atlas (TCGA) samples across 33 cancer types that had been used for the comprehensive characterization of cancer driver genes and mutations (Bailey et al, Cell, 2018). Receptor subtype and age at diagnosis of 1247 TCGA breast cancer samples were obtained from the UCSC Xena browser (Goldman et al, Nat Biotechnol, 2020). These datasets were combined to identify 119 patients with primary TNBC with harmonized high confidence mutation calls for analysis. We compared the overall number of non-silent mutations between patients ≤ 45 years vs. > 45 years using the Wilcoxon rank sum test. We also compared the proportion of patients with non-silent mutations in genes mutated at $> 10\%$ frequency between age groups using the Fisher Exact test.

Results:

Altogether, 25 patients ≤ 45 years and 94 patients > 45 years were identified with primary TNBC. No significant difference in the number of non-silent mutations among patients ≤ 45 years vs. > 45 years was seen (median [range], ≤ 45 years: 65 [5-228] vs. > 45 years: 74 [2-742], Wilcoxon rank sum $p=0.57$). In total, 35 unique genes were mutated at $> 10\%$ frequency in either patients ≤ 45 years (30 genes) or > 45 years (7 genes); notably, TP53 mutations were commonly seen in both age groups (≤ 45 years: 76%; > 45 years: 79%, $p=0.79$) and TTN mutations were also frequently mutated in both cohorts (≤ 45 years: 20%; > 45 years: 27%, $p=0.61$). Among the 35 genes identified, 12 genes were mutated at significantly different frequencies among patients ≤ 45 years vs. those > 45 years, as depicted in Table 1.

Conclusions:

Relatively high frequencies of TP53 and TTN mutations were seen in both patients ≤ 45 years and those > 45 years with primary TNBC. However, many genes associated with varying cellular functions including motility, signaling receptors, and growth were more frequently mutated in

patients ≤ 45 years. These results suggest that there are genomic differences of primary TNBC in patients ≤ 45 years vs. those >45 years. Further research is needed to validate these findings in a larger cohort of primary TNBC since genomic differences may affect tumor biology and clinical behavior.

Table 1. Significant Gene Mutation Differences in Primary TNBC Based on Age.

Gene Mutation	≤ 45 years	>45 years	p value
<i>HYDIN</i>	16%	1%	0.0068
<i>MUC4</i>	12%	0%	0.0084
<i>SEMA6A</i>	12%	0%	0.0084
<i>SNAP91</i>	12%	0%	0.0084
<i>UBE2R2</i>	12%	0%	0.0084
<i>RYR2</i>	16%	2%	0.017
<i>CDC42BPA</i>	12%	1%	0.029
<i>CDH23</i>	12%	1%	0.029
<i>DNAH17</i>	12%	1%	0.029
<i>PLIN4</i>	12%	1%	0.029
<i>RPL13A</i>	12%	1%	0.029
<i>PIK3CA</i>	0%	15%	0.039

PO5-04-01

Inetetamab combined with sirolimus and chemotherapy in HER2 positive metastatic breast cancer patients with abnormal activation of Pi3k/Akt/mTOR pathway after trastuzumab treatment

Presenting Author(s) and Co-Author(s):

Q. li. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China (People's Republic)

D. Lv. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China (People's Republic)

X. Sun. Cancer Hospital of Huanxing Chaoyang District, Beijing 100122, China., United States

M. Wang. Department of Breast surgery, Chongqing University Three Gorges Hospital, United States

L. Cai. Harbin Medical University Cancer Hospital, Harbin, China., China (People's Republic)

F. Liu. Fuyang Cancer Hospital, Anhui, China., China (People's Republic)

c. li. Anqing Cancer Hospital, Anhui, China., China (People's Republic)

J. Zhao. Qinghai University Affiliated Hospital, Qinghai, China., China (People's Republic)

j. sun. Anyang Cancer Hospital, Henan, China., United States

Y. Shi. Tianjin Medical University Cancer Institute and Hospital, Tianjin, China., China (People's Republic)

F. Ma. Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Objective: To explore the efficacy and safety of Inetetamab Combined with Sirolimus and Chemotherapy in the treatment of human epidermal factor receptor 2 (HER2) positive metastatic breast cancer patients with abnormal activation of Pi3k/Akt/mTOR (PAM) pathway after Trastuzumab treatment.

Methods: This prospective multicenter clinical study enrolled HER2 positive metastatic breast cancer patients at the National Cancer Center in China from July 2021 to September 2022 with PAM pathway mutation confirmed by histology or peripheral blood genetic testing. The inclusion criteria included: 1) Recurrent and metastatic breast cancer patients with HER2 positive confirmed histologically; 2) ECOG PS score \leq 2; 3) Patients who have progressed after previous treatment with Trastuzumab; 4) Patients with PAM pathway mutation confirmed by Genetic testing; 5) Patients' cardiac, pulmonary, liver and bone marrow functions are basically normal; 6) Patients voluntarily sign informed consent forms. The exclusion criteria included: 1) Patients previously treated with mTOR inhibitors or pyrotinib; 2) Patients who have used chronic Corticosteroid for more than 3 months or used Immunosuppressive drug within 4 weeks; 3) Patients with symptomatic central nervous system metastasis; 4) Patients with left ventricular Ejection fraction < 50% or clinical manifestations of obvious arrhythmia, myocardial ischemia, severe atrioventricular block, cardiac insufficiency, and severe valvular disease; 5) Diagnosed with other malignant tumors within five years. Patients were randomly divided into trial group and control group. The patients in the trial group received inetetamab combined with sirolimus and chemotherapy, and control group received pyrotinib and chemotherapy. RECISTv1.1 standard was used to evaluate the efficacy of patients. Descriptive statistics are used to summarize clinical pathological features. Kaplan Meier method was used to draw

survival curves. Log-rank test was used to compare progression free survival (PFS) differences between groups. $P < 0.05$ was considered statistically significant.

Results : A total of 59 HER2 positive metastatic breast cancer patients with abnormal activation of PAM pathway were included, of which 37 patients received the treatment of inetetamab group and 22 patients received the treatment of pyrotinib group. The median follow-up time was 5.33 months. In the intent-to-treat set, the median PFS of patients in the inetetamab group was 4.64 months, which was shorter than 5.69 months in the pyrotinib group. There was no statistically significant difference between the two groups ($P=0.51$; $HR=0.41$; 95% CI, 0.12-1.45). The objective response rate (ORR) of the inetetamab group and the pyrotinib group were 28.1% and 29.4%, respectively. In terms of safety, the incidence of adverse events (AE) in the experimental group was (33/37) 89.1%, while (16/21) 76.2% in the control group. The incidence of AE above level 3 in the inetetamab group and pyrotinib group were (13/37) 35.1% and (3/21) 14.3%, respectively.

Conclusion : For the metastatic HER2 positive breast cancer patients with abnormal activation of PAM pathway treated with trastuzumab previously, the combination of inetetamab with sirolimus and chemotherapy regimen are equivalent to the combination of pyrotinib and chemotherapy regimen. It demonstrated that combination of inetetamab with sirolimus and chemotherapy could be one of the treatment options for the metastatic HER2 positive breast cancer patients.

PO5-04-02

Combination of trastuzumab competing and non-competing fully human internalizing anti-Her2 monoclonal antibodies drug conjugates increases their inhibitory effect on the growth of HER2 positive metastatic breast cancer cells.

Presenting Author(s) and Co-Author(s):

G. Serrero. A&G Pharmaceutical Inc, Columbia, Maryland, United States

B. Yue. A&G Pharmaceutical, Columbia, Maryland, United States

J. Dong. A&G Pharmaceutical Inc., Columbia, Maryland, United States

J. Hayashi. Precision Antibody, Columbia, Maryland, United States

The human epidermal growth factor receptor (HER) family of receptors plays a key role in proliferation stimulator for several human cancers. In particular, HER2 is overexpressed in 15-30% of breast cancers with or without gene amplification with prognostic and predictive implications. HER2 overexpression is associated with shorter disease-free and overall survivals, resistance to hormonal agents and increased risk of brain metastasis. Trastuzumab is a humanized anti-HER2 monoclonal antibody that binds to domain IV of HER2 extracellular domain and blocks its signaling. More recently, two antibody drug conjugates using trastuzumab have been approved: Ado-Trastuzumab-Emtansine (Kadcyla) consisting of trastuzumab conjugated to the drug mertansine DM1 and fam-trastuzumab-deruxtecan-nhki (Enhertu) to deliver the topoisomerase inhibitor deruxtecan. We are reporting here the development of fully human internalizing anti-HER2 antibodies with distinct epitopes on the HER2 protein which compete or not with trastuzumab for binding to HER2. These monoclonal antibodies have been developed by immunizing fully human (TC-Mab mouse) mice with recombinant HER2 protein. After production of hybridoma secreting fully human immunoglobulins, the screening process included competition with trastuzumab for binding to Her2 by enzyme linked immunoassay and Octet epitope binning and affinity determination as well as internalization assay. Several internalizing antibodies able to compete or not with trastuzumab and with high affinity (Kd ranging from 10^{-9} M to 10^{-12} M) were selected. Their ability to deliver a cytotoxic payload in HER2 overexpressing breast cancer cells such as SKBR3, BT474 and AU565 was next investigated. Two groups of antibodies: one competing with trastuzumab and the other one non-competing were further characterized. Data related to these antibodies' biochemical characteristics as well as their ability to inhibit proliferation in vitro and in vivo in mouse xenografts studies will be presented here. In conclusion, the use of fully human mice to develop monoclonal antibodies provides a powerful and attractive approach to develop fully human monoclonal antibodies against cancer targets by-passing the need for humanization and affinity maturation of antibodies.

This work is supported by 5R44CA224718 SBIR grant from the National Cancer Institute.

PO5-04-04

Development of a method to detect very low levels of HER2 expression in Circulating Tumor Cells (CTCs) by liquid biopsy in patients with metastatic breast cancer.

Presenting Author(s) and Co-Author(s):

G. Di Caro. Epic Sciences, United States

D. Bourdon. Epic Sciences, San Diego, California, United States

A. Kunihiro. Epic Sciences, United States

A. Cunsolo. Epic Sciences, United States

E. Lam. Epic Sciences, United States

M. Slade. Epic Sciences, California, United States

M. Blankfard. Epic Sciences, United States

L. Schwartzberg. William N. Pennington Cancer Institute - Renown Health, United States

Introduction

Blood-based liquid biopsies are a non-invasive diagnostic approach for detecting circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) that may provide clinically actionable information for treatment decisions for metastatic breast cancer (MBC) patients when a conventional tissue biopsy is not feasible. Recently, the novel anti-HER2 antibody-drug conjugate, Trastuzumab Deruxtecan (T-DXd), has shown effectiveness against MBC with low HER2 expression detected by tissue biopsy characterized as HER2-low (immunohistochemically 1+ or 2+ and ERBB2 amplification-negative via in situ hybridization) and is being explored in an ultra-low population. Here we report on the application of a liquid biopsy platform designed to sensitively detect low levels of HER2 protein expression in CTCs from MBC patients.

Methods

Blood samples from 704 metastatic breast cancer patients as well as control cells lines were collected for cell-based and cell-free DNA analysis. After plasma isolation, nucleated cells deposited on glass slides went through immunofluorescent staining and imaging. CTCs were identified using Epic Sciences' digital imaging and machine learning algorithms, and a subset of CTCs were isolated and sequenced for genomic quantification of large scale-state transitions (LSTs) as well as copy number variants (CNVs). The HER2 status was based upon on ASCO-CAP guidelines and the previous tissue biopsy results from the ordering healthcare provider, as documented on the DefineMBC™ test requisition form.

Results

Within a DefineMBC early-access program (EAP), 93% of patients with MBC had detectable CTCs. Among ERBB2-non-amp patients tested with the DefineMBC assay, 25% of patients with MBC had findings that were reported as consistent with HER2-low in the CAP-CLIA setting. To explore the lower boundaries of HER2 protein expression, we created and validated an MCF-7 HER2-negative ERBB2 knock-out cell line and utilized its 95% confidence level threshold (271 MFI) as a negative fluorescence cutoff for very low HER2 expression. Based upon publicly available CCLE datasets, MDA-MB-453, MCF7, and MCF7 ERBB2 KO breast cancer cell lines were selected for their high and low HER2 RNA expression levels and were corroborated via observed HER2 immunofluorescence median levels of 15740, 381, and 188 MFI respectively. In an exploratory analysis, among ERBB2-non-amp patients, we retrospectively applied the 271 MFI HER2 cutoff to the EAP cohort and identified 38% of

patients with very low HER2 expression. We examined the impact of the HER2 ultra-low cutoff in patients not eligible for T-DXd treatment. Among patients reported as IHC=0 or with unknown IHC status from the most recent tissue biopsy, 44% and 42%, respectively, may qualify for treatment with T-DXd.

Conclusion

Using our higher sensitivity assay that combines CTC immunofluorescence and single-cell genomic analysis, we examined the lower boundary of HER2 protein expression. Feasibility data support further characterization of a very low HER2 expression phenotype, for the eventual inclusion into our comprehensive cancer profiling solution. To date, studies with biomarker expression have been limited to tissue biopsy, which may not always yield contemporaneous sampling in the metastatic setting. These results offer a liquid biopsy test that might identify patients potentially responsive to HER2-directed therapies.

PO5-04-05

Clinical validation of the concordance performance of ERBB2 status by single-cells genomics ERBB2 (HER2) amplification Assay in Circulating Tumor Cells (CTCs) from patients with matched HER2 status from metastatic tissue biopsies.

Presenting Author(s) and Co-Author(s):

G. Di Caro. Epic Sciences, United States

E. Lam. Epic Sciences, United States

M. Slade. Epic Sciences, California, United States

S. Huang. Stat4Ward, United States

R. Wenstrup. Epic Sciences, United States

L. Schwartzberg. William N. Pennington Cancer Institute - Renown Health, United States

Background

Liquid biopsies are a non-invasive diagnostic approach for detecting CTCs that may provide clinically actionable information for treatment decisions for metastatic breast cancer (MBC) patients when a conventional biopsy is infeasible. Blood-based liquid biopsy has the potential advantage that it allows broad sampling of metastatic tumor clones because it is capable of and likely to obtain cellular and genomic contributions from more than one metastatic site. Here we report the concordance performance of HER2 positivity by single-cell CTC genomics ERBB2 (HER2) amplification in patients with matched HER2 status from metastatic tissue biopsies.

Methods

A prospective Clinical Experience Program for CTC ERBB2 (HER2) Assay across 25 different United States-based cancer centers, was used to recruit 128 MBC patients with documented standard-of-care metastatic tissue biopsies performed within the last 5 years (Days from tissue biopsy to liquid biopsy, Median: 19.5; interquartile range: 40.75) CTCs from blood collection at each respective clinical site were isolated from plasma, nucleated cells were plated, & slides were bio-banked for Immunofluorescent staining & subsequent imaging in a CAP CLIA lab. CTCs were identified using Epic Sciences digital imaging & machine learning algorithms. Individual CTCs were sequenced for genomic quantification of chromosomal instability (LSTs) and ERBB2 (HER2) amplification.

Results

Within the clinical validation cohort of 128 MBC patients, 30% (38/128) were HER2-positive by standard pathologic criteria (IHC 3+ or IHC2+/ISH+) in metastatic tissue biopsies. Among the 64 out of 128 cases with reportable results by the CTC ERBB2 (HER2) amplification on chromosomally unstable CTCs, 31% (20/64) of patients had ERBB2 amplification. Concordance between CTC single cell genomics and available tissue results for HER2 positivity showed a sensitivity of 69% and specificity of 78%. We then addressed the effects of two known biological confounders to the use of tissue biopsy for HER2 status determination: 1) tissue biopsies performed on bone metastases, 2) tumor evolution driven by treatment pressure over time leading to potential HER2 conversion and tumor heterogeneity. Thus, we performed subgroup analysis including only validation set patients with tissue biopsies performed on non-bone tissues, which showed slightly improved concordance to the tissue comparator with a Sensitivity of 86%, and Specificity of 75%. Next, to exclude the possibility of tumor evolution we selected only patients with the HER2 status comparator performed on non-bone tissue biopsies contemporaneous (Days from tissue biopsy to liquid biopsy, Median: 14; interquartile range: 22)

to the blood draw for the CTC ERBB2 (HER2) amplification assay. This showed dramatically improved concordance performance with a Sensitivity of 100%, and a Specificity of 75%.

Conclusions

Blood and tissue are two biologically distinct sample types where variations in HER2 and other biomarker results might be expected due to analytic, temporal and clinical differences. These data indicate that determination of HER2 status by single cell genomic ERBB2 (HER2) amplification assay can aid in the clinical assessment of ERBB2 status in patients with metastatic breast cancer (MBC) for whom tissue biopsy for HER2 status is not available, or infeasible. Additionally, these results provide evidence of the contribution of site differences (bone) of metastatic biopsies and also tumor evolution to discordance between the CTC ERBB2 (HER2) Assay and tumor biopsy.

PO5-04-06

Enhancing Antitumor Activity of Her2 CAR T cells through TR2BB Co-Expression and Cytokine Signal 3 Incorporation.

Presenting Author(s) and Co-Author(s):

D. Chamorro. Baylor College of Medicine, Houston, Texas, United States

L. Somes. Baylor College of Medicine, Houston, Texas, United States

E. Madaras. Rice University, United States

S. Nalawade. Baylor College of Medicine, United States

P. Shafer. Baylor College of Medicine, United States

A. Mosquera. Baylor College of Medicine, United States

M. McKenna. Baylor College of Medicine, United States

V. Hoyos. Baylor College of Medicine, United States

Chimeric antigen receptor T cells (CARTs) targeting Her2 represent a promising approach for the treatment of patients with Her2 expressing breast cancers (BC). Her2 CARTs confront major challenges within the immune-suppressive tumor microenvironment (TME) of breast cancer, which inhibits sustained T cell proliferation and persistent antitumor activity. To bolster Her2 CARTs' expansion and persistence, we engineered a TNF-related apoptosis-inducing ligand receptor 2 (TR2) specific scFv connected to the endodomain of 4-1BB (TR2BB). TR2BB co-expressing Her2 CARTs exhibited enhanced antitumor potential against BC tumors by triggering myeloid derived suppressor cell (MDSC) apoptosis, thereby remodeling the TME and promoting T cell proliferation. Despite better tumor control in mice receiving CAR.TR2BB T cells, recent trials have demonstrated the importance of incorporating a cytokine signal for optimal tumor control in patients with solid tumors. Thus, we hypothesized that we could further augment anti-tumor activity of Her2 CAR.TR2BB T cells against BC by incorporating a cytokine signal 3 through IL-15 or C7R. We engineered the CARTs to (1) ectopically produce IL-15, a crucial T-cell homeostasis and survival cytokine, and (2) express a constitutively active IL-7 receptor (C7R) that triggers IL-7 receptor signaling independently of ligand or the common receptor gamma chain (γ_c).

Our repeat weekly tumor challenge assay revealed that CAR.TR2BB.IL15 T cells outperformed CAR.TR2BB.C7R and CAR.TR2BB in T cell proliferation. Both CAR.TR2BB.IL15 and CAR.TR2BB.C7R exhibited improved cytotoxic potential after three weeks of antigen stimulation compared to CAR.TR2BB alone in comparison with CAR.TR2BB alone. Furthermore, in our in vivo xenograft NSG mouse models implanted with Her2 expressing breast cancer cell line and MDSCs, CAR.TR2BB.IL15 T cells showed superior tumor control and improved survival rates.

In summary, the addition of IL15 transgene to our TME targeting Her2 CARTs provides an advantage in terms of T cell persistence, proliferation, and tumor control in in vitro and in vivo models. These promising preclinical results propel us to apply this optimized Her2 targeting CART therapy in a phase I clinical trial for patients with metastatic Her2-expressing breast cancers.

PO5-04-07

Characteristics of patients with metastatic HR+/HER2+ breast cancer in a Kaiser Permanente observational multi-site cohort

Presenting Author(s) and Co-Author(s):

S. Weinmann. Kaiser Permanent Center for Health Research, United States
D. Ritzwoller. Institute for Health Research, Colorado, United States
M. Kwan. Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States
R. Haque. Kaiser Permanente Research, United States
S. Stergiopoulos. Pfizer Inc., United States
A. Cha. Pfizer Inc., Fairfield, Connecticut, United States
E. Gauthier. Pfizer Inc, San Francisco, California, United States
D. Sapp. Kaiser Permanente Center for Health Research, United States
J. Dickerson. Kaiser Permanente Center for Health Research, United States
K. Richert-Boe. Kaiser Permanente Center for Health Research, United States
W. Hu. Kaiser Permanente Center for Health Research, United States
N. Carroll. Kaiser Permanente Institute for Health Research, United States
L. Chen. Kaiser Permanente Research, United States
V. Lee. Kaiser Permanente Division of Research, United States
R. Zalavadia. Kaiser Permanente Institute for Health Research, United States
M. O'Keeffe-Rosetti. Kaiser Permanente Center for Health Research, United States

Background: Approximately 10% of female breast cancer and 13% of male breast cancer tumors express hormone-receptor positive/human epidermal growth factor receptor 2 positive (HR+/HER2+) molecular subtype. Since HER2+ targeted agents were made available nearly 10 years ago, there has been limited innovation in treatment of patients with HR+/HER2+ metastatic breast cancer (mBC) to improve clinical outcomes. This study aims to characterize the HR+/HER2+ mBC patient population by describing demographic and clinical characteristics and treatment patterns in a racially diverse, insured, population-based cohort. This study includes data from 4 regions of the Kaiser Permanente (KP) health system -- Northwest, Northern California, Southern California, and Colorado.

Methods: Eligible study patients were adults age > 18 years with HR+/HER2+ invasive breast cancer who were either initially diagnosed with Stage IV disease or were diagnosed at an earlier stage and experienced recurrence with distant metastasis between 6/8/2012 and 12/31/2019 with data collected through 12/31/2021. Select information was extracted from electronic health records (EHR) of eligible patients and combined with manually abstracted data to create the analytic dataset. Breast cancer recurrence was identified by tumor registrars or obtained through a breast cancer recurrence detection algorithm and verified by chart review. Chart reviewers collected data on metastatic sites, disease progression, reasons for stopping systemic therapy medications, and verified use of medications.

Preliminary results: During the study period, we identified 492 subjects with HR+/HER2+ mBC. Seven were men and 485 were women. 221 (45%) had de novo Stage IV breast cancer at

diagnosis and 271 (55%) had recurrent mBC. Median age at metastatic diagnosis was 59 years for de novo cases and 62 years for recurrent cases. The cohort was racially and ethnically diverse, with 13% Asian subjects (11% de novo, 15% recurrent), 12% Black subjects (10% de novo, 14% recurrent), and 66% White subjects (71% de novo, 63% recurrent). 18% of cases were recorded as Hispanic (19% de novo, 18% recurrent) in the EHR. Major sites of metastases, including bone, liver, lung, brain, and distant lymph nodes, were similar in both the de novo and recurrent groups.

Among women (see table below), 28 (6%) received no systemic treatment for their metastatic disease (9% de novo, 3% recurrent). Among women with systemic treatment, 80% received anti-HER2 agents (90% de novo, 73% recurrent). Of women with recurrent mBC who received systemic therapy, 56% had received anti-HER2 therapy in the adjuvant setting.

Conclusion: This population-based study of a racially diverse cohort examined EHR-derived data to describe current demographics and treatment patterns for HR+/HER2+ mBC in an insured patient population. Over 90% of women received systemic therapy, and the majority of those received anti-HER2 therapy per current treatment guidelines. Future analyses will focus on clinical outcomes in this cohort with a goal of informing how prognosis can be improved.

	De Novo	Recurrent	Total
Number of women receiving systemic therapy	N	N	N
Total	217	268	485
No	19	9	28
Yes	198	259	457
Subset of women receiving anti-HER2 therapy	178	190	368
Recurrent case use of anti-HER2			
Used before metastatic diagnosis		54	
Used after metastatic diagnosis		46	
Used before and after metastatic diagnosis		90	

PO5-04-10

Clinical and prognostic value of MLN51 (Metastatic lymph node gene 51)/CASC3 (Cancer susceptibility candidate gene 3) in clinical breast cancer, connection with nodal and hormonal receptor status

Presenting Author(s) and Co-Author(s):

B. CONG. 1. Cardiff University School of Medicine; 2. Shandong Cancer Hospital and Institute, United States

T. Martin. Cardiff University, Cardiff, United States

X. CAO. 1. Cardiff University School of Medicine; 2. Tianjin Medical University; 3. Shandong Cancer Hospital and Institute., United States

R. MANSEL. University Llandough Hospital, United States

E. Davies. 3Wales Breast Centre, University Llandough Hospital, Cardiff CF64 2XX, UK, United States

W. Jiang. Cardiff University, United States

Introduction: Metastatic Lymph Node Gene 51 Protein (MLN51) also known as Cancer Susceptibility Candidate Gene 3 Protein (CASC3) or Barentsz (BTZ) is a molecule that was first identified in malignant breast tumours. The CASC3 gene encodes the protein that binds to mRNA and is a key component of the exon junction complex (EJC), playing an important role in the metabolism of mRNA and in cellular recovery after stress responses. It is not clear, however, if MLN51 has a clinical value in assessing the disease progression of breast cancer.

Methods: We analysed the transcription expression levels of MLN51 in a cohort of human breast cancer tissues and correlated the expression pattern with clinical outcome, pathological type and hormonal receptor status.

Results: High levels of MLN51 was found to be a favourable prognostic indicator for overall survival ($p=0.008$, Hazard Ratio [HR=0.262]), the prognostic value being independent of other clinical and pathological factors. Likewise, high levels of MLN51 were also a significant and independent predictive factor for disease free survival (DFS) ($p=0.003$, HR=0.262). It was found that the favourable prediction in both OS and DFS was associated with node positive tumours, with significance with OS ($p=0.004$), compared in node negative tumours ($p=0.143$) and to DFS ($p=0.001$ in node positive compared with $p=0.079$ in node negative tumours). Levels of MLN51 had a significant correlation with EGFR in both normal and tumour mammary tissues but correlated with Her-2 and Her-3 in tumour tissues only. The prognostic power of MLN51 for DFS was significant in both Her-2 positive and Her-2 negative ($p=0.003$ and $p=0.012$) tumours and in ER negative tumours ($p=0.003$). The prediction for OS by MLN51 was particularly strong for Her-2 positive and ER positive ($p=0.007$ for both) tumours.

Conclusions: MLN51 (CASC3) is a favourable prognostic factor in patients with breast cancer. This is clearly linked to the nodal status and hormone receptor status, particularly ER and HER-2.

PO5-04-11

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) beyond progression in hormone receptor positive advanced breast cancer: a systematic review and meta-analysis

Presenting Author(s) and Co-Author(s):

N. Pathak. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., Toronto, Ontario, Canada

S. Kumar. Sunnybrook Health Sciences Centre, Ontario, Canada

D. Malon Gimenez. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., United States

M. Di Iorio. Princess Margaret Cancer Centre, University of Toronto, United States

C. Molto Valiente. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., United States

D. Cuthbert. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., United States

M. Li. Princess Margaret Cancer Centre, Division of Medical Oncology, Toronto, ON, Canada. University of Toronto, Department of Medicine, Toronto, ON, Canada., United States

A. Batra. All India Institute of Medical Sciences, New Delhi, India, United States

M. Nadler. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

E. Amir. Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

A. Mittal. Health Sciences North, Northern Ontario School of Medicine, Sudbury, ON, Canada, United States

Introduction

The use of CDK 4/6i (palbociclib/ribociclib/abemaciclib) with endocrine therapy (ET) is a widely adopted first line standard treatment for hormone receptor positive advanced breast cancer (HR+ABC). Data supporting incorporation of CDK 4/6i ± ET beyond progression are less clear. Recent studies have evaluated either the continuation of or switching to a different CDK 4/6i, with a change in ET after progression on 1st line CDK4/6i with varying results. A pooled analysis of this strategy could be useful for clinical decision making.

Methods

We reviewed reports of both observational and clinical studies that evaluated continuing the same CDK4/6i or switching to a different agent after progression on first line CDK4/6i with ET. The search included the grey literature without exclusions for publication year or language. The mean overall response rate (ORR), clinical benefit rate (CBR) and progression free survival (PFS) weighted by study sample size were calculated. Meta-regression comprising linear regression weighted by sample size (mixed effects) was performed to explore the association between disease and treatment-related factors and benefit from continuing a CDK4/6i. Quantitative significance was assessed using the Burnand criteria. Analyses were performed using SPSS version 28 (IBM Corp, Armonk NY).

Results

Thirteen studies (N=1006 patients) were included; 7 were prospective trials and 2 cohorts of the

same retrospective study included separately). Study patients had a median age of 57.8 years and 66% had visceral metastases. Among patients whose type of first-line CDK 4/6i exposure was reported (84.5%), 81.21% received Palbociclib 3.28% received Ribociclib and 0.89% received Abemaciclib. Six patients received both Palbociclib and Ribociclib. The median duration of first line CDK 4/6i therapy was 13.8 months.

In the second line, the mean ORR was 12.8%, CBR 38.8%, and median PFS was 4.6 months. The ORRs for Palbociclib, Ribociclib and Abemaciclib, irrespective of type of prior CDK 4/6i, were 7.3%, 14.7% and 18.6%, respectively. The CBR for Palbociclib, Ribociclib and Abemaciclib were 33.1%, 42.2% and 46.8%, respectively. The median PFS based the CDK 4/6i used in second line was 4.2 (Palbociclib), 5.5 (Ribociclib) and 9.2 (Abemaciclib) months. Meta-regression analysis of PFS is included in the table.

Conclusion

Continuing a CDK 4/6i± ET beyond progression yields modest benefits. Switching CDK4/6i offers slightly better ORR and PFS. Continuing Palbociclib beyond progression does not seem beneficial. Longer duration of CDK4i exposure in the first line appears to be associated with shorter PFS in the second line. Small number of studies with limited number of patients likely affect results.

Variable	PFS		
	Beta coefficient	p-value	N studies
Age	-0.201	0.531	12
%Visceral metastases	-0.16	0.729	7
Median lines of Treatment	0.114	0.83	6
Prior Palbociclib (all CDK 4/6i)	-0.394	0.294	9
Prior Palbociclib (ribociclib/abemaciclib)	-0.617	0.267	5
PFS of prior CDK 4/6i	-0.371	0.412	9
ET: Aromatase inhibitor in 2 nd line	0.163	0.727	7
ET: fulvestrant in 2 nd line	-0.311	0.453	8

Meta-regression analysis of PFS of CDK 4/6i with or without ET in subsequent line of therapy.

PO5-04-12

Comparison of chemotherapy efficacy in metastatic lobular vs. ductal breast cancer

Presenting Author(s) and Co-Author(s):

B. Kirwin. Royal North Shore Hospital, United States

A. Chan. Breast Cancer Research Centre – Western Australia, Hollywood Consulting Centre, WA 6009, Nedlands, Western Australia, Australia

Comparison of chemotherapy efficacy in metastatic lobular vs. ductal breast cancer

Background: Invasive lobular carcinomas (ILC) are thought to be less chemo-sensitive than invasive ductal carcinomas (IDC), as reflected by lower rates of pathological complete response following neoadjuvant therapy. In the metastatic setting, evidence regarding chemotherapy (Cx) efficacy is limited. Methods: A retrospective review of prospectively collected data for consecutive patients (pts) with metastatic ILC (mILC) treated at a single institution between 2000 and 2023 was included. Pts with mILC were matched on a 1:2 ratio with a cohort of pts with metastatic IDC (mIDC) by age, era of diagnosis and initial metastatic burden. Primary outcome was efficacy of Cx in mILC vs. mIDC pts as measured by time to next treatment - TTNTc (months (m) between start date of first & second Cx). Key secondary endpoints included differences in efficacy of endocrine therapy between the two groups (as measured by TTNT and outcomes in pts with endocrine resistance (EnR) as defined by ESMO consensus guideline) and overall survival (time from diagnosis of metastatic breast cancer (BC) to death or last follow-up [OS]). Results: 376 pts were included, mILC (122) and mIDC (254) with median age 64y and 62y, respectively. A significantly higher proportion of mILC pts had hormone receptor positive/HER2 negative or lower proportion of triple negative disease ($p < 0.0001$). Compared to mIDC, mILC pts were more likely to have de novo disease (29% vs. 18%; $p=0.02$), lower grade ($p < 0.0001$), received endocrine therapy only ($p=0.03$) and were less likely to have visceral disease at diagnosis or any time after metastatic diagnosis (20% vs. 45% $p < 0.0001$, 35% vs. 51% $p < 0.0004$, respectively). Median time to commencing chemotherapy from metastatic diagnosis was longer in mILC pts (5.8 v 2.0 m, $p=0.03$). There was no significant differences in TTNTc for patients with mILC and mIDC except for those with visceral disease at diagnosis (Table 1). There was no significant difference in TTNTc by histological subtype of mILC ($p=0.46$) or by choice of first line chemotherapy used ($p=0.91$). In the entire population, no significant OS difference observed in mILC and mIDC (Table 1). BC outcome was assessed in pts receiving endocrine therapy as first-line treatment (mILC 65, mIDC 102). There was no difference in TTNT (mILC 14.6m vs. mIDC 14.8m). There were no differences in incidence of EnR between the groups. OS was shorter in mILC pts with primary EnR. The presence of primary, secondary or no resistance within each histological group was significantly associated with OS (Table 1). Conclusion: Pts with mILC have a longer time to commencing chemotherapy, but efficacy of chemotherapy is similar to pts with mIDC; irrespective of lobular histologic subtype, first line chemotherapy regimen used and sites of disease, except for those mILC with visceral disease. There was no significant difference in OS between mILC and mIDC pts treated in this single centre study. Efficacy of endocrine treatment when given as first line treatment was similar in both groups with no significant difference when pts were evaluated by presence or absence of endocrine resistance, except for primary EnR, but pt numbers were small in this group. Our results demonstrate equivalent chemotherapy efficacy in pts with mILC as compared to mIDC. References 1. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010

Table 1. TTNTc & OS

	IDC	ILC	IDC	ILC	
	No (%)		TTNT median (m)		P value
A. TTNTc (received \geq 2 lines Cx)					
• All pts	166 (65)	64 (53)	9.1	8.9	0.31
• Visceral disease at diagnosis	78 (31)	14 (12)	9.1	5.5	0.007
B. TTNT (received first-line endocrine therapy)	102 (40)	65 (53)	14.8	14.6	0.94
			OS median (m)		P value
C. Endocrine resistance	155 (61)	97 (80)			
Primary	30 (19)	14 (14)	33.1	22.6	0.017
Secondary	106 (68)	71 (73)	55.0	47.3	0.10
None	20 (13)	12 (13)	171.0	NR	0.59
OS across categories of resistance within group, p value			<0.0001	<0.0001	
D. OS Total population(n=376)	34.6	36.8			0.98

* Pts on first-line endocrine treatment or died without BC progression

PO5-04-13

Liquid Biopsy Testing in a Greek Cohort of ER-positive, HER2-negative metastatic breast cancer patients

Presenting Author(s) and Co-Author(s):

N. Tsoulos. GeneKor Medical SA, Greece
A. Meintani. GeneKor Medical SA, Gerakas, Greece
G. Kapetsis. GeneKor Medical SA, United States
C. Chatziannidou-Florou. GeneKor Medical SA, Gerakas, Greece
A. Tsantikidi. GeneKor Medical SA, Gerakas, Greece
S. Maxouri. GeneKor Medical SA, Gerakas, Greece
E. Thanou. GeneKor Medical SA, United States
K. Aggelaina. GeneKor Medical SA, Gerakas, Greece
V. Metaxa-Mariatou. GeneKor Medical SA, Gerakas, Greece
G. Tsaousis. GeneKor Medical SA, Greece
I. Natsiopoulos. Interbalkan European Medical Center, Greece
V. Venizelos. Metropolitan Hospital, Greece
C. Markopoulos. National Kapodistrian University of Athens, Greece
F. Zagouri. General Hospital of Athens Alexandra, Athens, Greece, United States
E. Kampletsas. University Hospital of Ioannina, Greece
E. Karyda. Hygeia Hospital, United States
D. Tryfonopoulos. Agios Savvas Anticancer Hospital, Greece
K. Papazisis. Euromedica, General Clinic of Thessaloniki, Greece, United States
D. Ziogas. Laiko University Hospital, Greece
I. Athanasiadis. Mitera Hospital, Greece
E. Papadopoulou. GeneKor Medical SA, Gerakas, Greece
G. Nasioulas. GeneKor Medical SA, Gerakas, Greece

AIM

Endocrine therapy (ET) represents the first line treatment for patients with ER+, HER2- breast cancer, however disease progression is observed in many cases. PIK3CA and ESR1 are the most encountered mutated genes that have been associated with targeted molecular treatment, as well as with resistance to Endocrine Therapy. Liquid biopsy is a non-invasive procedure, that can provide “real-time” monitoring of disease progression and response to treatment. The aim of this study is to determine the mutation rate of ESR1 and PIK3CA genes in a selected cohort of 200 Greek breast cancer patients, using liquid biopsies and NGS technology.

PATIENTS AND METHODS

Liquid biopsies were collected from 200 ER-positive, HER2-negative metastatic breast cancer patients who have received at least one previous line of endocrine treatment. cfDNA was extracted using the QIAamp Circulating Nucleic Acid Kit (Qiagen). Library preparation was performed using Oncomine™ Breast cfDNA Research Assay (ThermoFisher Scientific) and sequencing was carried out using Ion GeneStudio™ S5 System (ThermoFisher Scientific). Ion

Torrent Oncomine Knowledgebase Reporter was used in sequence analysis and interpretation of Copy number variations, SNPs, and indels.

RESULTS

Preliminary data of the first 49 examined samples demonstrated the prevalence of ESR1 and PIK3CA mutations in 20.4% (10/49) and 38.7% (19/49) of the cases respectively. The most frequently mutated codon in the ESR1 gene is the Y537, while in the PIK3CA gene, the H1047 codon is mainly altered. ESR1 and PIK3CA genes were co-mutated in 10.2% of the cases. Mutations in KRAS (6.1%) and TP53 (24%) were also detected.

CONCLUSION

More than 20% of the ER-positive, HER2-negative breast cancer patients with metastatic disease are eligible for targeted treatment with elacestrant. In addition, the high prevalence of mutations detected in our cohort indicates that liquid biopsy NGS panel testing can be used to monitor treatment response, track the development of resistance, and identify emerging genetic alterations that may guide treatment adjustments or the selection of alternative targeted therapies in breast cancer patients.

REFERENCES

1. Demir Cetinkaya B, Biray Avci C. Molecular perspective on targeted therapy in breast cancer: a review of current status. *Med Oncol.* 2022 Jul 14;39(10):149. doi: 10.1007/s12032-022-01749-1. PMID: 35834030; PMCID: PMC9281252.
2. Liao H, Huang W, Pei W, Li H. Detection of ESR1 Mutations Based on Liquid Biopsy in Estrogen Receptor-Positive Metastatic Breast Cancer: Clinical Impacts and Prospects. *Front Oncol.* 2020 Dec 15;10:587671. doi: 10.3389/fonc.2020.587671. PMID: 33384956; PMCID: PMC7770162.
3. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer>

PO5-04-14

Quality of Life (QoL) among metastatic hormone receptor positive, HER2 negative breast cancer patients during first line systemic treatment

Presenting Author(s) and Co-Author(s):

D. Gagliato. Hospital Beneficência Portuguesa, São Paulo, Brazil, Brazil

J. Antonio Araujo. BP, United States

B. Milena Verboski. BP de Sao Paulo, United States

G. William Marcelino. BP de Sao paulo, United States

F. Nogueira Momberg. BP de Sao Paulo, United States

G. Silveira da Silva. Bp de Sao Paulo, United States

R. Mesquita Ciconelli. Bp de Sao paulo, United States

A. Buzaid. Centro Oncológico Antonio Ermírio de Moraes - Beneficência Portuguesa de São Paulo, United States

Background

Current international guidelines recommend endocrine therapy combined with a CDK4/6 inhibitor as the preferred first line systemic treatment in patients diagnosed with metastatic hormone receptor positive (HR), HER2 negative breast cancer (BC). Randomized controlled trials that led to the approval of these agents in the first line disease setting are derived from controlled environments and selected patients. We aimed to assess real-world patients' characteristics, safety and health related quality of life in a non-select cohort of patients being managed in a Brazilian private Cancer Center.

Methods:

We performed a cross sectional study at Beneficencia Portuguesa de Sao Paulo evaluating quality of life among patients with metastatic HR+/HER2 negative treated in the first line disease setting. Inclusion criteria included patients that received the combination of a CDK4/6i with any endocrine therapy (ET) between January 2018 and April 2023. Primary endpoint was quality of life assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC QLQ-BR23, it is baseline, there is only one measurement for each patient.

Results:

We analyzed 72 patients who meet the inclusion criteria. Median age at diagnosis was 49 years old (ranging from 31 to 91). Approximately half of the population was premenopausal (51%). Palbociclib and abemaciclib were the most commonly used CDK4/6i, with 42 and 35% of patients, respectively. ECOG performance status was zero or one in almost the entire patient population analyzed (97%). 53% of the patients were diagnosed as de novo metastatic BC. Table 1 and 2 summarize the patients characteristics. Mean global health status was 75.4, with social and cognitive functioning scoring the highest (Mean 78.6 and 79.1, respectively). The most distressing symptom among the symptom scale was fatigue (Mean 27.2). Most symptoms and functioning scales did not meet the threshold for clinically meaningful differences between the different CDK4/6 inhibitors.

Conclusion:

Real-world data from our study is consistent with the historical expected health related quality of life among patients diagnosed with HR+/HER2 negative metastatic BC in the first line disease setting.

Table 1 –Baseline patient characteristics

Baseline characteristics		
Age, median (range)	55 (35-94)	
Age at diagnostic, median (range)	49 (31-91)	
Sex		
Female, n (%)	72 (100)	
Menopausal status		
Premenopausal	37 (51%)	
Postmenopausal	33 (46%)	
Unknow	2 (3%)	
Smoking status		
Never smoker	53 (96%)	
Former smoker	1 (2%)	
Smoker	1 (2%)	
Ethylism		
No	57 (97%)	
Yes	2 (3%)	
Performance status (ECOG)		
0-1	70 (97%)	
≥2	2 (3%)	
Body mass index, Kg/m ² , median (range)	26 (17,8-39,5)	
<i>de novo</i> mBC	38 (53%)	
Recurrent	34 (47%)	
Sites of metastases	<i>de novo</i> mBC	Recurrent
Bone	73%	50%
Lymph nodes	42%	35,3%
Visceral (Lung, Liver and Peritonium)	47,4%	38%
Central Nervous System	-	11,7%
Histology		
IDC	78%	
ILC	19%	
Other	3%	

Table 2 – Therapeutic intervention

Time of treatment, median (range)	xxx
CK4/6i	
Abemaciclib	25 (35%)
Palbociclib	30 (42%)
Ribocilib	17 (24%)
Endocrine therapy	
Aromatase inhibitor	31 (43%)
Fulvestrant	14 (19,5%)

PO5-05-01

ASSESSING THE CLINICAL AND SURVIVAL RESULTS OF PATIENTS WITH HR-POSITIVE, HER2 NEGATIVE ADVANCED BREAST CANCER TREATED WITH CDK 4/6 INHIBITORS IN A SPANISH COHORT

Presenting Author(s) and Co-Author(s):

A. Cano-Jimenez. Hospital Universitario de Jaen, United States

R. Urbano-Cubero. Hospital Universitario de Jaen, United States

R. Garcia-Muñoz. Hospital Universitario de Jaen, United States

A. Jaen-Morago. Hospital Universitario de Jaen, United States

M. Lomas-Garrido. Hospital Universitario de Jaen, United States

P. Sánchez-Rovira. Hospital Universitario de Jaén, Jaén, Spain, Andalucía, Spain

BACKGROUND

First line treatment of HR-positive, HER2 negative advanced breast cancer is based on endocrine therapy plus CDK 4/6 inhibitors (CDK 4/6i). Recently, there has been published in ASCO 2023 results from SONIA trial, which explores the use of CDK 4/6i in second-line treatment after monotherapy with endocrine therapy. This trial have shown using a CDK4/6i in the first-line setting did not significantly prolong the time from random assignment to progression on second-line therapy (PFS2) or overall survival (OS) when compared with deferred use until the second-line setting.

METHODS

We conducted a descriptive, observational and retrospective analyses of patients treated in our centre with CDK4/6i, comparing demographic, clinical and survival results. We also analysed different outcomes between first versus second line CDK4/6i.

RESULTS

A cohort of 153 patients were included, treated between January 2018 and June 2023, with a median age of 50 years.

At diagnosis, 49% were stage I-II and 31% stage IV. 59% had visceral metastases at the start of CDK4/6i treatment. Palbociclib was the most commonly CDK4/6i used (55%), followed by Ribociclib (32%) and Abemaciclib (12.5%). The most widely endocrine therapy used was letrozole (60%), followed by fulvestrant (38%). 58% received CDK4/6i in first-line setting while 9% received them in second-line.

The overall median progression-free survival (mPFS) was 18 months. In a subgroup analysis, the mPFS was 19 months with Palbociclib, 26 months with Ribociclib, and 31 months with Abemaciclib. Baseline characteristics were similar between subgroups of CDK4/6i.

Better survival data were obtained with letrozole than with fulvestrant (not reached versus 29 months OS respectively).

After CDK4/6i disease progression the most common subsequent treatment was chemotherapy (capecitabine, 23%).

The median OS with palbociclib and abemaciclib was 37 months, while not reached with

ribociclib.

We analysed PFS2 using CDK4/6i in the first-line setting compared with deferred use until the second-line. The use of CDK4/6i in second-line showed a PFS2 of 45 months, while first-line PFS2 was 26 months.

CONCLUSIONS

Our study results are consistent with previous studies assessing the efficacy of cyclin inhibitors in first and second-line setting.

Palbociclib seems to have a lower PFS rate. Patients treated with letrozole had a statistically significant benefit in survival outcomes.

Our data continue the trend observed in the SONIA trial in terms of PFS2.

Using endocrine therapy as first-line monotherapy may be a valid treatment option.

However, larger sample sizes are required to draw definitive conclusions. The identification of potential predictors of treatment response may help in the selection of the most effective treatment for patients with HR-positive HER2 negative advanced breast cancer.

PO5-05-02

Discovery of BTX-9341, a bifunctional degrader of CDK4 and CDK6 for HR+/HER2- breast cancer.

Presenting Author(s) and Co-Author(s):

H. Majeski. Biotheryx, United States
A. Okano. Biotheryx, United States
K. Chahal. Biotheryx, United States
A. Pasis. Biotheryx, United States
C. Carlson. Biotheryx, United States
A. Shakya. Biotheryx, United States
Q. Liu. Biotheryx, United States
S. Huang. Biotheryx, United States
A. Hoskote Chourasia. Biotheryx, United States
L. Fung. Biotheryx, United States

CDK4/6 inhibitors (CDK4/6i) such as palbociclib, abemaciclib and ribociclib are used to treat HR+/HER2- breast cancer, but patients can develop resistance via many mechanisms, several of which converge on the upregulation of cyclin D-CDK4/6 signaling node. This has been shown to limit the effectiveness of CDK4/6i in ER+ breast cancer with up to 20% patients exhibiting innate resistance and up to 70% patients developing acquired resistance after 3 years on therapy (Scheidemann, 2021). To address acquired resistance, we sought a degrader approach. We utilized our PRODEGY platform of Cereblon (CRBN) binders to synthesize CRBN mediated CDK4/6 bifunctional degraders and identified BTX-9341 as a development candidate due to its potency in vitro, in CDK4/6i resistant models and its effectiveness at inhibiting tumor growth in vivo. Degradation of CDK4/6 by immunoblot analysis of the triple negative breast cancer (TNBC) cell line, MDA-MB-231, treated with BTX-9341 for 6 hours showed up to 85% degradation of CDK4 and CDK6 with DC₅₀s of < 1nM. Similar degradation depth and DC₅₀ values were seen in HR+ breast cancer cells including T47D, MCF7 and ZR-751. CDK4/6 phosphorylates the protein RB which releases the transcription factor E2F, inducing the expression of genes which promote cell cycle progression. To determine the effect of CDK4/6 degradation on downstream signaling, we examined RB phosphorylation by in-cell western. Twenty-four hours treatment with BTX-9341 blocked RB phosphorylation robustly, with phospho-RB IC₅₀s at < 30nM in HR+ breast cancer cells as well as MDA-MB-231 cells. Cell cycle analysis by staining with propidium iodide after 24 hours of treatment with BTX-9341 caused G0/G1 cell cycle arrest at concentrations as low as 10nM. We used a 2D colony formation assay (CFA) as a readout for inhibition of proliferation by cell cycle arrest. BTX-9341 showed potent inhibition of cell proliferation with CFA IC₅₀s of < 50nM in TNBC cell lines and < 20nM in HR+ cell lines. We demonstrated that BTX-9341 was significantly more potent in vitro than the CDK4/6i, which had CFA values between 50 and 700nM in HR+ cell lines and between 100 and 1000nM in TNBC. This increased activity was due to CRBN mediated target degradation, as demonstrated by a shift in CFA IC₅₀ values in a CRBN knockout cell line towards the values seen with the inhibitors. In palbociclib-resistant HR+/HER2- cell lines models which exhibit high CDK6 expression, BTX-9341 maintained a low CFA IC₅₀ (< 150nM) while other CDK4/6 inhibitors displayed micromolar CFA IC₅₀s. BTX-9341 displays excellent pharmacokinetic properties and oral bioavailability, which allowed for oral dosing in xenograft

studies. MCF7 xenograft results with BTX-9341 showed dose-dependent tumor growth inhibition, tumor regression at higher doses and overall greater potency compared to the clinical CDK4/6i. BTX-9341 shows good exposure in the brain and exhibits tumor growth inhibition in an intracranial MCF-7 xenograft model, indicating that BTX-9341 could inhibit the growth of brain metastases. These results show that BTX-9341 displays excellent single agent activity in vitro and in vivo particularly in comparison to clinically approved CDK4/6i and that this activity is maintained in CDK4/6i resistant models. This indicates that a degrader approach to targeting this pathway may be more effective than current therapies, and that using this modality in a post CDK4/6i setting may be more effective than switching CDK4/6 inhibitors.

Reference: Scheidemann, Erin R, and Ayesha N Shajahan-Haq. "Resistance to CDK4/6 Inhibitors in Estrogen Receptor-Positive Breast Cancer." *International journal of molecular sciences* vol. 22,22 12292. 14 Nov. 2021, doi:10.3390/ijms222212292

PO5-05-03

Phase 1/2 Dose Expansion Study Evaluating First-In-Class eIF4A Inhibitor Zotatifin in Patients with ER+ Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

E. Rosen. Memorial Sloan Kettering Cancer Center, New York, New York, United States

M. Sharma. START Midwest, United States

D. Berz. Valkyrie Clinical Trials, United States

J. Caswell-Jin. Stanford, Stanford, California, United States

G. Fulgar. eFFECTOR Therapeutics, United States

M. Densel. eFFECTOR Therapeutics, United States

G. Chiang. eFFECTOR Therapeutics, United States

S. Sperry. eFFECTOR Therapeutics, United States

D. Warner. eFFECTOR Therapeutics, United States

F. Meric-Bernstam. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background

Zotatifin (eFT226) is a first-in-class, potent and sequence selective inhibitor of RNA helicase eIF4A that promotes a stable mRNA:eIF4A:drug ternary complex at specific polypurine motifs present within the 5'-UTR of select transcripts, thereby blocking production of the encoded proteins. In preclinical models zotatifin treatment simultaneously down-regulated translation of numerous oncogenes including CDK4, ER α , ERBB2, KRAS, and CCND1. Previous clinical research has demonstrated the activity of zotatifin in combination with other agents in ER+ metastatic breast cancer (MBC).

Methods

Part 1 is a 3+3 dose escalation portion of the protocol followed by Part 2 as a Simon's two-stage design in patients with ER+ MBC enrolled at the recommended phase 2 dose (RP2D) of zotatifin (0.07 mg/kg IV two weeks on/one week off) in combination with fulvestrant (ful) and abemaciclib (abema) (Z+F+A). Part 1a and Part 1b are 3+3 dose escalation portions evaluating zotatifin in combination with ful (Z+F) at QW IV and Q2W IV dosing schedules, respectively. Key eligibility criteria included at least one line of therapy for advanced/metastatic disease, progression on hormone therapy, and in addition, the Z+F cohorts required prior CDK 4/6 inhibitor (CDKi). Primary endpoint of Part 1a/1b was determination of RP2D and primary endpoint of part 2 was objective response rate (ORR) per RECIST v1.1. Additional endpoints included safety, progression-free survival (PFS) and other efficacy analyses, and characterization of pharmacodynamic (PD) markers and pharmacokinetics.

Results

As of a data cut-off of July 6, 2023, 20 pts were enrolled in the Z+F+A cohort and had a median of four prior metastatic lines of therapy. In 19 evaluable pts in Z+F+A cohort, there were four confirmed partial responses (PR), one unconfirmed PR, and 10 pts with best overall response (OR) of stable disease (SD). All pts with PR/unconfirmed PR received prior CDKi, ful, and chemotherapy for MBC. Confirmed PRs were observed in patients with and without mutations in ESR1 and PIK3CA. mPFS, while not yet mature, exceeds 20 weeks. In Z+F+A the most common adverse events (AEs) were diarrhea (80%, all grades (Gr)) and nausea (75%, all Gr

1/2) and the most common Gr 3/4 AE was diarrhea (15%). In Z+F cohorts of 0.07 mg/kg QW (n=3), 0.1 mg/kg Q2W (n=3), and 0.14 Q2W (n= 2) there were no dose-limiting toxicities or Gr 5 adverse events (AEs). There was one confirmed PR and one SD in 0.1 and 0.14 mg/kg Q2W cohorts, respectively, and no PR or SD in the 0.07 mg/kg QW cohort. In Z+F+A, 9 pts had paired pre- and on-treatment ctDNA analyzed by Guardant assay. Of the remaining 11 pts, 4 came off study prior to scheduled collection of the on-treatment sample and 5 had unavailable samples. Of the 9 patients with paired samples, 8 had ctDNA decreases of >50%, all of whom had SD or PR. In the Z+F Q2W cohort, 2 of 3 patients had ctDNA decreases >50%, one of whom had a PR. Reduction below the limit of detection was seen for mutant alleles in ESR1, PIK3CA and other genes with potential to confer resistance to endocrine therapy.

Conclusion

Z+F+A showed encouraging efficacy in heavily pretreated ER+ MBC patients, with results that compare favorably to other treatment options available after progression on CDKi plus endocrine treatment. Efficacy was seen independent of ESR1 or PIK3CA mutations, suggesting the potential to treat a broad, unrestricted patient population. Initial results with Z+F Q2W dosing are encouraging and support continued dose escalation of this regimen.

PO5-05-04

Advancing Treatment and Management of Patients with HR+/HER2- Breast Cancer: Findings from a Quality Improvement Initiative

Presenting Author(s) and Co-Author(s):

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

C. Anderson. PRIME Education, United States

I. Dewald. PRIME Education, United States

J. Carter. PRIME Education, United States

C. Heggen. PRIME Education, United States

K. McKinnon. PRIME Education, Georgia, United States

Background: With the advent of novel oral oncolytics, the cancer care delivery model for HR+/HER2- breast cancer (BC) is evolving, shifting the responsibility for medication adherence and monitoring and managing of side effects to patients and their caregivers. In this quality improvement (QI) initiative, we aimed to uncover and address gaps in patient and provider education, risk reduction, adverse event management, and shared decision-making in order to improve outcomes for HR+/HER2+ patients on oral oncolytics.

Methods: From 9/2022 to 12/2022, 54 HCPs who treat breast cancer and 111 HR+/HER2- BC patients from 4 US community oncology clinics completed surveys assessing attitudes, values, and challenges related to practice patterns, education, and therapy adherence in HR+/HER2- BC. HCPs participated in audit-feedback sessions to reflect on survey results and their own practice, and developed action plans to improve care, which were implemented in subsequent collaborative patient-provider learning sessions.

Results: Top reported HCP challenges in HR+/HER2- BC care include providing patient-centered supportive care measures (32%), patient adherence/lack of follow up (22%), and individualizing treatment plans (17%). Additionally, 43% of providers reported that improved collaboration across interprofessional teams would most improve care. Top reported patient challenges include worry about and/or difficulty managing side effects from treatment (26%), difficulty scheduling visits with many different HCPs/following up (24%), and difficulty communicating with healthcare teams (16%). In surveys, 28% of patients reported frequently or very frequently missing/skipping doses of oral breast cancer medication. Top reasons for missing/skipping doses included forgetting or not having it nearby (36%), cost (21%), and side effects (20%). To address the top challenges identified in baseline surveys, HCPs developed and implemented action plans, such as improving the identification of patients at high risk of recurrence, establishing patient-provider educational sessions, increasing the use of patient navigators, incorporating oral adherence toolkits, and educating patients and staff about available supportive care resources. After implementation of patient-provider collaborative education sessions at community clinics, patients reporting high levels of knowledge about BC treatment options and communicating side effects/symptoms increased from 27% to 57%, and 37% to 77%, respectively. At 60-day follow-up, 58% of patients reported taking a more active role in treatment decision-making, and 52% reported setting reminders/alarms/using apps to remember to take medication on time.

Conclusions: Patient adherence to oral oncolytic medications remains a challenge in BC treatment. This quality improvement initiative uncovered underlying barriers to effective

treatment management of HR+/HER2- breast cancer patients on oral oncolytics. Action plans and educational resources were developed and implemented to address identified barriers and optimize treatment management for HR+/HER2- BC. These methods and findings represent key opportunities for improvement that can be implemented in community oncology practices to improve adherence to oral oncolytics and overall HR+/HER2- breast cancer care.

PO5-05-05

Clinical outcomes of CDK4/6 inhibitors in patients with bone only metastatic breast cancer

Presenting Author(s) and Co-Author(s):

M. Mardani. Washington University in St. Louis School of Medicine, saint louis, United States

S. Noordeen. Washington University in St. Louis School of Medicine, United States

K. Clifton. Washington University in St Louis School of Medicine, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

J. Luo. Washington University in St Louis School of Medicine, United States

J. Xi. Washington University in St. Louis School of Medicine, United States

N. Bagegni. Washington University in St Louis School of Medicine, United States

F. Ademuyiwa. Washington University in St Louis School of Medicine, United States

R. Suresh. Washington University in St Louis School of Medicine, United States

A. Frith. Washington University in St Louis School of Medicine, United States

A. Davis. Washington University in St Louis School of Medicine, United States

R. Bose. Washington University School of Medicine, St. Louis, Missouri, United States

L. Peterson. Washington University in St Louis School of Medicine, St. Louis, Missouri, United States

S. Thomas. Washington University in St. Louis School of Medicine, Fenton, Missouri, United States

Y. Tao. Washington University St. Louis MO, United States

T. Kobayashi. Washington University in St. Louis School of Medicine, United States

J. Xiang. Washington University in St. Louis School of Medicine, United States

Y. Xu. Washington University in St.Louis school of medicine, United States

X. Su. Washington University in St.Louis, school of Medicine, United States

K. Weilbaecher. Washington University School of Medicine, United States

Background: CDK4/6 inhibitors (CDK 4/6i) have significantly advanced the treatment of hormone receptor-positive (HR+) metastatic breast cancer in the last decade. Several clinical trials including PALOMA, MONALEESA, and MONARCH have shown improved progression-free survival (PFS) rates when CDK4/6i were combined with endocrine therapy (ET). These results led to recommending their use in combination with ET as the first line of therapy in the metastatic settings. Bone metastasis is the most common site of disease in patients with HR+ metastatic breast cancer, about 40% of whom have bone as the only site of metastasis (bone-only disease [BoD]). While previous studies have shown that BoD can have a unique clinical course and a more favorable prognosis compared to non-BoD metastasis, most of the aforementioned CDK 4/6i clinical trials have not shown significant improvements in PFS in BoD subset of patients. Here we aimed to investigate the survival outcomes of BoD patients at a single institution center and evaluate CDK 4/6i activity in preclinical models of bone metastasis in breast cancer.

Patients and methods: Patients with HR+, HER2-negative metastatic breast cancer from a retrospective CDK4/6i study at Washington University School of Medicine were included in this

analysis. We selected all the patients who received CDK4/6i in the first- or second-line settings from June 2014 to March 2020. Outcomes were collected through June 10, 2023. The Kaplan-Meier method with log rank test and multivariable cox model were used for survival analysis.

Results: 114 female patients (n=75 first line, n=39 second line, n=20 African American, n=94 Caucasian) were included in this study. All patients received Palbociclib as the first exposure to CDK4/6 inhibitor in combination with ET for at least two months. Median age was 60 years (range, 28-87) and forty-seven patients (41%) were in the BoD group. Survival outcomes for BoD group were compared to the rest of patients who had either bone and visceral or visceral only metastatic lesions (BV group). Our results demonstrated a significantly reduced median PFS in BoD group compared to BV group (13.1 months [95%CI:8-18.2] vs 19.6 months [95%CI:6.8-32.4], $p=0.01$) respectively. There was no significant difference in overall survival between BoD and BV groups (36.6 months [95%CI:32.2-41] vs 41.7 months [95%CI 36.1-47.2] $p=0.74$) respectively. In multivariate analysis regarding the associated risk factors with PFS, after adjusting for age and race, BoD had a HR of 1.62 (95%CI:1.04-2.54) for PFS. Among the 75 patients who received CDK4/6i as their first line of therapy, BoD (n=32 patients [42.7%]) also showed an inferior ($p=0.05$) median PFS (20 months [95%CI 12.9-27]) compared to BV group (n=43 patients [57.3%], median PFS=28.4 months [95%CI: 16.3-40.4]).

To investigate potential treatment resistance mechanisms in bone metastases, we used the triple negative 4T1 and the ER+ luminal B PyMT Bo1 breast tumor cell line derived mammary gland models in immunocompetent mice. Single agent CDK4/6i, ribociclib, decreased primary mammary gland tumor burden. This effect was abrogated when CD8+ T-cells were depleted. In the bone colonization model using these cell lines, ribociclib had little effect on bone tumor burden. Arg1+ immune suppressive macrophages were significantly decreased in the primary mammary tumor but not in the bone tumor after ribociclib administration, suggesting a relative treatment resistance and immune suppression in the bone tumor microenvironment compared to the primary mammary gland.

Conclusion: CDK4/6i play a significant role in the treatment of patients with HR+ metastatic breast cancer. Our single institution, retrospective study and preclinical data suggests that CDK4/6i may not be as effective for the treatment of tumors residing in the bone microenvironment, warranting future studies to understand the mechanisms of CDK4/6 inhibitors action in bone versus visceral metastases.

PO5-05-07

Efficacy and safety of first line CDK4/6i plus endocrine therapy for patients with HR+/HER2- metastatic breast cancer:initial real-world experience at Ho Chi Minh city oncology hospital, Viet Nam

Presenting Author(s) and Co-Author(s):

H. Nguyen. HCMC, Oncology Hospital, United States

H. Phan-Thi. HCMC Oncology Hospital, United States

T. Le. HCMC Oncology Hospital, United States

Background

The cyclin-dependent kinases (CDK)4/6 inhibitors (CDK4/6i) palbociclib and ribociclib have been available in Viet Nam since 2021 for the treatment of hormone receptor-positive metastatic breast cancer (MBC). Data regarding CDK4/6i benefit in Vietnamese MBC are sparse. This study evaluated the impact of CDK4/6i in first-line HR⁺/HER2⁻ MBC using real-world experience at Ho Chi Minh City Oncology Hospital.

Methods

A single-institution study analyzed retrospective data from 108 patients treated with palbociclib or ribociclib with endocrine therapy in first-line in HR+/HER2- MBC patients at Ho Chi Minh city oncology hospital. Patient characteristics, PFS, treatment response, and toxicity profiles were analyzed.

Results

Baseline patients' characteristics are detailed in Table 1. The median follow-up was 12.5 months (95% CI: 10.9-13.3). Best responses by the line of therapy are in Table 2. The median PFS has still not been reached. The PFS rates at 6, 12 and 18 months were 94.4%, 93.5% and 91.5%, respectively. Patients with bone-only metastasis have a better PFS than visceral metastasis ($p = 0.059$). Patients with recurrent disease had shorter PFS ($p = 0.083$) than those presenting with de novo metastasis. The most common reasons for toxicity were neutropenia (92.6%), anemia (35.2%), thrombopenia (22.2%) and the incidence of diarrhea was only 2,8%. None were related to QTc-prolongation

Table 1. Patient Demographics and Baseline Disease

Characteristics (N=108)

Characteristics	N (%)
Age, y: Median	52
Stage	
Recurrent from earlier stage, stages 0–III	67 (62)
De novo, newly diagnosed stage IV at enrolment	41 (38)

DFI	
< 12 months	5 (4.6)
12-24 months	12 (11.1)
> 24 months	51 (47.2)
<hr/>	
No. of metastatic sites	
1	49 (45.4)
2	37 (34.3)
≥ 3	22 (20.4)
<hr/>	
Metastasis pattern	
Bone only	30 (27.8)
Other	78 (72.2)
<hr/>	
CDK4/6i	
Palbociclib	35 (32.4)
Ribociclib	73 (67.6)
<hr/>	
Partner ET	
Als	94 (87)
Fulvestrant	14 (13)
<hr/>	

Table 2. Best responses of therapy (N=108)

Best responses (N,%)

CR	2 (1.9)
----	---------

PR	29 (26.9)
SD	67 (62.1)
PD	10 (9.3)
Total	108 (100)
ORR	31 (28.8)
CBR	76 (70.3)

CBR

Conclusion The real-world effectiveness and safety with CDK4/6 inhibitors in our institution HR+/HER2- MBC patients mimics that observed in the clinical trials. This finding supports the use of CDK4/6i in combination with endocrine therapy as standard of care for HR+/HER2- MBC in Viet Nam. The study also suggests the need for more study of under-represented minority populations. Further studies are ongoing to validate these findings incorporating additional cancer centers. **Keywords:** advanced/metastatic breast cancer, Asia, CDK4/6 inhibitors, real world

Table 1. Patient Demographics and Baseline Disease

Characteristics (N=108)	N (%)
Age, y - Median	52
Stage	
Recurrent from earlier stage, stages 0-III	67 (62)
De novo, newly diagnosed stage IV at enrolment	41 (38)
DFI	
< 12 months	5 (4.6)
12-24 months	12 (11.1)
> 24 months	51 (47.2)
No. of metastatic sites	
1	49 (45.4)
2	37 (34.3)
≥ 3	22 (20.4)
Metastasis pattern	
Bone only	30 (27.8)
Other	78 (72.2)
CDK4/6i	
Palbociclib	35 (32.4)
Ribociclib	73 (67.6)
Partner ET	
Als	94 (87)
Fulvestrant	14 (13)

Table 2. Best responses of therapy (N=108)

	Best responses (N,%)
CR	2 (1.9)
PR	29 (26.9)
SD	67 (62.1)
PD	10 (9.3)
Total	108 (100)
ORR	31 (28.8)
CBR	76 (70.3)

PO5-05-08

LOSS OF SINGLEMINDED 2S RESULTS IN A PI3K SUBUNIT SWITCH WHICH DRIVES THERAPEUTIC RESISTANCE IN ESTROGEN RECEPTOR POSITIVE BREAST CANCER

Presenting Author(s) and Co-Author(s):

G. Wyatt. Texas A&M University, United States

R. Steinmetz. CU Anschutz Medical Campus, United States

T. Lyons. CU Anschutz Medical Campus, United States

W. Porter. Texas A&M University, United States

Estrogen receptor (ER) + breast cancer (BC) comprises over 70% of BC cases and are targeted via ER modulated therapies. Despite this, ER+BC patients can experience recurrence within 20 years and the majority of BC related deaths can be attributed to metastatic ER+BC. These distant metastases are commonly diagnosed as endocrine therapy resistant. Thus, there is an unmet need to identify novel biomarkers for treating ER+ patients with metastases. We have identified a tumor suppressor gene, single-minded 2s (SIM2s), expressed in breast epithelial cells that inhibits epithelial to mesenchymal transition and metastasis, and is downregulated in the progression of breast disease. In ER+BC cell lines, loss of SIM2s results in upregulation of mesenchymal markers and increased PI3K/Akt signaling. Dysregulation of the PI3K/Akt signaling pathway in ER+BC is involved with tumor progression and acquired therapeutic resistance. Our study suggests loss of SIM2s confers resistance in ER+BC through a PI3K subunit switch resulting in upregulation of pro-survival signaling. MCF7 SIM2 knock out cells exhibit increased expression of mesenchymal markers and undergo a phenotypic change compared to wild type cells. Utilizing a migration/invasion assay, MCF7 SIM2 knock out cells exemplify an increase in invasion potential compared to wild type cells. Furthermore, changes in PI3K subunit expression were observed via western blot and real time qPCR analysis. Clonogenic assays revealed an acquired resistance to PI3K α inhibition, but a susceptibility to PI3K δ inhibition. This is a significant finding as a current standard of care for patients with ER+ breast cancer recurrence is PI3K α inhibition. PI3K δ is an already approved therapeutic target in chronic lymphocytic leukemia, thus PI3K δ may present a new therapeutically targetable opportunity for ER+BC recurrence. Elucidating the mechanism for acquired therapeutic resistance is an integral avenue for understanding how breast cancer progresses and improving the prognosis of ER+BC patients.

PO5-05-09

Testing AI-Predicted Protein Motifs that Direct Constitutive Genomic AR Activity in Endocrine Resistant Breast Cancer

Presenting Author(s) and Co-Author(s):

A. Khan. University of Houston, Houston, Texas, United States

A. Peidl. University of Houston, United States

S. Bahnassy. Georgetown University, United States

H. Vo. AbbVie, United States

M. Castillo. UH Seq-N-Edit Core (SNEC), University of Houston, United States

S. Herzog. Baylor College of Medicine, United States

S. Fuqua. Baylor College of Medicine, United States

P. Gunaratne. University of Houston, United States

X. Gao. University of Houston, United States

S. Pakhrin. University of Houston-Downtown, United States

T. Bawa-Khalfe. University of Houston, United States

Testing AI-Predicted Protein Motifs that Direct Constitutive Genomic AR Activity in Endocrine-Resistant Breast Cancer Ashfia F. Khan ^{1,2}, Anthony S. Peidl ^{1,2}, Shaymaa Bahnassy ³, Henry Vo ², Micah B. Castillo ², Sarah K Herzog ^{4,5}, Suzanne AW Fuqua ^{4,6}, Preethi Gunaratne ², Xiaolian Gao ², Subash C. Pakhrin ⁷, Tasneem Bawa-Khalfe ^{1,2} ¹ Center for Nuclear Receptors & Cell Signaling, University of Houston, Houston, TX ² Department of Biology & Biochemistry, University of Houston, Houston, TX ³ Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC ⁴ Lester & Sue Smith Breast Center, Baylor College of Medicine, Houston, TX ⁵ Program in Integrative Molecular and Biomedical Sciences, Baylor College of Medicine, Houston, TX ⁶ Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX ⁷ Department of Computer Science & Engineering Technology, University of Houston-Downtown, Houston, TX Background: Endocrine therapy (ET) remains the first-line treatment for hormone-receptor positive (HR+) breast cancer (BCa). Approximately 15–20% of HR+ BCa are intrinsically resistant to ET, and 30–40% of patients acquire resistance. Resistance to ET (ET-R) supports cancer progression with reduced disease-free survival and greater incidence of metastatic disease. Hence, therapeutic strategies for ET-R HR+ BCa remain an overarching challenge. The androgen receptor (AR) is emerging as an attractive alternative target for BCa subtypes, and elevated AR levels drive HR+ BCa progression. Targeting AR in HR+ BCa is proving difficult with preclinical studies showing conflicting results for AR antagonists. Yet clinical trials with several AR-targeting drugs are ongoing. Our recent report highlights a unique constitutively active modified AR population that drives HR+ BCa metastatic properties and is insensitive to AR inhibitors. Our current objectives are to 1) use a novel machine-learning model to predict AR modifications and 2) establish a strategy to identify patients with high modified AR levels. Methods: An advanced artificial intelligence (AI) tool and mid-throughput microfluidic peptide array technology were used to map modification domains on AR. SUMO post-translational modification of AR (SUMO-AR) was eliminated in HR+ BCa using CRISPR-Cas9 technology. RNA-seq was employed to identify a unique gene signature for SUMO-AR, and comparative bioinformatic analysis stratified patients with high versus low SUMO-AR. Results:

A novel deep-learning AI platform SumoPred-PLM is trained to identify consensus, non-consensus, and SUMO2/3-specific motifs on AR. We verified SUMO2/3-specific sites on AR with a mid-throughput microfluidic peptide array. The identified SUMO2/3-acceptor site of AR is important for HR+ BCa cell pathophysiology; loss of this SUMO2/3-acceptor site impacts endogenous AR SUMOylation, cell morphology, and proliferation/ apoptosis. Using both high and low SUMO-AR BCa lines, a unique SUMO-AR gene profile was established. Our SUMO-AR gene signature identifies HR+ BCa patients with greater susceptibility to metastatic progression. Conclusion: Our studies present a unique pipeline that incorporates deep-learning AI technology to identify vulnerable motifs in AR for future drug discovery. Drug screens are currently ongoing. In addition, we establish a SUMO-AR gene signature that stratifies HR+ BCa patients with high/low SUMO-AR and predicts disease progression. We expect the results could be utilized to identify responders to AR inhibitors in ongoing clinical trials.

PO5-05-10

Analysis of Trends in Funding of Metastatic Breast Cancer Research

Presenting Author(s) and Co-Author(s):

M. Flowers. Breast Cancer Research Foundation, New York, New York, United States

T. Pollastro. University of Washington, Mercer Island, Washington, United States

K. Wojtanik. Susan G. Komen®, United States

K. McKenzie. California Breast Cancer Research Program, United States

K. Badovinac. Canadian Cancer Research Alliance, United States

M. Deoras-Sutliff. Metastatic Breast Cancer Alliance, United States

L. Davies. International Cancer Research Partnership, United States

Introduction To inform funding strategies for research in metastatic breast cancer (MBC), knowledge of the current research landscape and identification of potential gap areas requiring additional research are essential. In 2014, the Metastatic Breast Cancer Alliance (MBCA) published an analysis that showed that between 2000 and 2013, only 7% of all funds for breast cancer research were devoted to metastasis. As more people are living with MBC, addressing research priorities for those living with the disease is important, as is understanding gaps in the current funding landscape of MBC research to appropriately target investment. Methods A collaborative effort between funders and patients was undertaken to analyze breast cancer projects funded between 2014 and 2020 from the International Cancer Research Partnership database, the Health Resource Alliance database, and MBCA members, representing grants from 83 non-profit organizations worldwide. Project titles, abstracts, and classifications of these grants were extracted from these databases. Next, to identify research projects in the databases that are related to metastasis, a classification tool that uses a machine learning algorithm was built, trained on manually coded grants from the 2000-2013 analysis, and validated by expert coders. Projects were then coded according to a pre-established metastasis classification policy to categories such as type of research (e.g., treatment), genes or proteins studied, site of metastasis, breast cancer subtype, and patient priority questions. In terms of the latter, MBCA members living with MBC were surveyed about research priorities. Member advocates ranked survey questions according to highest patient priority, and these were converted to language that could be queried with the tool. Results Investment in MBC research nearly doubled from 2014 to 2020. Research into understanding and overcoming treatment resistance, which was the highest patient priority question, increased from 15% in 2014 to 26% of the MBC portfolio in 2020; this was a statistically significant increase above the rate of inflation. In terms of treatment resistance according to subtype, the highest number of projects focused on triple-negative MBC (>300). By contrast, < 20 projects were focused on overcoming treatment resistance in metastatic invasive lobular breast cancer. Of the six categories evaluated (e.g. biology and detection/diagnosis/prognosis), the largest increase in investment was for treatments. Discussion The coding tool allows for ongoing complex queries such as identification of funded research relevant to areas identified as important by MBC advocates (Table) and provides a funders' 'dashboard' to identify gap areas in need of further research funding. This collaborative effort between funders and patient advocates, and the resulting current and future analyses, can be used to focus advocacy efforts to drive research funding of priorities and understudied areas of MBC. Despite the increase in funding, the investment in metastatic research—the primary cause of death from breast cancer—remains insufficient.

Research Priorities of MBC Patient Advocates

Table: Research Priorities of MBC Patient Advocates

	Biology, Translational, and Clinical	New Drugs and Treatments	Quality of Life	Technology
Top Priorities	<ul style="list-style-type: none"> –Identify and define the role of somatic genes in metastatic tumors and the role of tumor heterogeneity in the selection of treatments for MBC 	<ul style="list-style-type: none"> –Understand how treatment resistance can be overcome in different subtypes –Define subsets of triple-negative MBC and appropriate treatments for those subsets –Identify better treatments for brain metastases and central nervous system metastases 	<ul style="list-style-type: none"> –Research that identifies how side effects of treatments can be better managed 	
Secondary Priorities	<ul style="list-style-type: none"> –Understand the immune system in each subtype and its potential role to keep metastasis in check and/or treat metastasis –Explore analysis of the tumor microenvironment to explain disease progression or help identify treatments –Identify the role of BRCA1, BRCA2, and other inherited genes in the development, progression, and treatment of MBC –Explore if the collection of serial biopsies in patients reveals the progression of MBC in various subtypes and identify if they are being tested in the clinic –Identify research that explores how bone metastasis impacts the spread of disease to other sites –Understand if pregnancy is a risk in developing MBC and identify how many grants are looking at pregnancy and MBC 	<ul style="list-style-type: none"> –Identify effective treatments for HER2-positive low tumors –Conduct comparative research between the three CDK4/6 inhibitors to determine which can all be used by the same patient –Identify effective treatments for lobular MBC –Identify better treatments for inflammatory breast cancer –Compare biosimilars to Herceptin to determine if they are as effective as Herceptin –Identify new treatments that strengthen bones, lessen osteoarthritis, and reduce pain in patients with bone metastases 		<ul style="list-style-type: none"> –Develop imaging that will identify the presence of lobular breast cancer and/or the progression of lobular breast cancer in patients –Conduct research that helps to establish new clinical guidelines for imaging newly diagnosed MBC patients for brain metastases –Research and define the abscopal effect in which radiation of one area results in shrinkage of tumors in other places –Research and define the use of Stereotactic Body Radiation Therapy as a treatment for oligo metastasis or oligo progression and its effect on overall survival

PO5-05-11

The effect of eribulin treatment for patients with HER2-low breast cancer

Presenting Author(s) and Co-Author(s):

W. Goto. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

S. Henmi. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

M. Nishikawa. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

A. Kouchi. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

R. Kouhashi. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

A. Yabumoto. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

K. Takada. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

Y. Asano. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

Y. Tauchi. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

K. Ogisawa. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

T. Morisaki. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

S. Kashiwagi. Japan / Osaka Metropolitan University Graduate School of Medicine / Department of Breast Surgical Oncology, United States

Background: Eribulin, a nontaxane, synthetic microtubule dynamics inhibitor, induces longer overall survival (OS) in patients with advanced or metastatic breast cancer (MBC). Interestingly, it also improves the tumor immune microenvironment via vascular remodeling. DESTINY-Breast04 trial showed that trastuzumab deruxtecan resulted in significantly longer OS of human epithelial growth receptor 2 (HER2)-low breast cancer patients, and this mechanism may also be related to tumor microenvironment. In this study, we investigated the effect of eribulin for patients with HER2-low breast cancer.

Materials and Methods: This retrospective study comprised 97 MBC treated with eribulin from August 2011 to April 2019 at our institute. HER2 levels were determined through tumor biopsy specimen at first medical examination. We evaluated the correlations between HER2 levels and clinicopathological features, including the prognosis and immune related markers in each breast cancer subtype. We also classified the progressive disease (PD) into progression due to pre-existing lesion (PPL) and progression due to new metastasis (PNM) based on systemic computed tomography findings, and investigated the relationships between HER2 expression and PD types.

Results: HER2-high group had significantly better OS than other groups ($p=0.021$, log-rank).

Hormone receptor (HR)-negative/HER2-low patients had significantly better progression-free survival (PFS) than HR-negative/HER2-negative ($p=0.024$, log-rank). Though we also examined HER2 levels of recurrent tumor specimen, it was not a significantly useful prognostic marker in patients with HR-negative breast cancer ($p=0.085$, log-rank). There was no significant correlation between HER2 expression and any tested clinicopathological parameter, including absolute lymphocyte count, neutrophil-to-lymphocyte ratio and tumor infiltrating lymphocytes. PD were observed in 64 patients (PPL: $n=47$, PNM: $n=17$). PD type of all HR-positive/HER2-high patients was PNM, whereas all HR-negative/HER2-high patients was PPL ($p=0.035$). HER2-low group tended to have a higher PPL rate than negative group (83.3% vs 69.2%).

Conclusions: In HR-negative/HER2-low group, PFS was improved by eribulin treatment, which might be due to unique anticancer effect of eribulin, suppression of epithelial-mesenchymal transition. Further study of this mechanism through basic research is important. Also, assessment of HER2 from primary tumor may be more useful than recurrent specimen.

PO5-05-12

Loco-regional Treatment in De Novo Bone Only Metastatic Breast Cancer; Prospective, Multi-Institutional Real-World Data, BOMETIN, Protocol MF14-1a

Presenting Author(s) and Co-Author(s):

A. Soran. UPMC Department of Surgery, Breast Health Working Group International, United States

S. Ozbas. Breast Health Working Group International, United States

L. Dogan. Breast Health Working Group International, United States

D. Trabulus. Bahcesehir University, Department of Surgery, Turkey

J. EL-AZRHI. KING FAHAD SPECIALIST HOSPITAL, DEPARTMENT OF SURGERY, United States

K. Senol. Uludag University, Faculty of Medicine, Department of Surgery, Turkey

B. GOKTEPE. Ege University, Medical Faculty, Dpartment of General Surgery, Izmir, Turkey

S. ZAVERI. MD ANDERSON CANCER CENTER, United States

S. Meas. MD Anderson Cancer Center, United States

U. Demirci. Ankara Memorial Hospital, Medical Oncology Center, Ankara, Turkey, Ankara, Turkey

H. Karanlik. Istanbul University Institute of Oncology, Department of Surgical Oncology, Istanbul, Turkey

A. Soyder. Acibadem University, Faculty of Medicine, Department of Surgery, Turkey

A. Dağ. Mersin University, Faculty of Medicine, Department of Surgery, Turkey

A. BILICI. MEDIPOL UNIVERSITY, DEPARTMENT OF MEDICAL ONCOLOGY, Turkey

M. Dogan. Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, United States

M. Sendur. Ankara City Hospital, Medical Oncology Clinic, Ankara, Turkey, Ankara, Turkey

H. KOKSAL. SELCUK UNIVERSITY MEDICAL SCHOOL, GENERAL SURGERY DEPARTMENT, United States

M. Gulcelik. University of Health Sciences, Gulhane Hospital, Department of Surgery, Turkey

N. Cabioğlu. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Bakırköy, Istanbul, Turkey

L. Yeniay. Ege University, Faculty of Medicine, Department of Surgery, Izmir, Turkey

N. Utkan. Kocaeli University, Faculty of Medicine, Department of Surgery, Turkey

N. Karadurmus. University of Health Sciences Gulhane Training and Research Hospital, Medical Oncology Clinic, Ankara, Turkey, Ankara, Ankara, Turkey

G. DAGLAR. PRIVATE PRACTICE, United States

T. SIMSEK. KOCAELI UNIVERSITY MEDICAL SCHOOL, GENERAL SURGERY DEPARTMENT, United States

B. YILDIZ. Elazig Medical Park Hospital, Medical Oncology Department, United States

C. URAS. Acibadem MAA University, Research Institute of Senology, Head, United States

M. Tukenmez. Istanbul University, Istanbul Faculty of Medicine, Department of Surgery, Turkey

C. OZASLAN. UNIVERSITY OF HEALTH SCIENCES, DR ABDURRAHMAN YURTASLAN ANKARA ONCOLOGY TRAINING AND RESEARCH HOSPITAL, GENERAL SURGERY DEPARTMENT, United States

N. Karaman. Ankara Oncology Hospital, Department of Surgery, Turkey

A. Isik. Istanbul Medeniyet University, United States

B. DEMIRORS. Bursa Yuksek Ihtisas Training and Research Hospital, General Surgery, Bursa, Turkey

E. Sezgin. Breast Health Working Group International, United States

V. OZMEN. ISTANBUL FLORENCE NIGHTINGALE HOSPITAL, DIRECTOR OF BREAST CENTER, United States

A. Lucci. MD Anderson Cancer Center, Houston, Texas, United States

Introduction: The impact of loco-regional treatment (LRT) on survival in de novo bone-only metastatic breast cancer (BC) is controversial. The aim of this study is to assess the effect of LRT on survival utilizing international, prospectively acquired data in this cohort of patients. **Materials and Methods:** Patients with de novo metastatic BC with bone-only metastases were divided into two groups: those receiving systemic therapy only (ST) and those undergoing LRT. Patients who received LRT were divided into two groups: those who received ST after LRT (LRT+ST arm) and those who received ST prior to LRT (ST+LRT arm). Solitary or multiple bone metastases were classified, and factors associated with disease progression were analyzed. **Results:** There were a total of 744 patients with de novo bone-only metastatic BC treated at each of the participating institutions between 2014 and 2022, with 372 (50%) participants in each arm. Median follow-up was 48 months (32-66, 25-75%). Patients in the LRT group were significantly younger than the ST group [50 (42, 60) vs 55 (44, 66), $p=0.0001$]. There were no significant differences in grade, Her2 neu and triple negative status, receipt of hormonal therapy and intervention to metastatic sites. During follow-up, 58% ($n=217$) of patients in ST arm and 32% ($n=120$) of patients in LRT arm died ($p<0.001$). Local progression was observed in 20% of the patients in the ST arm whereas it was 9% in the LRT arm ($p=0.0001$). Systemic progression occurred more in ST arm; 66% ($n=244$) compared to 41% ($n=152$) of patients in LRT group ($p<0.001$). The Hazard of death was 64% lower in LRT group than in ST group (HR: 0.36, 95% CI: 0.29-0.45), $p<0.0001$). The burden of metastatic disease was significantly different between groups with the solitary bone metastasis rate higher in LRT group than the ST only group (50% vs 24%, $p<0.001$). However, the LRT group had better overall survival for both solitary (HR: 0.38, 95% CI: 0.26-0.55) and multiple (HR: 0.38, 95% CI: 0.29-0.51) bone metastases patients. Within the LRT group, survival rates were similar whether the breast surgery was performed before or after ST. Multivariate Cox analysis showed that LRT and ER/PR positivity significantly decrease the hazard of death ($p<0.05$). **Conclusion:** Analysis of this large multi-institutional patient cohort provides further evidence that LRT improves overall survival and lowers loco-regional recurrence in patients with de novo bone-only metastatic BC. In breast cancer patients with bone-only metastases at presentation, the decision for LRT should be made through a multidisciplinary approach with consideration of surgical therapy at the primary tumor.

PO5-05-13

Clinical utility of whole body low dose computed tomography for detecting bone metastasis in breast cancer patients: A cross sectional study

Presenting Author(s) and Co-Author(s):

L. Mitra. All India Institute of Medical Sciences, New Delhi, Delhi, India

S. Suhani. All India Institute of Medical Sciences, New Delhi, Delhi, India

A. Goyal. All India Institute of Medical Sciences, Delhi, India

R. Kumar. All India Institute of Medical Sciences, Delhi, India

M. Joshi. All India Institute of Medical Sciences, Delhi, India

H. Bhattacharjee. All India Institute of Medical Sciences, Delhi, India

H. KP. All India Institute of Medical Sciences, Delhi, India

R. Sharma. All India Institute of Medical Sciences, Delhi, India

R. parshad. All India Institute of Medical Sciences, Delhi, India

Clinical utility of Whole Body Low Dose CT scan for detecting bone metastasis in Breast cancer patients: A cross sectional study

Background: Skeletal scintigraphy (Bone scan) is the imaging of choice to detect bone metastasis in locally advanced and metastatic breast cancer patients. Nuclear medicine facilities are however limited in their availability. As an alternative diagnostic modality to bone scan, we studied the diagnostic capability of Whole-Body Low Dose CT (WBLDCT) scan for detection of bone metastasis in these patients.

Materials and Method: This cross-sectional study was conducted from November 2021 to May 2023 at a tertiary healthcare center in India with an aim to study the clinical applicability of whole-body low dose computed tomography scan for detecting bone metastasis in patients with breast cancer. Breast cancer patients with primary tumor measuring 5cm or more, pathologically proven axillary lymph node metastasis, Stage III/IV disease, symptoms attributable to metastasis and suspected disease recurrence were included. All patients underwent WBLDCT and Bone scan within a period of about 2 weeks. WBLDCT was done during the same time as conventional dose CT scan was being done as part of metastatic workup. WBLDCT acquisition protocol was set in CT scan machine by modulating the technical parameters like Care dose 4D-automated, Care kV semi, rotation time & noise index. The image analysis was performed by Radiologist and Nuclear medicine experts in a blinded fashion. Data was recorded in MS Excel sheet. Sensitivity, specificity, positive and negative predicative value, and concordance rates were calculated using SPSS software ver 25.0. Agreement amongst WBLDCT and Bone scan was calculated using Inter-rater agreement. p value < 0.05 was taken as significant.

Results: 110 patients were enrolled in this study. The mean age of participants was 48.5 years and three fourth had stage III disease at presentation. Estrogen receptor positive disease was seen in 43.64% participants while 30% were triple negative. Her2neu positive disease was seen in 27.27% patients. Bone scan couldn't be done in 03 patients who deferred treatment (these had no bone metastasis on WBLDCT). Both bone scan and WBLDCT detected bone metastasis in 19 patients. Bone scan picked up additional metastasis in three patients which were missed on WBLDCT. WBLDCT detected bone metastasis additionally in three patients

which were not detected on Bone scan. Multiple lesions were most seen in vertebrae in 38.5% and 28.6% on bone scan and WBLDCT respectively. The sensitivity and specificity of WBLDCT for detection of bone metastasis was 86.36% and 96.47% respectively. The concordance rate between Bone scan and WBLDCT scan was 94.39% with an Inter-rater Kappa(k) quotient for agreement of 0.828 ($p < 0.0001$).

Conclusion: WBLDCT scan has comparable diagnostic capability to skeletal scintigraphy in detecting bone metastasis in breast cancer and may be a useful alternative specially in resource limited settings.

Keywords: WBLDCT, Bone scan, Diagnostic accuracy, Metastasis.

Table 1: Sensitivity, specificity, positive predictive value and negative predictive value of WBLDCT for detection of metastasis

Variables	Values
Sensitivity (95% CI)	86.36%
Specificity (95% CI)	96.47%
AUC (95% CI)	0.91
Positive Predictive Value (95% CI)	86.36%
Negative Predictive Value (95% CI)	96.47%
Diagnostic accuracy	94.39%
Inter-rater agreement (kappa)	0.828

Table 1: Sensitivity, specificity, positive predictive value and negative predictive value of WBLDCT for detection of metastasis

Variables	Values
Sensitivity (95% CI)	86.36%
Specificity (95% CI)	96.47%
AUC (95% CI)	0.91
Positive Predictive Value (95% CI)	86.36%
Negative Predictive Value (95% CI)	96.47%
Diagnostic accuracy	94.39%
Inter-rater agreement (kappa)	0.828

Table 1: Sensitivity, specificity, positive predictive value and negative predictive value of WBLDCT for detection of metastasis

PO5-05-14

Survival in Young Women with De Novo or Recurrent Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

L. Varella. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Y. Zheng. Dana-Farber Cancer Institute, United States

S. Rosenberg. Weill Cornell Medicine, New York, New York, United States

G. Kirkner. Medical Oncology, Dana-Farber Cancer Institute, United States

C. Snow. Dana-Farber Cancer Institute, United States

K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States

R. Tamimi. Weill Cornell Medicine, New York, NY, USA, United States

J. Peppercorn. Massachusetts General Hospital, Boston, MA, USA, United States

L. Schapira. Stanford Cancer Institute, Palo Alto, CA, USA, United States

V. Borges. University of Colorado Anschutz Medical Center, United States

S. Come. Beth Israel Deaconess Medical Center, Boston, MA, USA, United States

L. Collins. Beth Israel Deaconess Medical Center, United States

E. Warner. Sunnybrook Odette Cancer Centre, Toronto, Ontario, Canada

K. Dibble. Dana-Farber Cancer Institute, United States

E. Winer. Yale Cancer Center, New Haven, Connecticut, United States

A. Partridge. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background. Approximately 12,000 women aged 40 years or younger are diagnosed with breast cancer every year in the United States alone. Limited data exist regarding survival in young women with metastatic breast cancer (MBC), particularly when considering modern tumor subtyping and treatment, though previous studies have suggested that patients presenting with MBC at diagnosis (de novo stage IV) have better prognosis than those who develop recurrent MBC after initial diagnosis of stage 0-III disease. We sought to determine survival rates in young patients with MBC stratified by disease presentation (de novo versus recurrent) and subtype. **Methods.** The Young Women's Breast Cancer Study (YWS) is a multicenter, prospective cohort which enrolled 1,302 women diagnosed with stage 0-IV breast cancer at age ≤ 40 from 13 North American academic and community-based sites from 2006-2016. The current median follow-up is 10.1 (range 0.4-16.3) years. Histopathology slides were centrally reviewed for 97% of the participants, and clinical tumor molecular subtypes have been detailed. In the recurrent group, receptors were obtained from the initial breast surgery. Descriptive analyses were used to characterize patients with de novo or recurrent MBC, including demographic and disease characteristics, and survival rates. Overall survival was estimated using the Kaplan-Meier method and compared by log-rank test between those who presented with de novo and relapsed disease overall and within tumor subtypes. **Results.** Among 246 patients included in this analysis, 74.0% (n=182) had recurrent MBC and 26.0% (n=64) had de novo MBC. Most patients were white (n=208, 84.6%), while 6.9% were Asian (n=17), 4.5% Black (n=11), 0.8% Native American (n=2), 0.8% multiracial (n=2) and 2.4% other/unknown (n=6). A total of 4.5% of patients were Hispanic (n=11). Median age at diagnosis of de novo MBC was 37 years and 40 years for diagnosis of metastasis in the recurrent group. Median disease-free interval was 3.23 (range 0.32 – 13.84) years for the recurrent MBC group. Among all patients with MBC, most (55.7%, n=137) had estrogen receptor (ER) and/or

progesterone receptor (PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative disease, whereas 17.9% (n=44) had ER and/or PR-positive HER2-positive, 7.3% (n=18) had ER/PR-negative HER2-positive, and 18.7% (n=46) had triple-negative tumors. A greater proportion of participants (43.8%, n=28) had HER2-positive disease in the de novo group than in the recurrent group (18.7%, n=34), $P < 0.0001$. A total of 10.9% (n=7) of de novo patients had a germline BRCA mutation, compared to 13.7% (n=25) in the recurrent group. Median survival was 5.09 (95% CI: 3.74 – 6.38) years in the de novo group and 2.63 (95% CI: 1.98 – 3.21) years in the recurrent MBC group ($P=0.0004$). When stratifying by subtype, survival among patients with de novo ER and/or PR-positive HER2-positive disease was longer than among patients with recurrent disease ($P=0.0149$), whereas there were no statistically significant differences in survival between the de novo and recurrent disease groups in other disease subtypes (Table 1). Conclusion. Survival in young women with MBC is highly heterogeneous and varies substantially by tumor subtype and disease presentation. Those with de novo ER and/or PR-positive HER2-positive subtype appear to have better outcomes than those with recurrent MBC with the same subtype. These findings can inform patient care and potential future research to improve outcomes for young patients with MBC.

Table 1: Median survival by disease presentation and subtype

Tumor Subtype*	MBC Presentation (n)	Median OS (yrs)	95% CI	Log-rank test p-value
ER/PR+, HER2+	<i>De novo</i> (17)	10.24	4.47, -	0.0149
	Recurrent (27)	3.29	1.67, 7.01	
ER/PR+, HER2-	<i>De novo</i> (29)	4.07	3.08, 5.62	0.3568
	Recurrent (108)	3.21	2.44, 4.10	
ER/PR-, HER2+	<i>De novo</i> (11)	5.56	2.48, -	0.7848
	Recurrent (7)	11.39	2.59, 11.39	
ER/PR-, HER2-	<i>De novo</i> (7)	1.59	0.47, -	0.1142
	Recurrent (39)	0.98	0.38, 1.47	

* 1 patient with recurrent MBC was not included because the initial diagnosis was DCIS
MBC: metastatic breast cancer; OS: overall survival; CI: confidence interval; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2

PO5-06-01

Loss of hormone receptor expression in breast cancer is associated with increased brain tropism and accelerated progression of leptomeningeal disease.

Presenting Author(s) and Co-Author(s):

S. Pribus. Stanford University, United States

M. C. Umeh-Garcia. Stanford University, United States

B. Gu. Stanford University, United States

B. Godfrey. Stanford University, United States

S. Han. Stanford University, United States

S. Chernikova. Stanford University, United States

M. Hayden Gephart. Stanford University, United States

The four breast cancer subtypes—luminal A, luminal B, HER2-overexpressing, and triple-negative breast cancer (TNBC) – are classified based on gene expression profiles of hormone receptors (HRs) (estrogen receptor (ER) and progesterone receptor (PR)) and human epidermal growth factor receptor 2 (HER2/ERBB2).

Negative hormone receptor status is known to be associated with more aggressive breast cancer. Compared to other breast cancer subtypes, the HR-negative TNBC and HER2-overexpressing subtypes are characterized by high rates of recurrence and a notable increase in brain metastases and in particular, leptomeningeal disease (LMD). LMD – the most aggressive form of central nervous system (CNS) metastasis, in which cancer cells infiltrate leptomeninges of the brain and spine – carries a dismal prognosis due to a rapid progression, poor detection, and no effective treatment.

Several studies that investigated the link between HR status and LMD suggest that HR-negative breast cancers have a shorter time to LMD diagnosis. This shortened timeline is consistent with higher migratory capabilities reported for TNBC and HER2 breast cancer cells. However, as it is known that breast cancers exhibit subtype-specific metastatic tropism (i.e., luminal subtypes tend to metastasize to bone and liver, while TNBCs metastasize to the CNS), the longer time between primary breast cancer diagnosis and LMD diagnosis for HR-positive breast cancers may also reflect a longer metastatic route that first includes a non-CNS location.

In this study, we performed a retrospective analysis on 141 breast cancer patients with LMD treated at Stanford Hospital between 2008-2020. The Stanford LMD cohort was analyzed using linear regression analysis, Cox regression analysis, and Chi-squared analysis. HR status was recorded (when available) for local recurrences and distant metastases, and was included in our regression models as a time-dependent HR covariate. We tested if: (1) HR-negative breast cancers had shorter time between primary and LMD diagnosis as well as worse survival after LMD diagnosis versus HR-positive breast cancers, and if (2) HR loss (i.e., HR status changing from positive to negative) increased likelihood of the metastasis to CNS.

In agreement with published studies, the Stanford LMD cohort showed that HR-negative cancers had shorter time to development of LMD ($p = 0.0004$ for ER, $p = 0.0001$ for PR) and increased mortality following LMD ($p = 0.010$ for ER, $p = 0.009$ for PR). We found that HR-negative status at primary breast cancer diagnosis increased risk of first metastasis to CNS versus non-CNS locations ($p = 0.021$ for ER, $p = 0.043$ for PR). HR status switch (also known

as hormone discordance) between primary diagnosis and metastasis occurred in 15% of patients in Stanford cohort, consistent with other studies. Importantly, accounting for HR status switch strengthened the association between HR-negative status and the risk of CNS metastasis [Hazard Ratio = 2.506 (1.395 - 4.500) for “baseline ER status” versus Hazard Ratio = 3.509 (1.890 - 6.515) for “time-dependent ER status”, Hazard Ratio = 2.420 (1.310 - 4.471) for “baseline PR status” versus Hazard Ratio = 3.407 (1.815 - 6.395) for “time-dependent PR status”].

In conclusion, HR-negative status was associated with shorter time to development of LMD, higher CNS tropism, and shorter survival following LMD diagnosis. Taking into consideration hormone discordance between the primary tumor and metastatic sites strengthened this association. Our results suggest a potential value in testing HR status at all recurrences and advanced CNS monitoring following HR loss.

PO5-06-02

Phase II Trial of Combination of Atezolizumab, Cobimetinib and Eribulin (ACE) or Atezolizumab and Eribulin (AE) in patients with metastatic inflammatory breast cancer (IBC): Clinical data of both cohorts

Presenting Author(s) and Co-Author(s):

A. Alexander. UT MD Anderson Cancer Center, Houston, Texas, United States

H. Murphy. MD Anderson Cancer Center, United States

J. Reuben. University of Texas MD Anderson Cancer Center, United States

H. Le-Petross. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Lane. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

M. Huang. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

S. Krishnamurthy. MD Anderson cancer center, United States

Y. Gong. UT MD Anderson Cancer Center, United States

D. Gombos. UT MD Anderson Cancer Center, United States

N. Patel. UT MD Anderson Cancer Center, United States

R. Allen. UT MD Anderson Cancer Center, United States

S. Liu. The University of Texas MD Anderson Cancer Center, Texas, United States

A. Patel. The University of Texas MD Anderson Cancer Center, Texas, United States

A. Futreal. UT MD Anderson Cancer Center, United States

I. Wistuba. UT MD Anderson cancer center, Houston, TX, Texas, United States

R. Layman. The University of Texas MD Anderson Cancer Center, United States

N. Ueno. University of Hawai'i Cancer Center, Honolulu, HI, USA, United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

B. Lim. Baylor College of Medicine, Houston, Texas, United States

V. Valero. Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Bellaire, Texas, United States

Background: Metastatic IBC is an unmet clinical need due to the aggressiveness of this breast cancer subtype. Gene expression analysis of IBC samples post-neoadjuvant chemotherapy has revealed that dysregulation of immune pathways is common in tumors that do not have a complete pathologic response (pCR) to chemotherapy. The immune checkpoint PD-L1 is expressed in a third of IBC cases, and the MEK inhibitor, cobimetinib, has been shown to enhance the expression of PD-L1, the target of atezolizumab. Taken together, dual targeted therapy with atezolizumab and cobimetinib is hypothesized to be synergistic. Eribulin is a standard of care chemotherapy used in patients who have progressed on anthracycline-taxane based regimens.

Materials and Methods: Patients received triple or double combination therapy depending on the timing of their enrollment. Patients with metastatic IBC who had measurable disease after at least 1 standard regimen were eligible. Any receptor subtype was allowed, and PD-L1 positivity

was not required. The study began with a single cohort (n=17 patients) receiving all 3 agents with a lead-in phase to determine the MTD of cobimetinib in this setting. The study was later amended to include only atezolizumab and eribulin (cohort 2). Ten patients were treated in cohort 2. The study closed early due to lack of efficacy in cohort 2 and the changing landscape of metastatic breast cancer therapies. In cohort 1, atezolizumab was given every 2 weeks (840 mg), cobimetinib was given at 60/40/20 mg once daily, and eribulin was given at 1.4mg/m² on day 1 and day 8 of 21-day cycles. In cohort 2, atezolizumab was given every 3 weeks (1200 mg) during the PD window and cycles 1-4, and then every 4 weeks (1680 mg) during maintenance, and eribulin was given at 1.4mg/m² on day 1 and day 8 of 21-day cycles.

Results: The MTD of cobimetinib was 40mg. In cohort 1, 17 patients were treated, 14 had at least 1 restaging evaluation. Seven patients had a partial response (50%) and 3 stable disease. The cohort was predominantly triple receptor-negative (n=13/17), with a median age of 51 yrs. The median PFS for patients in cohort 1 was 6.2 months (0-54.1). There were 2 exceptional responders, both with triple negative subtype, one of whom remains on therapy for >4.5 years without evidence of disease. The median overall survival was 29.6 months (2.9-133). The AE profile was largely expected, with 3 irAEs (1 grade 5 colitis, and 2 grade 2 pneumonitis), and one other patient with cardiac dysfunction requiring discontinuation of cobimetinib and atezolizumab. The MTD of cobimetinib was 40 mg. Cobimetinib-related toxicities were mild and largely gastrointestinal tract related.

In cohort 2, only 1 patient experienced PR, and the median PFS was 3 months (1.2-6.2) and overall survival 8.3 months (1.8-19.9). One patient experienced autoimmune related hepatitis requiring discontinuation of protocol therapy. Due to excessive myelosuppression, dose of erublin was reduced to 1.1 mg per meter squared on day 1 and 8 and pegfilgastrim was added on day 9<

Conclusions: The response profile of the triple combination demonstrated promise, and suggests that MEK inhibition may warrant further investigation as a strategy in metastatic IBC in a larger sample size. However, there does not appear to be synergy between atezolizumab and eribulin without the addition of targeted therapy.

PO5-06-03

Impact of curative-intent treatment on survival for metastatic breast cancer limited to distant lymph nodes

Presenting Author(s) and Co-Author(s):

Y. Xu. Tom Baker Cancer Center, United States

BACKGROUND:

Metastatic breast cancer limited to distant lymph nodes is classified as stage IV but potentially represents an anatomically distinct entity amenable to curative treatment. Its optimal management is unclear, with existing studies limited by small sample sizes and short follow-up durations. We sought to investigate the impact of curative-intent treatment on breast cancer-specific survival (BCSS) and overall survival (OS) for patients with this diagnosis.

METHODS:

Three cohorts of patients diagnosed with breast cancer from 2010 to 2019 were identified from the Surveillance, Epidemiology, and End Results 17 registries database. The curative cohort consisted of patients with metastatic breast cancer involving only distant lymph nodes who received a combination of chemotherapy, surgery to the primary site, and radiotherapy (curative-intent treatment). The palliative cohort included patients who underwent chemotherapy but not curative-intent treatment. The N3c cohort was comprised of patients with ipsilateral supraclavicular lymph node metastases but no distant metastases who received curative-intent treatment. Weighting based on covariate balancing propensity scores was performed to balance age, sex, race, median household income, year of diagnosis, T stage, histology, pathological grade, and ER/PR/HER2 status between the cohorts. Weight-adjusted multivariable Cox regression models with the same covariates were then used to compare the BCSS and OS of the three cohorts.

RESULTS:

A total of 2,089 patients with a median follow-up of 37 months were eligible for analysis, of whom 577 (27.6%) were in the curative cohort, 905 (43.3%) were in the palliative cohort, and 607 (29.1%) were in the N3c cohort. After propensity score weighting, the maximal standardized mean difference for all covariates was less than 0.1. Five-year BCSS for patients in the weight-adjusted curative, palliative, and N3c cohorts were 63.0% (95% CI 58.1-68.3), 46.7% (42.4-51.4), and 66.4% (61.4-71.8), respectively; and five-year OS were 57.9% (53.0-63.2), 41.2% (37.2-45.7), and 62.2% (57.3-67.6), respectively. Compared to the palliative cohort, the curative cohort exhibited better BCSS (HR 0.47, 95% CI 0.38-0.57; $P < 0.001$) and OS (HR 0.48, 95% CI 0.40-0.58; $P < 0.001$). In contrast, the N3c cohort had similar BCSS (HR 0.93, 95% CI 0.73-1.17; $P = 0.53$) and OS (HR 0.96, 95% CI 0.77-1.19; $P = 0.68$) to the curative cohort.

CONCLUSIONS:

Patients treated curatively for metastatic breast cancer limited to distant lymph nodes had higher BCSS and OS than those receiving palliative chemotherapy and similar BCSS and OS to patients receiving curative-intent treatment for ipsilateral supraclavicular lymph node metastases. These results support the use of aggressive multimodal therapy for select stage IV breast cancer patients with only distant nodal metastases and, if confirmed, suggest that a substantial portion of such patients may be undertreated.

PO5-06-04

EMSY amplification co-occurs with FGF/FGFR axis amplification in Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

D. Prasad. George Mason University, United States

E. Blais. Perthera inc, United States

R. Dunetz. Side Out Foundation, United States

E. Petricoin. George Mason University, Manassas, Virginia, United States

M. Pierobon. George Mason University, United States

Background: Amplification of FGFR and its ligands play an important role in breast cancer onset and progression and mutations of this signaling axis are emerging as mechanisms of resistance to targeted treatments. Understanding the molecular landscape of tumors that harbor aberrations in the FGF/FGFR (FGF/R) axis may help define the biology of these tumors and lead to the development of novel personalized approaches for more effective treatments in this group of patients. Using publicly available datasets, this study aimed at identifying genomic alterations co-occurring with amplification (amp) of the FGF/R axis in Metastatic Breast Cancer (mBC) patients. **Methods:** We utilized data from three cohorts of mBC patients. The first cohort (c1) included 176 patients with mBC from an ongoing precision medicine program sponsored by the Side-Out Foundation where genomic testing was performed, using a targeted gene panel, in real-world settings by commercial labs based predominantly on tumor specimens collected between 2019 and 2023. Whole exome sequencing data was obtained from AACR Genomics Evidence Neoplasia Information Exchange (GENIE) to establish a second cohort (c2) of 301 patients and a third cohort (c3) of 216 patients with mBC. Lastly, we included a fourth cohort (c4, n=122) of patients with early breast cancer (eBC). Chi2 test and Fisher's Exact test were used to find significant co-occurring events. Python, pandas, and shell scripting were used for data manipulation, analysis and performing statistical tests. **Results:** Alterations of the FGF/R axis occurred in 26% (n=46) of patients in c1 of which 76% (n=35) were HR+ tumors and 24% (n=11) were Triple Negative Breast Cancers. Specifically, we detected amp of FGF3 (n=24, 52%), FGF4 (n=23, 50%), FGF19 (n=17, 37%), FGFR1 (n=18, 39%). In patients with alteration of the FGF/R axis, the most frequent aberrations were CCND1 (n=22, 48%), ZNF703 (n=12, 26%), MYC (n=9, 20%), and EMSY (n=8, 17%) amp, along with mutations of PIK3CA (n=17, 37%) and TP53 (n=18, 39%). EMSY amp was found in none of the patients without alterations of the FGF/R axis and co-amplified with the FGF/R axis in 8 patients (100%) (p< 0.0001). Similar results were also detected in the two independent cohorts of patients retrieved from the GENIE database. In c2, co-amp of EMSY and FGF/R axis was found in 53 of the 56 patients (95%) harboring EMSY amp (p< 0.0001). In c3, 17 patients (89%) had co-amp of EMSY and FGF/R axis of the 19 patients with EMSY amp (p< 0.0001). However, when we looked at patients with eBC in c4, of the 10 patients with EMSY amp, 7 patients (70%) had co-amp of EMSY and FGF/R axis and this association was not significant (p = 0.09). **Conclusion:** Amplification of EMSY has been mostly reported in ovarian (~17%) and sporadic breast cancers (~13%). EMSY has been reported to behave as an oncogene and a transcriptional repressor. It is well known that it can interact with the BRCA2 protein and potentially contributes to the "BRCAness" of tumors harboring its amp. Studies have also suggested that EMSY may act as a transcriptional repressor that modulates the expression of antimetastatic microRNAs in breast cancer. In the three mBC cohorts included in this analysis, EMSY amp was detected in 8, 56, and 19 cases, respectively. However, when the analysis was restricted to tumors harboring amps of both EMSY and FGF/R axis, EMSY was amplified

in 100%, 95%, and 89% of those cases. While co-amplification of the EMSY gene with members of the FGF/R axis may be explained by its close proximity to the FGF3/4/19, and CCND1 genes on chromosome 11, in our analysis these co-amplifications were significant only in patients with metastatic disease. As dissecting the complex molecular landscape of mBC continues to be an essential step for advancing personalized treatment and better patient care, understanding the phenotypic effects of these co-amplifications may provide unique opportunities for devising combinatorial treatments for these patients.

PO5-06-05

DISCORDANCE BETWEEN HORMONE RECEPTORS AND HER2 STATUS IN BREAST CANCER PATIENTS RELAPSE

Presenting Author(s) and Co-Author(s):

K. Roque. 1.Instituto Nacional de Enfermedades Neoplásicas Lima-Perú 2. Post graduation programme in Medicine, Faculty of Medicine, Nine of July University (UNINOVE), São Paulo, Brazil, Lima, Peru

I. Otoyá. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Surquillo, Lima, Peru

N. VALDIVIESO. ecancer, Lima, Peru

Z. Morante. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

H. Fuentes. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

S. Neciosup. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

H. Gómez. Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica, Lima, Peru and Universidad Ricardo Palma, Lima, Peru

J. Cotito. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

G. Ziegler. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

E. Peña. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

T. Vidaurre. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

R. Andrade de Mello. Post graduation programme in Medicine, Faculty of Medicine, Nine of July University (UNINOVE), São Paulo, Brazil, Sao Paulo, Brazil

C. Castañeda. Instituto Nacional de Enfermedades Neoplásicas Lima-Perú, Lima, Peru

Introduction:

Breast cancer (BC) is a heterogeneous disease, and during its progression, the tumor phenotype can undergo changes that are often associated with a poor prognosis. In this study, we aim to compare the discordance in estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER-2), and Ki-67 expression between primary and recurrent/metastatic lesions.

Methods:

This study is a retrospective analysis of 132 non-advanced breast cancer patients who experienced confirmed recurrence/metastasis at the Instituto Nacional de Enfermedades Neoplásicas between 2011 and 2022. Descriptive analysis was conducted to assess the expressions of ER, PgR, HER-2, and Ki-67 in primary and metastatic breast cancer, as well as clinical variables. Normality tests, including Kolmogorov-Smirnov and Shapiro-Wilk, were performed. The paired samples Wilcoxon test was used to determine significant differences between primary and recurrent/metastatic tumors. Additionally, Spearman's rank correlation coefficient was employed to evaluate the relationships of expression discordance.

Results:

Fifty-nine percent of patients presented locoregional recurrence, while 41% presented visceral metastasis. In the primary tumor, ER and PR expression were found in 63.6% and 55.3% of cases, respectively. HER2 status was determined as 0 (36.3%), +1 (22%), +2 (14.4%), +3 (26.5%), and not determined (0.8%) by IHC. For the recurrent/metastatic tumor, ER and PR expression were found in 59% and 34% of cases, respectively. HER2 status was determined as

0 (27.3%), +1 (19.7%), +2 (25%), +3 (25%), and not determined (3%). The median Ki-67 levels were 37% in the primary tumor and 40% in the recurrent/metastatic tumor. Significant differences were found for ER ($p=0.014$), PR ($p< 0.001$), and HER2 ($p=0.019$), but not for Ki-67 percentage ($p=0.139$). The discordance rates of ER, PR, HER2, and Ki-67 expression were 27.9%, 47.7%, and 26.3%, respectively.

Conclusions:

Discordance in hormone receptor expression between primary and recurrent/metastatic tumors is a common phenomenon, with ER showing a discordance rate of 27.9% and PR showing a higher rate of 47.7%. HER2 status also displayed significant discordance, with a 26.3% rate of discordant expression between primary and recurrent/metastatic tumors. The findings from this study emphasize the dynamic nature of breast cancer and the importance of comprehensive evaluation of biomarker expression in both primary and recurrent/metastatic tumors, to choose the best treatment options.

PO5-06-06

Tumor/stromal expression of CD3/CD8/PD-1/PD-L1 and overall survival (OS) in patients (pts) with metastatic (met) HER2+ breast cancer (BC).

Presenting Author(s) and Co-Author(s):

D. Collins. Cancer Biotherapeutics, National Institute for Cellular Biotechnology, Dublin City University, Dublin, Ireland, Dublin, Dublin, Ireland

J. McCormack. UCD Conway Institute, Dublin, Dublin, Ireland

L. Ivers. Dublin City University, Dublin 9, Dublin, Ireland

J. Berenguer-Pina. Dept of Medical Oncology, Saint Vincent's University Hospital, Dublin, Ireland, United States

J. Ballot. Department of Medical Oncology, St Vincent's University Hospital, Dublin, Ireland, United States

C. Quinn. St. Vincent's University Hospital, Dublin, Ireland, United States

D. Skrobo. Galway University hospital, United States

A. Eustace. Dublin City University, Ireland

N. Walsh. Dublin City University, Dublin 9, Dublin, Ireland

A. Fabre. Saint Vincent's University Hospital, Dublin, Ireland, United States

J. Crown. St Vincent's University Hospital, Dublin 4, Dublin, Ireland

Background: The "Thousand Patient HER-2 database" project at Saint Vincent's University Hospital (SVUH) Dublin contains a cohort of met HER2+ BC pts treated with trastuzumab, with OS ranging from short term to durable complete response (never relapsed). While the majority of pts progress on treatment, higher stromal tumor immune infiltrate has been associated with longer OS in met HER2+ BC. Using the SVUH database, we have identified a cohort of met HER2+ BC pts that received trastuzumab and have a broad OS range (0.3 months (mos) to 200.9 mos). This study examines the tumor and stromal levels of pan T cell marker CD3, cytotoxic T cell marker CD8, and immune checkpoints PD-L1 and PD-1 by immunohistochemistry (IHC) in primary and met samples from this cohort. Methods: Clinico-pathological data was available for formalin-fixed, paraffin-embedded biopsy specimens (n=45 primary, n=25 matched met biopsies). IHC staining was conducted for CD3 (Agilent IR50361-2), CD8 (Agilent IR62361-2), PD-L1, (Agilent M365329-2), and PD-1 (Roche 07099029001). A DAKO Link 48 Autostainer was utilised for staining, incorporating positive (tonsil tissue) and negative controls (isotype controls). Slide processing used an Aperio AT2 Digital Slide Scanner (Leica Biosystems), Aperio ImageScope 12.4 software (Leica Biosystems) and QuPath analysis software (University of Edinburgh). Following annotation of tumor areas, an algorithm was trained to identify immune cells and designate them as tumor or stromal. Data was expressed as the number of positively stained cells/mm² tissue. A median cut-off was applied to denote "high" and "low" expression for CD3 and CD8. For PD-1 and PD-L1, samples with ≥ 1 stained cell/mm² were designated as positive (pos) and samples with zero stained cells as negative (neg). The Kaplan Meier method was utilised for survival studies. A paired Student's t test was utilised for primary vs metastatic site comparisons. Results: 51.1% of primary samples displayed high CD3 (23/45) and CD8 (23/45) expression in both the stromal and tumor compartments. Within the tumor compartment, 18.6% (8/43) of samples were pos for PD-L1 expression, and 57.8% (26/45) were pos for PD-1 expression. In the stromal compartment, 30.2% (13/43) of samples were pos for PD-L1 expression, and 68.9% (31/45) were pos for PD-1 expression. High tumor levels of CD3 (median OS CD3 high 113.4 mos vs CD3 low 7.9 mos,

HR 0.2938 (95% CI 0.130-0.618), $p=0.0012$) and CD8 (median OS CD8 high 73.9 mos vs CD8 low 10.8 mos, HR 0.4764 (95% CI 0.238-0.954), $p=0.0365$), but not stromal levels of these markers, were associated with improved OS. There were no significant differences in CD3, CD8, PD-1 and PD-L1 levels between matched primary and met samples ($p > 0.05$). Tumor, but not stromal, PD-L1 expression was associated with longer OS (HR 0.3120 (95% CI 0.146-0.667), $p=0.0027$). Interestingly, stromal PD-1 expression, but not tumor PD-1 expression, was also associated with longer OS (median OS PD-1 pos 64.7 mos vs. PD-1 neg 5.6 mos, HR 0.158 (95% CI 0.060-0.411), $p=0.0002$). Conclusion: Our results report a link between OS and tumor (CD3+, CD8+ and PD-L1+)/stromal (PD-1+) immune cell infiltrate in met HER2+ BC patients treated with trastuzumab. Further expansion of this preliminary dataset is warranted.

PO5-06-07

Unravelling the role of PKC-eta in modulating the Hippo Pathway: a novel therapeutic strategy for triple-negative breast cancer metastasis.

Presenting Author(s) and Co-Author(s):

L. Vijaya Steltar Belsamma. Ben-Gurion University of the Negev, Beersheva, Israel, United States

A. Muraleedharan. Ben-Gurion University of the Negev, Beersheva, Israel, Israel

D. Ram Jayaram. Ben-Gurion University of the Negev, Beersheva, Israel, United States

K. Waidha. Ben-Gurion University of the Negev, Beersheva, Israel, United States

S. Jagadeeshan. Ben-Gurion University of the Negev, Beersheva, Israel, United States

R. Sinay. Ben-Gurion University of the Negev, Beersheva, Israel, Israel

E. Eremenko. Ben-Gurion University of the Negev, Beersheva, Israel, Israel

O. Berner. Ben-Gurion University of the Negev, Beersheva, Israel, United States

M. Elkabets. Ben-Gurion University of the Negev, Beersheva, Israel, United States

E. Livneh. Ben-Gurion University of the Negev, Beersheva, Israel, Israel

Breast cancer (BC) is the leading cause of cancer-related deaths in women, with metastasis being the primary reason for BC mortality. Triple-Negative Breast Cancer (TNBC) is aggressive and highly metastatic, having fewer treatment options than other types of breast cancer. Protein kinase C eta (PKC η), an anti-apoptotic kinase of the novel PKC subfamily, is associated with poor prognosis in invasive BC patients. In this study, we show the role of PKC η in promoting cell migration and invasion, and we demonstrate that its expression is required to maintain the mesenchymal state during EMT. Furthermore, we show that PKC η activates YAP/TAZ, tumor aggressiveness, and metastasis using in vitro and in vivo models.

PKC η promotes metastasis in TNBC cells, showing that the PKC η -YAP signaling axis mediates this. Data analysis of BC patients with a high metastatic invasive propensity and low survival BC revealed a positive correlation between the elevated expression levels of PKC η and the expression of YAP. Knockout of PKC η (PKC η ^{KO}) in the TNBC cells 4T1 and MDA-MB-231 markedly inhibited their invasion and migration capability. We further show that PKC η enhances cell survival and anoikis prevention ability, which have crucial roles in metastasis formation, allowing cancer cells to circulate and home to distant sites in the body. Further substantiated by in vivo experiments with 4T1 xenografts in NSG mice, demonstrating that 4T1 PKC η ^{KO} cells depicted reduced primary tumor size and a significant decrease in size and number of tumor metastases in the lungs, with fewer tumor nodules. MDA-MB-231 PKC η ^{KO} xenografts also expressed reduced metastasis in the distant brain, lung, and liver organs.

Mechanistically, we show that PKC η regulates epithelial-to-mesenchymal transition (EMT) markers as knockout of PKC η in TNBC cell lines increased expression of E-cadherin, EpCAM, and slug, and decreased expression of vimentin and ZEB1. Further profiling of the Hippo-YAP axis showed that PKC η is a negative regulator of the Hippo pathway that leads to YAP stabilization and is associated with phosphorylation at Ser128, which allows YAP to translocate to the nucleus and contributes to metastasis of TNBC cells. Moreover, our data support direct interaction between PKC η and YAP1 in TNBC cells. Finally, we show that treatment of TNBC cells with uPEP2 (a uORF-encoded peptide of the PKC η transcript) downregulates the PKC η

expression, activates the Hippo signaling pathway and promotes YAP degradation. Our findings highlight the importance of PKC η in TNBC metastasis and provide a new avenue for therapeutic intervention in this aggressive and lethal disease.

In conclusion, our studies identify a novel role of PKC η as a negative regulator of the Hippo pathway and reveal its function in promoting EMT and metastasis by modulating YAP /TAZ activity in TNBC. Results suggest that PKC η may represent a therapeutic target for this highly lethal and metastatic TNBC.

PO5-06-08

Real-world analysis of efficacy, adverse events and predictive biomarkers for advanced triple negative breast cancer (TNBC) treated with immune check point Inhibitors (ICI): A single center experience

Presenting Author(s) and Co-Author(s):

A. Patel. Roswell Park Comprehensive Cancer Center, United States

A. Roy. Roswell Park Comprehensive Cancer Center, Amherst, New York, United States

M. Alharbi. Roswell Park Comprehensive Cancer Center, United States

K. Attwood. Roswell Park Comprehensive Cancer Center, United States

C. Hong. Roswell Park Comprehensive Cancer Center, United States

S. Yao. Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

T. Khoury. Department of Pathology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

A. Early. Roswell Park Comprehensive Cancer Center, United States

T. O'Connor. Roswell Park Comprehensive Cancer Center, United States

E. Levine. Roswell Park Comprehensive Cancer Center, United States

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

Introduction KEYNOTE-355 investigated the addition of pembrolizumab to chemotherapy in advanced TNBC patients (pts) with PD-L1 positive tumors showing median overall survival (OS) of 23.0 months (mos) and median progression-free survival (PFS) of 16.1 mos. Given significant OS benefit with pembrolizumab, it is the current standard of care while the indication of atezolizumab has been withdrawn due to lack of OS benefit in IMPASSION-130. Clinical efficacy and adverse events in pts on this treatment regimen in clinical practice is unknown and understanding the real-world outcomes of this regimen is critical. Methods We conducted a retrospective, single-center observational study among TNBC pts treated with ICI (Pembrolizumab or Atezolizumab) at Roswell Park Comprehensive Cancer Center from January 2017 to May 2023. Demographics and clinicopathological variables were collected including comorbidities, laboratory data, sites of metastases (mets), treatment received, immune related adverse events (irAEs), and clinical outcomes. Adverse events were reported using the Common Terminology Criteria for Adverse Events v5.0. Serial CT scans were reviewed and response rate was determined using RECIST v1.1. Patient demographic, clinical and outcome characteristics were summarized by treatment and survival outcomes were obtained using standard Kaplan-Meier methods. Associations between survival outcomes and baseline or treatment characteristics were evaluated using Cox regression models using Firth's method. All analyses were conducted in SAS v9.4 at a significance level of 0.05. Results A total of 44 pts with advanced TNBC treated with ICI were included (23 received pembrolizumab and 21 received Atezolizumab). The study population consisted of all female pts with stage IV disease, median age 53.7 years (IQR 30.4-85.2), 68.2 % (30/44) White, 25.0% (11/44) Black, 34.1% (15/44) obese (BMI \geq 30). 27.3% (12/44) pts developed any grade irAEs which included myocarditis (4.5%), rash (9.1%), hyperthyroidism (6.8%), hypothyroidism (4.5%), adrenal insufficiency (2.3%), diabetes mellitus (2.4%), colitis (2.3%), and transaminitis (2.3%). Distribution of reported irAE was 25% grade 1 (3/12), 66.7% grade 2 (8/12) and 8.3% grade 3 (1/12). 75% pts (33/44) received standard treatment (ICI+ chemotherapy) of which 72.7 % (24/33) received it in the first-line setting. Median OS in pts treated in first line was 16.2 mos

(95% CI, 10.7-NR) and median PFS was 4.4 mos (95% CI, 2.7-8.4). Overall response rate (ORR) was 29.1% (7/24) of which 8.3% (2/24) had complete response and 20.8% (5/24) had partial response. ORR was 22.2 % (2/9) in pembrolizumab cohort and 33.3 % (5/15) in atezolizumab cohort. Among pts with first line treatment, obese pts were found to have improved PFS compared to non-obese (11.5 vs 3.8 mos, univariate hazard ratio (HR) 0.46, 95% CI 0.23-0.93, p= 0.031), and this difference was maintained in multivariable analysis even after adjusting for age (adjusted HR (aHR) 0.40, 95% CI 0.17-0.98, p= 0.044). Pts with brain mets had poor extracranial PFS compared to those without brain mets (2.8 vs. 5.2 mos, HR 2.25, 95% CI 1.08-4.68, p= 0.036), however this difference was not observed when further adjusted for age (aHR 2.27, 95% CI= 0.91-5.68, p= 0.08). Conclusion Clinical outcomes in our study were inferior to KEYNOTE-355 where median PFS was 16.1 mos and OS was 23.0 mos and ORR was 52.7% for PD-L1 positive population. This may reflect a more heterogeneous population of pts treated in routine clinical practice who are typically less fit than pts on clinical trials. Our study found improved outcomes among obese patients, similar to data reported in other disease settings. These data warrant multi-center validation with larger number of patients.

PO5-06-09

Metastatic triple negative breast cancer has distinct tumor immune landscape

Presenting Author(s) and Co-Author(s):

R. Seager. Omniseg, United States

H. Ko. Labcorp Oncology, United States

S. Pabla. Omniseg, United States

M. Senosain. Omniseg (Labcorp Oncology), United States

E. Van Roey. Omniseg (Labcorp Oncology), United States

S. Gao. Labcorp, Buffalo, New York, United States

K. Strickland. Labcorp Oncology, United States

R. Previs. Labcorp Oncology, United States

M. Nesline. Labcorp Oncology, United States

S. Hastings. Labcorp Oncology, United States

S. Zhang. Labcorp Oncology, United States

J. Conroy. OmniSeq, Inc., Buffalo, New York, United States

T. Jensen. Labcorp Oncology, United States

M. Eisenberg. Labcorp, United States

B. Caveney. Labcorp, United States

E. Severson. Labcorp Oncology, United States

S. Ramkissoon. Labcorp Oncology, United States

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

Background: Triple negative breast cancer (TNBC) is considered the most immunogenic breast cancer subtype due to higher levels of tumor infiltrating immune cells (TILS), elevated tumor mutational burden and PD-L1 expression, providing a rationale for immunotherapy. Here we aimed to investigate the differences in the immune microenvironment of primary vs. metastatic sites in TNBC vs. non-TNBC and their impact on survival. Methods: Comprehensive immune profiling, including PD-L1 IHC and the expression of 395 immune genes, was performed on 147 real-world FFPE breast cancer samples (32 primary, 115 metastatic). 37 samples were, by definition, triple negative for ER, PR, and HER2 overexpression. PD-L1 (CPS positive $\geq 1\%$ and CPS positive $\geq 10\%$) was determined using immunohistochemistry (22C3). mRNA expression signatures of tumor inflammation (TIGS, weak/moderate/strong) and cell proliferation (CP, poor/moderate/high) were determined by RNA-sequencing. Demographic and clinicopathologic variables were collected. Statistical comparisons of biomarkers between groups were calculated using the Wilcoxon Rank-Sum test for continuous variables and the proportions test for categorical variables ($p \leq 0.05$ for significance). Survival differences were quantified by Cox proportional hazards analysis ($p \leq 0.05$ for significance). Results: Triple negative status was associated with current use of alcohol [$p=0.03$]. Black patients were also more likely to have TNBC, constituting 24% of TNBC patients while only making up 14% of the total cohort [$p=0.04$]. Conversely, white patients were less likely to have TNBC, constituting 73% of TNBC patients while making up 84% of the total cohort [$p=0.04$]. Comparing TNBC and non-TNBC cases, TNBC cases were observed to have significantly higher TIGS [$p=0.014$] and PD-L1 expression [$p=4.4 \times 10^{-7}$]. Additionally, TNBC cases trended towards exhibiting greater cell

proliferation [p=0.069]. These differences were found to be driven primarily by metastatic tumors, among which TNBC tumors showed significantly higher TIGS [p=0.015], cell proliferation [p=0.021], and PD-L1 expression [p=2.9×10⁻⁷] than non-TNBC tumors, while none of these significant associations were observed among primary tumors. Triple negative status was significantly associated with PD-L1 expression (assessed by IHC), with a majority of PD-L1 positive cases determined to be triple negative [70% of CPS≥1% cases, p=5×10⁻⁵; 59% of CPS≥10% cases, p=6×10⁻⁴]. Several immune-related genes and immune checkpoint molecules were over-expressed in triple negative breast cancer, including CD8, GZMB, PRF1, CCL5, IFNG, TIGIT and CXCL10. A number of genes were also significantly overexpressed in metastatic tumors: KRT5 [p=0.02], TFRC [p=0.04], ABCF1 [p=0.04], FCRLA [p=0.05], LAMP3 [p=0.05], and underexpressed in metastatic tumors: ENTPD1 [p=0.05], IGSF6 [p=0.03], and ITGA1 [p=0.03]. Conclusions: Our comprehensive biomarker analyses showed that metastatic TNBC has a more inflamed tumor microenvironment and higher checkpoint target expression compared to non-TNBC. Further analysis of immune expression by site-specific metastases and correlation with immunotherapy outcomes is warranted to guide clinicians in selection of the ideal metastatic site to biopsy for therapeutic decision making. However, in a collective TNBC context, these data support the use of immunotherapy in metastatic TNBC.

PO5-06-10

Evaluating Disparities in Access to Quality Cancer Care for Black Women with Triple Negative Breast Cancer in the US: A Provider Perspective

Presenting Author(s) and Co-Author(s):

D. Effange. Association of Community Cancer Centers (ACCC), United States

N. Dixit. University of California, San Francisco, United States

R. O'Regan. University of Rochester Medical Center, Rochester, New York, United States

O. Kalu. Tigerlily Foundation., United States

R. Norcereto. Middlesex Health Cancer Center, United States

R. Simonds. University of Houston-Downtown, United States

E. Valencia. Mayo Clinic Alix School of Medicine, United States

L. Bolds-Johnson. Tigerlily Foundation, United States

A. Van Kirk Villalobos. Rhizome, LLC, United States

C. Mangir. Rhizome, LLC, United States

e. Plotkin. Association of Community Cancer Centers, United States

K. Tacka. Association of Community Cancer Centers, United States

L. Boehmer. Association of Community Cancer Centers, United States

Introduction: Triple-negative breast cancer (TNBC) presents unique challenges due to its aggressive nature and limited treatment options. Black women are disproportionately affected by TNBC, experiencing higher incidence rates and poorer outcomes compared to other racial/ethnic groups. This study aims to evaluate disparities in access to quality cancer care for Black women with TNBC from the perspective of oncology healthcare providers. **Methods:** From December 2022 to February 2023, the Association of Community Cancer Centers conducted a survey of 84 multidisciplinary care team members who provided care to Black patients with TNBC. The online survey captured quantitative and qualitative data on challenges related to accessing timely TNBC diagnosis and treatment services, care coordination for work-up and biomarker testing, confidence in TNBC treatment, clinical trial enrollment, supportive care services, and related referrals. Additionally, a follow-up focus group was conducted in May 2023 to further interpret select survey data, with a focus on shared decision-making, patient-provider communication, and ways to support cancer programs in improving screening, biomarker testing, and care coordination for individuals with TNBC. **Results:**

Respondents reported several barriers to accessing timely diagnosis and treatment services for Black women with TNBC, including challenges in coordinating care for work-up and biomarker testing, providers' confidence in providing guideline-concordant comprehensive cancer care services for this patient population, enrolling patients in clinical trials, and making referrals for supportive care services. The survey revealed that community cancer programs treated an average of 21-50 patients with TNBC annually, with 31% of them being Black. Perceived patient-level factors contributing to challenges in accessing TNBC diagnosis and treatment included geographic distance to care facilities (14%), health literacy (18%), and insurance-related factors (21%). Practice-level barriers included limited accessibility of practice location (19%), capacity to accommodate new patients (27%), and insurance-related factors (34%). Additional findings highlighted slightly lower provider confidence in areas such as tobacco cessation (only 54% very confident), breast reconstruction (59% very confident), fertility counseling (52% very confident), and coordinating care across a fragmented healthcare system

(52% very confident). Respondents identified the most commonly offered comprehensive cancer care services as palliative care (82%), nutrition support (77%), telemedicine (68%), psychological counseling (68%), and financial advocacy (68%). Less commonly offered services include recreational therapy (21%), legal aid (17%), and childcare (16%). Conclusion: This study highlighted the barriers faced by providers in delivering quality cancer care to Black women with TNBC. The findings underscore the importance of addressing challenges related to timely diagnosis and treatment services, care coordination, confidence in treatment options, clinical trial enrollment, and referrals for supportive care services. Insights from the focus group discussions further highlight the need for shared decision-making, improved patient-provider communication, and identification of opportunities to support cancer programs in addressing the specific needs of Black women with TNBC. To advance equity in cancer care, targeted interventions should focus on enhancing provider education, improving care coordination systems, and promoting cultural sensitivity. Efforts should also be made to overcome barriers related to limited accessibility of practice location, and insurance-related factors. By addressing these gaps, providers can play a crucial role in reducing disparities and improving outcomes for Black women with TNBC.

PO5-06-11

RPL27A promotes the growth and metastasis of triple negative breast cancer by regulating Ribosome biogenesis

Presenting Author(s) and Co-Author(s):

W. Zhao. Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

j. Zhang. National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

y. Zhu. National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

x. Yang. National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, United States

X. Li. Tianjin Normal University, United States

Background: Ribosome is a complex structure in cells for protein synthesis. It has been considered always have a constant composition. Recent studies have revealed that the Ribosome composition of tumor cells is heterogeneous. The Ribosome protein composition, post-translational modification, rRNA modification, and rRNA variants can lead to the existence of specialized "onco-ribosomes" in tumor cells, which regulates the rate of translation and protein synthesis, and can affect the occurrence and development of tumors significantly. The abnormal expression of multiple Ribosome proteins in triple-negative breast cancer may be the target of its diagnosis and treatment, also, an independent factor in prognosis evaluation.

Methods: To learn the expression levels of Ribosome biogenesis related genes in normal breast cells and abnormal breast cells with different pathological subtypes of breast cancer, the following studies have been done: 1. Bioinformatics analysis on TCGA database and single-cell sequencing data; 2. IHC detection on TNBC tissue and adjacent tissues; 3. Determine the expression level of RPL27A in TNBC cells, and analyze the correlation between the expression of RPL27A and clinical information of patients. To explore the effect of RPL27A on Ribosome biogenesis, protein synthesis and other signaling pathways through Proteomics and molecular biology experiments have been designed and tested. The effects of RPL27A on malignant biological behaviors such as proliferation, migration, infiltration, and clonal formation of TNBC cells were studied through cell biology experiments and mouse experiments. Results: The analysis of TCGA database and single-cell sequencing data showed that the RPL27A was significantly increased in TNBC group. Immunohistochemical experiments showed that RPL27A was highly expressed in TNBC tissue and was impressively positively correlated with tumor size, lymph node metastasis, and bone metastasis. There was significantly negatively correlated with overall survival (OS) and disease free survival (DFS). It can be an independent factor for evaluating the prognosis of TNBC. By knocking out RPL27A in TNBC cell line, label free proteomics analysis showed that Ribosome biogenesis, protein synthesis, cell cycle regulation and other signaling pathways were obviously down regulated. Cell biology experiments have implied that the high expression of RPL27A in TNBC promotes cell proliferation, enhances cell migration, infiltration, and cloning ability, leads to more malignant biological behavior of tumor cells. Further research demonstrates that the high expression of RPL27A in TNBC significantly activated the EIF3C signal, cause changes in the composition of Ribosome in TNBC cells, promoted the formation of "onco-ribosomes", and distinctly increased the rate of protein synthesis. The study of PDX mice and Organoid showed that the knock out of RPL27A significantly reduced the growth rate and transfer ability of TNBC. Conclusion: The

obvious over expressing of RPL27A in TNBC, which can significantly promote the growth and metastasis of tumor cells by influencing the Ribosome biogenesis process.

PO5-06-12

Genetic screen identifies epigenetic drivers of breast cancer brain metastasis

Presenting Author(s) and Co-Author(s):

J. Chen. Yale University, United States

W. Cai. Yale University, United States

P. Xu. Yale University, United States

D. Nguyen. Yale University, United States

Q. Yan. Yale University, United States

Metastatic breast cancer remains a major cause of cancer-related deaths in women, and there are few effective therapies against this advanced disease. Brain metastases, found in 15~35% of patients with breast cancer, are often incurable. Accumulating evidence suggests that key steps of tumor progression and metastasis are controlled by reversible epigenetic mechanisms. To systematically identify the druggable epigenetic regulators essential for breast cancer brain metastasis, we conducted an *in vivo* shRNA screen and identified multiple epigenetic regulators, including RNA acetyltransferase NAT10 as drivers of breast cancer brain metastasis. Knockdown of NAT10 significantly restrains breast cancer cell proliferation and migration *in vitro* and brain metastases *in vivo*. NAT10 promotes breast cancer cell growth through its RNA helicase activity but not its acetyltransferase activity. Integrative analyses of transcriptomics, proteomics, and NAT10 eCLIP-Seq data identify NAT10 downstream targets critical for breast cancer progression and metastasis. Thus, these results reveal novel therapeutic strategies to treat metastatic breast cancer.

PO5-06-13

Impact of Therapy on Sites of Metastases in Triple Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

H. Chang. University of Texas at Southwestern, Dallas, Texas, United States

P. Dev. University of Texas at Southwestern, United States

L. Froessl. University of Texas at Southwestern, United States

S. Huang. University of Texas at Southwestern, United States

C. Hodgdon. Grasp Cancer, United States

J. Maues. GRASP, Washington, District of Columbia, United States

I. Chan. University of Texas Southwestern Medical Center, United States

Background: Metastatic triple negative breast cancer (TNBC) is a diverse disease with the propensity to spread to visceral organs and the central nervous system (CNS). While systemic chemotherapy is commonly used, there is a growing utilization of immune checkpoint inhibitors (ICI) and antibody drug conjugates (ADC). However, few studies have examined the impact of specific therapies on individual metastatic sites, limiting clinical guidance for solitary metastases. Objective: This study aimed to evaluate the efficacy of various systemic therapies in TNBC patients with lung, liver, and CNS metastases. Methods: We analyzed data from the Dallas Metastatic Breast Cancer Study, a retrospective cohort study that includes all patients with metastatic breast cancer treated at a single academic medical center and identified 52 TNBC patients with visceral and CNS metastases diagnosed between 2009 and 2021. We correlated the site of metastasis with and treatment response, which was assessed based on imaging findings using RECIST 1.1 criteria. Results and Discussion: The median age at diagnosis of visceral metastatic disease was 52 years. Of the patients, 60% presented with de novo metastatic disease, while 40% experienced disease recurrence. The most prevalent metastatic sites were the lung (n=28), CNS (n=28), and liver (n=9). Among patients with detectable circulating tumor DNA, the most prevalent gene mutations in lung metastases were TP53 (36%), PTEN (13%), and PIK3R1 (10%). In liver metastases, TP53 (53%) and BRCA1 (15%) mutations were the most frequently observed. Similarly, in CNS metastases, TP53 (40%) and BRCA1 (13%) mutations were again most frequently detected. The notable frequency of TP53 mutations indicates the necessity for further investigations to explore potential differences in treatment approaches for patients with these mutations. The median overall survival (OS) was 14.43 months \pm 15.53, with the longest survival observed in patients with lung metastases (15 months), followed by liver metastases (6 months) and CNS metastases (5 months). Patients with involvement of a single visceral or CNS site had a mean OS of 15.80 \pm 18.19 months, whereas those with two sites of involvement had a mean OS of 13.08 \pm 10.18 months. Patients with metastases in all three sites had a mean OS of 8.33 \pm 8.50 months. Treatment modalities varied among patients. For liver metastases, chemotherapy (n=6), ICI (n=2), ADC (n=1), radiation therapy (n=2), and surgery (n=1) were administered. Lung metastases were treated with chemotherapy (n=26), ICI (n=4), ADC (n=5), radiation therapy (n=4), and surgery (n=1). CNS metastases were managed with chemotherapy (n=14), ICI (n=2), ADC (n=1), radiation therapy (n=21), and surgery (n=4). Systemic therapy for liver metastases resulted in stable disease (75%) and progressive disease (25%). In lung metastases, it led to stable disease (56%), partial response (23%), complete response (13%), and progressive disease (8%). CNS metastases treated with systemic therapy demonstrated stable disease (86%) and progressive disease (14%). The most commonly used systemic therapy was paclitaxel. Immunotherapy achieved a partial response (60%), stable disease

(20%), and progressive disease (20%) in metastatic lesions. Treatment with ADCs resulted in stable disease (43%), partial response (29%), and progressive disease (29%). Compared to lung metastases, liver and CNS metastases exhibited lower response rates and overall survival. CNS metastases were less likely to receive systemic therapies, indicating a need for improvement. These findings highlight the importance of personalized treatment strategies tailored to individual metastatic sites in TNBC.

PO5-06-14

Genomic Landscape and Clinical Outcomes of Triple-Negative Invasive Lobular Carcinoma

Presenting Author(s) and Co-Author(s):

H. Batra-Sharma. University of California San Diego Moores Cancer Center, United States

S. Sivakumar. Foundation Medicine Inc., United States

P. Ashok Kumar. SUNY Upstate Medical University, Syracuse, New York, United States

E. Sokol. Foundation Medicine Inc, United States

R. Shatsky. University of California at San Diego, United States

J. Ross. Foundation Medicine Inc., United States

Background: Triple-negative (TN) invasive lobular carcinoma (ILC) of the breast is a rare entity, comprising roughly 2% of primary ILC. Clinicopathologic studies have shown that TN ILC is associated with more pleomorphism, higher nuclear grade, older patient age, and worse disease-related outcomes compared to estrogen receptor-positive (ER+) ILC. Intrinsic subtyping indicates that TN ILC less frequently expresses basal markers than TN invasive ductal carcinoma (IDC). This prompted investigation of the genomic landscape and clinical management of TN ILC to provide insight into potential therapeutic approaches. Methods: Twenty patients with TN ILC were included in this study. Three patients were treated at a single academic center and underwent comprehensive genomic profiling (CGP) of breast or metastatic tissue; clinicopathologic details were obtained from their electronic health records. Seventeen patients with TN ILC who underwent CGP of breast or metastatic biopsies were included from the Foundation Medicine, Inc. database. PD-L1 testing for all patients was determined by immunohistochemistry (IHC) using the VENTANA SP142 or Dako 22C3 commercial assays. HER2 expression was determined by IHC. Negative HER2 expression was defined as an IHC score of 0, or IHC 1+ or 2+ with non-amplified fluorescence in situ hybridization (FISH). Results: In the Foundation Medicine database of patients with TN ILC, the most frequent genomic alterations were in CDH1 (15/17 patients [88.2%]), TP53 (10/17 patients [58.8%]), and PIK3CA (10/17 patients [58.8%]). Short variant mutations in ERBB2 were found in 3/17 patients (17.6%). Fourteen patients were HER2-low (HER2 IHC 1+ or 2+ with non-amplified FISH). No cases were MSI high or expressed PD-L1 (8 of 17 cases underwent PD-L1 assessment by SP142). Median tumor mutational burden (TMB) was 5 muts/Mb. Among the three patients with TN ILC treated at a single center, the most common somatic mutations were in CDH1 and TP53, and no cases were MSI high or expressed PD-L1 (by SP142 or 22C3). All three patients had pleomorphic ILC, histologic grade 2 or 3, and HER2 IHC 0. One patient with mpT1cN1a(sn) ER+/HER2- ILC of the right breast in 2011 received adjuvant TAC (docetaxel, doxorubicin, cyclophosphamide), breast/axillary radiation, and ten years of adjuvant endocrine therapy. She was diagnosed with TN ILC of the left supraclavicular nodes in 2022; she did not exhibit a response to docetaxel and carboplatin with pembrolizumab, and she subsequently received palliative radiation followed by capecitabine. Another patient with locally advanced TN ILC progressed on the KEYNOTE-522 regimen, immediately developed metastases, and is currently receiving palliative sacituzumab govitecan. The third patient with cT3N1 TN ILC progressed on neoadjuvant therapy (through the I-SPY 2 trial) with oral paclitaxel, encequidar, and dostarlimab, followed by dostarlimab with dose-dense doxorubicin and cyclophosphamide. Her surgical pathology demonstrated ypT3N3a disease with 10x7 cm of tumor, and she developed skin metastases on the chest wall within weeks post-operatively. She received comprehensive chest wall and nodal radiation and is currently

receiving palliative capecitabine with neratinib given a high variant allele frequency driver somatic ERBB2 mutation. Conclusions: The most common somatic mutations among TN ILC patients included in this study were in CDH1, TP53, and PIK3CA. Currently the management of TN ILC is extrapolated from that of TN IDC, however our patients did not respond to chemoimmunotherapy. The presence of HER2-low status or somatic ERBB2 mutations may provide opportunities for treatment with an anti-HER2 antibody-drug conjugate or tyrosine kinase inhibitor. Studies with larger sample sizes of TN ILC are needed for molecular profiling and assessment of outcomes with specific therapeutic approaches.

PO5-07-01

A novel clinical risk score that can accurately predict the survival of young breast cancer patients: A UAE-based cohort study.

Presenting Author(s) and Co-Author(s):

A. Al-Awadhi. department of Medical Oncology, Tawam hospital - SEHA, United States

M. Hourani. Department of Medical Oncology -Tawam hospital - Abu Dhabi Health Services Company - Al Ain - UAE, United States

M. Hussein. Department of Medical Oncology -Tawam hospital - Abu Dhabi Health Services Company - Al Ain - UAE, United States

F. Alkindi. Department of Internal Medicine -Tawam hospital - Abu Dhabi Health Services Company - Al Ain - UAE, United States

L. Wahba. Department of Clinical Pharmacy -Tawam hospital - Abu Dhabi Health Services Company - Al Ain - UAE, United States

A. AlAgha. Department of internal Medicine -Tawam hospital - Abu Dhabi Health Services Company - Al Ain - UAE, United States

A. Shoqeir. Department of Academic affairs -Tawam hospital - Abu Dhabi Health Services Company - Al Ain - UAE, Abu Dhabi, United Arab Emirates

M. AlShebli. Department of Internal Medicine, University of Toronto, Canada, United States

A. Abusanad. Faculty of medicine, King Abdulaziz university, United States

A. Ahmad. New York University Abu Dhabi, Cancer Research UK (CRUK), United States

Introduction: Breast cancer (BC) in women below the age of 40 accounts for approximately 7% of all BC cases. According to studies, BC in younger women is more likely to have negative tumor characteristics and outcomes compared to older women. The rate of early-onset breast cancer in the United Arab Emirates (UAE) is higher than in the Western population (24%, previously reported). Young breast cancer patients in the UAE have worse adverse features, including a higher grade, a larger tumor size, and lymph node involvement, as we reported previously. Therefore, combining several clinical indicators to predict recurrence risk in our unique, heterogeneous young breast cancer group is needed.

Aim:The aim of this study is to develop a statistical machine learning model that can predict survival and the risk of recurrence in a young breast cancer population seen and treated in a large-volume tertiary cancer center in the United Arab Emirates (Tawam Hospital).

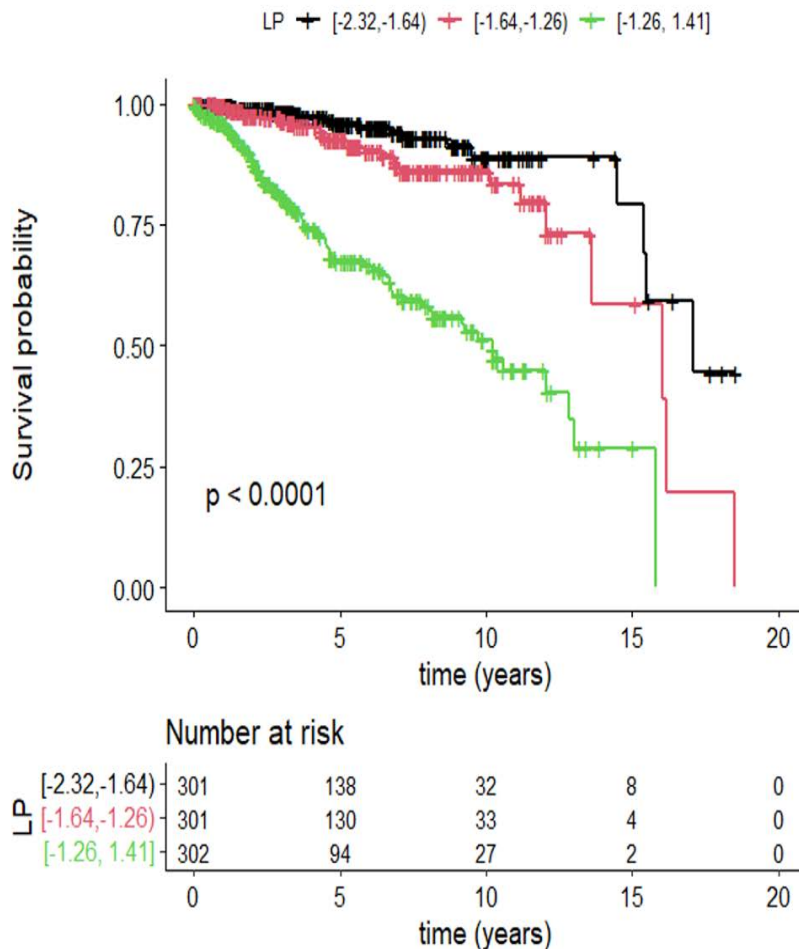
Methods: Early-onset breast cancer patients from a retrospective observational cohort study were included in this study (N = 904). A broad range of clinical data was collected. A multivariate ridge Cox regression model was performed using age, histology, molecular type (ER,PR,HER-2 status), T-stage, N-Stage, M-stage, grade, and BMI, and the interaction term age*BMI at the time of diagnosis. The primary outcome was time-to-death. A novel breast cancer risk score (BCRS) was developed as the linear predictor of the fitted-ridge Cox regression model. Breast cancer patients were categorized into low, medium, and high risk using the 33th and 66th centiles of the novel BCRS. A univariate Cox regression model was performed with a categorized BCRS as a predictor of time-to-death. Hazard ratios (HR) with a 95% confidence interval (95% CI) were estimated. Kaplan-Meier (KM) curves were plotted and compared using the log-rank test. Time-dependent sensitivity and specificity were computed at five- and ten-year follow-ups, respectively. Statistical analyses were performed in R version

4.2.3.

Results: The median age was 36 years (IQR: 32–38), and 64% were Arabic. Fifteen percent had an event with a median duration of follow-up of 15.4 years (95% CI: 13.6–17.1). The estimated HR of the categorized novel BCRS in a univariate Cox regression model was 1.968 (95% CI: 1.075- 3.601) and 8.040 (95% CI: 4.695–13.769) for the intermediate and high-risk groups as compared to the low-risk group, respectively. KM curves show a clear separation in terms of survival between the three risk groups, $p < 0.0001$ (Figure 1). A cutoff value of -1.733 gives a sensitivity of 93.8 and 90.6 with corresponding specificities of 31.42 and 31.31 at five- and ten-year follow-up, respectively.

Conclusion: This is the first study in the region that uses clinical data that combines several clinical characteristics and aims to design a statistical machine learning model to predict the risk of death from breast cancer. Our novel model can be used in daily clinical practice to identify high risk breast cancer patients and aid clinical decision-making in patients with breast cancer. However, further validation studies are needed.

Figure 1:KM curves of breast-cancer survival for patients with low-risk (BCRS in [-2.32, -1.63], black curve), intermediate-risk (BCRS in [-1.64, -1.25], red curve), and high-risk BCRS in [-1.26, 1.41], green curve).



PO5-07-02

AI-assisted interpretation of PD-L1 CPS improves the precision medicine in Triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

J. Li. Department of Pathology, The Fourth Hospital of Hebei Medical University, United States

X. Wang. Department of Pathology, The Fourth Hospital of Hebei Medical University, United States

Y. Liu. Department of Pathology, The Fourth Hospital of Hebei Medical University, United States

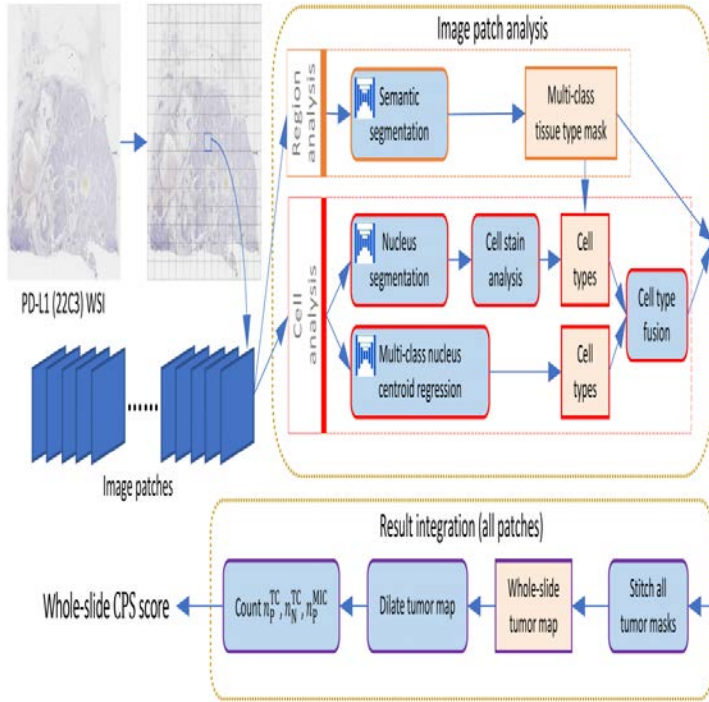
Objective: The IMpassion 031 and KEYNOTE-355 clinical trial demonstrated the advantages of atezolizumab and pembrolizumab in the treatment of Triple-negative breast cancer (TNBC). However, the application of CPS in assessing PD-L1 expression is challenging. Pathologists have great variability in interpretation of PD-L1 CPS, the daily diagnostic workload is too heavy and their diagnostic efficiency is low, and they still have deficiencies in terms of accurate enumeration. It is of necessity to establish an objective and effective method which is highly repeatable.

Methods: In this study, we established a deep learning-based artificial intelligence-assisted (AI-assisted) model which using cell detection and region segmentation algorithm. Three rounds of ring studies (RSs) were conducted. 12 pathologists of different level evaluate the CPS of PD-L1 (DAKO 22C3) in TNBC patients by visual assessment and AI-assisted model. Compare the difference, consistency and accuracy of the interpretation. Our research evaluated PD-L1 CPS expression with continuous score. Shapiro-Wilk (S-W) method performs normality test, difference analysis using Friedman M and Bonferroni calibration tests, consistency analysis is studied by intraclass correlation coefficient (ICC) and heat maps and box plots.

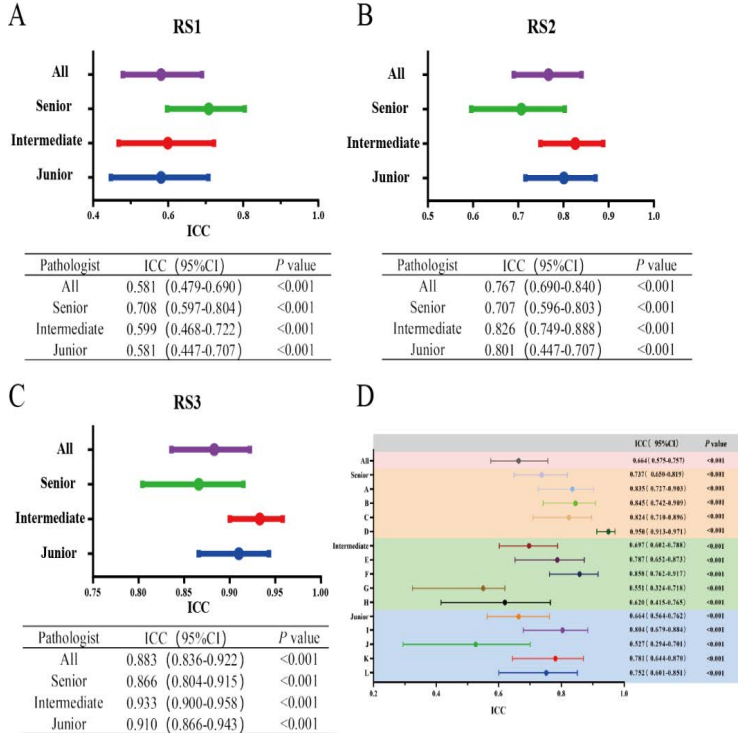
Results: In the visual assessment, the interpretation results of PD-L1 (DAKO 22C3) CPS in different level pathologists have significant differences ($P < 0.05$), and the consistency of all the pathologists interpretation results was weak. Due to this strong inconsistency, it may result in a number of patients losing the opportunity to use ICIs for treatment. Moreover, the internal consistency of all pathologists in the visual assessment is moderate, in which the repeatability of junior pathologists is the worst · the ICC value is 0.664 (95%CI: 0.564-0.762). Through AI-assisted interpretation, there is no significant difference between all pathologists ($P = 0.425$), and the ICC value increased to 0.883 (95%CI : 0.836-0.922) which improved the consistency of the interpretation results. In addition, through AI-assisted interpretation, the repeatability and accuracy of the interpretation results has been further upgraded. At the same time, the acceptance of AI results by junior pathologists are high, and 80% of the AI results are accepted.

Conclusions: With the help of the AI-assisted diagnostic model, different levels of all the pathologists have achieved excellent consistency and repeatability in the interpretation of PD-L1 (DAKO 22C3) CPS. Moreover, the level of interpretation has been sought the rapid enhancement. It can be seen that AI-assisted diagnostic model provides a good approach to strengthen the consistency and repeatability in clinical practice. Our research also shows that PD-L1 CPS can receive precise interpretation from pathologists, so more patients have the opportunity to use ICIs. Therefore, these patients can benefit from treatment and achieve better survival.

The interpretation results and system diagram of PD-L1 CPS by AI-assisted model.

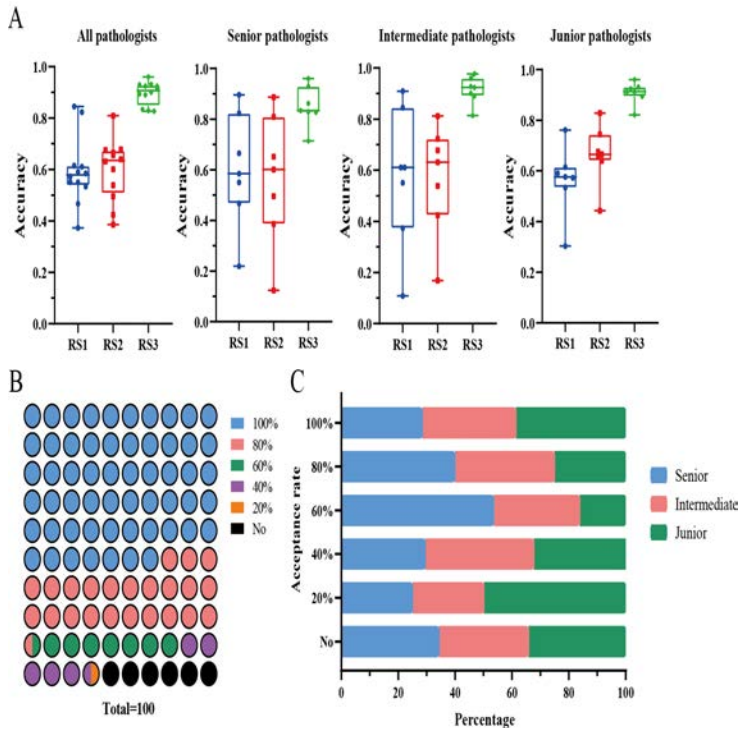


The consistency and repeatability of the interpretation results.



(A)-(C) The consistency of the PD-L1 CPS interpretation among the different level of pathologists in three ring studies. (D)The repeatability of the interpretation results between 12 pathologists in RS1 and RS2.

Accuracies and acceptance rates of different experienced pathologists.



(A) Boxplots of scoring accuracies for pathologists in different levels. (B) Acceptance rates of all pathologists in total 50 slides. (C) Percent stacked column chart of different levels of pathologists with AI score acceptance.

PO5-07-03

Integrating mechanism-based and data-driven modeling to predict the response of triple negative breast cancer to therapy

Presenting Author(s) and Co-Author(s):

C. Stowers. University of Texas at Austin, Austin, Texas, United States

C. Wu. UT Austin, Texas, United States

S. Kumar. University of Texas at Austin, United States

Z. Xu. MD Anderson Cancer Center, Texas, United States

C. Yam. Breast Medical Oncology Department, The University of Texas MD Anderson Cancer Center, United States

J. Son. University of Texas MD Anderson Cancer Center, United States

J. Ma. University of Texas MD Anderson Cancer Center, United States

J. Tamir. University of Texas at Austin, United States

G. Rauch. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

T. Yankeelov. UT Austin, United States

Introduction Neoadjuvant chemotherapy (NAC) is the standard-of-care (SOC) for patients with locally advanced triple-negative breast cancer (TNBC) [1]. Unfortunately, only about half of TNBC patients achieve a pathological complete response (pCR) at the completion of NAC [2]. With the recent FDA approval of immunotherapy, the response rate improved by about 8% [3]. To try to further improve NAC response rates, we build upon methods that predict treatment response to optimize interventions and outcomes. Our previous studies have demonstrated that excellent predictive accuracy of TNBC response to NAC was achieved through calibrating mechanism-based models to both pre- and on- treatment imaging data [4]. However, by requiring on-treatment imaging data, therapy optimization can only occur after a patient begins NAC. Here, our goal is to relax the requirement of on-treatment imaging data such that we can predict, and potentially optimize, a patient's response to NAC before initiating it. We will accomplish this through combining data-driven approaches with mechanism-based modeling to obtain spatiotemporal predictions of tumor response prior to NAC. More specifically, we integrate a reaction-diffusion equation based mathematical model with a U-Net based convolutional neural network (CNN). Methods The reaction-diffusion equation models the development of tumor cellularity over time as the sum of tumor cell diffusion, controlled by a fixed diffusivity, and tumor cell proliferation, controlled by a calibrated net proliferation rate. The net proliferation rate implicitly accounts for both proliferative and drug induced death effects. We calibrated the net proliferation rates in this model on a patient-specific basis for 128 patients from the ARTEMIS trial (NCT02276443) using three imaging timepoints – pre- (V1), post two cycles (V2), and post four cycles (V3) of A/C. We then employed a CNN to characterize the relationship between the calibrated net proliferation rates and the pre-treatment imaging data. The CNN takes pretreatment imaging inputs of the apparent diffusion coefficient map, percent enhancement maps from the dynamic contrast enhanced MRI timecourse, and precontrast T₁ map. The CNN outputs an estimate of the calibrated net proliferation rate which can be used to run the mathematical model forward in time to predict cellularity maps at V2/3. In training the CNN, our loss considers both the concordance correlation coefficient (CCC) and the normalized root mean square error (NRMSE). We calculated loss on the net proliferation rate predictions as NRMSE with a CCC penalty to aid in characterizing the non-Gaussian distribution of the net

proliferation rate. We calculated loss on the cellularity predictions as the CCC between predicted and measured voxel-wise cellularity. The CNN was trained using the Adam optimizer and a fivefold cross validation with a withheld test set of 26 patients. Results Using the CNN predictions to forward run the mechanism-based model in time to V3 we calculated change in total tumor cellularity and volume from V1 to V3. In the test cohort, we obtained CCC values between the predicted and measured changes of 0.95 and 0.91 for cellularity and volume, respectively. Discussion and summary Through integrating mechanistic modeling and deep learning, we can accurately predict the spatiotemporal development of TNBC response to NAC using only pretreatment imaging data. We will build upon these results by expanding our model to include separate proliferation and drug induced death terms to allow for therapy intervention and optimization. Additionally, we will incorporate other pretreatment data types including genetic data. [1] Liedtke et al., J of Clin Oncol, 2008. [2] Spring et al., Clin Cancer Res, 2020. [3] Schmid et al., NEJM, 2020. [4] Wu et al., Cancer Res, 2022.

PO5-07-04

Machine learning models can help physicians reduce unnecessary ultrasound guided breast biopsies

Presenting Author(s) and Co-Author(s):

I. Buzatto. Ribeirão Preto Medical School, University of São Paulo, Brazil

D. Carlotti. Departamento de Ciência da Computação, Instituto de Matemática e Estatística, University of São Paulo, Brazil

N. Onari. Barretos Cancer Hospital, Barretos, Brazil, United States

A. Faim. Barretos Cancer Hospital, Barretos, Brazil, Brazil

S. Recife. Women's Health Reference Center of Ribeirão Preto (MATER), Ribeirão Preto Medical School, University of São Paulo, Brazil

L. Miguel. Women's Health Reference Center of Ribeirão Preto (MATER), Ribeirão Preto Medical School, University of São Paulo, Brazil

R. Bonini. Barretos Cancer Hospital, Campo Grande, Brazil, Brazil

L. Silvestre. Ribeirão Preto Medical School, University of São Paulo, Brazil

L. Figueira. Faculdade Estadual de Tecnologia de Ribeirão Preto - Centro Paula Souza, Brazil, Brazil

D. Guimarães Tiezzi. University of Sao Paulo, United States

Background Breast ultrasound is widely used as a diagnostic tool, the weakness of the method though is a high false positive rate, leading to unnecessary biopsies. In recent years, machine learning (ML) is gaining attention for its excellent performance in image-recognition tasks. The objective of this study was to train and validate ML models to predict malignancy of breast masses identified by ultrasound using clinical features of the patients, image information from the ultrasound reports and attributes extracted from the images. **Methods** We prospectively collected clinical and ultrasonographic attributes as well as the images from 927 lesions classified as BI-RADS 2, 3, 4a, 4b, 4c, 5 and 6 submitted to percutaneous biopsy in four institutions. Images in PNG format were loaded with OpenCV library and converted to gray scale. A total of nine attributes were extracted from the annotated area. We trained and validated five ML algorithms (histogram gradient boosting, logistic regression, a pipeline of these two classifiers, stacking ensemble of several classifiers and lightgbm), randomly sampling 80% of the dataset for training and 20% for validation using a cross fold strategy. We trained and tested the models with five different combinations of the data collected and compared the performances. The model with the lowest mean errors was selected and the threshold tuned to minimize the cases that the model classified as benign and were truly cancer ("false not cancer"). Image preprocessing, attribute extraction, and traditional machine learning was performed in Python. **Results** The clinical characteristics of the patients and ultrasonographic attributes of the lesions withdrawn from the exam reports are described in Table 1. The biopsy results distribution across the BI-RADS classification of the ultrasound report is shown in Table 2 and are in accordance with the literature. Among the five tested models, the logistic regression was the one with the lowest mean errors and was selected to tune the thresholds minimizing "false not cancer" cases. Our target was up to 2% of this error to stay within the BI-RADS 3 classification and thus dismiss biopsy. Table 3 describes five different combinations of data used to construct the models. All these combinations had < 0.5% of "false not cancer", way below the 2% threshold from the BI-RADS 3 category. The mean error of the models classifying benign lesions as cancer and inducing unnecessary biopsies

varied from 22.7% to 23.3% depending on the combination of data used. Conclusions Machine learning models can potentially help physicians avoid unnecessary ultrasound guided breast biopsies using unsophisticated clinical features and attributes from the images missing < 0.5% of cancer cases.

Table 1. Clinical characteristics of the included patients and ultrasound features of the breast lesions.

Age: mean	51.7
Lesion size in mm: mean	16.5
Palpable: n (%)	497 (53.6)
Presence of internal vessels in the Doppler study: n (%)	486 (52.4)
Resistance Index of the vessel (when present): median (range)	0.75 (0.39-1)
Shape: n (%)	
Oval	320 (34.5)
Round	46 (4.9)
Irregular	561 (60.5)
Margins: n (%)	
Circumscribed	264 (28.4)
angular/microlobulated/indistinct	448 (48.3)
Spiculated	215 (23.2)
Orientation: n (%)	
Parallel	689 (74)
not parallel	238 (26)
Histology: n (%)	
Benign	477 (51.4)
Malignant	450 (48.5)

Table 2. Histology (malignant or benign) distribution across BI-RADS® classification.

BI-RADS® (n - total)	Benign: n (%)	Malignant: n (%)
2 (2)	2 (100)	0 (0)
3 (26)	26 (100)	0 (0)
4a (358)	350 (97.7)	8 (2.3)
4b (127)	85 (67)	42 (33)
4c (138)	11 (7.9)	127 (92)
5 (173)	1 (0.6)	172 (99.4)
6 (98)	0 (0)	98 (100)

*We had five lesions missing this data.

Table 3. Mean performances of the five models and parameters used to build them.

Dataset used	Age	Age	Age	Age	Age
	Palpable	Palpable	Palpable	Palpable	Palpable
	Size	Size	Size	Size	Size
	Shape, margin, and orientation (US report)	Shape, margin, and orientation (US report)	Shape, margin, and orientation (US report)		
	Doppler analysis (US report)		Doppler analysis (US report)	Doppler analysis (US report)	
		Attributes extracted from the images	Attributes extracted from the images	Attributes extracted from the images	Attributes extracted from the images
	Mean "false cancer"	22.7%	23.3%	22.8%	22.7%
Mean "false not cancer"	0.43%	0.43%	0.43%	0.43%	0.43%

PO5-07-05

Deep learning can diagnose axillary lymph node metastases on optical virtual histologic images in breast cancer patients during surgery

Presenting Author(s) and Co-Author(s):

S. Zhang. Peking University People's Hospital Breast Center, United States

H. Yang. Peking University People's Hospital Breast Center, United States

J. Zhao. Peking University People's Hospital Breast Center, United States

S. Wang. Peking University People's Hospital Breast Center, United States

Background: Reliable identification of axillary lymph node (ALN) involvement in patients with breast cancer allows for definitive axillary dissection at the time of the initial surgery, thus avoiding the need for a separate axillary surgery. However, conventional intraoperative ALN diagnostic methods are time-consuming and labor-intensive and can result in tissue destruction. Dynamic full field optical coherence tomography, also called dynamic cell imaging (DCI), has been developed and validated to offer rapid and label-free histologic approximations of metastatic and non-metastatic ALNs. In this study, we aim to optimize the diagnostic pipeline with an automated approach and present the results of using a deep learning (DL) algorithm with DCI to predict ALN status intraoperatively in patients with breast cancer. Methods: Breast cancer patients who required ALN staging were enrolled prospectively in this study. DCI was applied to bisected fresh lymph nodes in a non-destructive manner, and the specimens were subsequently sent for histopathological examination, regarded as the gold standard for comparison. A DL model was trained and fine-tuned on over 80,000 DCI images, and the results were mapped to slide level to predict ALN diagnosis. Results: Total 607 DCI slides of ALNs with 112,852 cropped patches were included in the study. The DL model was trained and validated on a dataset containing 481 slides and tested on an independent testing dataset with 126 slides. In the test set, the DL algorithm yielded accuracy for prediction of ALN status, with sensitivity and specificity of 91.9% and 95.5% and an area under the receiver operating characteristic curve (AUC) of 0.937 (95% confidence interval [CI]: 0.912-0.957) at slide level. Conclusion: These results demonstrate that the integration of DCI with DL is rapid, reduces labor requirements and minimizes tissue destruction. Meanwhile, this algorithm had high classification accuracy to predict the metastatic burden of ALNs for patients with breast cancer.

PO5-07-06

Impact of patient-specific factors on quantitative breast parenchymal texture features

Presenting Author(s) and Co-Author(s):

S. Nyante. University of North Carolina at Chapel Hill, United States

Y. Kajita. University of North Carolina at Chapel Hill, United States

W. Mankowski. University of Pennsylvania, Philadelphia, Pennsylvania, United States

L. Killeya. University of North Carolina at Chapel Hill, United States

D. Kontos. Department of Radiology, University of Pennsylvania, United States

X. Tan. UNC Lineberger Comprehensive Cancer Center, United States

E. Cohen. University of Pennsylvania, United States

C. Kuzmiak. University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

Breast parenchymal texture characterizes the spatial and structural patterns of breast tissue and is an independent predictor of breast cancer risk. Although it has conceptual similarities with another breast composition measure, breast density, parenchymal texture is more complex and is represented by multiple quantitative measures. The extent to which the epidemiology and biological basis of parenchymal texture and breast density differ has not been well described.

In this cross-sectional study, we evaluated quantitative measures of parenchymal texture among 308 postmenopausal women aged ≥ 45 years who participated in a routine breast cancer screening at an academic medical center between 2020 and 2022. After providing informed consent, participants completed a short interview-based questionnaire. Additional demographic and breast cancer risk factor information was obtained from the medical record. Parenchymal texture features were measured from craniocaudal views of full-field digital mammograms. Measured texture values were standardized and averaged across left and right breasts. For this analysis, we evaluated associations between features previously validated as being associated with breast cancer risk (fractal dimension, grey-level mean, co-occurrence entropy and inverse difference moment) and patient personal and clinical characteristics reported at the time of screening. Associations between texture features and participant characteristics were evaluated using Pearson correlations (continuous variables) or the Kruskal-Wallis test (categorical variables). Generalized linear models were used to adjust for technical factors associated with image acquisition, including mammography machine, compression force, and software version. P-values less than 0.05 were considered statistically significant.

Among the 308 participants, 70% were White, 24% were Black, 1% were Asian, 1% were American Indian, and 4% were another race that was not specified. 4% of participants reported Hispanic ethnicity. The mean age was 64.7 years (range 45 – 84 years). Fewer than half of the women were reported by a radiologist to have dense breasts (heterogeneously dense – 24%, extremely dense – 5%, vs. almost entirely fatty – 21%, scattered fibroglandular densities – 50%). The mean body mass index (BMI) was 29.4 kg/m² (range 19.4 to 53.1 kg/m²) and 77% of the women were parous.

BMI was strongly correlated with fractal dimension ($r=0.62$, $P < 0.01$) and grey-level mean ($r=-0.48$, $P < 0.01$), and had a weaker correlation with co-occurrence entropy ($r=-0.19$, $P < 0.01$).

Age was weakly correlated with co-occurrence inverse difference moment ($r=-0.12$, $P=0.03$). BI-RADS breast density was inversely associated with fractal dimension, grey-level mean, and co-occurrence entropy (all $P < 0.01$). Adjustment for technical factors attenuated some associations, but BMI associations with fractal dimension ($P < 0.01$) and gray-level mean ($P < 0.01$), and breast density associations with fractal dimension, grey-level mean, and co-occurrence entropy (all $P < 0.01$) all remained statistically significant. Parity was not associated with any of the features evaluated in unadjusted or adjusted analyses (all $P > 0.05$).

These data suggest that, in postmenopausal women, risk-associated parenchymal texture features are associated with measures affected by body size and adiposity, but not with measures related to age or reproductive status. Longitudinal studies are needed to understand the temporality of these associations. Additionally, future studies will address the joint effects of texture features and the impact of endogenous estrogen levels on the features, which will provide insight into the biological mechanisms that influence texture feature associations with personal characteristics and breast cancer risk.

PO5-07-07

The biological basis of breast MRI background parenchymal enhancement in women with high breast cancer risk

Presenting Author(s) and Co-Author(s):

P. Khoshpouri. University of Washington, Seattle, Washington, United States

A. Kazerouni. University of Washington, United States

S. Parsian. University of Washington, United States

D. Hippe. University of Washington, United States

O. Walsh. University of Washington, United States

L. Koch. University of Washington, United States

S. Partridge. University of Washington, United States

H. Rahbar. University of Washington, United States

Introduction:

The amount and degree of the fibroglandular tissue (FGT) enhancement on breast MRI, known as background parenchymal enhancement (BPE), is an emerging marker of breast cancer risk. Higher qualitative and quantitative BPE levels have been shown to correlate with both future risk of initial breast cancer diagnosis and breast cancer recurrence after treatment. Furthermore, adjuvant and preventative therapies such as radiation and endocrine therapy have been shown to lower BPE in many women, potentially serving as a marker of treatment efficacy. However, the biological basis of BPE remains unclear and elucidation of this mechanism could identify novel targeted prevention strategies. The goal of this study was to assess the association of BPE levels with markers of inflammation, vascularity, proliferation, and estrogen sensitivity in a cohort of high-risk women.

Materials and Methods:

In this IRB-approved retrospective study, we identified asymptomatic high-risk women who underwent at least one dynamic contrast-enhanced (DCE) breast MRI within one year of prophylactic bilateral mastectomy. Qualitative BPE assessments were obtained from clinical reports. Quantitative BPE measures were obtained using in-house semi-automated software: whole breast FGT was first segmented on pre-contrast images, percent enhancement (PE) was calculated for each voxel as $(S1-S0)/S0 \times 100\%$, where $S0$ and $S1$ are pre- and early post-contrast signal intensity, respectively, and quantitative BPE was then defined as the mean PE of the FGT. Additionally, the BPE volume ratio was calculated as the fraction of FGT that had a PE >50%. Histopathology markers of inflammation (COX-2), vascularity (VEGF), proliferation (Ki-67), and estrogen receptor status (ER) were prospectively measured on archived mastectomy specimens of each breast. BPE metrics were correlated with histopathological markers using Spearman's rank correlation, with and without adjustment by menopausal status of the patient. All tests were based on generalized estimating equations models to account for the non-independence of the two breasts per patient. A p-value < 0.05 was considered significant.

Results:

We identified 56 women (median age: 39; range: 26-63 years) for this study, of which 39% were post-menopausal (N=22). Distribution of qualitative BPE levels were 41% minimal (N=23), 29% mild (N=16), 18% moderate (N=10), and 12% marked (N=7). Qualitative BPE and quantitative BPE markers were moderately positively correlated ($r=0.37-0.54$, $p < 0.01$). Table 1

lists the correlations between BPE metrics and histopathology markers. After adjusting for menopausal status, qualitative BPE was positively associated with ER ($r=0.27$, $p=0.02$) and VEGF ($r=0.24$, $p<0.01$; $r=0.21$, $p=0.02$ adjusted). Quantitative BPE and BPE volume ratio were both positively correlated with VEGF ($p<0.04$) and negatively correlated with COX2 ($p<0.05$). No significant associations were observed between BPE and Ki-67.

Discussion:

Our study suggests that increased BPE on MRI positively correlates with increased vascularity and higher estrogen receptor expression but not inflammation or proliferation within normal breast tissue in high-risk women. These findings, along with established associations between BPE and cancer risk, could be useful to select and assess efficacy of targeted preventative treatments.

Spearman rank correlations between BPE metrics and histopathological markers.

	Qualitative BPE		Quantitative BPE		BPE Volume Ratio	
	ρ	ρ_{adj}	ρ	ρ_{adj}	ρ	ρ_{adj}
ER	0.23	0.27*	0.11	0.11	0.13	0.14
VEGF	0.24**	0.21*	0.19*	0.19*	0.21*	0.21*
COX2	-0.09	-0.14	-0.21*	-0.21*	-0.23*	-0.24*
Ki67	0.07	0.03	-0.05	-0.05	-0.02	-0.03

ρ_{adj} is adjusted by menopausal status.

*, $p<0.05$; **, $p<0.01$

PO5-07-08

A Serum Biomarker for the Early Detection of Breast cancer

Presenting Author(s) and Co-Author(s):

c. chavany. Milagen, Inc., United States

J. Dea. Milagen, Inc., United States

M. Guevara. Instituto Nacional de Ciencias Medicas y Nutricion, United States

R. Hernandez-Gonzalez. Instituto Nacional de Ciencias Medicas y Nutricion, United States

P. Ferroni. IRCCS San Raffaele Pisana Research Center, United States

F. Guadagni. IRCCS San Raffaele Pisana Research Center, United States

R. Valle. Milagen, Inc., United States

M. Jendoubi. Milagen, Inc., United States

Background: After decades of use, clinicians and medical societies are still debating on the clinical utility of mammography, the standard of care for breast cancer (BC) screening, because of its limitations such as subjective visual interpretation, high rate of false-positive and false-negative (in dense breast) and concerns over radiation exposure. There are 55 million women, and about 45% of them considered dense breast, in need of an accurate, easy to use test for the screening of BC regardless of breast tissue complexities to differentiate between BC and benign findings such as calcification and fibrosis. To this date there is no blood protein biomarker (BM) in clinical use for the early detection of BC. We have developed a novel BC specific protein biomarker -based blood test to detect patients with early-stage BC and established herein the diagnostic performance of our BM in discriminating BC patients from healthy individuals and benign breast cases. Methods: A total of 433 serum samples (318 primary BC, 32 benign breast and 83 normal breast) were obtained from the Cooperative Human Tissue Network and from the IRCCS San Raffaele Pisana Research Center (blind samples). 247 BC samples were provided as blind samples and were used to validate the screening utility. Serum samples were tested with our BC specific BM by sandwich ELISA. Receiver operating characteristic (ROC) curves were calculated to evaluate the diagnostic performance, by determining sensitivity (SE), specificity (SP), area under the curve (AUC), and confidence interval (CI). Statistical analysis, ROC curves and scatter plots were performed with GraphPad Prism 7.0. Results: BM elevation in early cancer cases (stage I-II, Ductal Carcinoma) was found to be statistically significant ($p < 0.0001$) as compared to healthy and benign cases. Our test discriminated early BC patients from non-cancer cases with 87.3% SE at 85.2% SP and was further validated in a blind set including 247 BC (Ductal & Lobular Carcinoma, stage I-III), 30 benign and 83 normal breast cases (88%SE, 86%SP). The sensitivity for early-stage (I-II) and late stage (III) BC was 86.8% and 94.3%, respectively. While lobular carcinoma is particularly not well detected by mammography with a sensitivity as low as 57% and much lower for women with dense breast, it was detected with high sensitivity (90%) in our test. 80% of fibrocystic changes (FCC), the most common form of benign breast disease in women over 50 years of age were negative with our test. Although it is a benign condition, FCC may be misdiagnosed as a malignant lesion by physical examination and imaging. Conclusion: Our results support the utility of our blood-based test for the early detection of breast cancer which presents improved features over mammography such as higher lobular cancer sensitivity, lower detection rate of common form of benign condition often misdiagnosed by imaging, absence of radiation and expected high compliance. Further testing is needed to confirm accuracy of our test in the dense breast population.

PO5-07-09

ACCURACY OF STEREOTACTIC VACCUUM-ASSISTED BREAST BIOPSY FOR INVESTIGATING SUSPICIOUS CALCIFICATIONS IN 2,021 PATIENTS A PUBLIC HOSPITAL IN BRAZIL

Presenting Author(s) and Co-Author(s):

A. Amorim. Perola Byington Hospital, United States

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

M. ANTONINI. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, Sao Paulo, Sao Paulo, Brazil

R. COELHO LOPES. HOSPITAL DO SERVIDOR PUBLICO ESTADUAL, United States

L. Damous. Hospital do Servidor Público Estadual – Francisco Morato de Oliveira, São Paulo, Brazil., United States

L. Gebrim. Perola Byington Hospital, United States

M. Diogenes. HOSPITAL PEROLA BYINGTON, SÃO PAULO, Sao Paulo, Brazil

M. Ramos. Perola Byington Hospital, United States

Background: the gold standard for breast biopsy procedures is currently an open excision of the suspected lesion. The cost and morbidity associated with this procedure has prompted many physicians to evaluate less invasive, alternative procedures. More recently, image-guided percutaneous core-needle biopsy has become a frequently used method for diagnosing palpable and non-palpable breast lesions. Although sensitivity rates for core-needle biopsy are high, it has the disadvantage of histological underestimation. Vacuum-assisted stereotactic biopsy (VASB) was developed to overcome some of these negative aspects of core-needle biopsy. Objectives: to evaluate the accuracy of vacuum-assisted stereotactic biopsy (VASB) in the investigation of non palpable suspicious calcifications. Methods: it was a retrospective study from July 2012 to December 2020, in which 2,021 women with suspicious calcifications detected on mammography (BI-RADS 4 and 5) had VASB performed at Hospital Estadual Pérola Byington, São Paulo, Brazil. Fragments were obtained and sent to anatomopathological study; a metal clip was placed on the biopsy site. Four groups were analyzed, based on the biopsy results: benign, precursor lesions, Ductal Carcinoma In Situ (DCIS) and Invasive Ductal Carcinoma (ICD). Results: patients median age was 55y (49-63y). Pathology results on VASB were classified respectively as benign n=1,340 (66.3%), precursor lesions n=84 (4.1%), DCIS n=441 (21.8%) and ICD n=156 (7.7%). The 60 patients with results benign on VASB, because anatomopathological disagreement, surgery was performed, with the following results: benign n=30 (50%), ICD e DCIS n=21 (35%) e precursor lesions n=9 (15%). The sensitivity of the method was 91.7 %, specificity was 97.1%, false negative rate was 3%, positive predictive value was 92.4%, negative predictive value was 96.9%. Conclusion: the VASB method has a good accuracy to distinguish lower and higher risk lesions groups comparing to the gold standard. It has high predictive value in both benign and malignant lesions, guiding therapeutic planning. Keywords: Calcifications; Vacuum-assisted stereotactic biopsy; Breast cancer; Diagnosis.

PO5-07-10

CONTRAST MAMMOGRAPHY FOR PREOPERATIVE STAGING OF PATIENTS WITH EARLY BREAST CANCER: PRELIMINARY RESULTS

Presenting Author(s) and Co-Author(s):

A. Amorim. Perola Byington Hospital, United States

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

A. Bitencourt. DASA, United States

P. Moraes. DASA, United States

F. Fingerman. DASA, United States

a) Brief description of the objective(s) The aim of this study is to compare contrast-enhanced mammography (CM) with magnetic resonance imaging (MRI) for preoperative locoregional staging of patients with early-stage breast cancer. b) Material(s) and method(s) Prospective, single-center study, approved by the Research Ethics Committee, which included patients with a histological diagnosis of invasive breast carcinoma, candidates for initial medical treatment. Patients treated with neoadjuvant chemotherapy and those in whom the tumor was completely resected in the initial biopsy were excluded. CM and MRI were performed in the week before surgery and the anatomopathological result of the surgical specimen was considered the gold standard. Pearson's modification (r) was used to compare tumor size between different methods. c) Results and discussion Thirty-seven patients were included, with a mean age of 54.5 ± 6.9 years (43-70 years). The mean size of the tumors in pathology was 2.9 ± 1.4 cm (1.1-8.0 cm) and the most common histological type was invasive ductal carcinoma (n=34;87.2%). The clinical stage was IA for 14 patients (37.8%) and IIA for 23 patients (62.2%). The main tumor was identified in 33 cases (89.2%) on conventional mammography and in all cases (100%) on both CM and MRI. There was excellent elasticity between tumor size measured on CM and MRI ($r=0.897$; $p < 0.01$). When compared with tumor size in pathology, both methods were adopted in a good way ($p < 0.01$), however, MRI was functionally superior to CM ($r=0.847$ vs. 0.683), while mammography conventional showed no therapeutic effect ($r=0.222$; $p=0.21$). Multifocal lesions were observed on CM in 2 cases (5.4%) and on MRI in 6 cases (16.2%), with 1 case confirmed as multifocal and the others presenting DCIS associated with the surgical specimen. Suspicious additional lesions were seen in 4 patients (10.8%) on CM and in 3 patients (8.1%) on MRI, of which one was confirmed as malignant in the contralateral breast, which had not been identified in previous exams. d) Conclusions CM showed good adaptability with MRI for assessing tumor size and searching for additional lesions, and may be a cheaper and more accessible alternative for preoperative staging in patients at an early clinical stage.

PO5-07-11

Use of ^{64}Cu -DOTA trastuzumab -PET to predict response to trastuzumab-deruxtecan (TDXd) in patients with metastatic disease to the brain: Study in Progress

Presenting Author(s) and Co-Author(s):

J. Mortimer. City of Hope, Duarte, California, United States

K. Poku. City of Hope, United States

J. liu. City of Hope, United States

R. Rockne. Beckman Research Institute, United States

c. Bihong. City of Hope, United States

R. Woodall. City of Hope, United States

V. Adhikarla. Beckman Research Institute, United States

Background: We have utilized ^{64}Cu -DOTA trastuzumab-PET imaging in patients with advanced breast cancer. In our experience, uptake on ^{64}Cu -DOTA trastuzumab-PET correlated with the qualitative assessment of HER2 by IHC. In women treated with the antibody-drug conjugate (ADC), ado-trastuzumab emtansine (TDM1), we identified a threshold level of ^{64}Cu -DOTA trastuzumab-PET uptake that predicted for lack of response to TDM1. As patients are living longer with advanced breast cancer, the incidence of brain metastasis has increased. The ADC, trastuzumab-deruxtecan (T-DXd) has demonstrated activity in patients with metastatic HER2 positive breast cancer with brain metastases. The DESTINY 04 trial included patients with HER2 1+ and 2+ disease and demonstrated superior survival compared to standard of care. It is not feasible to biopsy all brain metastases to determine tumor markers. Given the increased incidence of brain metastases in this population and the efficacy of T-DXd in patients with HER2+ metastatic disease to the brain, we initiated a study of ^{64}Cu -DOTA trastuzumab-PET/MRI of the brain prior to institution of T-DXd. Endpoints Primary: 1. ^{64}Cu -DOTA-trastuzumab PET-CT will identify tumor heterogeneity of trastuzumab uptake in women with metastatic breast cancers. 2. The degree of uptake of ^{64}Cu -DOTA-trastuzumab PET-CT will predict for response to Enhertu. Secondary: 1. Uptake of ^{64}Cu -DOTA-trastuzumab PET-CT will be predictive of response duration to Enhertu. Eligibility: Patients must have documented recurrent breast cancer that is HER2 1+, 2+ or 3+, evidence of brain metastases by CT or MRI of the brain and are candidate for treatment with trastuzumab-deruxtecan. The CNS disease must be stable and not in need of intervention. Methods: Prior to treatment staging workups includes pathologic review of HER2 status, disease staging with ^{18}F FDG-PET or CT of the chest/abdomen/pelvis and bone scan, and ^{64}Cu -DOTA-trastuzumab PET/MRI of the brain. After initiation of T-DXd, MRI of the brain is repeated every 6 weeks for the first 24 weeks and every 9 weeks thereafter. Progress: We have enrolled 1 patients to date, received PET and dynamic contrast-enhanced MRI. Four lesions were analyzed in this patient. The mean values of K^{trans} (volumetric perfusion to tumor, s^{-1}) in these lesions near a prior resection cavity were 0.210 s^{-1} , indicating sufficient perfusion for ADC uptake. Corresponding to this perfusion data, the mean SUV_{max} of these lesions on the ^{64}Cu -DOTA-trastuzumab PET scans was 5.38.

PO5-07-12

Feasibility of organized population-based mass-level mammography screening (0.2 million women) –Report from LMIC-Uzbekistan

Presenting Author(s) and Co-Author(s):

M. Tillyashaykhov. Republic Specialised scientific practical medical center of Oncology and Radiology of Uzbekistan, United States

A. Seytmuratova. Republic Specialised scientific practical medical center of Oncology and Radiology of Uzbekistan, United States

A. Ososkov. Republic Specialised scientific practical medical center of Oncology and Radiology of Uzbekistan, United States

S. Djanklich. Republic Specialised scientific practical medical center of Oncology and Radiology of Uzbekistan, United States

Y. Ziyaev. Republic Specialised scientific practical medical center of Oncology and Radiology of Uzbekistan, United States

D. Pendharlkar. Sarvodaya cancer institute, Faridabad, Haryana, India

Background. Breast cancer is one of the leading diseases worldwide. The early detection of breast cancer is the best way to improve survival. Mammography is included in the standard guidelines of all the leading organizations. The procedure is technically demanding and cost sensitive. Despite being a standard, it is not practical in many countries, and more so in LMIC. The state of Uzbekistan embarked on a massive, unique, organized population-based program of mass-level mammography screening, starting from one region of the country and expanding to others. Here, we report the process of such establishment and the feasibility of this innovative model.

Methods. Realizing the importance of breast cancer screening, the Republic of Uzbekistan initiated a pilot project in the Bukhara Region. The area is divided into 12 districts. Every district was equipped with a stationary mammography machine in a regional polyclinic and one mobile van. The personnel were appropriately trained and a selection process was established to invite women for screening. The invitation was sent using the local area's existing municipality residential directory, which contains the complete demographic details of every individual living in the area. The state has 100 % coverage in the registry. The study targeted every woman aged 45-65 starting May 2021. All mammographs were digitally recorded and sent in real time to a centralized server at the National Republican Cancer Center in Tashkent, Uzbekistan. Reporting is performed at a centralized reading center on the information system platform. The program envisages a complete care pathway, from screening to diagnosis and treatment.

Results. Over a period of two years, 140506 women in the age range 45-65 underwent mammography screening. Depending on the size of the target group of the district, an average of 30-60 mammograms were performed per day. A reported preliminary analysis shows the presence of BIRADS 0 in 4495, BIRADS 1 IN 78634, BIRADS 2 in 64345, BIRADS 4 in 4998, BIRADS 5 in 893. All women with BIRADS 4 and 5 were referred to the regional comprehensive cancer center for further evaluation.

A total of 7570 patients underwent cytology and 408 underwent core biopsy. Depending on the reports, the patients were appropriately managed. A total of 1885 patients were recalled for additional screening owing to their inappropriate quality. After a year of function, the project was

expanded with “Mobile Vans” to other regions of the country. An additional 13 mobile mammography vans were added after 1.5 years. From January 2023, approximately 50000 mammograms were additionally performed, taking the total number of screened women to 190506.

Conclusion. Thus, it is feasible to plan and successfully implement state-owned mass-level mammography screenings. This project has the potential for duplication in any part of the world, and other organizations can learn from this extensive, wide program.

PO5-08-01

Investigating the Link between APC I1307K Mutation and Breast Cancer in Arab Population

Presenting Author(s) and Co-Author(s):

B. sharaf. King Hussien Cancer Center, amman, Jordan

H. Bani Hani. King Hussien Cancer Center, United States

A. Zayed. Khcc, Jordan

M. Barbar. king hussien cancer center, United States

A. Hushki. KING HUSSIEN CANCER CENTER, United States

R. Abdel-Razeq. King Hussein Cancer Center, Amman, Jordan

M. Titi. KING HUSSIEN CANCER CENTER, United States

R. Al-Halalshah. king hussien cancer center, United States

S. Mahafdah. King Hussein cancer center, United States

H. Abdel-Razeq. King Hussein Cancer Center, Amman, Jordan

Background: Identifying asymptomatic individuals with an increased risk of hereditary breast cancer may significantly enhance early detection and prevention strategies and may inform treatment decision of patients who carry such variants. The APC I1307K missense mutation is known to be unrelated to conditions such as familial adenomatous polyposis (FAP), attenuated FAP, or gastric adenocarcinoma. However, individuals of Ashkenazi Jewish ancestry who carry this variant, have increase risk of colon cancer compared to the general population. The association of this variant with other cancer types, such as breast cancer, and in individuals of other ancestries, like Arabs, remains unknown. In this study, we investigate the potential association between APC gene (I1307K variant) and breast cancer risk.

Method: Over a course of 18 months, all newly diagnosed patients with solid tumors were offered to participate in a universal germline genetic screening study, utilizing a standard 21-gene or an investigational 84-gene panel testing. A retrospective analysis was conducted on the 153 patients within the study group who carry the APCI1307K missense variant irrespective of cancer type. Patients were classified as meeting the criteria or not meeting the criteria of the National Comprehensive Cancer Network (NCCN) v.1.2020. Data were extracted from electronic medical records and our institutional cancer registry. Descriptive statistics test was employed.

Results: Among the screened cancer patients (n=3400), 153 (4.5%) were tested positive for the APC I1307K missense mutation are included in this analysis. Median age at cancer diagnosis was 52 (range, 19-80) years, and 99 (64.7%) were female. Breast cancer was the most common primary tumor (n=67, 43.8%) followed by colorectal (n=38, 24.8%), lung (n=7, 4.6%) and pancreatic cancer (n=6, 3.9%). Among the 67 breast cancer patients included, 16 (23.9%) were not eligible for genetic testing as per the NCCN guidelines, and were tested as part of the universal genetic testing study. Among the patients with breast cancer, 53 (79.1%) had screening colonoscopy and 9 (17.0%) were found to have polyps (range, 1-3); 8 (88.9%) were low-grade dysplasia, while the other 44 (83.0%) had completely normal colonoscopy.

On the other hand, among the 38 patients with colorectal cancer, 21 (55.3%) had tumors presenting as polyps, or exhibited concomitant polyps (range, 1-3), or displayed abnormalities

in the background that were polypoid in nature. Notably, 24 (63.2%) of patients with colorectal cancer, have a family history of breast cancer.

Conclusions: APC I1307K variant is unexpectedly common among our cohort of Arab patients. Individuals who carry this variant may face an elevated risk of developing breast cancer; potentially contributing to hereditary and familial cases, and such patients are at higher risk for colorectal cancer, too.

PO5-08-02

Endocrine Disruptors and Life STILe in Patients Carrying BRCA Pathogenic VARIants With Breast and/or Ovarian CANcer and Women Without Neoplasm: the STILVARCA study

Presenting Author(s) and Co-Author(s):

A. Franco. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, United States

A. Rossi. University of Rome "Foro Italico", Rome, Italy., United States

D. Terribile. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, United States

E. Lucci Cordisco. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, United States

I. Paris. Fondazione Policlinico Universitario A. Gemelli IRCCS Rome - Italy, United States

M. Muratore. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, United States

E. Florio. Azienda Ospedaliera Universitaria Integrata Verona, United States

V. Salutari. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, United States

F. Pavese. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, Italy

F. L'Erario. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, United States

A. Palazzo. Fondazione Policlinico Universitario A. Gemelli IRCCS Rome - Italy, United States

E. Di Guglielmo. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, United States

G. Borghesiani. Azienda Ospedaliera Universitaria Integrata Verona, United States

L. Cardinali. University of Rome "Foro Italico", Rome, Italy., United States

E. Ferretti. "Sapienza" University, Rome, Italy, United States

G. Terrana. University of Rome "Foro Italico", Rome, Italy., United States

D. Giannarelli. Biostatistic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy., Italy

g. Scambia. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, Italy

S. Migliaccio. University of Rome "Foro Italico", Rome, Italy., United States

A. Fabi. Precision Medicine in Breast Cancer, Fondazione Policlinico Universitario A. Gemelli, IRCCS Rome - Italy, Rome, Italy

Background. Pathogenetic variants (PVs) in the BRCA1/2 genes can be found in 20% of patients with breast (BC) or/and ovarian (OC) cancers. In subjects carrying PVs in these genes, the absence of repair of damage to the DNA double helix causes its accumulation favoring neoplasm development. Exposure to environmental pollutants (e.g. Cadmium (Cd), through contaminated food and drinking water, cigarette smoke, dust and fumes inhalation) may play a role in the development of BC and OC. Cd acts as an "endocrine disruptor" through its binding to the estrogen receptor, promoting cell proliferation and increase in mutation rate. Individual lifestyle habits may be associated with cancer onset and progression in these patients. Our aim

was to evaluate the interference of environmental factors in the development of BC and/or OC in women carrying PVs in BRCA1/2 genes.

Methods. We conducted an observational, multicentric, case-control, retrospective study of patients with PV in BRCA1/2 genes and with BC, OC, or both diagnosed from 2012 to 2020 (Group 1, G1), or without cancer (Group 2, G2). 89 patients (82.4%) developed BC, 17 (15.8%) OC, and 2 (1.8%) experienced both BC and OCs. We collect data about demographics, body mass index (BMI), occupation (divided in employed, educative professions/students, healthcare professions, unemployed/retired and other), type of BRCA mutation (mBRCA), smoking habits (SH), pack/year index, estroprogestinic (EP) use and duration, adherence to Mediterranean diet (with PREDIMED questionnaire) and physical activity (using IPAQ questionnaire). Fisher's exact test and Anova were used to compare patient's features among the two group. A univariate and multivariable model were fitted to investigate the relationship between adherence to Mediterranean diet, physical activity, Cd exposure through smoking habits (SH), EP use, and cancer development.

Results. We evaluated 208 patients, 108 (51.9%) in Group 1 and 100 (48.1%) in Group 2. Table 1 shows the features of enrolled patients. 128 (61.5%) had a mBRCA1, 80 (38.5%) a mBRCA2. Analysis of the two groups revealed significant differences in age (47.2 vs 35.6 years in G1 and G2, respectively; $p < .001$), SH (38.9% in G1 and 20.0% in G2; $p = .002$), EP use (36.1% in G1 and 21.0% in G2; $p = .021$), and occupation (office workers develop cancer more easily, while professions associated with education/students have a lower possibility of developing cancer). No difference was found regarding pack/year index, EP intake duration, adherence to Mediterranean diet, and physical activity. At univariate analysis, predictive factors for cancer incidence were: SH (OR 2.545; 95% CI 1.363 – 4.752 - $p = .003$); EP use (OR 2.126; 95% CI 1.143 – 3.957 - $p = .017$); adherence to Mediterranean diet (OR 1.500; 95% CI 1.016 – 2.215 – $p = .041$). No relationship was found with BMI, occupation and physical activity. At multivariable analysis, SH (OR 2.606; 95% CI 1.370 – 4.959 - $p = .004$), EP use (2.340; 95% CI 1.224 – 4.474 - $p = .010$), and adherence to Mediterranean diet (OR 1.544; 95% CI 1.027 – 2.320 – $p = .037$) were predictive of cancer development.

Conclusion. In this preliminary analysis, the risk of development of BC or/and OC in patients with BRCA mutation was influenced by SH, EP use, and adherence to Mediterranean diet. Many environmental factors seem to play a role in the carcinogenesis of mBRCA VP patients. Paths of lifestyle education are highly recommended in BRCAm-carrying women.

Table 1. Characteristics of enrolled patients

<i>Characteristics</i>	<i>All Patients</i>	<i>Group 1 (108 – 51.9%)</i>	<i>Group 2 (100 – 48.1%)</i>	<i>p-value</i>
Age (y)	41.6 ± 15.7	47.2 ± 10.1	35.6 ± 18.4	<0.0001
BMI (Kg/m²)	48.0 ± 70.6	47.5 ± 73.1	48.5 ± 68.1	0.923
Type of mBRCA				
- 1	128 (61.5%)	67 (62.0%)	61 (61.0%)	0.888
- 2	80 (38.5%)	41 (38.0%)	39 (39.0%)	
Smoking habits	62 (29.8%)	42 (38.9%)	20 (20.0%)	0.002
Pack/year	8.6 ± 7.9	9.3 ± 8.6	6.9 ± 6.1	0.247
Estroprogestinic use	60 (28.8%)	39 (36.1%)	21 (21.0%)	0.021
Duration of Estroprogestinic intake	8.53 ± 7.0	8.9 ± 7.2	6.0 ± 6.1	0.446
Occupation				
- Employed	104 (50%)	57 (52.8%)	47 (47.0%)	0.029
- Educative professions/students	33 (15.9%)	12 (11.1%)	21 (21.0%)	
- Healthcare professions	32 (15.4%)	17 (15.7%)	15 (15.0%)	
- Unemployed/retired	23 (11.1%)	17 (15.7%)	6 (6.0%)	
- Other	16 (7.7%)	5 (4.6%)	11 (11.0%)	
Adherence to Mediterranean diet				
- Low				0.124
- Moderate	35 (16.8%)	14 (13.0%)	21 (21.0%)	
- High	93 (44.7%)	46 (42.6%)	47 (47.0%)	
	80 (38.5%)	48 (44.4%)	32 (32.0%)	
Physical activity				
- Inactive	62 (29.8%)	30 (27.8%)	32 (32.0%)	0.511
- Moderate	97 (46.6%)	49 (45.4%)	48 (48.0%)	
- Active	49 (23.6%)	29 (26.8%)	20 (20.0%)	

PO5-08-03

Breastfeeding and Breast Cancer Screening Among Carriers of Pathogenic Variants in BRCA 1 and BRCA 2 and Other High Penetrance Genes: Knowledge and Perspectives

Presenting Author(s) and Co-Author(s):

L. Pacheco-Spann. Mayo Clinic, United States

M. Sherman. Mayo Clinic, United States

S. Friedman. Facing Our Risk of Cancer Empowered, United States

D. Rose. Facing Our Risk of Cancer Empowered, United States

M. Levi. Mayo Clinic, United States

A. hochwald. Mayo Clinic, United States

J. Ridgeway. Mayo Clinic, United States

S. Blumenfeld. Mayo Clinic, United States

Objectives:

Carriers of pathogenic variants in high penetrance mutations, including BRCA 1 or BRCA 2 face higher lifetime risks of developing breast and tubo-ovarian cancers, and possibly endometrial cancers, than non-carriers. In particular, relative risks are higher among carriers than non-carriers at younger ages, suggesting the value of early initiation of breast cancer screening and the use of sensitive imaging methods, such as magnetic resonance imaging (MRI). Further, breastfeeding appears protective for these three cancers in the general population, and potentially among mutation carriers, albeit based on limited evidence. Given that data related to knowledge and perspectives of carriers about these issues are limited, we surveyed mutation carriers regarding breastfeeding, cancer risk, and the deferral of breast cancer screening coinciding with reproductive events. These data may guide future cancer prevention research and developing of targeted communication campaigns.

Methods:

Researchers at Mayo Clinic, in collaboration with Facing Our Risk of Cancer Empowered (FORCE) – a large, national non-profit organization that addresses the needs of people and families affected by inherited mutations linked to cancer – designed and conducted a survey using the Mayo Clinic's external RedCap system. The survey covered genetic testing and results, history of live births and breastfeeding history for mothers, history of risk-reducing surgery, personal cancer history, sources of information about cancer screening, breastfeeding knowledge, and breast cancer screening at various times, including during pregnancy, while breastfeeding, and after weaning. The survey was disseminated through FORCE's electronic newsletter, website, social media pages, and advocacy partners. Survey responses were collected anonymously and analyzed descriptively using standard descriptive statistics, including frequency and percentages for categorical responses and means (SD) or medians (IQR) for continuously scaled responses. The open-ended responses were analyzed qualitatively using standard qualitative methodology.

Results:

Respondents included 253 women, of whom 88.7% were U.S. residents and 92.9% were white. The mean age + SD was 47(13) years, 61.7% were parous, with a mean age at first birth of 22.58 (13.16) years. Approximately 60% of women were carriers of mutations in BRCA1 or BRCA2 or both genes and all but two of the remaining women reported mutations in other genes linked to increased cancer risk. At the time of the survey, 92% of women had undergone

a mammogram, with first screen at a mean age of 35 (6.49) years, and 85.3% had undergone breast MRI, with first screen at a mean age of 43 (12.39) years. Among 34.3% of participants, their 1st postpartum mammogram occurred >3 years after the birth of their last child and 57% had 1st MRI 3 years postpartum. Preliminarily, our analysis shows that nearly 90% of women were unaware of their mutation status prior to pregnancy and approximately 1/3 did not undergo radiologic screening until 3 years postpartum. While 62.6% of respondents believed that breastfeeding lowers breast cancer risk, 74.2% of participants responded that nursing had no effect on tubo-ovarian cancer risk, and 78.2% considered that nursing did not impact endometrial cancer risk.

Discussion and Conclusions:

Preliminarily, we conclude that most women in the surveyed population were unaware of their mutation status when pregnant years earlier and many had not undergone screening until years after delivery. Many participants did not consider breastfeeding a potentially protective factor for women's cancers. These data raise issues about the potential value of discussing genetic testing with women when considering family planning and mutation carriers, addressing complex issues about breast cancer screening while pregnant and breastfeeding.

PO5-08-04

Characteristics of breast cancer in carriers of pathogenic variant in ATM in a large academic health center

Presenting Author(s) and Co-Author(s):

U. Karki. Corewell Health William Beaumont University Hospital, United States

T. Rangarajan. Corewell Health - Nancy & James Grosfeld Cancer Genetics Center, United States

D. Zakalik. Corewell Health - Nancy & James Grosfeld Cancer Genetics Center, United States

Background:

Pathogenic variants (PVs) in ATM are associated with an increased risk of breast, pancreas, and other cancers. The clinical and pathological characteristics of ATM-associated breast cancers have not been well defined.

Methods:

Patients who underwent multigene panel testing between December 2012 and May 2023 and were identified to harbor ATM PVs were included in the study. We analyzed demographics, germline findings, histopathology, genomic recurrence score, and management of ATM PV carriers with breast cancer.

Results:

A total of 222 individuals were identified to have PVs in ATM, of whom 184 (83%) were female. The majority were Caucasian (n = 179, 81%) and of those, 22 (12%) had Ashkenazi Jewish ancestry. The median age at genetic testing was 52y, with a range of 20-90y. A total of 111 patients (50%) had a personal cancer diagnosis, the most common of which was breast cancer (n = 70; 63%). The median age at breast cancer diagnosis was 53y, with a range of 25-84y. The most common histopathology was invasive ductal carcinoma (74%), followed by DCIS (21%), and invasive lobular carcinoma (5%). The majority of patients had breast tumors with stage 2 or 3 (78%), grade 2 or 3 (92%), ER and/or PR positive (92%) and HER2 negative (70%). One patient had triple-negative breast cancer. Forty-four percent of breast cancers were less than two centimeters, 23% were lymph node-positive, and 29% had lymphovascular invasion. Thirty-eight percent of patients underwent bilateral mastectomy, 54% received radiation therapy, 40% received adjuvant chemotherapy, 24% received neoadjuvant chemotherapy, and 70% received hormonal therapy. Of the 15 breast cancers with known 21-gene recurrence scores, 47% were intermediate (11-26), 33% were high (≥ 26) and 20% were low (≤ 10). Other notable cancers observed were pancreas (n = 9), colorectal (n = 6), prostate (n = 5), uterine (n = 4), melanoma (n = 4), and thyroid (n = 4).

Conclusion:

Our study outlines the clinical and pathological characteristics of ATM-associated breast cancer in a large academic center. The majority of breast cancers were invasive ductal type, early stage, intermediate or high grade, and hormone receptor-positive with an intermediate or high recurrence score. Despite the early stage, a significant proportion of patients underwent bilateral mastectomy. Further studies are needed to better elucidate the unique characteristics of breast cancer in ATM PV carriers in order to provide tailored management guidelines for this population.

PO5-08-05

Breast Cancer in PMS2 related Lynch Syndrome: evidence of a possible association?

Presenting Author(s) and Co-Author(s):

U. Karki. Corewell Health William Beaumont University Hospital, United States

T. Rangarajan. Corewell Health - Nancy & James Grosfeld Cancer Genetics Center, United States

D. Zakalik. Corewell Health - Nancy & James Grosfeld Cancer Genetics Center, United States

Background:

Lynch syndrome (LS) is a hereditary cancer predisposition syndrome caused by pathogenic variants (PVs) in mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. LS is associated with increased risk of colorectal, and endometrial cancers but breast cancer risk is uncertain, with some studies suggesting MSH6 and PMS2 PVs may have a higher risk for breast cancer. Our study outlines the incidence and clinical characteristics of breast cancer in PMS2-related LS identified at a large academic center.

Methods:

Patients with PMS2 PVs identified between July 2009 and May 2023 were selected from a database at the Nancy and James Grosfeld Cancer Genetic Center at Beaumont Health. Data on demographics, genetic testing, cancer types, and breast cancer characteristics were retrospectively analyzed.

Results:

A total of 108 patients from 74 families were found to carry a pathogenic or likely pathogenic variant in PMS2, of whom the majority were female (75%) and Caucasian (85%). The median age at genetic testing was 52y (19 to 95y). The most common variant was c.137G > T (p.Ser46Ile), seen in 15 of 74 (20%) families. Forty-seven patients (46%) had a personal history of cancer, with a median age at diagnosis of 58y. Of these forty-seven patients, sixteen (34%) had multiple malignancies, including one patient with six separate cancers. The most common malignancies were breast (19; 40%), colon (16; 34%), followed by uterine cancer (7), pancreas (4), and prostate (3). The median age at breast cancer diagnosis was 53y, with a range of 41-78y. The most common histopathology was invasive ductal carcinoma (54%), followed by DCIS (31%), and invasive lobular carcinoma (15%). The majority of patients had breast tumors with stage 0 or 1 (75%), grade 2 (63%), ER-positive (92%), PR positive (67%), and HER2-negative (88%). One patient had triple-negative breast cancer. Sixty-seven percent of breast cancers were less than two centimeters, and 92% were lymph node-negative. Fifty-nine percent received radiation therapy and 53% received chemotherapy.

Conclusion:

Our study outlines the incidence and clinical characteristics of breast cancer in PMS2-related LS. Breast cancer was the most common malignancy in our cohort of PMS2 PV carriers, accounting for 40% of all cancers, supporting a possible association between PMS2 and breast cancer. The majority of PMS2-related breast cancers were invasive ductal type, early stage, intermediate grade, and hormone receptor-positive. Further studies with larger diverse cohorts of patients with LS are needed to better characterize a possible association in order to provide tailored breast cancer screening and management guidelines for this population.

PO5-08-06

Metabolic shift to serine pathway induced by lipids confers oncogenic properties in non-transformed breast cells

Presenting Author(s) and Co-Author(s):

M. Bustamante Eduardo. Surgery, Breast Surgery Division; Feinberg School of Medicine, United States

G. Cottone. Northwestern University, United States

S. Liu. Duke University, United States

M. Zappia. University of Illinois at Chicago, United States

E. Benevolenskaya. University of Illinois at Chicago, United States

A. Islam. University of Illinois at Chicago, United States

M. Frolov. University of Illinois at Chicago, United States

S. Khan. Northwestern University, Chicago, Illinois, United States

S. Clare. Surgery, Breast Surgery Division, Feinberg School of Medicine, United States

Introduction. Oncogenic factors that are local/in-breast are of great interest as they may be more specifically targetable for breast cancer prevention than systemic factors. We have identified a lipid metabolism gene signature that is enriched in breast tissue at risk for estrogen negative breast cancer (ER- BC). Utilizing the medium chain fatty acid Octanoic acid (OA) to probe lipid metabolism in non-transformed breast epithelial cells, we observed increased flux through several metabolic reactions and altered histone methylation with consequent changes in gene expression (e.g. neural genes). Neuronal signaling and regulatory circuits are observed in cancer cells of multiple origins, not just ones with ontological relationships to neurons. We hypothesize that the first and rate limiting step in the de novo serine pathway, which is catalyzed by Phosphoglycerate Dehydrogenase (PHGDH) is key to these observations. In the forward direction, PHGDH participates in the serine, one-carbon, glycine (SOG) and methionine pathways that produce the methyl donor S-adenosylmethionine (SAM) and in the reverse direction produces the oncometabolite 2-Hydroxyglycerate (2-HG). Methods. Non-transformed MCF-10A cells exposed to OA were utilized for U13C-glucose tracing. SAM and 2-HG concentrations following treatment with OA \pm PHGDH inhibitor were measured by liquid chromatography. CUT&RUN for H3K4me3 was performed and genes affected by OA (PMID: 28263391) were compared with OA-responsive peaks. Single cell RNA-sequencing was carried out using breast microstructures derived from reduction mammaplasty tissue exposed to vehicle or OA. Microstructures were dissociated into single cells and sequenced using the 10x Genomics platform. The digital expression matrix file containing UMIs were analyzed with Seurat. Alkaline comet assay was performed to detect DNA breaks. Results. U13C-glucose tracing in presence of OA revealed that one-carbon-THF was redirected to the methionine cycle increasing flux to methylation. Concentrations of SAM and 2-HG increased after 15- and 30-min OA exposure, respectively; PHGDH inhibitor blocked these increases. H3K4me3 CUT&RUN revealed 661 differential peaks (FDR < 0.05) comparing OA to control. 73% of H3K4me3 OA-associated peaks were in regulatory regions of OA-induced genes (FDR < 0.01), these genes are involved in neural pathways, EMT and ER- BC. Motif analysis revealed an overrepresentation of binding sites for transcription factors ATF3/4 ($p < 0.05$), which are regulators of the serine pathway. Single cell RNA-sequencing revealed OA not only affected the distribution of cell subpopulations but also modulated the expression of many genes within each subcluster. The percentage of luminal progenitor subcluster 3 increased upon OA from

less than 1% to about 13%. Within basal subcluster 3, OA drives the expression of ATF3, along with two of the enzymes in the de novo serine pathway: PHGDH and PSAT1. Alkaline comet assay showed DNA breaks in OA- and control 2-HG- treated cells. Conclusions. Metabolism of OA in preference to glucose and glutamine results in a metabolic shift toward the serine pathway increasing the production of SAM and 2-HG, with implications for oncogenesis: 1. SAM production results in epigenetic fostered plasticity leading to reprogramming/selecting cells that express genes consistent with a neural/neural crest-like state. These co-opted neuronal regulatory mechanisms can make critical contributions to the acquired functional capabilities that drive cancer development. 2. 2-HG exposure results in appearance of DNA breaks, which are likely consequent to the inhibition of the alpha-ketoglutarate-dependent dioxygenases KDM 4A/B by 2-HG. Their catalytic activity is required for homologous recombination repair; inhibition results in metabolic "BRCAness".

PO5-08-07

Ki-67 Expression in Breast Cancer associated with ATM, BRCA1, BRCA2, CHEK2 and PALB2 Pathogenic Variants

Presenting Author(s) and Co-Author(s):

R. Scheel. Mayo Clinic - Rochester, United States

G. Choong. Mayo Clinic, United States

T. Rao. Mayo Clinic - Rochester, United States

N. Boddicker. Mayo Clinic, United States

C. Hu. Mayo Clinic, United States

J. Na. Mayo Clinic, United States

V. Kaggal. Mayo Clinic - Rochester, United States

S. Murphy. Mayo Clinic - Rochester, United States

K. Giridhar. Mayo Clinic, Rochester, Minnesota, United States

S. Yasir. Mayo Clinic - Rochester, United States

M. Goetz. Mayo Clinic, Rochester, Minnesota, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

S. Yadav. Mayo Clinic, Rochester, Minnesota, United States

Background: Germline Pathogenic Variants (PVs) in ATM, BRCA1, BRCA2, CHEK2, and PALB2 are known to increase breast cancer (BCa) risk, but the effect of these PVs on tumor biology is not well-understood. Ki-67 is an established prognostic marker in hormone receptor (HR) positive breast cancer but the distribution of Ki-67 in breast cancer associated with germline PVs is not known. **Methods:** The study included patients with loco-regional (Stage I-III) HR-positive (ER+ or PR+), HER2-negative invasive ductal or lobular breast cancer evaluated at Mayo Clinic for curative intent treatment between 2012 and 2021. PV carrier status was ascertained in more than two-thirds of cases from germline whole exome sequencing (Regeneron) of patients who participated in a prospective registry at Mayo Clinic. Additional PV carriers were identified through a review of the results of clinical germline genetic testing in electronic medical records aided by natural language processing. Clinically performed Ki-67 values were abstracted from electronic medical records and analyzed as continuous and categorical variables (low: < 20% vs. high: ≥20%). Throughout the timeline of the study, a consistent method for assessment of Ki-67 was utilized at Mayo Clinic, Rochester: Immunohistochemical staining of the Ki-67 antigen in formalin-fixed paraffin-embedded tissue was performed using MIB-1 clone, the scanned slides were reviewed by a technologist and traced areas further analyzed for Ki-67 using Aperio Software. Patients who received neoadjuvant therapy prior to the assessment of Ki-67, with metastatic disease at diagnosis, with PVs in two or more genes of interest, or unknown germline PV or Ki-67 status were excluded from the analysis. Multiple primary tumors in the same patient diagnosed within one year of each other were analyzed independently. The control (non-carrier) group included randomly selected patients from the prospective registry who tested negative for PVs in the five genes over the same time period. Ki-67 values were compared between germline PV carriers and non-carriers in a multivariable logistic regression analysis adjusting for sex, race, age at diagnosis, stage at presentation, and histology of the tumor. **Results:** A total of 113 HR+/HER2- tumors from 111 PV carriers (ATM: 27, BRCA1: 24, BRCA2: 28, CHEK2: 22, and PALB2:12) along with 431 HR+/HER2- tumors from 422 randomly selected non-carriers were

evaluated. The majority (>95%) of patients were non-Hispanic White. Germline PV carriers in each gene were diagnosed at a significantly younger age ($P < 0.05$) compared to non-carriers. The median Ki-67 value was 12 (Range: 1 to 93) for non-carriers, 16 (Range: 0 to 79) for ATM, 31 (Range: 4 to 86) for BRCA1, 30 (Range: 6 to 80) for BRCA2, 13 (Range: 1 to 38) for CHEK2, and 20 (Range: 3 to 46) for PALB2 PV carriers. In multivariable analysis, compared to non-carriers, we observed significantly higher odds of a high Ki67 value ($\geq 20\%$) for tumors arising from germline PV carriers in BRCA1 (Odds Ratio (OR): 7.3, 95%CI: 2.3 – 23.3, $p < 0.001$), BRCA2 (OR: 3.0, 95%CI: 1.2 – 7.4, $p = 0.02$) and PALB2 (OR: 3.9, 95%CI: 1.1 – 14.5, $p = 0.04$). No such relationship was observed with either ATM (OR: 1.1, 95%CI: 0.4 – 2.9, $p = 0.81$) or CHEK2 (OR: 0.8, 95%CI: 0.3 – 2.2, $p = 0.63$). Conclusion: This study reveals that HR+/HER2- tumors in BRCA1, BRCA2, and PALB2 PV carriers have a significantly higher Ki-67 expression compared to non-carriers. These findings have implications for understanding prognosis and endocrine response PV with HR+ breast cancer. Further exploration of the relationships between Ki67 and germline PV status is necessary to personalize systemic therapy options in germline PV carriers. Acknowledgments: Thank you to Regeneron Genetics Center. The study was funded in part by the NIH Specialized Program of Research Excellence in Breast Cancer [P50CA116201] to Mayo Clinic, Mayo Clinic Department of Oncology Small Grants Program, and the Paul Calabresi Program at Mayo Clinic

PO5-08-08

Tumor Registry Guided Genetic Testing: Opportunities Unlocked

Presenting Author(s) and Co-Author(s):

K. Hughes. Medical University of South Carolina, United States

A. Finianos. Medical University of South Carolina, United States

K. Meeder. Medical University of South Carolina, United States

Introduction With the expansion of guidelines for germline genetic testing, more patients are eligible for testing. Unfortunately, many remain untested. Testing is critical, as patients with pathogenic variants (and their families) can benefit from more aggressive screening and preventative strategies, as well as targeted therapies (e.g., poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors) if cancer does occur. **Objectives** To study the prevalence of Hereditary Breast Ovarian Cancer (HBOC) genetic testing eligibility and uptake among cancer patients from the tumor registry at the Medical University of South Carolina (MUSC) in order to identify a group of living patients who require testing now. **Methods** This Quality Improvement study included patients 18 years of age or older diagnosed with breast, ovarian/fallopian/primary peritoneal, pancreas and prostate cancers between 1991 and 2021 as reported to the MUSC Tumor Registry. Each patient was evaluated using the latest National Comprehensive Cancer Network (NCCN) criteria for breast-ovarian genetic testing (Excluding family history criteria, which were not available in the tumor registry). Using our genetic testing database, we also determined which had had testing. We describe the prevalence of genetic testing performed vs the number of patients that would benefit from testing under the newest guidelines. **Results** Patients identified as eligible for testing included 399 breast cancer patients, all 544 ovarian/fallopian/primary peritoneal cancer patients, all 1534 pancreas cancer patients and 872 prostate cancer patients. Reported testing of eligible patients was low (breast: 35%, Ovarian: 33%, pancreas: 4%, and prostate cancer: 6%). Of eligible patients not tested, 310 patients with breast cancer, 343 patients with ovarian/fallopian/primary peritoneal cancer, 717 patients with pancreas cancer and 763 patients with prostate cancer, are alive and eligible for testing (2133 patients) **Discussion** Using Tumor Registry data plus genetic testing data allowed us to detect a large number of living patients with cancer that would be eligible for HBOC genetic testing. This is despite the fact that this approach underestimates the number of patients that would benefit from further testing as it does not include family history and other factors. A similar approach for colorectal or other cancers will yield additional patients. **Conclusion** Most cancer patients eligible for breast ovarian genetic testing have not been tested. There is an opportunity to use Tumor Registry and genetic testing data to identify a large number of living patients who can be approached for testing. As we showed in our study, by adopting updated cancer genetic testing guidelines, there is increased opportunity to detect more patients that would benefit from such testing. In our study this benefit is shown especially in the prostate and pancreas cancer groups. Next steps will be to determine how best to notify and make testing available to these patients.

Table 1. Testing Status Comparison

Cancer	Tested No. (%)	Not tested No. (%)	Total No.
Breast Overall	138 (35%)	261 (65%)	399
Breast Alive	115 (37%)	195 (63%)	310
Breast Dead	23 (26%)	66 (74%)	89
Ovarian/Fallopian/Primary peritoneum (OFPP) Overall	177 (33%)	367 (67%)	544
OFPP Alive	125 (36%)	218 (64%)	343
OFPP Dead	52 (26%)	149 (74%)	201
Pancreas Overall	63 (4%)	1471 (96%)	1534
Pancreas Alive	37 (5%)	680 (95%)	717
Pancreas Dead	26 (3%)	791 (97%)	817
Prostate Overall	54 (6%)	818 (94%)	872
Prostate Alive	52 (7%)	711 (93%)	763
Prostate Dead	2 (2%)	107 (98%)	109

Assessing Genetic Testing Rates Using Tumor Registry Among Eligible Patients with Breast, Ovarian/Fallopian/Primary Peritoneum, Pancreas and Prostate cancer as per the New Testing Guidelines

PO5-08-09

Li Fraumeni Syndrome in Breast Cancer Patients of Ceará/Brazil: correlations of genotype - fenotype

Presenting Author(s) and Co-Author(s):

R. Sant'Ana. Instituto do Câncer do Ceará, FORTALEZA, Ceara, Brazil

I. Fernandes. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

M. Luciano. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

M. Bezerra. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

F. Bitencourt. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

C. Albuquerque. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

P. Silva. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

J. De Moura. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

F. Oliveira. Instituto do Câncer do Ceará, Fortaleza, Ceara, Brazil

Introduction: Li Fraumeni Syndrome (LFS) is a rare condition determined by germline mutation of TP53 gene. LFS has penetrance near 100% with a broad spectrum of malignances such as breast, lung, sarcomas, choroid plexus, adrenocortical carcinomas, gliomas, leukemia and other starting from early childhood. Breast cancer is the most frequent cancer type of adults with LFS, followed by soft tissue sarcomas. Individuals with LFS has an aggressive prognosis of multiple neoplasms lifetime. In Brazil the most described variant of TP53 is c.1010G >A; p.R337H (the Brazilian variant). This variant affects predominantly individuals of South and Southeastern regions. Usually presents with the same spectrum of tumor of other variants however R337H presents lower penetrance, higher frequency of adrenocortical carcinomas, later onset of tumors. Ceará is a northeastern state of Brazil highly miscegenated distinct from populations of South where predominates European colonization. At Ceará originals there are no description of R337H. The present study describes Clinical and tumoral characteristics of breast cancer patients with LFS of Cancer Reference Center of Ceará. Methods: from 2018 to 2021 breast cancer patients admitted in Instituto do Câncer do Ceará-ICC filling NCCN criteria for hereditary breast cancer were screened for germline variants. After assigned consent it was offer NGS germline genetic panel of 33 genes and clinical and pathologic data were recorded. Results: 460 BC patients were recruited, of them 6 had germline pathogenic mutation of TP53. Table 1 list these women and their variants. The mean age of the first tumor was 30 years (range 18-44), only one patient had no knowledge of familiar history (HF) of child and adults cancer, all the other listed HF of early onset of breast cancer, lung cancer, osteosarcoma, rbdomyosarcoma, GBM and gastrointestinal cancers. One had bilateral metachronic breast cancer, 3 of them had HER2 positive tumor, 1 had a metaplastic TNBC, and 1 had a Luminal B tumor. 2 variants were not found at populational database (a exons 2-10 microdeletion and a c.637C >T variant). About half of relatives recruited for genetic test confirmed to the carriers and 3 of them developed neoplasms (GBM and breast cancer). Two patient had early recurrence (one of them had a third tumor of ovarian – carcinosarcoma) and died at age of 30 and 39 years old. Conclusion: The Northeast of Brazil has a distint clinical and genetic pattern of LFS from the South. No R337H variant were found in our population. We identified different variants in all patients with LFS. The BC subtype more commom was HER2 positive. The bias of our study is the original objective that evolved determination of prevalence of hereditary breast and ovarian cancer. Based on these results we are now recruiting exclusively cancer patients with clinical criteria for LFS.

Table 1 - LFS patients characteristics

ID	Age	Stage	Molecular Subtype	Variant	HF
1	33	<u>Ia</u>	RH+HER2+	c.524G>A	BC
83	25	IIb	TNBC	c.742C>T	No
90	18	IIIa	RH-HER2+	c.818G>A	BC, <u>osteossarcoma</u>
225	33	<u>Ia/IV</u>	RH+HER2+	Exon 2-10 <u>deletion</u>	BC, <u>rabdomiossarcoma,</u> <u>biliar cancer, lung,</u> <u>osteossarcoma</u>
444	44	<u>Ia</u>	Luminal B	c.637C>T	BC, GBM
496	28	IIIa	RH-HER2+	c.824G>A	BC, SNC, CCR

PO5-08-10

Breast cancer risk prediction performance of polygenic risk score in Taiwanese female with dense breast: A nested case-control study

Presenting Author(s) and Co-Author(s):

C. Lum. TaiChung Veterans General Hospital, Taichung, Taiwan (Republic of China)

C. Hung. Taichung Veterans General Hospital, United States

C. Huang. Taipei Veterans General Hospital, United States

T. Hsiao. Taichung Veterans General Hospital, United States

S. Moi. Kaohsiung Medical University, United States

Introduction:

Breast cancer is the most common cancer among women in Taiwan and the incidence rate of breast cancer has been increasing steadily over the past 30 years. To address this, a nationwide screening program with biennial mammography for women aged 40-69 was implemented in 2004, which has contributed to a significant reduction in breast cancer mortality. Asian women are more likely to have dense breast tissue, and studies have shown a correlation between breast density and the risk of developing breast cancer, with higher breast density values associated with increased risk.

Polygenic risk scores (PRS) are calculated based on an individual's genetic information and can estimate their risk of developing a particular disease. Although PRS can identify low-penetrance risk variants, its use in breast cancer risk estimation is typically limited to gene-only models, and integration with breast cancer screening databases is rare. Hence, the aim of this specific study was to evaluate the predictive capacity of PRS in women with dense breast tissue by exploring potential genetic markers and constructing a PRS to investigate the genetic factors associated with clinical characteristics and the risk of developing breast cancer.

Methods:

The PRS was developed using genetic information from the Taiwan Precision Medicine Initiative genotyping data. A total of 6335 patients were enrolled, and 101 single nucleotide polymorphisms (SNPs) were selected as candidate markers based on the PGS Catalog (PGS000001).

Clinical characteristics of the study cohort were summarised using median and range, or frequency and percentage. The distribution of characteristics between breast cancer and controls was estimated using an independent two-sample t-test, chi-square, and Fisher's exact test. The association of the PRS and related characteristics with breast cancer risk in the study cohort was estimated using univariate and multivariate binomial logistic regression. Harrel's C-index was reported to demonstrate the predictive performance of PRS in both univariate and multivariate models. All p-values were two-sided, and a p less than .05 is considered statistically significant. All analyses were performed using R 4.1.2 (R core team, 2023)

Results:

The results showed that breast cancer patients constituted a higher proportion of individuals in PRS Q4 (37.8% vs 24.8% in controls). The model's predictive performance for breast cancer risk increased from 0.565 (95% CI = 0.520-0.611) to 0.699 (95% CI = 0.644-0.755) by adding related clinical characteristics compared to the PRS-only model. Patients characterized with benign breast disease (OR = 0.50, 95% CI = 0.31-0.79, P = 0.004) showed a decreased breast

cancer risk, and patients with mastalgia or palpable breast lesion (OR = 6.87, 95% CI = 4.29-10.8, $P < 0.001$) predicted significant greater breast cancer risk. Subgroup analysis of patients without breast symptoms was conducted as they may be overlooked or underestimated for breast cancer screening. For dense breast patients without symptoms, the high PRS group (Q4) consistently showed a significantly elevated breast cancer risk compared to the low PRS group (Q1-Q3) in both univariate (OR = 2.25, 95% CI = 1.43-3.50, $P < 0.001$) and multivariate analyses (OR = 2.22, 95% CI = 1.41-3.46, $P < 0.001$).

Conclusion:

Breast cancer screening has undergone a shift from a general approach to a personalized, risk-based approach. Besides breast cancer screening using family history as the only risk factor, our proposed model identifies both genetic and clinical risk factors using big data analyses including the EHR, cancer screening, and registry from a single institute. The study suggests that integrating PRS into personalized screening strategies could improve risk prediction for Taiwanese females with dense breasts without prominent symptoms.

Table 1. Clinical characteristics of study cohort (n=6335).

Characteristics	Overall	Controls	Breast cancer	<i>P</i>
Patients no.	6335	6224	111	
Age at mammography	57 (40-71)	57 (40-71)	56 (44-70)	0.337
Education				0.732
Without education	67 (1.1%)	66 (1.1%)	1 (0.9%)	
Primary	752 (11.9%)	743 (11.9%)	9 (8.1%)	
Secondary	803 (12.7%)	787 (12.6%)	16 (14.4%)	
High/Professional	2,024 (31.9%)	1,990 (32.0%)	34 (30.6%)	
Bachelor	2,683 (42.4%)	2,632 (42.3%)	51 (45.9%)	
Refused to answer	6 (0.1%)	6 (0.1%)	-	
Breast cancer family history				
Overall	565 (8.9%)	552 (8.9%)	13 (11.7%)	0.298
First-degree relative	208 (3.3%)	205 (3.3%)	3 (2.7%)	1.000
Second-degree relative	354 (5.6%)	344 (5.5%)	10 (9.0%)	0.113
Previous fertility	5,509 (87.0%)	5,412 (87.0%)	97 (87.4%)	0.893
Breast surgery history	470 (7.4%)	458 (7.4%)	12 (10.8%)	0.169
Benign breast disease	2,088 (33.0%)	2,058 (33.1%)	30 (27.0%)	0.180
Self-exam experience	1,181 (18.6%)	1,160 (18.6%)	21 (18.9%)	0.940
Breast symptom				<0.001
No symptom	5,914 (93.4%)	5,834 (93.7%)	80 (72.1%)	
Mastalgia/palpable	421 (6.6%)	390 (6.3%)	31 (27.9%)	
Other cancer history	463 (7.3%)	459 (7.4%)	4 (3.6%)	0.130
Previous mammogram				-
None	3,729 (58.9%)	3,634 (58.4%)	95 (85.6%)	
1 episode	1,808 (28.5%)	1,794 (28.8%)	14 (12.6%)	
2 episodes	798 (12.6%)	796 (12.8%)	2 (1.8%)	

Table 2. Association of the PRS quartiles in breast cancer risk.

Characteristics	Overall	Controls	Breast cancer	OR (95% CI)	P
PRS quartile					
Q1	1,584 (25.0%)	1,562 (25.1%)	22 (19.8%)	Referent	
Q2	1,584 (25.0%)	1,559 (25.0%)	25 (22.5%)	1.14 (0.64, 2.04)	0.700
Q3	1,583 (25.0%)	1,561 (25.1%)	22 (19.8%)	1.00 (0.55, 1.82)	1.000
Q4	1,584 (25.0%)	1,542 (24.8%)	42 (37.8%)	1.93 (1.16, 3.31)	0.013
PRS subgroup					
Low (Q1-Q3)	4,751 (75.0%)	4,682 (75.2%)	69 (62.2%)	Referent	
High (Q4)	1,584 (25.0%)	1,542 (24.8%)	42 (37.8%)	1.85 (1.25, 2.71)	0.002

OR, Odds ratio. CI, confidence interval.

Table 3. Predictive performance of PRS for breast cancer risk.

Characteristics	Comparison	Univariate		Multivariate	
		OR (95% CI)	P	OR (95% CI)	P
Overall (n=6,335)					
PRS subgroup	high vs low	1.85 (1.25, 2.71)	0.002	1.85 (1.24, 2.73)	0.002
Age at mammography	years	0.99 (0.96, 1.01)	0.356	1.00 (0.97, 1.02)	0.754
Family history of BC	yes vs no	1.36 (0.72, 2.36)	0.299	1.46 (0.77, 2.54)	0.214
Previous fertility	yes vs no	1.04 (0.61, 1.91)	0.893	1.16 (0.67, 2.17)	0.611
Breast surgery history	yes vs no	1.53 (0.79, 2.69)	0.172	1.65 (0.81, 3.16)	0.145
Benign breast disease	yes vs no	0.75 (0.48, 1.13)	0.181	0.50 (0.31, 0.79)	0.004
Self-exam experience	yes vs no	1.02 (0.61, 1.61)	0.940	1.43 (0.85, 2.34)	0.160
Breast symptom	yes vs no	5.80 (3.73, 8.79)	<0.001	6.87 (4.29, 10.8)	<0.001
Others cancer	yes vs no	0.47 (0.14, 1.12)	0.139	0.39 (0.12, 0.96)	0.072
Harrel's C-index (95% CI)		0.565 (0.520-0.611) ^a		0.699 (0.644-0.755) ^b	
No symptom (n=5,914)					
PRS subgroup	high vs low	2.25 (1.43, 3.50)	<0.001	2.22 (1.41, 3.46)	<0.001
Age at mammography	years	0.99 (0.96, 1.02)	0.531	0.99 (0.96, 1.02)	0.641
Family history of BC	yes vs no	1.31 (0.61, 2.49)	0.454	1.32 (0.61, 2.54)	0.434
Previous fertility	yes vs no	1.15 (0.61, 2.49)	0.689	1.21 (0.62, 2.64)	0.606
Breast surgery history	yes vs no	1.31 (0.55, 2.68)	0.495	1.81 (0.72, 4.00)	0.170
Benign breast disease	yes vs no	0.67 (0.39, 1.10)	0.128	0.55 (0.31, 0.96)	0.042
Self-exam experience	yes vs no	1.43 (0.85, 2.33)	0.159	1.44 (0.85, 2.34)	0.158
Others cancer	yes vs no	0.48 (0.12, 1.30)	0.219	0.41 (0.10, 1.13)	0.140
Harrel's C-index (95% CI)		0.589 (0.534-0.644) ^a		0.629 (0.563-0.696) ^b	

BC, breast cancer.

^a Harrel's C-index for PRS subgroup in univariate model.

^b Harrel's C-index for multivariate model with all retained variables.

PO5-08-11

Genetic Landscape of Early Breast Cancer in an Ashkenazi Jewish Cohort

Presenting Author(s) and Co-Author(s):

L. Munoz Arcos. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, New York, United States

E. Nicolò. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

M. Pires. New York Presbyterian/Weill Cornell Medical Center, New York, United States

L. Pontolillo. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, United States

L. Varella. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

T. Cigler. Weill Cornell Medical College, New York, United States

E. Andreopolu. New York Presbyterian/Weill Cornell Medical Center/Columbia University, New York, NY, United States

A. Moore. Weill Cornell Medical College, New York, United States

A. Schreier. Weill Cornell Medical College, New York, United States

C. Munoz-Zuluaga. New York Presbyterian/Weill Cornell Medical Center, New York, United States

L. Newman. Weill Cornell Medicine, New York, New York, United States

G. Syrnioti. Weill Cornell Medical College, New York, United States

M. Cristofanilli. Weill Cornell Medicine, United States

Background: The Ashkenazi Jewish (AJ) population exhibits a distinctive mutation profile in BRCA1 and BRCA2 (BRCA1/2), characterized by 3 common founder mutations: BRCA1 185delAG, BRCA1 5382insC, and BRCA2 6174delT. These 3 mutations are associated with 10% of invasive breast cancer (BC) cases among AJ women. However, the frequency of non-founder pathogenic variants in BRCA1/2 and other BC-related genes in AJ women with BC remains unclear. **Methods:** This retrospective study included AJ patients diagnosed with stage I-II human epidermal receptor growth factor 2 negative BC between 2004-2022 at the Weill Cornell Breast Center. We collected clinicopathological characteristics and genetic information to determine the frequency of predisposing mutations in BC and non-BC related genes in AJ patients with early BC. We also analyzed the clinicopathological characteristics and outcomes of patients with and without germline mutations in these genes. **Results:** The study included 232 self-identified AJ patients, with 98% being females. The median age at BC diagnosis was 62 years (IQR: 50-70). Stage I and II cancers accounted for 68% and 32% of cases, respectively. Hormone receptor positivity (HR+) was observed in 71% of patients, while 29% had triple-negative tumors. Genetic testing was performed on 88% (n=203) of the patients, while 5% of patients declined to undergo genetic testing. Among the tested patients, 12% (n=25/203) had pathogenic variants in BRCA1 or BRCA2, with 44% and 16% of these corresponding to the BRCA1 and BRCA2 founder mutations, respectively. Testing beyond BRCA1/2 genes was conducted on 154 patients, and only 6% (n=9/154) were found to have pathogenic variants in CHEK2, while no mutations were detected in other prevalent BC-related genes, including PALB2 and ATM. Fourteen-percent of patients had pathogenic mutations in other genes including APC, CFTR, FH, DIS3L2, FANCC, MUTYH, NF1 and VHL. The

frequency of pathogenic BRCA1/2 variants was inversely proportional to the age at BC diagnosis: 50% (n=8/16), 21% (n=8/39), 15% (n=6/40), and 3% (n=3/108) of patients diagnosed at age < 40, 40-49, 50-59, and >60 years, respectively, had a pathogenic variant in either BRCA1 or BRCA2. The frequency of founder mutations varied according to age at diagnosis: 63%, 75%, 17%, and 100% for patients aged < 40, 40-49, 50-59, and >60 years, respectively. Patients with BRCA1/2 mutations exhibited higher-risk clinicopathological features compared to those without mutations, including a higher proportion of high histological grade (88%), and triple-negative tumors (76%). Mastectomy was the primary surgical treatment for 56% and 23% of patients with and without BRCA1/2 mutations, respectively. No difference in disease-free survival was found between patients with and without BRCA1/2 mutations with a median follow up of 3 years (IQR: 1-4). Conclusions: In our cohort, 17% of AJ patients with early BC carried a pathogenic variant in a BC-related gene, with BRCA1/2 being the most commonly affected genes. The proportion of pathogenic variants in BRCA1/2 showed an inverse correlation with the age at BC diagnosis, reaching up to 50% in patients diagnosed under the age of 40. These findings contrast with the lower prevalence of pathogenic variants in BRCA1/2 (38%) reported in the existing literature for this age group. Additionally, 8% of patients had pathogenic variants in other tested cancer genes carrying a genetic predisposition to colorectal cancer (CRC). These findings contribute to our understanding of the genetic landscape of early BC in the AJ population and emphasize the importance of comprehensive genetic testing, particularly among young patients. These results also suggest the need for earlier and more frequent CRC screening in a population of BC patients that may not be adhering to recommended guidelines. Furthermore, our study provides insight into how this genetic landscape may vary when analyzing late-stage BC in women of AJ heritage.

PO5-08-12

Ethnic Admixture Affects Breast Cancer Incidence in Native Hawaiians: The Multiethnic Cohort

Presenting Author(s) and Co-Author(s):

D. Valdez. University of Hawaii Cancer Center, United States

A. Bunnell. University of Hawaii at Manoa, United States

D. Bogumil. University of Southern California, United States

G. Maskarinec. University of Hawaii Cancer Center, United States

J. Shepherd. University of Hawaii Cancer Center, United States

Ethnic Admixture Affects Breast Cancer Incidence in Native Hawaiians: The Multiethnic Cohort Dustin Valdez^{1,2}, Arianna Bunnell^{1,2}, David Bogumil³, Gertraud Maskarinec¹, John A. Shepherd¹ 1 University of Hawaii Cancer Center, Honolulu, HI 2 University of Hawaii at Manoa, Honolulu, HI 3 University of Southern California, Los Angeles, CA Background Native Hawaiians (NH) have the highest breast cancer incidence and the poorest survival of any ethnic group in Hawaii [1]. Since it has been shown that different ethnic groups have disparate risk of breast cancer in Hawaii and NHs are commonly of mixed ancestry, it is possible that the specific ethnic admixture may present an altered risk profile. For example, NH with Asian admixture was associated with higher risk for type 2 diabetes independent of known risk factors [2] compared to those without. The objective of this study was to calculate crude and age-adjusted breast cancer incidences by ethnic admixture group among participants of the Multiethnic Cohort (MEC). Methods: Based on self-reports, 106,525 eligible women were categorized by broad ethnic categories: Native Hawaiian, White, Black, Latino, and Japanese. In total there were 9257 breast cancer cases in the MEC cohort (1996-2019) at time of analysis. The Native Hawaiian population was further categorized into the following subgroups: Native Hawaiian only, Native Hawaiian & White, Native Hawaiian & Chinese, Native Hawaiian & White & Chinese. Crude and age-adjusted incidence rates (per 1000 person-years) were calculated for the various groups. The direct method of age adjustment using the US 2000 Standard population was used. Results: The ethnicity with the highest crude incidence were White=88.46, followed by Black=85.20, Latino=84.27, Japanese=84.90, and Native Hawaiian=81.28. However, after age-adjustment the highest were Japanese=159.1, White=153.8, Latino=148.3, Black=147.4, and Native Hawaiian=139.1. Crude incidence rates for Native Hawaiian ethnic admixture was found to be highest for Native Hawaiian & White=83.5, Native Hawaiian only=82.5, Native Hawaiian & Chinese=80.8, and Native Hawaiian & White & Chinese=80.4. After age adjustment, the highest was Native Hawaiian & Chinese=173.9, followed by Native Hawaiian & White=154.3, Native Hawaiian only=148.7, and finally Native Hawaiian & White & Chinese=120.8. Conclusion: These findings indicate that ethnic admixture in Native Hawaiians may be at elevated age-adjusted breast cancer incidence when compared to Native Hawaiian alone. When a woman was Native Hawaiian and Chinese the incidence was notably higher than any other group at 173.9 when compared to all Native Hawaiian=139.1. Furthermore, the group that had the lowest age-adjusted incidence was the mixed group of Native Hawaiian & White & Chinese=120.8 which seems to account for why the overall Native Hawaiian group=139.1 had one of the lowest incidence rates of the 5 major ethnic groups. 1. Loo, L.W., M. Williams, and B.Y. Hernandez, The high and heterogeneous burden of breast cancer in Hawaii: A unique multiethnic US Population. *Cancer epidemiology*, 2019. 58: p. 71-76. 2. Maskarinec, G., et al., Ethnic admixture affects diabetes risk in native Hawaiians: the Multiethnic Cohort. *Eur J Clin Nutr*, 2016. 70(9): p. 1022-7.

PO5-09-01

Relative low body mass index (BMI) and fat quantity predicts prognosis better than absolute BMI in hormone receptor-positive, HER2-negative breast cancer

Presenting Author(s) and Co-Author(s):

E. Kang. Seoul National Univ. Hospital, Surgery, Republic of Korea

J. Jung. Seoul National Univ. Hospital, Surgery, Korea, United States

I. Shin. Department of Surgery, Seoul National University Hospital, United States

H. Lee. Department of Surgery, Seoul National University Hospital, United States

J. Byeon. Department of Surgery, Seoul National University Hospital, United States

C. Lim. Seoul National Univ. Hospital, Surgery, Korea, United States

H. Kim. Seoul National Univ. Hospital, Surgery, Korea, United States

H. Moon. Seoul National University, Republic of Korea

W. Han. Seoul National University Hospital, Seoul, Republic of Korea

J. Cheun. Seoul Metropolitan Government Seoul National University Boramae Medical Center, United States

S. Yoon. Department of Radiology, Seoul National University College of medicine, United States

H. Lee. Seoul National University Hospital, United States

Purpose: Most existing research about obesity and prognosis in breast cancer patients primarily compares obese and non-obese individuals according to standard body mass index (BMI) categories. With a notably high percentage of Asian patients presenting with young age onset and normal weight, the prevalence of overweight and obesity based on absolute BMI values is lower in Asia (according to WHO guideline, BMI under 18.5 means underweight, and BMI over 25 means overweight). Understanding the impact of relatively low and high weight on prognosis can provide more insightful data than assessments based on absolute BMI thresholds. This study aimed to investigate the impact of relative low/high BMI on the prognosis of breast cancer and to explore the influence of body fat quantity (FQ), which is closely related to BMI. **Methods:** The study population consisted of 3,663 patients who received surgery for primary breast cancer at Seoul National University Hospital from 2006 to 2015. Pre-treatment BMI was divided into quartiles, defining low-BMI (Q1) as ≤ 21.33 , high-BMI (Q4) as > 25.53 , and mid-BMI as values between the two. Fat quantity (FQ) was derived from chest CT using the deep learning-based FDA-approved DeepCatch software. It measures the fat volume at the L1 level then divides this value by the square of the patient's height. It was then also divided into quartiles, establishing the definitions of low-, mid-, and high-FQ. The associations of BMI and FQ with distant metastasis-free survival (DMFS) and overall survival (OS) were examined. **Results:** The high-BMI group demonstrated older median age and higher T and N stages ($p < 0.001$). The high- and low-BMI groups also showed a higher prevalence of estrogen receptor positive cancer compared to the mid-BMI group. A strong correlation (Pearson correlation coefficient 0.83) was observed between BMI and FQ. In HR-positive, HER2-negative breast cancer, high-BMI patients had a 1.55 times higher risk of distant metastasis (95% CI: 1.15-2.11, $p = 0.005$), and a 1.78 times higher risk of mortality (95% CI: 1.22-2.58, $p = 0.003$) compared to mid-BMI patients, while low-BMI patients demonstrated better outcomes regarding DMFS (HR 0.67, $p=0.035$) and OS (HR 0.59, $p=0.04$). Comparison of FQ with prognosis revealed that the low-FQ patients exhibited better DMFS (HR 0.59, $p=0.005$) and OS

(HR = 0.44, p=0.002) compared to mid-FQ patients in HR-positive, HER2-negative breast cancer. However, when adjusted for T and N stages, low-BMI patients in the HR-positive, HER2-negative group showed no difference in prognosis from mid-BMI patients but better prognosis compared to high-BMI patients. In contrast, when defined using absolute BMI, underweight patients did not show a difference in DMFS (HR 0.72 vs. normal BMI, p = 0.515) and OS (HR 0.91 vs. normal BMI, p = 0.87) compared to those with normal weight and overweight. The low-FQ group had the best prognosis regarding DMFS (HR 0.66 vs. mid-FQ, p=0.032) and OS (HR 0.50 vs. mid-FQ, p=0.008). Conclusions: Low-BMI is a favorable prognostic factor compared to high-BMI for DMFS and OS in HR-positive, HER2-negative breast cancer. The relative BMI defined according to BMI quartiles was a better prognostic factor than to absolute BMI standards. Investigations with FQ showed similar tendencies, suggesting that low BMI's favorable prognostic influence may be associated with fat. Future investigations should aim to validate these results and delve deeper into the underlying mechanisms. Declaration of Competing Interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Soon Ho Yoon work as chief medical officer in MEDICALIP. This author did not involve data/statistical analysis. Other authors have no competing interest to declare.

PO5-09-02

Breast Tissue Proteomic Profile of Breast Cancer in Premenopausal Women and Association with Mammographic Breast Density

Presenting Author(s) and Co-Author(s):

S. Tapiavala. Washington University School of Medicine, St. Louis, United States

M. Son. Washington University School of Medicine, St. Louis, United States

G. Colditz. Washington University School of Medicine, Saint Louis, Missouri, United States

A. Goo. Washington University School of Medicine, St. Louis, United States

A. Toriola. Washington University School of Medicine, St. Louis, Missouri, United States

Introduction: Breast cancer incidence is rising in premenopausal, hence, there is a critical need to understand factors underlying premenopausal breast cancer development in order to guide targeted prevention. Mammographic breast density is a strong risk factor for, as well as an intermediate phenotype for premenopausal breast cancer. Yet, the molecular mechanisms underlying the associations of dense breasts with breast cancer are not well understood. Our objectives in this study are to perform proteomic analysis in breast tissues to (i) identify proteins that are associated with breast cancer development in premenopausal women; (ii) determine which of these proteins are also associated with dense breasts. **Methods:** We performed proteomic analysis on tumor and adjacent normal tissues from 50 premenopausal women with breast cancer who had breast tissue samples archived at the St. Louis Breast Tumor Registry. Samples were analyzed on Orbitrap Eclipse Tribrid coupled with Vanquish Neo LC system (Thermo Fisher Scientific). Database search was performed using MaxQuant and MS1 LFQ intensities were used for further data analysis. We performed multiple imputation using Bayesian Principal Component Analysis and hierarchical clustering analysis using 'ConsensusClusterPlus' package in R. Pathway enrichment analysis was performed using Reactome Pathway database. 10 times repeated 5-fold cross validation using Logistic Regression (LR) was performed for model development. Top 10 proteins were selected by variable importance in logistic regression, and recursive feature elimination was performed for feature selection. We corrected for multiple testing by setting the false discovery rate, FDR, p -value < 0.05 . **Results:** After imputing for missing values, we identified 3,571 proteins that were expressed in tumor and normal breast tissues. We selected 1,640 proteins for further analysis using median absolute deviation analysis. In multivariable-adjusted analysis, 451 proteins were up-regulated, and 180 proteins were down-regulated in tumor tissues compared to adjacent normal tissues (FDR < 0.05). 53 of the 451 proteins that were upregulated in tumor tissues were also upregulated in dense breasts. Some of the top proteins that were upregulated in both tumor tissues and dense breasts were AIMP2, ALDH18A1, BZW1, CKAP5, COPG1, ERGIC1, GSPT1, ILF2, IPO7, LRBA, and PSMD12. Mammographic breast density protein clusters were highly correlated with hormone receptor positivity clusters and were enriched in ESR-mediated signaling, IGF1R signaling, NOTCH4, PTEN regulation, and NFkB pathway. **Discussion:** Using untargeted proteomics, we identified proteomic signatures of breast cancer development in premenopausal women. We further identified protein biomarkers and pathways that are shared between breast tumors and dense breast tissues in premenopausal women. Our novel findings highlight mammographic breast density as a strong intermediate phenotype that can be targeted in breast cancer prevention in premenopausal women. Larger studies are needed to validate our findings.

PO5-09-03

Multi-tissue transcriptome-wide association studies identified genes for intrinsic subtypes of breast cancer.

Presenting Author(s) and Co-Author(s):

J. Li. Department of Public Health Sciences, University of Chicago, United States

J. McClellan. Department of Public Health Sciences, University of Chicago, United States

H. Zhang. National Cancer Institute, Division of Cancer Epidemiology and Genetics, United States

G. Gao. University of Chicago, United States

D. Huo. Department of Public Health Sciences, University of Chicago and Center for Clinical Cancer Genetics & Global Health, Section of Hematology and Oncology, Department of Medicine, University of Chicago, Chicago, Illinois, United States

Background: Though several genome-wide association studies (GWAS) of breast cancer (BC) have identified common variants which differ between intrinsic subtypes, the genes through which these variants act through to impact BC risk have not been fully established.

Furthermore, transcriptome-wide association studies (TWAS) have thus far been primarily employed to identify genes associated with overall BC risk, while overlooking how the influence of common variation on gene expression may contribute to subtype-specific differences.

Methods: In this study, we performed two complementary multi-tissue TWASs for each of the following BC intrinsic subtypes: Luminal A-like, Luminal B-like, Luminal B/HER2-negative-like, HER2-enriched-like, Triple Negative BC. These two approaches included 1) an expression-based approach that collated TWAS signals from expression quantitative trait loci (eQTLs) across multiple tissues using the Aggregated Cauchy Association Test (ACAT) and 2) a splicing-based approach that utilized two applications of ACAT to collate splicing QTLs (sQTLs) for a given gene in a tissue and then across tissues. To perform these two TWASs, we utilized e/sQTL models trained in 11 tissues from the Genotype-Tissue Expression Project including breast, ovary, uterus, vagina, EBV-transformed lymphocytes, whole blood, spleen, liver, subcutaneous adipose, visceral adipose, and cell-cultured fibroblasts. GWAS summary statistics were previously generated from 133,384 BC cases and 113,789 controls who were participants in the Breast Cancer Association Consortium (BCAC). We further performed our TWAS while conditioning e/sQTL effect sizes on nearby GWAS index SNPs. Additionally, we utilized gene-based fine-mapping of eQTLs and sQTL to identify candidate causal genes for each intrinsic subtype. Results: Overall, we identified 164 genes in 69 loci that were associated with Luminal A-like, 19 genes in 9 loci with Luminal B-like, 18 genes in 11 loci with Luminal B/HER2-negative-like, 10 genes in 7 loci with HER2-enriched-like, and 29 genes in 12 loci with TNBC. Among these genes, 17 genes had not been reported in previous TWAS of BC, and 140 genes, 1 gene, 2 genes, 2 genes, and 16 genes were uniquely associated with each of the intrinsic subtypes, respectively. Additionally, we identified one gene associated with Luminal A-like and one gene with Luminal B-like BC that were each in a locus located at least 1.4 Mb from published GWAS hits. Furthermore, we identified 106, 11, 10, 5, and 21 candidate causal genes for each of the intrinsic subtypes, respectively, that had a posterior inclusion probability of 0.9 in at least one e/sQTL. Conclusion: In summary, our multi-tissue TWAS corroborated previous GWAS loci for overall BC risk and intrinsic subtypes, while underscoring how common variation impacts BC etiology by modulating the expression and splicing of genes in multiple tissue types.

PO5-09-04

Oncotype DX Breast Recurrence Score® analysis in early-stage breast cancer associated with CHEK2, ATM and PALB2 germline pathogenic variants.

Presenting Author(s) and Co-Author(s):

F. Akkoc Mustafayev. University of Texas MD Anderson Cancer Center, United States

A. Gutierrez Barrera. University of MD Anderson Cancer Center, United States

D. Liu. UT MD Anderson Cancer Center, United States

B. Arun. UT MD Anderson Cancer Center, Houston, Texas, United States

Background: The 21-gene assay (Oncotype DX Recurrence Score, RS) is the only clinically validated assay to determine the prognosis in hormone-positive, HER2-negative breast cancer (BC) patients treated with endocrine therapy alone by predicting locoregional and distant recurrence. Outcomes of Oncotype RS in BRCA-associated BC has been studied previously, but the results of RS analysis in BC patients with the other BC susceptibility genes have not been documented. This study evaluates the clinical and pathological characteristics of BC patients with ATM, CHEK2 and PALB2 germline pathogenic variants (PV). Methods: Patients with invasive hormone-positive, HER2-negative BC who have had Oncotype DX Breast Recurrence Score® testing and who underwent genetic testing in the Breast Medical Oncology and the Breast Clinical Cancer Genetics Clinic at the University of Texas MD Anderson Cancer Center (MDACC) were identified from the prospectively maintained research database. Clinical and tumor characteristics were analyzed using descriptive statistics. Results: Between 1996 and June 2023, 5652 patients with Oncotype RS were included in this analysis. Amongst those 828 BC patients had genetic testing and 81 patients were found to have a pathogenic variant: 17 patients with a CHEK2 mutation, 10 patients with an ATM mutation, and 18 patients with a PALB2 mutation. Among patients with CHEK2 PV, median Oncotype RS was 17 (5–32) overall, 21 (13–32) for patients age < 50, and 14.5 (5–28) for patients age ≥50 (p= 0.2). Among patients with ATM PV, median RS was 16.5 (3–54) overall, 25 (10–54) for patients age < 50, and 14.5 (3–29) for patients age ≥50 (p= 0.19). Among patients with PALB2 PV, median RS was 26.5 (15–40) overall, 20 (15–40) for patients age < 50, and 31 (26–37) for patients age ≥50 (p= 0.012). Further patient and tumor characteristics are shown in Table 1. Conclusion: This is a single-institutional cohort of hormone-positive, HER2-negative BC patients who had Oncotype RS and who underwent genetic testing. Further analysis on clinical and tumor pathological characteristics and long-term outcome is ongoing.

Table1. Patient and tumor characteristics

Table1. Patient and tumor characteristics

	CHEK2 (n, %)	ATM (n, %)	PALB2 (n, %)
Age at diagnosis			
<50	9 (53)	4 (40)	11 (61)
≥50	8 (47)	6 (60)	7 (39)
Histology			
Ductal	15 (88)	10 (100)	17 (94)
Lobular	2 (12)	0	0
Mixed	0	0	1 (6)
Estrogen receptor			
POS	17 (100)	10 (100)	17 (94)
NEG	0	0	1 (6)
Progesterone receptor			
POS	17 (100)	10 (100)	15 (83)
NEG	0	0	3 (17)
RS			
<16	7 (41)	5 (50)	1 (6)
≥16	10 (59)	5 (50)	17 (94)
<26	14 (82)	7 (70)	8 (44)
≥26	3 (18)	3 (30)	10 (56)

PO5-09-05

Characteristics of newly diagnosed breast cancer patients at a large safety-net system: Implications for health equity and care delivery

Presenting Author(s) and Co-Author(s):

S. Kashanian. University of Texas Southwestern Medical Center, Dallas, Texas, United States

S. Kanjwal. University of Texas Southwestern Medical Center, United States

L. Brown. Parkland Health, United States

A. Semlow. Parkland Health, United States

M. Hodges. Parkland Health, United States

R. Cobb. Parkland Health, United States

B. Walsh. Parkland Health, United States

U. Dickerson. Parkland Health, United States

N. Sadeghi. University of Texas Southwestern Medical Center, Dallas, Texas, United States

Introduction:

Despite the increased awareness and advocacy for health equity, racial and socioeconomic disparities remain prevalent among breast cancer patients. Since lack of access to care is a major barrier, safety-net systems that provide services for the uninsured/underinsured play a significant role in promoting health equity and eliminating disparities. Understanding the patient population treated within these systems, which are often resource-limited, can help develop strategies to improve care delivery and outcomes. Here, we describe characteristics of breast cancer patients treated at a large safety-net system.

Methods:

Parkland Health (PH) is the safety-net system for Dallas County, and is affiliated with the University of Texas Southwestern Harold C. Simmons Comprehensive Cancer Center (NCI-CCC). Electronic medical records of patients with a new invasive breast cancer diagnosis between 2018 to 2020 at PH were reviewed and data on demographics and clinical presentation were collected. Categorical data was summarized with counts and percentages and continuous data was summarized with median and interquartile range. Statistical comparisons used Chi-square test for categorical data and rank sum test for continuous data with a significance level of 0.05. Data from the National Cancer Database (NCDB) for the same period was used for comparison.

Results:

A total of 657 patients at PH were included in the analysis (50.2% Hispanic; 32.3% Black). Median age at diagnosis was 53 years (range 46-61), with 39.1% of patients < 50 (12.3% < 40). The majority of patients were uninsured at the time of diagnosis (67.0%). Hispanic patients were younger than others (median age 49 years (range 43-57) vs 57 (range 48-63), $p < 0.01$), with 51.2% < 50. Late-stage diagnosis was observed in 30.6% of patients (stage III 16.4%, stage IV 14.2%), and triple negative breast cancer (TNBC) accounted for 22.8% of cases. While the stage distribution was not statistically different between racial and ethnic subgroups ($p=0.66$), black patients were diagnosed with TNBC at a significantly higher rate compared to others (30.2% vs 19.3%, $p < 0.01$). Although a trend towards higher rate of HER2(+) disease was noted among Hispanics, this difference did not reach the level of statistical significance (22.7% vs 16.5%, $p=0.06$). One hundred eighty-nine patients (28.8%) were diagnosed outside

PH. Compared to Black patients, Hispanic patients were more often diagnosed in the community (22.2% vs 32.4%, $p=0.01$). Of the 564 patients with stage I-III, 340 (60.3%) had T2-4 and 203 (36.0%) had node positive disease at diagnosis. Median time to treatment initiation (TTI) was 51 days (range 35-76) and was significantly longer in patients who were diagnosed in the community compared to those diagnosed at PH, median 63 days (range 44-96) vs 48 (range 34-70), $p < 0.01$. Compared to the NCDB, PH patients were younger (39.1% vs 18.4% < 50 years, $p < 0.01$), presented at a higher rate with late-stage disease (30.6% vs 13.2%, $p < 0.01$) and TNBC (22.8% vs 10.7%, $p < 0.01$), and had a longer median time from diagnosis to treatment initiation - 51 days (range 35-76) vs 33 (range 21-49), $p < 0.01$.

Conclusion:

Breast cancer patients at PH were significantly different from the national average, with over a third below the USPSTF recommended breast cancer screening age. The rate of late-stage diagnosis at PH was more than two-fold the national average. Lowering the screening age to 40, expansion of outreach mammography programs, improving patient navigation, and simplifying access to indigent care programs are among strategies to promote health equity. Considering the high disease burden among safety-net patients, a systematic effort to increase resources at safety-net health systems is warranted.

PO5-09-06

Outcomes of breast cancer in a minority-enriched population treated at a large safety-net system: Is site of care a predictor of poor outcomes?

Presenting Author(s) and Co-Author(s):

S. Kashanian. University of Texas Southwestern Medical Center, Dallas, Texas, United States

S. Kanjwal. University of Texas Southwestern Medical Center, United States

L. Brown. Parkland Health, United States

A. Semlow. Parkland Health, United States

M. Hodges. Parkland Health, United States

R. Cobb. Parkland Health, United States

B. Walsh. Parkland Health, United States

U. Dickerson. Parkland Health, United States

N. Sadeghi. University of Texas Southwestern Medical Center, Dallas, Texas, United States

Background:

Breast cancer outcomes in the United States continue to improve, but sociodemographic disparities remain prevalent and impact care delivery and outcomes in vulnerable populations. Safety-net health systems are intended to address inequities by providing access to care for the uninsured/underinsured. Care delivery in a safety-net setting is often inherently complicated by limited resources at these institutions. Here, we present the overall survival (OS) data of breast cancer patients treated at a large safety-net system, compared to the national average.

Methods:

Parkland Health (PH) is the safety-net system for Dallas County and is affiliated with the University of Texas Southwestern Harold C. Simmons Comprehensive Cancer Center (NCI-CCC). Electronic medical records of patients diagnosed with invasive breast cancer between 2018 to 2020 at PH were reviewed and data on demographics, treatment, and outcomes were collected. Categorical data was summarized with counts and percentages and continuous data was summarized with median and interquartile range. Statistical comparisons used Chi-square test for categorical data and rank sum test for continuous data with a significance level of 0.05. Survival data was analyzed using Cox proportional hazard model. Data from the National Cancer Database (NCDB) for the same period was used for comparison.

Results:

Of the 657 patients included in the study, the majority (82.5%) belonged to racial and ethnic minorities (Hispanic 50.2%; Black 32.3%). Compared to the NCDB, PH patients were more often uninsured (67% vs 1.6%) or enrolled on Medicaid (14.5% vs 6.9%), and less often on Medicare (8.5% v. 43%) ($p < 0.01$). Triple negative breast cancer (TNBC) phenotype and late-stage diagnosis (stage III/IV) rates were higher at PH compared to NCDB (TNBC 22.8% vs 10.7%, $p < 0.01$; late stage 30.6% vs 13.2%, $p < 0.01$). At a median follow up of 33 (range 24-43) months in PH and 28 (range 21-36) months in NCDB, the unadjusted OS for the PH population was 86.3% vs 92.6% for the NCDB population ($p < 0.01$). Within the PH population, Black race, higher stage, and TNBC were associated with decreased OS. There was a significant interaction between Black race and TNBC. When combining all patients (PH+NCDB), site of care (PH) was associated with a higher risk of death from breast cancer (HR 1.467, 95% CI 1.192-1.805, $p < 0.0005$), however, multivariate analysis did not show a

significant difference based on site of care. Factors associated with a significantly increased risk of death in this multivariate analysis (corrected for interaction between Black race and TNBC phenotype) included age, late-stage diagnosis, TNBC, Black race, and uninsured status (Table 1).

Conclusions:

Breast cancer patients treated at PH were more likely to have adverse disease characteristics compared to the NCDDB population. When accounting for these risk factors in multivariate analysis, patients treated at PH had similar outcomes compared to the national average. Our findings reinforce the critical role of safety-net systems in promoting health equity and eliminating disparities.

Table 1

Table 1

Factors Associated with Risk of Death in a Multivariate Analysis*

	Hazard Ratio	Confidence Interval	p-value
PH v NCDDB	1.060	0.857-1.310	0.591
Black Race	1.513	1.461-1.568	<0.001
Stage III or IV	7.578	7.405-7.755	<0.001
TNBC	1.745	1.691-1.801	<0.001
Age	1.052	1.051-1.053	<0.001
Uninsured	1.509	1.420-1.603	<0.001

*Corrected for interaction between Black race and TNBC phenotype

PO5-09-08

Cancer Health Disparities among non-Hispanic African women: A systematic review of the disparities, reasons and probable intervention

Presenting Author(s) and Co-Author(s):

T. Khan efa. University of Texas Health Science at Houston, Arlington, Texas, United States

Health equity places health inequities in historical and social context and calls for action to address injustice and enhance health. As an ethical and human rights value that drives us to end health inequities, health equality is defined as everyone having a fair and just opportunity to be as healthy as feasible. According to this perspective, structural discrimination and marginalization cause health disparities that can be avoided. If these issues are not resolved, social and economic injustices, bias, and unfavorable outcomes that affect all of us will continue to exist. The idea of cancer health equality recognizes that there is still considerable work to be done to change the social structures and historical momentum that have contributed to different cancer outcomes, and that this work can only succeed if it is done.

In USA, non-Hispanic black women experience a complicated and multifaceted disparity in breast cancer incidence and outcome. It's possible that social, economic, and behavioral variables contribute to discrepancies. Black women are less likely to breastfeed after childbirth, statistically more likely to have diabetes, heart disease, and obesity, all of which are risk factors for breast cancer. Compared to white women, they are more likely to lack adequate health insurance or access to medical facilities, which could have an impact on screening, follow-up treatment, and therapy completion.

It has become evident via more study that biology also plays a part. Black women are more likely to be diagnosed at younger ages and at higher rates with more aggressive subtypes of breast cancer, such as triple-negative breast cancer (TNBC) and inflammatory breast cancer.

The National Institute on Minority Health and Health Disparities (NIMHD) established a research framework to characterize the multiple domains of influence (biological, behavioral, physical environment, sociocultural environment, and health care system) that may act across various levels of influence to impact health. A literature search was conducted using the National Library of Medicine's PubMed search engine. Triple negative breast cancer (TNBC) is a common malignancy in African American women. The incidence of TNBC is higher in women of African ancestry and is associated with overall poor prognosis. This disparity is due to the presence/absence of oncogenes/tumor suppressor genes, mutations and altered signaling pathways that might predispose premenopausal African American women to TNBC. Multiple socioeconomic factors influence the access to standard care, novel treatments and inclusion in clinical trials and contribute to overall prognoses. This review focuses on the epidemiology, molecular alterations, and treatment-related disparities in African Americans with breast cancer.

This poster will elaborate the racial disparity in terms of breast cancer among the African-American women in USA, the reasons and it's effects on health equity.

PO5-09-09

Incidence of Breast Cancer in Hispanic Women Across the US: A Focus on Texas

Presenting Author(s) and Co-Author(s):

C. Esguerra. Protean BioDiagnostics, United States

K. Santos Barbosa. Protean BioDiagnostics, United States

R. Khalife. Protean BioDiagnostics, Orlando, Florida, United States

A. Magliocco. Protean BioDiagnostics, Orlando, Florida, United States

Incidence of Breast Cancer in Hispanic Women Across the US: A Focus on Texas

Catalina Esguerra ¹, Kemely Santos Barbosa ¹, Roy Khalife ¹, Anthony Magliocco ¹

¹ Protean BioDiagnostics Inc, Orlando, FL

Introduction

Breast cancer (BC) is one of the most common cancers affecting the female population in the United States, particularly among the Hispanic community. According to the CDC, the incidence rate of new breast cancer cases in Hispanic women is 95.6 per 100,000 annually, and the mortality rate is 13.7 per 100,000 women annually. Texas is home to one of the largest Hispanic communities in the US. By analyzing the prevalence, mortality, and access to healthcare services in Texas, we can shed light on the unique aspects of breast cancer within the Hispanic population. Overall, this study will provide valuable insights and identify potential avenues for reducing disparities and improving healthcare outcomes for Hispanic women affected by breast cancer.

Materials and methods

This study used comparative data from State Cancer Profiles on the CDC and NIH databases. The database was used to generate an overall comparison of breast cancer in Hispanic women across different US states. Comparison factors analyzed include incidence, mortality, insurance, and screening efforts. Significant differences were noted especially in Texas. Graphs and quantitative data for comparison factors were generated. This data is from 2015-2019 unless noted.

Results

The incidence of breast cancer in Hispanic women in Texas (TX) is 93.5 (Age-Adjusted Incidence Rate-cases per 100,000) with a CI of (92.2-94.8). The incidence of BC in Hispanic women in the US averages 99.0 with a CI of 98.7-99.9. From the incidence data, Hispanic women in Texas have a lower overall incidence of BC compared to the rest of the Hispanic females in the US. When analyzing the mortality rate, Hispanic women in TX have an Age-Adjusted Death Rate (deaths per 100,000) of 15.2 (CI of 14.7-15.8). In the US, Hispanic women have an Age-Adjusted Death Rate (deaths per 100,000) of 13.0 (CI of 13.4-13.9).

To analyze preventative measures, a graph reporting mammogram use in 2020 by state was gathered. In TX 2020, the estimated age-adjusted prevalence of mammograms among Hispanic females from 50-74 years old was 75.0% (CI of 67.0%-81.7%). Nationally, the age-adjusted prevalence among Hispanic females 50-74 years who reported mammogram screening in 2 years was 79.7% (CI of 76.6 – 82.4).

As for Texas insurance rates in 2020, Hispanic women under 65 years old, 27.4 % reported

being uninsured. In comparison, other ethnicities such as African American (non-Hispanic) women, 16.5% reported to be uninsured, and white (non-Hispanic) women in Texas 11.8 % reported to be uninsured.

Additionally, to further analyze if the lack of preventative measures was causing women to have a higher mortality rate, the instance of late-stage diagnosis of BC in Texan Hispanic women was analyzed. The age-adjusted incidence rate of late-stage breast cancer in Hispanic women was reported to be 33.4 (CI of 32.6-34.2) and the national incidence of late-stage BC in Hispanic women is 35.0 (CI of 35.1-35.8).

Conclusion

Even with Texas having one of the largest Hispanic communities, Hispanic women with breast cancer in Texas are faced with obstacles that lead to an increase in their mortality rate. As seen in the results, Hispanic women have less incidence of BC (including late stage) than their equivalent across the US but Hispanic women in TX have higher mortality rates in comparison. This is additionally accompanied by a decrease in insured women and a decrease in the utilization of cancer screenings. Lack of access to affordable healthcare and lack of regulatory cancer screenings cause Hispanic women to meet their premature death. Further analysis of the effects of affordable health care or further molecular investigation of this population is encouraged to research to fully conclude the reason behind this population's disparities.

PO5-09-10

Inflammatory Breast Cancer Patient Profile in a Population of Puerto Rican Women

Presenting Author(s) and Co-Author(s):

L. ARROYO-CRUZ. Universidad Central del Caribe, Bayamón, Not Applicable, Puerto Rico

M. Martinez-Montemayor. Universidad Central del Caribe, Bayamón, Not Applicable, Puerto Rico

Background: Breast cancer (BC) is the most frequently diagnosed cancer type, as well as the leading cause of cancer death among women in Puerto Rico (PR). Moreover, inflammatory breast cancer (IBC) is a highly aggressive BC subtype. The current study aimed to describe the patient profile and the clinicopathological characteristics of IBC tumors in Hispanic women living in Puerto Rico.

Methods: This is a retrospective, population-based study using the Puerto Rico Central Cancer Registry (PRCCR) database and the Health Insurance Linkage Database (PRCCR-HILD) to identify and describe the patient profile of Puerto Rican women diagnosed with IBC from 2008 to 2018. Variables such as age at diagnosis, staging variables, tumor receptor subtypes, treatment received, and overall survival (OS) were studied. Statistical analysis methods were employed to describe the population, estimate survival curves and examine the risk of dying.

Results: We identified a total of 51 patients. The mean age at diagnosis of IBC in the current study was 59 years old, which is older than the mean age at diagnosis of IBC for women in the mainland US, but younger than the mean age of women that are diagnosed with BC in PR (63 years old). A total of 62.8% of patients had no metastases at diagnosis and 64.7% were diagnosed with stage III disease. Most tumors presented with ER+/PR+/Her2- (21.6%), or a triple-negative (ER-/PR-/Her2-, 15.7%) tumor concordance. The OS during the 12 months post-diagnosis was 66%, whereas at 36 months, OS decreased to 39%. The triple-negative subtype had the worst survival at 36 months (36%). Women with stage IV disease and those with ER-/PR- tumor subtype had a higher risk of dying.

Conclusions: This is the first research to describe the patient profile and characteristics of women diagnosed with IBC in Puerto Rico. Our results suggest that the Puerto Rican IBC patient population presents unique characteristics. This research increases awareness about this lethal disease in PR.

PO5-09-11

Abrupt involution of mouse mammary gland leads to inflammatory systemic changes along with mammary specific metabolic shifts that may enhance risk of breast cancer.

Presenting Author(s) and Co-Author(s):

K. Ormiston. The Ohio State University Medical Center, Westerville, Ohio, United States

K. Kaul. The Ohio State University Medical Center, United States

N. Shinde. The Ohio State University Medical Center, United States

D. Bennouna. The Ohio State University, United States

R. Kopec. The Ohio State University, United States

R. Ganju. The Ohio State University Medical Center, United States

S. Majumder. The Ohio State University, United States

B. Ramaswamy. The Ohio State University Comprehensive Cancer Center, United States

Epidemiological data links higher parity and lack of breastfeeding with increased risk of breast cancer, specifically aggressive triple negative breast cancer (TNBC), and higher mortality rate. Following pregnancy and lactation, breast remodels to near pre-pregnancy stage through apoptotic cell death and adipocyte repopulation process. Long-term breastfeeding and gradual weaning of an infant leads to gradual involution (GI) of the breast, while lack of or abrupt discontinuation of breastfeeding after birth leads to abrupt involution (AI), when rapid and massive cell death takes place. Our studies have shown several precancerous changes, such as increased collagen deposition, inflammation, and hyperplasia in the mammary gland of mice after AI. However, the systemic impact of AI and how this increases risk of breast cancer is yet to be elucidated.

Objectives: Our objective is to evaluate the systemic effects that are prompted by the AI mammary gland. We hypothesize that AI leads to marked alteration in lipid metabolism and systemic inflammation that enhances risk for breast cancer.

Methods: FVB/n mice (8week old) were paired for breeding. At partum (day 0), dams were randomized to AI or GI cohort and standardized to 6 pups. AI mice had pups removed on day 7 postpartum (ppm) to mimic short-term breastfeeding. For GI mice 3 pups each were removed on day 28 and 31ppm to mimic gradual weaning. Tissues harvested on day 28, 56, and 120 postpartum. Body composition was measured by echo MRI. Glucose tolerance test (GTT) was performed after a 6 hour fast using a 2g/kg glucose intraperitoneal injection. Blood glucose was measured by glucometer. Serum insulin was analyzed by ELISA. HOMA-IR was calculated using blood glucose and serum insulin results. Serum was analyzed using multiplex ELISA by MesoScale Diagnostics. Mammary glands were subjected to untargeted lipidomics.

Results: There were no significant differences in body weight, percent body fat or lean mass between AI and GI groups at any time point. However, at day 120 ppm (4 months after partum), we have observed significantly larger amount (1.29-fold increase) of perigonadal adipose tissue (visceral adipose) in AI mice than GI mice ($p=0.0112$; $n=24-38$ /group). There were no significant differences in blood glucose, serum insulin, HOMA-IR, or GTT results between AI and GI groups at day 120. AI mice had significantly higher levels of cytokines IL-1 β (3.1-fold increase, $p=0.0417$) and KC/GRO (1.5-fold increase, $p=0.0196$) than GI mice at day 120. At day 28, AI mammary glands had significantly higher amounts of level 3 identified oxidized ceramide containing sphingolipids that were linked to insulin resistance and diabetes. At day

56, GI mammary glands had significantly higher amounts of level 2 and 3 identified metabolites linked to cellular signaling and lipid metabolism. On day 120, there were no significant differences in lipid metabolites between groups.

Conclusion: Although histologically GI and AI mammary glands return to near pre-pregnancy state within a month after partum, our data shows specific lipid changes in the AI mammary gland similar to what has been shown in women with TNBC. Furthermore, AI of the mammary gland leads to systemic effects on adiposity and inflammation that could be key to increased breast cancer risk. Further studies along these lines are in progress to understand the whole-body effects of AI and stratify preventive measures for women who cannot breast feed.

Significance: Lack of breastfeeding is more prevalent in African American (AA) women and linked to higher risk of developing aggressive TNBC¹. Our novel animal models of AI and GI help to link the impact of AI and systemic changes that may enhance breast cancer risk. In particular, we see an increase in visceral adiposity with AI. Understanding this mechanism will help identify strategies to reduce risk in women who are unable or choose not to breastfeed and ultimately help to reduce TNBC and TNBC-related mortality in AA women.

PO5-09-12

Unraveling the Intricacies of Racial Disparities in Breast Cancer in Brazil

Presenting Author(s) and Co-Author(s):

J. da Silva. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

A. De Melo. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

M. Rodrigues. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

L. de Albuquerque. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

L. Thuler. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

Abstract Background: Over the past three decades, numerous countries have experienced a substantial decrease in breast cancer (BC) fatality, attributed to heightened consciousness, widened and earlier screening, and enhanced therapeutic interventions. However, these advancements have not eradicated the disparity in BC treatment across different racial and ethnic groups. In Brazil, the causes of these disparities are diverse and intricate, resembling health inequalities among ethnic communities observed in other countries. This study aimed to investigate the trends in BC incidence and mortality rates in Brazil, considering clinicopathological and sociodemographic variations, and placing particular emphasis on the severity of racial disparity concerning race/skin color. **Patients and methods:** Incidence trends for women with BC were analyzed using data from 13 Brazilian Population-Based Cancer Registries covering the period 2010-2015. Crude incidence ratios (CIRs) and the annual average percent change (AAPC) were calculated. Clinical and sociodemographic information from 348 Hospital-Based Cancer Registries spanning from 2000 to 2019 was also utilized. Meanwhile, mortality data for the years 2000-2020 were obtained from the National Mortality Information System. Racial and skin color data were collected through a self-declaration process, following the classification proposed by the Brazilian Institute of Geography and Statistics, which included categories such as white, black, and brown/mixed race. In the analysis, black and brown/mixed race categories were combined as black. Yellow and indigenous categories were excluded. Statistical significance was defined as a p-value less than 0.05. To determine clinically relevant differences, a threshold of more than 5% disparity in proportional values was used as an arbitrary criterion. **Results:** Between 2010 and 2015, a total of 70,896 newly diagnosed cases of BC were recorded. Mean CIRs were 83.9/100,000 for the overall population, 101.3/100,000 for white women, and 59.7/100,000 for black women. Neither the group of white women (AAPC -1.7; 95% CI: -7.9 to 4.9; p = 0.506) nor the group of black women (AAPC -0.4; 95% CI: -5.0 to 4.5; p = 0.831) exhibited any significant changes in the incidence rate. Black women predominantly originated from underdeveloped regions (56.4%, p < 0.001), were referred by the public healthcare system in Brazil (79.0%, p < 0.001), had ≤ 8 years of schooling (68.7%, p < 0.001), were unmarried (50.9%, p < 0.001), reported alcohol consumption (20.9%, p < 0.001), and were diagnosed with advanced stage disease (60.1%, p < 0.001). The escalation in mortality rates among black women exhibited a notable difference, amounting to 3.8 times the increase observed among white women (AAPC + 2.3; 95% CI: 2.1 to 2.5; p < 0.001) (AAPC + 0.6; 95% CI: 0.5 to 0.7; p < 0.001). **Conclusion:** Despite the lower incidence of BC in black women compared to their white counterparts, there is a concerning rise in BC-related mortality rates among black women. This group exhibits a significantly unfavorable sociodemographic and clinicopathological profile. These results highlight the pressing need to address the multifaceted factors contributing to these disparities, encompassing socioeconomic disparities and unequal healthcare access. **Keywords:** Breast cancer; racial disparities; incidence; mortality.

PO5-10-02

Neighborhood deprivation index and time to initiation in patients with metastatic breast cancer

Presenting Author(s) and Co-Author(s):

S. Rajendran. University of Pittsburgh Medical Center, United States

D. Ren. University of Pittsburgh Medical Center, United States

M. Petruzzi. University of Pittsburgh Medical Center, United States

M. Rosenzweig. University of Pittsburgh School of Nursing, PITTSBURGH, Pennsylvania, United States

Background Cyclin-dependent kinase 4 and 6 inhibitors (CDKi) are first-line therapy for patients with estrogen-positive (ER+) metastatic breast cancer (MBC). The accessibility, usability, and outcomes according to demographic factors have not been well studied in real world practice. Methods Retrospective review of patients with ER+ MBC prescribed first line CDKi therapy at a large NCI-designated cancer center from January 2015 through December 2022. Patient records were abstracted for outcomes including 1) time from CDKi prescription to drug initiation (TTI), 2) time from CDKi initiation to progression, and 3) time from CDKi initiation to death /or 6/30/2022. Patient variables collected were: patient age (continuous), race (patient self-report – Black, White, Other), partner status (Married, Not married), Insurance type (Medicare, Medicaid, Private); Mean BMI; Number of comorbidities (5 categories). Neighborhood deprivation index (NDI) was determined from the patient's address with higher scores indicating more deprivation. Descriptive, comparative, and correlational statistics were used. Results A total of 173 patients were included in the analysis. Mean age – 63.1, (SD 12.7, range 24-94); race – White n=157, Black n=16; marital status – Married n=102, Not married n=71; mean NDI – 61.0 (SD 23.7, range 6-100); mean BMI – 28.9 (SD 6.9, range 16-48); number of comorbidities – 0 n=35, 1-2 n= 35, 3-4 n = 55, 5-6 n = 20, 7+ n = 28; insurance type – Medicare n = 115, Medicaid n = 21, Private n = 37. TTI: the median TTI was 14 days. There were no statistically significant differences in TTI based on age, race, NDI, or other demographic variables. Time to progression: in the multivariate model, younger age at diagnosis and Medicaid insurance were associated with shorter time to progression. Overall survival: not married, younger age at diagnosis, and Medicaid insurance were associated with shorter overall survival. Discussion Demographic factors are associated with diverse outcomes of MBC therapy, not attributed to delay in CDKi treatment initiation. Personalization of support during MBC illness according to risk factors for worse outcomes may help to equalize incomes.

PO5-10-03

A Translational Epidemiologic Approach to Understand Disparities in Triple Negative Breast Cancer: Integrating Germline Genomics, Genetic Ancestry, and Neighborhood Disadvantage

Presenting Author(s) and Co-Author(s):

N. Goel. University of Miami Department of Surgery, United States

A. Hernandez. Sylvester Comprehensive Cancer Center, University of Miami Health System, United States

S. Kesmodel. University of Miami DeWitt Daughtry Dept. Surgery, United States

E. Kobetz. University of Miami, United States

N. Merchant. University of Miami Miller School of Medicine, United States

T. Rebbeck. Dana Farber Cancer Institute, United States

Background: Triple-negative breast cancer (TNBC) disproportionately affects women of West African ancestry and those living in neighborhood disadvantage (ND). However, these studies were limited in their ability to control for both ancestry and socioeconomic data. To overcome this limitation, we utilized the epidemiologic-genomic infrastructure of the Miami Breast Cancer Disparities (MBCD) study to evaluate the impact of ND on relative risk (RR) of TNBC, independent of West African ancestry.

Methods: A prospective cohort of 502 women with breast cancer enrolled in the MBCD study from 2020-2022. Genetic ancestry, median neighborhood-level income quartiles (ND), germline genetic mutations, and tumor characteristics were assessed. Multinomial logistic regression was used to determine the RR between West African ancestry and TNBC (compared to ER+/HER2- and HER2+ disease) after controlling for access to care measures which might impact TNBC distributions and known TNBC risk factors (e.g., age, ND, BRCA 1 mutation, obesity, screening mammography).

Results: Of the 502 women, 333 (66.33%) had ER+/HER2- disease, 67 (13.35%) had ER+/HER2+ disease, 22 (4.38%) had ER-/HER2+ disease, and 80 (15.94%) had TNBC. On univariable analysis, the highest West African quartile (RR 3.58 95%CI 1.72-7.42, $p < 0.001$), a BRCA 1 mutation (RR 7.89 95%CI 2.25-27.64, $p = 0.001$) were associated with a higher RR of TNBC. Conversely, decreasing ND was associated with a lower RR of TNBC (RR 0.42 95%CI 0.21-0.83, $p = 0.013$). On covariate adjusted multivariable analysis, decreasing ND (RR 0.45 95%CI 0.22-0.99, $p = 0.047$) and a BRCA 1 mutation (RR 12.68 95%CI 3.19-50.35, $p < 0.0001$) were both significantly associated with TNBC compared to ER+/HER2- and HER2+ disease.

Conclusions: To our knowledge, this prospective study is the first to evaluate the combined impact of genetic ancestry, germline genomics, and social factors on RR of TNBC. We discovered that ND and BRCA 1 mutations are independent predictors of TNBC, even after accounting for known TNBC risk factors (e.g., West African ancestry). These findings suggest a potential association between ND and TNBC, thus emphasizing the importance of a translational epidemiologic approach to understand TNBC disparities that considers both genomic and non-genomic factors.

Adjusted Multinomial Logistic Regression of Patient Genetic Ancestry, Sociodemographic and Tumor Characteristics Predictors of Breast Cancer Subtype

Table: Adjusted Multinomial Logistic Regression of Patient Genetic Ancestry, Sociodemographic and Tumor Characteristics Predictors of Breast Cancer Subtype

	HER2+ (ref. ER+/HER2-)		TNBC (ref. ER+/HER2-)	
	RR (95%CI)	P-value	RR (95%CI)	P-value
<i>Age</i>	0.98 (0.96 -1.01)	0.14	1.02 (0.99-1.04)	0.18
Genetic Ancestry				
%West African (quartiles)				
0.001-2.6 (ref)				
2.7-6.9	0.83 (0.37-1.86)	0.66	1.89 (0.75-4.78)	0.18
7.0-21.0	1.05 (0.45-2.41)	0.92	1.50 (0.53- 4.27)	0.45
21.1-98.0	0.76 (0.27-2.16)	0.61	2.87 (0.75-10.96)	0.12
%European (quartiles)				
0.001-4.9 (ref)				
4.9-31.0	0.73 (0.33-1.63)	0.45	1.03 (0.45-2.33)	0.95
31.0-84.0	0.97 (0.39-2.46)	0.95	1.02 (0.35-2.97)	0.97
84.0-99.0	0.39 (0.12-1.21)	0.10	0.79 (0.19-3.20)	0.74
%Native American (quartiles)				
0.001-2.1 (ref)				
2.1-15.0	0.93 (0.42-2.04)	0.86	1.55 (0.70-3.47)	0.28
15.0-66.0	0.90 (0.37-2.16)	0.81	0.71 (0.26-1.91)	0.49
66.0-99.0	0.40 (0.13-1.23)	0.11	1.07 (0.28-4.14)	0.92
BRCAl Mutation				
Yes	0.86 (.09-8.10)	0.90	12.68 (3.19-50.35)	<0.0001
Neighborhood-level income (quartiles)				
19,138-36,051 (ref)				
36,052-48,450	1.30 (0.64-2.63)	0.46	0.49 (0.24-1.04)	0.06
48,451-61,917	1.17(0.56-2.44)	0.68	0.49 (0.23-1.09)	0.08
61,918-154,868	1.03 (0.48-2.17)	0.95	0.45 (0.20-0.99)	0.047
BMI	1.01 (0.97-1.05)	0.52	1.00 (0.96-1.05)	0.92
Found on Screening				
Yes	0.85 (0.55-1.30)	0.45	0.83 (0.53-1.32)	0.44

PO5-10-04

Rare to Care: Assessing Awareness and Health Disparity Factors Related to Inflammatory Breast Cancer in the Primary Care Setting

Presenting Author(s) and Co-Author(s):

G. Devi. Department of Surgery, Duke University School of Medicine; Duke Consortium for Inflammatory Breast Cancer, Duke Cancer Institute, Durham, North Carolina, United States

L. Greenblatt. Duke University School of Medicine; Northern Piedmont Community Care, Durham, North Carolina, United States

R. Saincher. Duke Primary Care, North Carolina, United States

V. Keck. Duke Outpatient Clinic, Durham, North Carolina, United States

B. Blass. Duke University School of Medicine, United States

S. Weaver. Duke University School of Medicine, Durham, North Carolina, United States

A. Bennion. Trinity College of Arts and Sciences, Duke University, North Carolina, United States

A. Tran. Duke University School of Medicine, Durham, North Carolina, United States

Background: The diagnosis of inflammatory breast cancer (IBC) is life-changing as it is a rare, highly aggressive breast cancer variant designated by NIH as a cancer health disparity. Given the unique presentation of diffuse tumor cell spread in the absence of a solid mass, which is not easily detected by self-breast exams or mammograms, IBC patients often face delays in diagnosis and treatment. Therefore, an individualized and a multifaceted approach that addresses the unique needs of the patient with input from both providers and the community is an unmet need. To address this, we are investigating the current knowledge and perspectives of providers and public related to rare cancers like IBC in primary care practices. Methods: Researchers and advanced practice providers collaboratively drafted and piloted the initial surveys with guidance from a Community Advisory Board, comprising of members from academic institutions, primary care practices in urban and rural setting, topical experts, and patient advocates, in order to assess primary care providers (PCPs) and general public knowledge, attitudes and health seeking practices related to rare cancer like IBC. Results: The surveys are currently being administered statewide specific to PCPs or public via cognitive interviews and/or using an online survey tool within North Carolina as a model of a large state (100 counties) with a range of population densities, race, ethnicities, and environmental burdens. Challenges elaborated at the PCP level include communicating rare cancer information, gaps in confidence in diagnosing IBC, timely follow-up with patients, and accessing specialty care and an unmet need for developing PCP educational modules to improve guideline-concordant care. Public data analyzed to date is from a Duke Outpatient Clinic, an urban ambulatory care teaching practice serving primarily low-income, medically complex patients in Durham (n=14) included 69% Black, 93% female, with 68% in households earning under \$50,000 annually). 71% had not heard of IBC; 64% did not identify high BMI as a risk factor; 36% did not know there is differential race-related incidence; 74% did not recognize IBC-specific symptoms. 50% noted lack of insurance, transportation, religious reasons, or difficulty or fear of talking to a physician contributed in general delay in seeking health care. Most importantly, 93% expressed feeling comfortable sharing information about IBC with others. Majority expressed that adding visual aids and providing educational materials about IBC at the time of survey would be helpful. Conclusions: The results highlight the role of PCPs, including physicians, physician assistants, and nurse practitioners, who are often the first point of contact when patients begin to notice signs or symptoms. The general public and the patients with

common breast cancer subtypes can provide valuable insight into their own health care experiences, what works for them and what barriers they face in their communities, which can be used to compare with experience of patients with IBC and other rare cancers. Overall, the lessons from this study inform the development of effective tools to educate PCPs and patients for this understudied cancer that contributes to disparities in clinical and survival outcomes in minoritized and marginalized populations. Support in part from the Duke Cancer Institute pilot as part of the P30 Cancer Center Support Grant (P30CA014236) and Duke School of Medicine Behavioral Health and Survey Research Core Facility Award (GRD, ANT); Duke Advanced Practice Provider Leadership Institute scholarship (VK, GRD), Department of Surgery (GRD); Duke Ahead Education grant; NIH/NCI RO1CA264529-01 (GRD); ACS Mission Boost grant MBG-20-141-01-MBG (GRD), Nakayama Public Service Scholar Award (AB).

PO5-10-06

A Pilot Study for Clinical Research Nurse Navigation at an Urban NCI-Designated Comprehensive Cancer Center

Presenting Author(s) and Co-Author(s):

L. Huckaby. Winship Cancer Institute, Emory University, United States

M. Ratcliffe. Winship Cancer Institute, Emory University, United States

M. Canning. Winship Cancer Institute, Emory University, United States

D. Smith-Graziani. Dept of Hematology and Medical Oncology, Emory University School of Medicine, United States

K. Kalinsky. Winship Cancer Institute at Emory University, Atlanta, Georgia, United States

M. Bhawe. Emory University School of Medicine, Atlanta, Georgia, United States

Background: Breast cancer is now the leading cause of cancer death for non-Hispanic Black women in Georgia with non-Hispanic Black women 40% more likely to die of breast cancer compared to White women. Inadequate representation of patients in clinical trials may contribute to health care inequity, though prior work has also shown disparate outcomes on similar clinical trials at Emory, suggesting differences in tumor biology may also be contributing to the disparity. Improving diversity in trial participation is imperative to better understand these differences, particularly with newer molecularly targeted therapies. We aimed to utilize Clinical Trials Nurse Navigation to increase clinical trial enrollment at an urban NCI-designated comprehensive care center in Atlanta, Georgia. Methods: A prospective pilot study was conducted investigating the role of a Clinical Research Nurse as a dedicated Clinical Trials Nurse Navigator to identify, pre-screen, and refer potential patients to both breast and next generation sequencing (NGS)-driven basket clinical trials at the Winship Cancer Institute at Emory University. The role also included centralizing all molecular data from patients with stage IV breast cancer into a database as a tool to refer patients to NGS-driven clinical trials. This role expands upon the Institute's current research nursing scope to better meet the needs of our diverse patient population. Our catchment area is 35% non-Hispanic Black or African American. The nurse prescreened patients with stage IV breast cancer from breast oncology clinic templates and the breast NGS database to match them with clinical trials, with a particular emphasis on patients with stage IV triple negative breast cancer. The study began in January 2022 and is currently ongoing. Results: Since study initiation in January 2022, there has been a 27% increase in breast cancer clinical trial enrollment over a 12-month period. Over the last 6 months from January 2023, this has increased even further with 57 patients enrolled onto breast cancer clinical trials compared to a total enrollment of 70 patients onto breast cancer clinical trials in 2022 (Table 1). Of these patients, 11% enrolled in NGS-driven clinical trials in 2022 to present compared to 0% in 2021. Twenty-two (31.4%) non-Hispanic Black women enrolled onto breast cancer clinical trials in 2022 with another 21 (36.8%) non-Hispanic Black women enrolled thus far in 2023 (Table 1). Conclusion: Disparities in clinical trial enrollment may contribute to racial inequities in breast cancer outcomes. Implementation of clinical research nurse navigation has successfully improved clinical trial enrollment and diversity in clinical trial enrollment at our urban cancer center. Through increasing clinical trial prescreening, centralizing an NGS database, and dedicated nurse support to allow patients to navigate onto clinical trials, we achieved a 21% improvement in clinical trial enrollment from 2021 to 2022 and are on track to increase enrollment by 200% by the end of 2023. Clinical trials nurse navigators serve as an essential link between clinical trial patients and their providers, and should strongly be considered a key component of all clinical trials programs.

Table 1

Covariate	Year				
	2019	2020	2021	2022	2023 (1/01/23- 6/30/23)
Race (N, %)					
<i>African American</i>	8 (40.0%)	8 (34.8%)	21 (36.8%)	22 (31.4%)	21 (36.8%)
<i>Asian</i>	1 (5.0%)	4 (17.4%)	2 (3.5%)	3 (4.3%)	3 (5.3%)
<i>White</i>	9 (45.0%)	11 (47.8%)	33 (52.9%)	37 (52.9%)	29 (50.9%)
Ethnicity (N, %)					
<i>Hispanic</i>	0 (0.0%)	1 (4.3%)	2 (3.5%)	0 (0.0%)	1 (1.8%)
<i>Non-Hispanic</i>	20 (100.0%)	22 (95.7%)	51 (89.5%)	61 (87.1%)	51 (89.5%)
<i>Overall</i>	20	23	57	70	57

Breast Working Group Patient Enrollment by Race and Ethnicity, 2019-2023

PO5-10-07

Risk factors associated with secondary cancers in AYA patients with breast cancer. A SEER database study

Presenting Author(s) and Co-Author(s):

S. Ba Aqeel. Roswell Park Comprehensive Cancer Center, United States

A. Taneja. Roswell Park Comprehensive Cancer Center, United States

S. Gandhi. Roswell Park Comprehensive Cancer Center, United States

Background Adolescents and young adults (AYA) diagnosed with breast cancer face unique challenges and have distinct characteristics compared to older patients. While primary breast cancer remains a significant concern, the risk of developing secondary cancers in this population is also of great importance. This study aimed to identify these risk factors by analyzing a large cohort of AYA breast cancer patients using SEER (Surveillance Epidemiology and End Result) Database. Methods Patients were identified from SEER Research Data 17, from 2000 to 2019. Patients aged 18-39 years with breast cancer and at least 1 year of survival were identified. Secondary cancers were then identified and included any disease site. Patient demographic and clinical characteristics were summarized by secondary cancer status using Mann-Whitney U and Fisher's exact tests. Overall survival from the initial breast cancer diagnosis was summarized by secondary cancer status using standard Kaplan-Meier methods, where the median and 3/5-year rates were estimated with 95% confidence intervals. Comparisons were made using the log-rank test. SAS v9.4 (Cary, NC) was used at a significance level of 0.05. Results A total of 47,912 AYA breast cancer patients were identified, of which 2,886 (6.0%) developed a secondary cancer at least 1 year after the initial breast cancer diagnosis. When comparing patients with and without secondary cancers, we observed significant differences with respect to age at initial breast cancer diagnosis, race, stage, nodal status, surgical procedure, ER status, PR status, Her2 status, and sub-type (Table1). The analysis of overall survival showed that, from the time of breast cancer diagnosis, there was no statistically significant difference between patients with and without secondary cancers. However, this may be due to an immortal time bias. Breast was the most common site of secondary cancer (67%) followed by gynecological (7%), colorectal (3.7%), skin (3.4%) lung and hematologic (2.7%) Compared to other subtypes, TNBC patients were found to have much shorter time to secondary cancer development of 38 months compared to Her2+ and ER/PR+ (40 and 45 months respectively, $P < 0.001$). Black and Hispanic individuals were found to have higher rates (7.4% and 6.3%) and earlier development of secondary cancer (76 months and 74 months) as compared to whites and Asians (5.9% and 5%, 88 months and 81 months, $P < 0.001$ and $P < 0.002$ respectively). Conclusion This study identified several risk factors associated with the development of secondary cancers in AYA breast cancer patients such as age at initial breast cancer diagnosis, race, stage, nodal status, surgical procedure and sub-type. Higher rates and early development of secondary cancer were observed among TNBC subtype and Black and Hispanic races that calls for further investigation and tailored interventions to improve outcomes in specific patient populations.

Table 1

		No Secondary Ca	Secondary Ca	P value
	N	45,026 (94.0)	2,886 (6.0)	
Age at BCa	Mean/Std/N	34.8/3.8/45026	34.9/3.8/2886	0.024
Sex	Female	99.7%	99.9%	0.088
Race	White	53.4%	51.9%	<.001
	Black	14.2%	17.7%	
	Asian	11.8%	9.6%	
	Hispanic	19.2%	20.1%	
	Native American	0.8%	0.6%	
	Not Reported	0.6%		
Stage	0	0.1%	0.0%	<.001
	I	27.5%	31.5%	
	II	44.6%	47.6%	
	III	16.5%	12.8%	
	IV	5.4%	2.6%	
Nodes	negative	46.4%	52.4%	<.001
	positive	40.5%	38.4%	
Size (cm)	Mean/Std/N	3.2/2.7/7535	3.3/3.2/54	0.470
Surgery	None	7.0%	4.1%	<.001
	Partial Mastectomy	36.6%	55.5%	
	Total Mastectomy	26.6%	14.2%	
	Radical Mastectomy	28.8%	25.5%	
ER Status	negative	29.2%	34.5%	<.001
	positive	69.7%	64.6%	
PR Status	negative	36.7%	39.7%	0.003
	positive	62.1%	59.4%	
Her2 Status	negative	34.5%	11.6%	<.001
	positive	15.4%	4.9%	
Subtype	HR+/HER2-	25.7%	9.0%	<.001
	HER2+	15.4%	4.9%	
	TNBC	8.8%	2.6%	

Table 1 showing significant differences in characteristics AYA breast cancer patients who developed secondary breast cancer compared to those who did not

PO5-10-08

Clinical Value of Molecular Targets and Genome-Targeted Cancer Therapies Recommended by the National Comprehensive Cancer Network for Advanced Breast Cancer

Presenting Author(s) and Co-Author(s):

A. Tibau. Program On Regulation, Therapeutics, And Law (PORTAL) Division of Pharmacoepidemiology and Pharmacoeconomics Brigham and Women's Hospital and Harvard Medical School, United States

T. Hwang. Cancer Innovation and Regulation Initiative, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, Massachusetts, United States

J. Avorn. Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA, United States

A. Kesselheim. Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA, United States

Background: Genomic testing has expanded the possibilities of precision cancer medicine, particularly for advanced, treatment-resistant breast cancer cases. However, the clinical significance of most genetic alterations remains uncertain, potentially overestimating tailored therapies. The National Comprehensive Cancer Network (NCCN) guidelines are evidence-based cancer-specific recommendations used in clinical practice and that are often determinative for insurance coverage. In this study, we assessed the validity of the targets and the clinical benefit of genome-targeted cancer drugs recommended in the NCCN guidelines for metastatic breast cancer.

Methods: We identified genome-targeted oncology therapies supporting advanced breast cancer recommendations in the most recent NCCN breast cancer guideline (version 4.2023). Genome-targeted drugs were defined as involving use of a genomic test in which the drug targeted a genomic alteration. We analyzed data from trials supporting advanced genome-targeted breast cancer drugs recommendations. When multiple (or overlapping) articles for the same study were identified, the most recent publication was included. We extracted key details of each trial, including trial design, blinding, phase of clinical trial and primary efficacy end points. We cross-referenced the FDA-approved indications as of 30 June 2023 with the NCCN recommendations for each drug. Strength of evidence supporting molecular targetability was evaluated using the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT). Clinical benefit for genome-targeted oncology therapies was assessed using the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). We considered a substantial clinical benefit as a grade of 4 or 5. Molecular targets qualifying for ESCAT category level I-A and I-B associated with substantial clinical benefit by ESMO-MCBS were rated as high-benefit genomic-targeted breast cancer treatments.

Results: We identified 47 recommendations supporting 17 genome-targeted drugs, which targeted 11 driver alterations. Out of these recommendations, 29 (62%) aligned with the FDA indications. We associated 47 trials with these recommendations, most randomized (24, 51%), phase 3 (23, 49%) and open-label (42, 89%). The most common primary endpoint (22, 47%) was overall response rate, followed by progression-free survival/time to progression (21, 45%).

Twenty-four trials (51%) had a I-A ESCAT targetability, 7 (15%) had a I-B targetability, 6 (13%) had a I-C targetability score and 10 (21%) were categorized as II-B. ERBB2 amplification, germline BRCA1/2 mutations, PIK3CA mutations, and ESR1 mutation were mainly classified as tier I-A based on randomized trials demonstrating the effectiveness of approved targeted therapies in patients with these alterations. By contrast, RET fusions, NTRK fusions, high-tumor mutational burden and microsatellite instability were ranked as tier I-C and somatic BRCA mutations, germline PALB2 mutations and HER-2 mutations as II-B. Six trials (14%, 6/42) supporting drug approval demonstrated substantial ESMO-MCBS clinical benefit. Overall, 6 recommendations (14%) had high-benefit genomic-based cancer treatments.

Conclusions: Fewer than one-fifth of molecular-targeted cancer therapies recommended in NCCN guidelines for metastatic breast cancer demonstrated substantial patient benefits. Value frameworks like ESCAT and ESMO-MCBS can help stakeholders identify therapies with the greatest potential.

PO5-10-09

Capturing Experiences: Navigating Breast Cancer Treatment of Nigerian Patients and Healthcare Providers Using Qualitative Interviews

Presenting Author(s) and Co-Author(s):

B. Nwachukwu. University of Illinois Chicago, Chicago, Illinois, United States

E. Papautsky. University of Illinois at Chicago, United States

Introduction

A notable shift has occurred in medical relationships, placing greater emphasis on the role of patients within the healthcare system. A nascent body of literature in the US captures the experiences of patients following a diagnosis, but this is lacking in Nigeria. We used Systems Engineering Initiative for Patient Safety (SEIPS 2.0) as a theoretical framework from the discipline of human factors that serves as a guide for characterizing complex sociotechnical systems comprised of factors, work processes, and outcomes - with the patient and clinicians at the center. We specifically focused on the patient work network, which refers to individuals and communities that play role in supporting patient work. The objective of this study was to elicit the experiences of Nigerian breast cancer patients and healthcare providers by qualitative interviews and characterize productive and counterproductive activities of the patient work network.

Methods

The study was approved by the IRB. We used snowball sampling and social media to recruit Nigerian breast cancer patients and health care providers with experience treating breast cancer. One researcher conducted interviews that lasted 30–60 min using teleconferencing technology and an interview guide developed for this study. Questions for both patients and healthcare providers covered topics such as patient response to diagnosis, barriers and facilitators to care including people and communities within the patient's network. We calculated descriptive statistics for demographics. Using thematic analysis, we carried out the analysis in the following stages: data review, category coding and data extraction, and synthesis and integration of findings.

Results

We interviewed 18 female patients (29-67 yrs old) and 6 healthcare providers (31-42 yrs old; 3 males). Twelve patients received treatment in urban areas and 6 in rural. Four patients had a bachelor's degree. Healthcare providers included primary, specialty, palliative, treatment, diagnostic care. We highlight a subset of the dataset with focus on productive versus unproductive work conducted by family and by religious community, with unproductive defined as potentially having negative impact on the patient and their experience (Table 1).

Providers stated that patients who receive family support exhibit better health outcomes compared to those who do not. Providers shared that religious community can perpetuate patient denial in their diagnosis. Both patients and providers discussed an inclination towards seeking traditional care. Despite recognizing the challenges and pressures faced by patients, providers lacked in-depth understanding of the specific experiences patients encountered.

Conclusion

Our findings highlight the role of family and religious community in conducting activities that are both productive and unproductive facilitating productive activities and its influence on the decision-making process of patients. Alternatively, both family and religious community engage

in activities counterproductive to the patient and their illness. Findings emphasize the importance of comprehensive support systems, education, and targeted interventions to improve the experiences and outcomes of Nigerian breast cancer patients. Effective strategies should address cultural beliefs, empower patients to make informed decisions, and enhance provider knowledge regarding the unique challenges faced by patients within the identified barriers.

Productive versus unproductive work conducted by family and by religious community

	Productive Work	Counterproductive Work
Family	<ul style="list-style-type: none"> ▪ Acquisition of supplies e.g., medication, PPE. ▪ Helps with house chores, meal prep. ▪ Helps with transportation (geographically distant facilities at an average of 3-4 hours) and participate during appointments. ▪ Sourcing informational materials on breast cancer. 	<ul style="list-style-type: none"> ▪ Pressure to utilize traditional medicine as a standard treatment plan. ▪ Decision-making in treatment planning is heavily influenced by individuals providing financial support. ▪ Fear of stigmatization leads to the concealment of diagnoses and a lack of support. ▪ Blame game due to fertility issues, resulting in lack of support.
Religious community/Clergy	<ul style="list-style-type: none"> ▪ Comfort through prayer and guidance from clergy. ▪ Raise funds for treatment. ▪ Building a community of counsellors and support system. 	<ul style="list-style-type: none"> ▪ Misinformed guidance towards seeking medical care and reliance on "miracles." ▪ Providing guidance on treatment plans outside area of expertise.

PO5-10-10

Disparities in Work RVUs for Breast and Prostate Cancer Operations

Presenting Author(s) and Co-Author(s):

N. Khosrowzadeh. University of Miami Miller School of Medicine, United States

K. Chambers. University of Miami Miller School of Medicine, United States

M. Gompels. University of Miami Miller School of Medicine, United States

C. Washington. Sylvester Cancer Center, United States

J. Meshman. University of Miami, United States

Introduction: In a vast array of different methods used to quantify healthcare processes, the Relative Value Unit (RVUs) has become the federal precedent set by the Centers for Medicare and Medicaid Services (CMS) to assign value to different procedures and processes. The current RVU conversion factor in 2023 is \$33.06 per unit. Physician work RVUs, malpractice RVUs (MP RVUs) and practice expense RVUs (PE RVUs) were first implemented in 1992 as a system for assigning payment to physicians while providing administrative budgeting based on clinical and liability expenditures. These values are subject to reevaluation every 5 years at minimum, or as new services become available. The CMS updates its RVU model by consulting the American Medical Association's Specialty Society Relative Value Scale Update Committee (RUC), which controversially sets higher values in certain fields of medicine than others. This article will objectively analyze the RVUs provided by the CMS to surgical oncologists treating breast cancer and compare them to the RVUs compensated to urologists treating prostate cancer, across multiple modalities.

Methods: Work RVUs, practice expense RVUs, and malpractice RVUs were obtained from the CMS 2023 physician fee schedule, using the HCPCS codes to identify the services from their database. Estimated pre-evaluation times, intra-procedure times, immediate post service times, and total procedural times were gathered from the CY 2023 Final Rule Physician Work Time database provided by CMS.

The HCPCS codes used for mastectomy variations were 19301 for partial mastectomy, 19302 for partial mastectomy with lymph node removal, 19303 for a simple complete mastectomy, 19305 for a radical mastectomy, 19306 for an urban type radical mastectomy, and 19307 for a modified radical mastectomy. The HCPCS codes used for armpit lymph nodes were 38740 and 38745 for axillary lymph node dissections.

The HCPCS codes used for prostatectomy variations were 55810 and 55812 for a radical perineal prostatectomy, 55840 and 55845 for a radical retropubic prostatectomy, and 55866 for a laparoscopic retropubic radical prostatectomy. The HCPCS codes used for pelvic lymph nodes were 38571-38573 for laparoscopic lymphadenectomies.

Work RVUs were compared between mastectomy and prostatectomy procedures, and axillary node procedures were compared to those of pelvic lymph nodes. To further assess any true disparities in the values assigned to the operations, a second analysis of work RVUs divided by total operation times were compared between their surgical counterparts.

Conclusion: Values collected from CMS indicate 59% more RVUs are provided to urologists for prostatectomies than breast surgeons for mastectomies per procedure, and 12% more per hour of total procedure time. Additionally, the CMS indicates on average 29% more work RVUs are provided to urologists for pelvic lymph node removals than breast surgeons for axillary lymph

node removals, and 3.4% more per hour of total procedure time (appendix 1). Breast cancer and prostate cancer have similar incidence and mortality rates, but one affects mostly women and the other only men. The decision by the Center of Medicare and Medicaid Services to place a higher value in prostate cancer management is unknown, and elicits future analysis with surveyed procedural data across the nation for statistical significance determination.

Appendix 1

HCPCS Code	Short Description	Work RVU	Fully Implemented Non-FAC PE RVU	Fully Implemented Facility PE RVU	MP RVU	Pre Evaluation Time (min)	Pre Positioning Time (min)	Pre Service Scrub Dress Wait time (min)	Median Intra Service Time (min)	Immediate Post Service Time (min)	Total Time (min)	Work RVU/Total Time (min)	Work RVU/Total Time (hours)
Mastectomy													
19301	Partial mastectomy	10.13	7.18	7.18	2.48	30	10	15	60	20	216	0.0469	2.81
19302	P-mastectomy w/ln removal	13.99	9.74	9.74	3.44	40	3	15	100	20	276	0.0507	3.04
19303	Mast simple complete	15	10.01	10.01	3.67	40	3	15	90	30	283	0.053	3.18
19305	Mast radical	17.46	12.74	12.74	4.3	44	0	25	137	26	463.5	0.0377	2.26
19306	Mast rad urban type	18.13	13.91	13.91	4.54	50	0	25	166	29	544.5	0.0333	2
19307	Mast mod rad	17.99	12.93	12.93	4.43	40	10	15	120	30	343	0.0524	3.15
Averages	Average Mastectomy	15.45	11.085	11.085	3.81						354.333333	0.04566667	2.74
Breast LN													
38740	Remove armpit lymph nodes	10.7	7.71	7.71	2.61	60	0	0	60	30	231	0.0463	2.8
38745	Remove armpit lymph nodes	13.87	9.15	9.15	3.37	57.5	0	0	90	25	270.5	0.0513	3.08
Averages	Average Axillary LN	12.285	8.43	8.43	2.99						250.75	0.0488	2.94
Prostatectomy													
55810	Prostatectomy rad perineal	24.29	11.23	11.23	2.88	42	0	25	186	25	515	0.0472	2.83
55812	Prostatectomy rad perineal	29.89	13.77	13.77	3.57	46	0	25	262	31	684	0.0437	2.62
55840	Prostatectomy rad retropubic	21.36	10.48	10.48	2.55	33	3	15	180	33	448	0.0477	2.86
55845	Prostatectomy rad retropubic	25.18	11.8	11.8	3.02	33	3	15	198	33	466	0.054	3.24
55866	Laps surg prstsect rpbic rad	22.46	10.04	10.04	2.68	40	15	12	180	50	362	0.062	3.72
Averages	Average Prostatectomy	24.64	11.46	11.46	2.94						495	0.0509	3.06
Pelvic LN													
38571	Laparoscopy lymphadenectomy	12	6.04	6.04	1.54	40	3	10	90	30	250	0.048	2.88
38572	Laparoscopy lymphadenectomy	15.6	8.88	8.88	2.45	40	15	15	120	30	321	0.0486	2.92
38573	Laps pelvic lymphadec	20	11.63	11.63	3.35	40	13	15	180	30	360	0.0556	3.33
Averages	Average Pelvic LN	15.87	8.85	8.85	2.45						310.33	0.0507	3.04

allocated work RVUs, practice expense RVUs, malpractice RVUs, and median operative times for prostate cancer and breast cancer operations.

PO5-10-11

BREAST CANCER DIAGNOSIS AND TREATMENT AMONG DISPLACED AND HOST POPULATIONS IN NORTH-WEST SYRIA

Presenting Author(s) and Co-Author(s):

A. Chagpar. Yale University, New Haven, Connecticut, United States

A. Abbara. Syrian-American Medical Society, United States

A. Alshemali. Faculty of medicine University Free Aleppo, United States

F. Alahdab. Houston Methodist Academic Institute, United States

M. Hamze. Syrian-American Medical Society, United States

B. Attassi. Syrian-American Medical Society, United States

J. Alawa. Stanford University, United States

S. Cech. Yale University, United States

L. Tang. Yale University, United States

K. Khoshnood. Yale School of Public Health, United States

INTRODUCTION: The protracted Syrian conflict has forcibly displaced more than half the pre-conflict population of 22 million people with 6.7 million IDPs (internally displaced people.) 80% of IDPs are women and children. Given a lack of humanitarian funding for oncology services, NGOs like the Syrian-American Medical Society (SAMS), have used private funding to establish oncology services. We sought to explore differences in breast cancer diagnosis and treatment among IDPs and host populations in SAMS oncology centre in Idlib governorate.

METHODS: Charts of women seen diagnosed with breast cancer at the SAMS Oncology Centre in Idlib governorate between March 2018 and February 2021 were reviewed. Clinicopathologic data was extracted, and non-parametric statistical analyses were performed to compare citizens vs. those who were displaced.

RESULTS: Data for 188 patients were available; for 108/188 (57%) details of IDP versus host status was available. 61/108 (56%) were IDPs, 47 (44%) were host. The median age at diagnosis was similar between citizens and those who were displaced. Further, the clinicopathologic features and treatment between these two groups were similar. The time between onset of symptoms and diagnosis was similar between the host population and IDPs (median 125.5 days vs. 77 days, respectively, $p=0.255$), although there was a trend towards a shorter time from diagnosis to initiation of treatment for IDPs (median 19 days vs. 14 days, $p=0.051$).

CONCLUSION: From this cohort study, it is notable that there were no significant differences in the tumor size, node positivity or grade at diagnosis. Further, although IDPs are usually considered to have more challenging access to healthcare services compared to host populations, it was notable that there was no significant difference between the time of onset of symptoms to diagnosis between the two groups, and a trend towards a shorter time to treatment. Although this may be related to the relatively small sample size, it may also reflect other commitments of host populations (e.g., employment) that may delay care, or the work of humanitarian organizations in reaching displaced populations. Further, given that in northwest Syria, more than 65% of the 4-4.6 million people in the area are IDPs, access to care between the two groups may be similar. Further work is required to explore this.

Feature	Host	IDP	p-value
Median age at diagnosis	50	43	0.109
Median tumor size	4.5	4	0.164
Node positive	34 (81.0%)	47 (83.9%)	0.790
Median number of positive nodes	4	4	0.963
Grade 3	12 (31.6%)	17 (37.8%)	0.673
Triple negative	5 (10.9%)	3 (5.5%)	0.463

PO5-11-01

Audit of multidisciplinary team meetings for improving breast cancer care

Presenting Author(s) and Co-Author(s):

K. Sharma. AIIMS, New Delhi, New Delhi, Delhi, India

G. Puri. AIIMS, New Delhi, New Delhi, Delhi, India

Introduction: Multidisciplinary team (MDT) meeting is a well-established method of optimising care for breast cancer patients. However, its effectiveness has not been proven yet. The present study aims to audit the functioning of MDT at a tertiary care hospital in a low-middle income country. **Methods:** This study examines the prospectively maintained database of patients being discussed in MDT meetings occurring from August 2018 till June 2023. The MDT was suspended for few months in between owing to the COVID pandemic. The analysis was done in terms of indications of discussion, referring department, modification in the pre-MDT plan, new investigation advised, radiological and pathological concordance, significant change in management strategy and interesting cases. The analysis is both qualitative and quantitative. Quantitative analysis involves percentages, mean and median. **Results:** MDT at our institute was conducted every Saturday at 12 noon as an in-person meeting. The MDT was suspended from May 2020 till June 2021 in view of the pandemic. It was restarted in July 2021, on an online platform and is continued as such. A total of 473 cases were discussed with 181 (38.2%) benign causes and rest were malignant. The most common indication of discussion for malignant cases was feasibility of breast conservation (59.9%) followed by ruling out recurrence/residual disease (17.4%). The indication for benign cases was rad-path concordance and ruling out phyllodes in a case of fibroepithelial lesion. In 31.4% of the cases the plan was modified from the pre-MDT plan and there was improved care. 34.7% cases were advised to get a new investigation done in form of contrast enhanced mammogram or MRI. Seventy nine percent cases were feasible for BCS, and it was done involving few complex surgeries as well. The most common indication for deferring BCS was extensive DCIS. The total number of man hours spent in preparation as well as MDT were analysed with improved clinical care and revealed the MDT to be a time intensive exercise with poor efficacy in terms of hours spent per patient. The time to decision making was increased at an average of 7.5 days for these patients. **Conclusion:** MDT helps to achieve goals of superior clinical care for both benign and malignant breast disorders at the cost of increased time to decision. It is labour intensive with capability of changing decision in one third of the cases. However, MDT needs regular audit to ensure optimum care with available resources.

PO5-11-03

Associations among BMI and patient-reported body image dissatisfaction after breast reconstruction

Presenting Author(s) and Co-Author(s):

S. Bouhali. University of Houston, Sugar Land, Texas, United States

N. Noufail. University of Houston, Sugar Land, Texas, United States

T. Chen. University of Houston, United States

M. Bordes. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

G. Reece. MD Anderson Cancer Center / Department of Plastic and Reconstructive Surgery, United States

M. Markey. The University of Texas at Austin, Austin, Texas, United States

F. Merchant. University of Houston, Houston, Texas, United States

D. Chopra. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

INTRODUCTION

Breast reconstruction surgery helps women restore their physical appearance and contributes to overall well-being. We assessed body image concerns in the context of breast reconstruction using patient-reported outcome measures: Body Image Scale (BIS), Brief Symptom Inventory (BSI), Appearance Schemas Inventory (ASI-R), and BREAST-Q. Since obesity is known to be associated with body image dissatisfaction¹, body size may influence a patient's adjustment to bodily changes arising from breast cancer and its treatment. Thus, we investigated the associations among BMI and patient-reported body image dissatisfaction after immediate autologous breast reconstruction.

MATERIAL AND METHODS

Patients undergoing breast reconstruction surgery were enrolled in an IRB approved study from 2011 to 2014 at The University of Texas MD Anderson Cancer Center. Participants (N=44) included patients who underwent immediate autologous (DIEP/TRAM) reconstruction and completed the BIS, BSI, ASI-R, and BREAST-Q, both preoperatively and postoperatively at 12+ months. Descriptive statistics including means, standard deviations, and medians were used to summarize continuous variables, while frequencies and percentages were used to summarize the categorical clinical and demographic characteristics. Univariate analyses were conducted to identify potential factors among preoperative variables for subsequent multivariable regression analysis: age, race, ethnicity, BMI, laterality, BIS, BSI, ASI-R, BREAST-Q psychosocial wellbeing score (PWBS), and BREAST-Q satisfaction with breast score (SWBS). Factors with a t test p-value \leq 0.2 were considered potential predictive variables for the postoperative dependent variables BIS, BREAST-Q PWBS, and BREAST-Q SWBS. Multivariable linear regression models were used to assess the relationship between the dependent and the selected predictive variables. A multivariable linear regression model was fitted using stepwise selection procedure, and the model with the highest adjusted R-squared value and the lowest Akaike information criterion (AIC) was chosen. All tests were two-sided with p-value $<$ 0.05 considered statistically significant, and for each significant predictor, we report the unstandardized coefficient β . Analyses were performed using SPSS 29.0.0 and SAS 9.4.

RESULTS

Results from the selected models are summarized in Table 1. Age and BMI were significant predictors for postoperative BIS score. Older patients and those with BMI categorized as overweight and obese tend to feel less dissatisfied with their body image after immediate autologous breast reconstruction compared to patients with healthy BMI. Preoperative BSI anxiety was identified as significant predictor for postoperative BREAST-Q PWBS, i.e., patients with higher preoperative anxiety scores tend to have lower postoperative BREAST-Q PWBS. Preoperative BSI anxiety and laterality were significant predictors for postoperative BREAST-Q SWBS. Patients with higher preoperative anxiety scores tend to be less satisfied with their breasts after immediate autologous reconstruction and patients who underwent unilateral reconstruction tend to be less satisfied with their breasts postoperatively compared to patients with bilateral reconstruction.

CONCLUSION

Women with higher BMI may experience improved body image after undergoing immediate autologous breast reconstruction, as compared to women with healthy BMI. The use of BIS may provide more insight to plastic surgeons compared to relying solely on the body image correlates provided by the BREAST-Q. Moreover, body image counseling can be beneficial for individuals across all BMI categories, including those with healthy BMI.

REFERENCES

1. Weinberger, N.A., et al., Body Dissatisfaction in Individuals with Obesity Compared to Normal-Weight Individuals: A Systematic Review and Meta-Analysis. *Obes Facts*, 2016. 9(6): p. 424-441.

Table 1:

Dependent Variable (Postoperative)	R ² (AIC)	Predictors	coefficients (β)	Std Error	t	p-value	95.0% Confidence interval for β
BIS (130.48)	0.437	(Intercept)	13.399	2.542	5.270	<0.001	8.227 to 18.572
		Age	-0.412	0.092	-4.489	<0.001	-0.598 to -0.225
		BMI group					
		Healthy	reference				
		Overweight	-9.034	2.756	-3.278	0.002	-14.641 to -3.428
Obese	-5.844	2.755	-2.121	0.042	-11.449 to -0.239		
BREAST-Q PWBS (265.86)	0.210	(Intercept)	76.469	3.361	22.750	<0.001	69.652 to 83.286
		Preoperative BSI Anxiety score	-2.921	-	-3.522	0.001	-4.603 to -1.239
				0.829			
BREAST-Q SWBS (267.34)	0.205	(Intercept)	75.259	4.175	18.027	<0.001	66.783 to 83.734
		Preoperative BSI Anxiety score	-2.812	-	-3.582	0.001	-4.405 to -1.218
		Laterality					
		Bilateral	reference				
		Unilateral	-13.311	6.432	-2.069	0.046	-26.369 to -0.253

Table for reporting selected multivariable linear regression models; (a) Postoperative BIS with explanatory variables age and BMI category, (b) Postoperative BREAST-Q PWBS with explanatory variable Preoperative BSI anxiety score, (c) Postoperative BREAST-Q SWBS with explanatory variables Preoperative BSI anxiety score and laterality.

PO5-11-04

Sexuality and fertility profiles, Health-Related Quality of Life and other living conditions of young breast cancer survivors in France: a national cross-sectional study by the French Network of Cancer Registries (FRANCIM)

Presenting Author(s) and Co-Author(s):

E. Assogba. Breast and Gynaecologic Cancer Registry of Côte d'Or, Epidemiology and Quality of Life Research Unit, Georges François Leclerc Comprehensive Cancer Centre - UNICANCER, Dijon Cedex, Bourgogne, France

C. Mollévi. Département de l'Information Médicale - Unité de Recherche Clinique & Epidémiologie - CHU Montpellier – Hôpital La Colombière, United States

A. Woronoff. Cancer Registry of Doubs, Besançon University Hospital, United States

A. Dumas. Clinical Epidemiology and Economic Evaluation Applied to Vulnerable Populations (Epidémiologie Clinique et Évaluation Économique appliquée aux Populations Vulnérables [ECEVE])—INSERM UMR 1123, University of Paris—Site Villemin, United States

A. Mamguem. Centre Georges François Leclerc, Dijon, United States

C. COUTANT. Centre Georges-François Leclerc, France

I. Desmoulins. Centre Georges-François Leclerc, Dijon, France

S. Ladoire. Centre Georges François Leclerc, France

S. Dabakuyo. Centre George François Leclerc, Dijon, France

Introduction In recent decades, the living conditions of breast cancer (BC) survivors have received particular attention, especially among the youngest who face problems related to fertility and sexuality. The main objective of this population-based study was to identify clinical, social and economic determinants of sexuality, fertility and Health Related Quality of Life (HRQoL), and describe other living conditions of young BC survivors in France. **Methods** Non-metastatic invasive BC women diagnosed from 2009 to 2016, aged ≤ 40 years at diagnosis were identified through the FRANCIM Network. Participants completed self-reported questionnaires including standardized measures (sexuality, HRQoL, anxiety, depression, social deprivation and social support), and fertility issues from June 2021 to December 2022. Sexuality profiles were identified by ascending hierarchical classification and fertility profiles were identified by latent class models. The main determinants of HRQoL were identified using mixed regression model. **Results** In total, 563 BC survivors from 14 French cancers Registries participated in the survey (response rate of 31%). The mean age at diagnosis was 35.9 (SD=3.8). Main tumors characteristics were AJCC stage 2-3 (61%), Hormone Receptor positive (76%), HER2 positive (24%), and Tumor grade ≥ 2 (91%). Patients underwent lumpectomy (72%), chemotherapy (85%), radiotherapy (85%), endocrine therapy (71%) and targeted therapies (23%). More than 5 years after diagnosis, 48% reported sexual dysfunction. About 47% of women received information about the impact of BC treatment on fertility, and 34% about fertility preservation. Among 18% of women who had a pregnancy project at diagnosis, 35% became pregnant after treatment. The number of spontaneous pregnancies decreases from 97% before diagnosis to 36% after treatment whereas the number of pregnancies with Medically Assisted procreation increases respectively from 8% to 10%. The average score of general health scale was 60.9. The highest average score of HRQoL was in the physical functioning scale (82.2) and the lowest was in vitality (48.2). Ascending hierarchical clustering allowed to identify 3 distinct sexuality profiles from worse sexual function to better respectively: profile 1 (20%), profile 2 (30%) and profile 3 (50%) of the studied population. Social deprivation

and treatment with endocrine therapy (especially tamoxifen) were associated with an increased risk of sexual dysfunction. We identified 3 classes using a latent class model. In class 1, women had a pregnancy project at diagnosis but few of them had children and were referred to a reproduction specialist. At the end of treatments, the pregnancy rate was high in this group. Class 2 includes women who have a pregnancy project at diagnosis and who have given up at the end of treatment. At diagnosis, women in class 3 had children and had no specific pregnancy plans and they were menopausal at time of study with therefore a low rate of pregnancy after treatments. Classes differed in age at diagnosis ($p=0.0000$), fertility preservation ($p=0.0000$), information received about treatment impact on fertility ($p=0.0002$) and fertility preservation ($p=0.0000$), comorbidities ($p=0.0040$) and income ($p=0.0000$). The main determinants of general health were anxiety ($p=0.0006$), depression ($p<0.0001$) and comorbidities ($p=0.0065$). Conclusions This study showed that more than five years after the diagnosis of BC, almost one in two young BC survivors, diagnosed before 40 years old, experienced difficulties related to sexuality. Specific interventions in the field of supportive care (recourse to specialists, psychological support and improvement of communication within the couple) for this population should focus in managing sexual dysfunction and improving HRQoL. It would also be suitable for women to receive the necessary information on fertility at diagnosis in order to prepare them for after cancer.

PO5-11-05

Fertility, sexuality and other unmet needs of young breast cancer survivor during and at the end of treatment in France : a national qualitative study by the French Network of Cancer Registries (FRANCIM)

Presenting Author(s) and Co-Author(s):

E. Assogba. Breast and Gynaecologic Cancer Registry of Côte d'Or, Epidemiology and Quality of Life Research Unit, Georges François Leclerc Comprehensive Cancer Centre - UNICANCER, Dijon Cedex, Bourgogne, France

A. Dumas. Clinical Epidemiology and Economic Evaluation Applied to Vulnerable Populations (Epidémiologie Clinique et Évaluation Économique appliquée aux Populations Vulnérables [ECEVE])—INSERM UMR 1123, University of Paris—Site Villemin, United States

C. Morgny. Regional Health Observatory Burgundy Franche-Comté, United States

M. Borel. Regional Health Observatory Burgundy Franche-Comté, United States

V. Brun. Regional Health Observatory Burgundy Franche-Comté, United States

N. Nicolas Meunier-Beillard. Clinical Investigation Center - CIC INSERM 1432 - EC Module (Clinical Epidemiology) - Faculty of Medicine and Pharmacy, Burgundy Franche-Comté University, United States

A. Mamguem. Centre Georges François Leclerc, Dijon, United States

C. COUTANT. Centre Georges-François Leclerc, France

I. Desmoulins. Centre Georges-François Leclerc, Dijon, France

S. Dabakuyo. Centre George François Leclerc, Dijon, France

Introduction In recent decades, the living conditions of breast cancer (BC) survivors have received particular attention, especially among the youngest who face problems related to fertility and sexuality. Integrating women's needs into medical decisions is becoming increasingly essential for high-quality care. This study aimed to describe and understand the experiences of young women after BC, examined the scope and content of information transmitted on fertility and sexuality during routine appointments during the management of BC, and identify unmet support needs. **Methods** This study follows on from a quantitative study using self-questionnaires, in which patients met the following inclusion criteria (Non-metastatic invasive BC women diagnosed from 2009 to 2016, aged ≤ 40 years at diagnosis were identified through the FRANCIM Network). Interviews were conducted with a sample of 29 women drawn at random from among eligible women who completed the self-questionnaires in the quantitative study. The sample were stratified by age, department, socio-professional category and socio-economic level. Individual face-to-face semi-structured interviews were conducted either by videoconference or face-to-face, in patient's homes or in any other location of their choice during October to December 2022. The interviews were audio-recorded, transcribed verbatim, and analyzed thematically. **Results** Findings revealed that during treatments, women would like physicians (oncologists, surgeons, radiologists, gynecologist, etc.) to be more empathetic, more humane, and show tact and attentiveness when announcing the disease and treatments during the course of care. They would like to be better informed about the post-treatment side effects and better prepared by the physicians, for the feeling of abandonment felt in the aftermath of cancer due to the absence of medical appointments. The mains unmet needs of BC survivors were more numerous at the end of the treatments. In fact they more deplore the lack of coverage and reimbursement of aesthetic care and paramedical care essential to women to compensate for the persistent side effects and the repercussions of the

disease and post-cancer treatments (eg: a more aesthetic and better reimbursed breast reconstruction at the end of the treatments, support by psychologists, etc.). With regard to sexuality, in the absence of systematic information for patients on the side effects of treatments on sexuality at diagnosis, it would be desirable to ask the woman if she would like to be informed. In addition, psychological support for the couple during and after treatment in terms of sexuality is necessary to avoid divorce and separation. In terms of fertility, there is a lack of systematic information for young women on the side effects of treatment on fertility, as well as questioning by physicians about any pregnancy plans women may have at the time of diagnosis. The introduction of fertility preservation with the possibility of it being systematically offered to all young women at diagnosis is important (or, failing that, the subject should be discussed more with the women), as it represents a gap in support). For women who had a pregnancy plan at diagnosis, the majority felt a lack of listening by doctors and adaptation of care to their pregnancy plan at diagnosis. **Conclusions** This study showed that, despite the high quality of care provided to young women diagnosed with BC in France, they felt they had unmet needs in terms of sexuality, fertility and access to paramedical care at the end of treatment. Indeed, these women face psychological suffering that they would like physicians to see beyond their physical suffering based on their experience. The results of this study could help public authorities and physicians improve care and life after cancer for young women diagnosed with BC.

PO5-11-06

Initial Results from a Cohort Study on the Impact of Breast Cancer on Employment in Mexican Patients

Presenting Author(s) and Co-Author(s):

A. Ramirez-Cisneros. Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, United States

D. Gonzalez-Sanchez. Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, Mexico

D. Vazquez-Juarez. Breast Cancer Center, Hospital Zambrano Hellion TecSalud, United States

A. Platas. Instituto Nacional de Cancerología, United States

A. Platas. Breast Medical Oncology Department, Instituto Nacional de Cancerología, Mexico

F. Mesa-Chavez. Hospital Zambrano Hellion - TecSalud, Tecnologico de Monterrey, Nuevo Leon, Mexico

G. Carrillo. Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, Mexico

C. Villarreal-Garza. Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, Mexico

BACKGROUND

As breast cancer (BC) survival has increased, care must focus beyond the traditional role of curing a disease and provide further attention to patients' quality of life. In Mexico, women represent an important part of the labor force; and the impact of BC diagnosis and treatment on patients' employment status has not been thoroughly evaluated. This study shows the initial results of a nation-wide effort to understand the changes in the employment status of Mexican BC patients after their initial treatment.

METHODS

An online survey was created and distributed in June 2023 through the social media networks of Médicos e Investigadores en la Lucha Contra el Cáncer, a BC NGO. BC patients who had initiated treatment and lived in Mexico were invited to participate. The survey consisted of multiple-choice questions and the opportunity to explain certain responses. Results were analyzed using REDCap, Excel and SPSS.

RESULTS

67 patients completed the survey and were employed: 51% had a full-time job, 33% were self-employed, and 16% had a part-time job. Their average age was 50 years (25-68). Only 43% reported having medical insurance from their jobs; of these, 83% included cancer treatment.

Most participants (39, 58%) reported having support from their bosses and co-workers at the moment of diagnosis, 13 (19%) did not disclose their diagnosis in their workplace, 10 (15%) perceived an indifferent attitude, and 5 (7%) reported lack of support. Table 1 describes the changes in work status during their initial part of treatment (including surgery, chemotherapy, radiation).

After their treatment ended, from the 67 who were initially employed, 34 (51%) patients became unemployed, 26 (39%) were employed, and 7 (10%) were employed with temporary disability. Of the 26 employed patients, 12 (46%) had a full-time job, 7 (27%) had a part-time job and 5

(19%) were self-employed. Of those who were unemployed, 14 (41%) were actively looking for a job.

Of the 26 employed participants, 17 (65%) worked at the same place they did before BC diagnosis, 6 (23%) worked at a different place, and 1 (4%) had a second job. Reintegration for most patients was gradual (15, 58%) or immediate (7, 27%). The majority (18, 69.2%) felt supported by their workplace during reintegration. Of note, 11 (42%) patients described having to decrease their work hours/load.

When asked about their disease as an obstacle in their work, 8 (31%) patients had to slow down their job rhythm, 8 (31%) had to endure symptoms while working, 6 (23%) had no impediments, and 2 (8%) could only do partial work. Most patients (21, 81%) reported having permits to attend medical consultations or receive treatment, and 9 (35%) mentioned having salary discounts due to their medical appointments. The main motivations to return to work were economic need (11, 42%), returning to “normal life” (10, 39%) and personal growth (3, 12%).

Of the 67 patients that were employed before their BC diagnosis, 44 (66%) considered their current health status as an obstacle for their reintegration into the workforce. Moreover, 25 (37%) considered not having any limitations, but 20 (30%) and 14 (21%) reported physical and psychological limitations, respectively, as impediments to their successful reintegration.

CONCLUSION

BC can represent an obstacle when returning to “normalcy”, given the psychological and physical burden that the diagnosis and its treatment entail. In this study, half of the participants became unemployed upon finishing their BC treatment. This study represents the first necessary step to design strategies that favor the continuation and successful laboral reintegration of BC patients who wish to do so.

Table 1: Change of work status during BC treatment

Type of change in work status	n=67	
Resignation	16	24%
Work accommodation (eg. reduced hours)	14	21%
Firing /laid off	6	9%
Permanent disability/Retirement	2	3%
Temporal disability with pay	9	13%
Temporal disability without pay	9	13%
Transition to home office	4	6%
No change	7	11%

BC: Breast Cancer

PO5-11-07

Short- and long-term treatment-related effects on physical health in breast cancer survivors

Presenting Author(s) and Co-Author(s):

C. Bodelon. American Cancer Society, United States

M. Masters. American Cancer Institute, United States

L. McCullough. American Cancer Society, United States

A. Patel. American Cancer Society, United States

L. Teras. American Cancer Society, United States

Background. Breast cancer (BC) survivors experience greater physical health declines compared to cancer-free women of the same age, which is thought to be caused by their cancer and its treatment. However, the short- and long-term effects of different types of treatment on physical health are not well understood, especially for hormone therapy. Moreover, whether specific aspects of physical health, such as activities of daily living (ADL), are affected by treatment is unknown. **Methods.** This analysis was conducted in the Cancer Prevention Study 3 (CPS-3), a prospective cohort study with approximately 300,000 participants enrolled between 2006-2013. Participants returned a baseline survey and triennial follow-up surveys beginning in 2015. Incident, non-metastatic, female BC patients were included in this analysis if they returned a survey at least 90 days after their diagnosis through June 30, 2020, the end of follow-up for this analysis. All 2,551 BC patients included in this study had pre- and post-diagnostic surveys and underwent breast surgery if they were diagnosed with invasive disease. They were matched to up to five cancer-free women on age and year of survey returns (N=12,704). Self-reported physical health and ADL were assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Scale instrument. Treatment information was obtained from cancer registries and self-report and included surgery, chemotherapy, radiation and hormonal therapy. Odds Ratios (OR) and 95% confidence intervals (CI) between treatment received and self-reported physical function were estimated using multivariable ordinal logistic regression models at three time points relative to the case's diagnosis date: before diagnosis, within 90 days to 5 years after diagnosis, and more than 5 years after diagnosis. **Results.** Median age at diagnosis was 56 years (interquartile range (IQR): 50-62). Approximately 82% of the tumors were hormone-receptor positive. The median times from the three physical health measurements to diagnoses were 1.7 years before diagnosis (IQR: 0.9 – 2.7), 1.7 years (IQR: 0.9 – 2.5) from 90 days to 5 years post-diagnosis and 6.6 years (IQR: 5.5-7.0) for more than 5 years post-diagnosis. There was a significant risk of physical decline within 5 years of diagnosis for women who received chemotherapy or hormonal therapy compared to cancer-free women (Table 1). However, more than 5 years after diagnosis, the risk of physical decline was only observed among those who received chemotherapy. Treatment combinations that included chemotherapy were also associated with a decline in the ability to carry out ADL during the first 5 years. Patients who received hormonal therapy without chemotherapy were comparable to cancer-free women in their ability to carry out ADL during the post-diagnosis period. BC patients who received surgery only or surgery and radiation reported physical health and ADLs similar to cancer-free women within 5 and >5 years after diagnosis. **Conclusions.** Post-diagnosis physical health decline is time and treatment dependent. Patients receiving chemotherapy have the greatest overall physical health decline and it is long-lasting. Beyond five years from diagnosis, physical health of breast cancer patients who did not receive chemotherapy were similar to cancer-free women. Strategies are

needed to help BC patients receiving chemotherapy overcome the long-term physical function limitations of their cancer treatment.

Associations between treatment received and physical health and ability to carry out activities of daily living.

	Pre-diagnosis		90 days to ≤ 5 years post-diagnosis		> 5 years after diagnosis	
	N (%)	OR (95% CI)*	N (%)	OR (95% CI)*	N (%)	OR (95% CI)*
Physical health						
Cancer free	12,771 (84.6)	1.00 (reference)	11,956 (84.6)	1.00 (reference)	2,646 (84.5)	1.00 (reference)
Surgery only	260 (1.7)	0.81 (0.63, 1.04)	239 (1.7)	1.07 (0.84, 1.36)	60 (1.9)	1.04 (0.65, 1.68)
Surgery + radiation	138 (0.9)	0.83 (0.59, 1.17)	130 (0.9)	1.30 (0.94, 1.79)	35 (1.1)	1.09 (0.57, 2.08)
Surgery + chemo	83 (0.5)	1.96 (1.28, 3.02)	78 (0.6)	3.98 (2.62, 6.07)	17 (0.5)	2.41 (1.05, 5.54)
Surgery + hormone	291 (1.9)	0.97 (0.77, 1.22)	276 (2.0)	1.74 (1.39, 2.16)	51 (1.6)	0.96 (0.58, 1.59)
Surgery + radio + chemo	162 (1.1)	1.14 (0.85, 1.54)	148 (1.0)	2.74 (2.02, 3.72)	36 (1.1)	2.78 (1.48, 5.22)
Surgery + radio + horm	810 (5.4)	1.01 (0.87, 1.16)	769 (5.4)	1.71 (1.49, 1.96)	156 (5.0)	1.07 (0.79, 1.45)
Surgery + chemo + horm	150 (1.0)	1.34 (0.96, 1.86)	138 (1.0)	3.28 (2.36, 4.55)	33 (1.1)	3.37 (1.81, 6.32)
Surgery + radio + chemo + horm	436 (2.9)	1.35 (1.12, 1.63)	403 (2.9)	2.86 (2.38, 3.44)	99 (3.2)	1.99 (1.37, 2.89)
Activities of daily living						
Cancer free	4,706 (84.7)	1.00 (ref)	1,222 (84.0)	1.00 (ref)	2,545 (84.3)	1.00 (ref)
Surgery only	90 (1.6)	1.17 (0.67, 1.92)	31 (2.1)	1.34 (0.99, 1.78)	58 (1.9)	1.05 (0.56, 1.87)
Surgery + radiation	42 (0.8)	0.68 (0.26, 1.51)	13 (0.9)	1.24 (0.82, 1.82)	35 (1.2)	1.04 (0.44, 2.20)
Surgery + chemo	17 (0.3)	0.34 (0.02, 1.68)	12 (0.8)	1.25 (0.71, 2.12)	17 (0.6)	1.64 (0.58, 4.13)
Surgery + hormone	108 (1.9)	0.98 (0.58, 1.56)	24 (1.6)	1.09 (0.81, 1.45)	51 (1.7)	0.90 (0.44, 1.70)
Surgery + radio + chemo	64 (1.2)	0.90 (0.34, 2.04)	18 (1.2)	2.19 (1.56, 3.05)	35 (1.2)	2.75 (1.42, 5.14)
Surgery + radio + horm	332 (6.0)	1.18 (0.90, 1.53)	72 (4.9)	1.14 (0.96, 1.35)	151 (5.0)	0.93 (0.62, 1.36)
Surgery + chemo + horm	37 (0.7)	2.00 (1.17, 3.30)	19 (1.3)	1.72 (1.17, 2.47)	32 (1.1)	1.75 (0.82, 3.51)
Surgery + radio + chemo + horm	161 (2.9)	1.27 (0.86, 1.83)	44 (3.0)	2.23 (1.82, 2.73)	96 (3.2)	1.35 (0.85, 2.08)

OR: Odds Ratio; CI: confidence interval; chemo: chemotherapy; radio: radiation therapy; horm: hormonal therapy.

*Associations were adjusted for matching factors, which included age and time from diagnosis to measurement of physical health.

PO5-11-08

Assessing practice patterns of antidepressant medication and tamoxifen use among patients with hormone receptor-positive breast cancer

Presenting Author(s) and Co-Author(s):

M. Ondeck. Cleveland Clinic Foundation, United States

B. Osantowski. Cleveland Clinic Foundation, United States

N. Lopetegui-Lia. Cleveland Clinic Foundation, Cleveland, Ohio, United States

W. Wei. Cleveland Clinic, United States

A. Murray. Cleveland Clinic Foundation, United States

A. Maggiotto. Cleveland Clinic Foundation, United States

H. Moore. Cleveland Clinic, United States

E. Roesch. Cleveland Clinic, Ohio, United States

Background:

Treatment with endocrine therapy such as tamoxifen has been identified as one of the most important variables linked with survival among women with hormone receptor-positive breast cancer (BC). There is significant risk reduction of BC recurrence and BC mortality at 15 years among patients treated with tamoxifen for 5 years compared to no endocrine therapy. Tamoxifen is metabolized in the liver via multiple cytochrome P (CYP) isoforms. To ensure optimal efficacy of tamoxifen, consideration must be given to concomitant use of other commonly prescribed drugs such as antidepressants. Some selective serotonin reuptake inhibitors (SSRIs) are potent inhibitors of CYP2D6, an enzyme that metabolizes tamoxifen into its active metabolite, endoxifen, which has anti-tumor effect. Such inhibition can reduce the plasma concentration of endoxifen which could lead to higher rates of BC recurrence. This resulted in an FDA black box warning discouraging concurrent prescriptions of tamoxifen and SSRIs, yet clinical data to support this warning is lacking.

Our aim is to describe the practice patterns of concomitant use of tamoxifen and antidepressant medication at our institution.

Methods:

This is a single institution retrospective study that included adult women, ages 18-99, with stage I-IV BC, who received adjuvant tamoxifen and were taking an antidepressant medication between years 2016-2021. Patients were identified from a tumor registry database. Patient demographics and tumor characteristics were collected via electronic medical record.

Results:

A total of 419 patients met the inclusion criteria. At the start of tamoxifen therapy, 348 women were on at least one antidepressant, mostly for Major Depressive Disorder (86%). Of those women, 22% were prescribed a strong/moderately potent CYP inhibitor (paroxetine, fluoxetine, duloxetine, or bupropion) and 43% were prescribed weak or non-CYP inhibiting SSRIs (citalopram, escitalopram, fluvoxamine, and sertraline). The most commonly prescribed antidepressants at the start of tamoxifen, alone or in combination with a second antidepressant, were: venlafaxine (30%), escitalopram (17%), sertraline (13%), citalopram (12%) and duloxetine (10%). Main prescribers of antidepressants were primary care physicians (70%), psychiatrists (10%) followed by academic medical oncologists (7%) and regional medical

oncologists (6%). Interestingly, the majority of women continued taking the same antidepressant after starting tamoxifen (76%) while, at least 10% of patients changed antidepressant classes prior to starting tamoxifen, due to concern for drug-drug interaction. When a different class of antidepressant was chosen after starting tamoxifen (22%), serotonin and norepinephrine reuptake inhibitors (SNRIs) were the most frequent class (48%), followed by a different SSRI (42%). The time in which the antidepressant change occurred was variable, but most commonly prior to initiating tamoxifen.

Conclusion:

Concurrent use of tamoxifen and antidepressant medications is common. Theoretical risk of reduced efficacy of tamoxifen with inhibitors of CYP leads to medication changes for some but not all patients requiring tamoxifen and an antidepressant medication. This can have clinical implications as stability on a specific antidepressant is important for patients and adjustment may impact control of their mood disorder. In some cases, even if a drug-drug interaction was identified, some patients chose to continue their current antidepressant due to concerns of mood de-stabilization, and in other cases, aromatase inhibitors were started as an alternative. These findings highlight differences in practice patterns for which additional guidance may be helpful in bringing awareness and standardization to care.

PO5-11-09

Participants' experience with an online mindfulness-based stress reduction intervention for anxiety management in breast cancer survivors: A secondary analysis of a randomized trial

Presenting Author(s) and Co-Author(s):

H. Verduzco-Aguirre. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

M. Pompa Mansilla. Coordinación de Universidad Abierta, Innovación Educativa y Educación a Distancia, CUAIEED-UNAM, United States

M. Salazar-Alejo. Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, Mexico

J. Gutierrez Ornelas. Centro de Mindfulness Monterrey, United States

F. Mesa-Chavez. Breast Cancer Center, Hospital Zambrano Hellion, Tecnologico de Monterrey, Mexico

A. Ferrigno Guajardo. Yale University School of Medicine, New Haven, Connecticut, United States

C. Villarreal-Garza. Tecnologico de Monterrey, Nuevo Leon, Mexico

Background

Breast cancer (BC) diagnosis and treatment can lead to multiple symptoms with a negative impact on the quality of life of survivors. Mindfulness-based stress reduction (MBSR) interventions have shown to improve anxiety, depression, and stress in patients with cancer across multiple settings. However, the effectiveness of an online MBSR program has not been studied.

Methods

This is an explanatory qualitative sub-study of a randomized trial of an online MBSR intervention versus a waitlist control. Participants were Mexican women aged ≥ 18 years diagnosed with stage 0-III BC 1-5 years prior to inclusion, not currently undergoing chemotherapy or radiotherapy, with moderate to severe anxiety (baseline GAD-7 score ≥ 10). The intervention consisted of 8 weekly 2-hour Zoom sessions with body scan meditation and yoga practice led by a certified instructor. Participants received a digital manual with exercises, audio for guided practice, and a video of postures for balance and flexibility. The primary outcome of the trial was anxiety at 2, 5, and 8 months after the intervention.

Two focus groups were conducted via Zoom; 21 participants from the intervention arm were selected and invited according to the difference in GAD-7 scores between baseline and 8 months. The first group consisted of 7 participants (median age 53 years, range 39-62) with a decrease in GAD-7 score of ≥ 4 points (mean -9.1, SD 3.7); the second group consisted of 7 participants (median age 54 years, range 44-64) with a decrease of < 4 points or an increase in GAD-7 score (mean -1.2, SD 1.9). Each focus group was conducted 14 and 9 months after the MBSR intervention, respectively, and had a duration of 110 and 113 minutes, respectively. Audio and video were recorded and transcribed verbatim. Transcripts were analyzed and themes were developed, focusing on participants' experience with the online intervention and its perceived benefits.

Results

The weekly sessions and at-home practice functioned as a “personal haven” for participants. At-home deliberate practice and the additional audio and video materials were considered essential for the effectiveness of the intervention. Participants no longer needed to consciously follow step-by-step directions, as the practices had become a part of who they were, even several months after the intervention. Breathing exercises were frequently used by participants on a day-to-day basis.

Regarding the mindfulness practice itself, some participants indicated that they noticed positive changes in their character and demeanor, and in their reactions to everyday and BC-related stressors, including situations such as medical consultations and possible news regarding their treatment. In that sense, they mentioned that all they learned is useful for their life in general, and not exclusive to BC survivors. Despite differences in improvement of anxiety by GAD-7 scores between the focus groups, most participants in both groups referred to the intervention as “life-changing”.

Most participants in both groups perceived the online format of the intervention as positive: it allowed them to join in from any location and fit the program into their daily routine with less time commitment. Likewise, the privacy of their homes made them feel more comfortable expressing themselves during the weekly sessions. A high level of recognition, appreciation and gratitude towards the instructor was observed. Some participants noted that contact with the instructor and other participants was limited due to the online format, preventing them from forming friendships or a sense of community.

Conclusion

BC survivors’ opinion of an online MBSR program was largely positive regarding the benefits of the intervention and its delivery format. Moreover, the intervention was successful at facilitating participants’ adoption of mindfulness practice in their daily lives and at improving other aspects of their lives beyond BC.

PO5-11-10

Quality of life in Brazilian women with early breast cancer on adjuvant endocrine therapy

Presenting Author(s) and Co-Author(s):

- D. Santos. Hemolabor, Goiânia, Goiás, Brazil, Goiânia, Goiás, Brazil
- C. Souza. Hospital de Câncer de Barretos, Barretos, Brazil
- M. Magalhães. Hospital Universitário Evangélico Mackenzie, CURITIBA, Parana, Brazil
- D. Pereira. ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, Brazil
- F. Moura. Hospital Sírio-Libanês, Brasília DF, Brazil , Instituto Hospital de Base do Distrito Federal, DF, Brazil, Brazil
- S. Oliveira. Liga Norte Riograndense contra o Câncer , RN, Brazil, Brazil
- A. Galvão. Uniceub, DF, Brazil, Brazil
- B. Souza. DASA Oncologia/Hospital Brasília, Brasília, DF, Brazil, Brazil
- A. Castro. Hospital Sírio-Libanês, Brasília DF, Brazil, Brazil
- M. Andrade. Liga Norte Riograndense contra o Câncer , RN, Brazil, United States
- A. Shimada. Hospital Sirio Libanês, São Paulo , Brazil, Brazil
- Y. Beckedorff. Hospital Sirio Libanês, São Paulo, Brazil, Brazil
- C. Paiva. Barretos Cancer Hospital, Barretos, Brazil
- H. Resende. Hospital Jardim Amália, United States
- A. Rodrigues. Universidade Federal de Minas Gerais, Brazil; ONCOCENTRO, Grupo Oncoclinicas Belo Horizonte, Brazil, United States
- D. Rosa. Hospital Moinhos de Vento, RS, Brazil, United States
- D. Assad-Suzuki. Hospital Sírio-Libanês, Brasília, Brazil, Brazil
- R. Barroso-Sousa. Dasa Oncology, United States

Background: There is a significant scarcity of quality of life (QOL) data among the Brazilian population with breast cancer. This study aims to evaluate QOL in Brazilian women with early breast cancer treated with adjuvant endocrine therapy (ET) and to explore its relationships with patients' clinical and social characteristics, type and duration of endocrine therapy and type of healthcare insurance.

Methodology: Women with a history of early-stage estrogen-receptor positive invasive carcinoma of the breast on adjuvant endocrine therapy for at least 6 months were invited to participate of this study. QOL assessment was conducted using the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. Demographic and medical information were collected from medical records. Data collection performed using RedCap software. Qualitative variables were compared between groups using the Chi-square or exact Chi-square test and for quantitative variables the non-parametric Mann-Whitney test was used. Multivariable analysis was performed using Multiple linear regression models with Stepwise procedure. $P < 0.05$ was considered significant. Analyses were performed in SAS 9.4.

Results: From June 2021 to May 2023, a total of 461 women with ER+ early-stage breast cancer from 12 Brazilian institutions were included in this analysis. A total of 233 women (50.54%) were treated in private institutions. Mean age was 56.02 years (range 22-93), 47.69% were non-white and 38.7% were premenopausal. A total of 62.34% had prior lumpectomy,

43.1% had tumor stage II, 61.69% received prior chemotherapy and 15.18% were HER2 positive. Regarding ET, 45.2% were on aromatase inhibitors (AI), 40.61% on tamoxifen (TMX) and 14.19% on ovarian function suppression plus ET (OFS). Median duration of ET use was 2.78 years. From the adjustment of the multiple regression model, it was found that the variable patients with a higher educational level were a significant predictor for the Physical Functioning score ($p < 0.0001$). The Role Functioning score had the variables treatment in a private hospital ($p = 0.0462$) and a higher educational level ($p = 0.0357$) as significant predictors. The variables age > 60 years ($p = 0.0006$) and marital status: single ($p = 0.0267$) were significant predictors for the Emotional Functioning score. Cognitive Functioning was correlated with the variables age > 60 years ($p < 0.0001$) and treatment duration < 2 years ($p = 0.0475$). Social Functioning had significant predictors such as hormone therapy with AI ($p = 0.0305$) and hormone therapy with TMX ($p = 0.0267$) when compared to OFS, as well as treatment duration < 2 years ($p = 0.0175$). The variable age > 60 years was a predictor for the Fatigue score ($p = 0.0233$). The Pain score correlated with variables such as higher educational level ($p = 0.0003$) and treatment duration < 2 years ($p = 0.0032$). The variables treatment in a public hospital ($p = 0.0066$), age < 60 years ($p = 0.0471$), and treatment duration < 2 years ($p = 0.0054$) were predictors for a higher Arm Symptoms score. Regarding the Breast Symptoms score, the variables treatment in a public hospital ($p = 0.0005$), Caucasian ethnicity ($p = 0.0006$), radiation therapy ($p = 0.0098$), and treatment duration < 2 years ($p = 0.0203$) were predictors for the total score. Body Image correlated with variables such as age > 60 years ($p = 0.0322$), surgical approach: mastectomy ($p = 0.0445$), tumor size $< 50\text{mm}$ ($p = 0.0446$), and radiation therapy ($p = 0.0405$). The Global health status score did not correlate with any variable.

Conclusion: Lower educational level, age < 60 years, duration of ET less than 2 years had a significant impact in many domains of QOL. Radiotherapy was the treatment modality with more impact in QOL scores. The identification of modifiable factors related to QOL in this study provides valuable insights for the development of a customized intervention in Brazilian population.

PO5-11-11

Risk Assessment, Prevention and Early Detection of Breast Cancer Related Lymphedema – Objective Measurements and Patient Reported Outcomes

Presenting Author(s) and Co-Author(s):

A. Desai. University Of Miami, Florida, United States

O. Eldar. university of miami, United States

G. Halfteck. university of miami, United States

M. Moller. University Of Miami, United States

S. Kesmodel. University of Miami DeWitt Daughtry Dept. Surgery, United States

D. Franceschi. University Of Miami, United States

N. Goel. University of Miami Department of Surgery, United States

J. Crystal. University of Miami/Sylvester Comprehensive Cancer Center, Miami, Florida, United States

L. Huang. University Of Miami, United States

J. Hu. University of Miami, United States

K. Tulay. University Of Miami, United States

W. Zhao. University Of Miami, United States

A. Narvaez-Rojas. university of miami, United States

E. Avisar. University of miami, United States

Background Breast cancer-related lymphedema (BCRL) affects the quality of life, but there is no consensus regarding early detection and monitoring. Patient-reported outcomes (PROs) are important in assessing cancer survivor outcomes, and different questionnaires have been developed. LYMPHA (Lymphatic Microsurgical Preventive Healing Approach) and S-LYMPHA (Simplified LYMPHA) have reduced BCRL rates. This study aims to identify the most reliable PRO in a South Florida multi-ethnic population and to study correlations between PROs and objective measurements in the first 6 months after axillary surgery. Methods Patients undergoing axillary lymph node dissection (ALND) or axillary radiation were included. L-Dex score (Bioimpedance Spectroscopy) and three validated questionnaires (LyQLI, Lymphedema Quality of Life Inventory; LyQOL, Lymphedema Quality of Life and FACT-B4+ Functional Assessment of Cancer Therapy – Lymphedema) were recorded at baseline, and 6 months post-surgery to assess the agreement between patient-reported symptoms and BCRL. L-Dex score outside the normal range or a 10 unit increase above baseline was considered lymphedema. Additional variables such as demographics, tumor characteristics, and treatment modalities were recorded. Results Out of 40 recruited patients, 39 were analyzed (excluding one deceased patient). Patient and treatment characteristics are described in Table 1. Patients were divided into three cohorts (Figure 1) for analysis: ALND with no axillary radiation (7.69%; n=33), Sentinel Lymph Node Biopsy (SLNB) with axillary radiation (7.69 %; n=3), and ALND with axillary radiation (85%; n=3). In the first cohort, LYMPHA or S-LYMPHA were associated with lower rates of lymphedema (19% vs, 50%) (p=0.116). No patients in the second or third cohort developed lymphedema. There were 4 out of 20 (20%) patients with lymphedema with scores above the median for FACT B4+ (p= 0.480) and a lower score (higher quality of life) correlated with lower L-Dex (p=0.76). The higher value in the physical domain of LyQLI showed higher L-Dex (p=0.826). There was a significant inter-domain correlation in LyQLI and LyQOL (p= < 0.001). Conclusion These results validate the use of PROs alongside objective

measurements to assess BCRL. In addition, LYMPHA and S-LYMPHA significantly reduce lymphedema rates. Larger numbers will be necessary to reach statistical significance and to identify the best PRO.

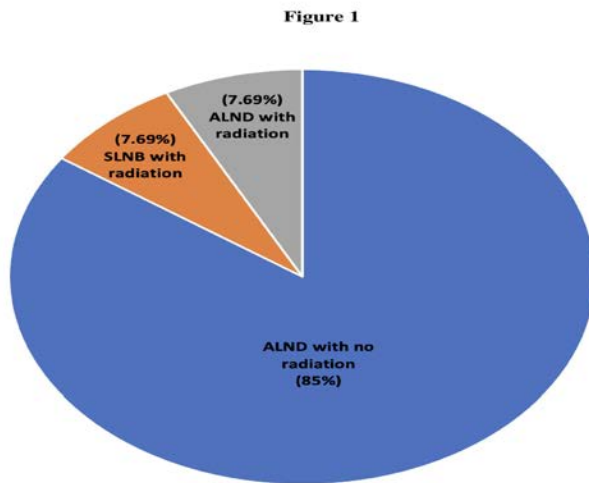
Table 1

Table 1 : Patient and Treatment Characteristics

Gender	Male 2.56% (n=1) Female 97.4%(n=38)
Menopausal Status (Females)	Pre-menopausal 47.3% (n=18) Post-menopausal 52.6% (n= 20)
Ethnicity	Hispanic: 58.9 %(n=23) Non-Hispanic: 42.1% (n=16)
Race	White 79.4% (n=31) African American 10.25 % (n=4) Others 10.25%(n=4)
Breast Cancer Stage	Stage 1: 2.56 %(n=1) Stage 2 :51.2% (n=22) Stage 3 :41% (n=16)
Neoadjuvant Treatment	Neo-adjuvant chemotherapy: 89.7% (n=35) Neo-adjuvant hormone treatment :10.25% (n=4)
Type Of Breast Surgery	Lumpectomy: 33.33% (n=13) Mastectomy : 66.66% (n=26)
Breast Reconstruction	Reconstruction : 46.15% (n=18) No Reconstruction: 53.8% (n=21)

Demographic and Treatment Summary

Figure 1



Cohort 1: ALND with no axillary radiation (7.69%; n=33)
 Cohort 2: SLNB with axillary radiation (7.69 %; n=3)
 Cohort 3: ALND with axillary radiation (85%; n=3)

Division of patient population into three cohorts

PO5-11-12

The use of wearable sensors and patient-reported outcomes in breast cancer research: A literature survey

Presenting Author(s) and Co-Author(s):

K. Dumais. Clario, United States

A. Jagodinsky. Clario, United States

S. Khakwani. Clario, United States

R. Bonaker. Clario, United States

B. McDowell. Clario, United States

K. Sowalsky. Clario, United States

Background: Clinical outcome assessments (COAs) related to physical activity, sleep, and functional mobility (gait and balance) are common in breast cancer research as they provide insight into treatment effects and overall quality of life. Wearable sensors offer utility in supplementing traditional COAs by providing objective data by passive, continuous measurement, thereby gaining unique insight on functioning while reducing patient burden. However, a comprehensive understanding of how wearables are being used in breast cancer research and how they correlate with subjective measurement of functioning is lacking. Our aim was to identify how wearable sensors and patient-reported outcomes (PROs) are being utilized in breast cancer research, the common areas of overlap, as well as areas in which expanded use of wearable sensors may be beneficial in clinical breast cancer research. Methods: We conducted a non-systematic survey of breast cancer literature using electronic databases (PubMed, Web of Science, Elsevier and Clinicaltrials.gov) to identify oncology trials using both wearable sensors and PROs. Details such as PROs used, types of sensors used, and the data collected from these were extracted and summarized. There were no restrictions placed on the date and year of publication. Results: A total of 15 breast cancer studies, which used both wearable sensors and PROs to measure patient outcomes, were included in analysis. Accelerometers were implemented most frequently in the studies analyzed (73%) followed by pedometers (40%). The most common outcomes measured using wearable sensors were physical activity (47%) and sleep (47%), with only 1 study (7%) measuring functional mobility (gait and balance). The most common outcomes measured using PROs were sleep (47%), followed by quality of life (40%), physical activity (33%), and "other" parameters (40%; e.g., mood, fatigue, pain). Correlation between PRO and sensor metrics were sparse (20%), yet sensor measures of physical activity, sleep, and gait/balance correlated respectively with PROs of activity, sleep, and quality of life. Conclusions: Sleep, quality of life, and physical activity were the most common outcomes measured by PROs, while physical activity and sleep were the most common outcomes captured using wearable sensors. These results suggest there is alignment in outcomes gathered from wearable sensors and PROs, however additional insight may be gained by incorporating wearable sensors for assessment of functional mobility (e.g. walk or balance tests) as these areas are known to impact quality of life in cancer patients and cancer survivors. Further, few studies analyzed correlations between the two measurement systems, suggesting a greater need in understanding how objective measures via wearable sensors and subjective measurements relate.

PO5-12-01

Characteristics of Patients Served by Participants in a Survivorship Navigator Learning Collaborative

Presenting Author(s) and Co-Author(s):

T. Hamlish. University of Illinois at Chicago, Chicago, USA, Illinois, United States

T. Holzman Castetllands. University of Illinois at Chicago, Chicago, USA, Illinois, United States

Patient navigation is demonstrated to be a successful model for improving breast cancer screening and early detection, particularly for women in under-resourced communities. The effectiveness of this model has not yet been explored in cancer survivorship. Our research assesses the feasibility of community-based patient navigation after a breast cancer diagnosis. This analysis focuses on the role of patient navigators in providing community-based peer support for women living with breast cancer.

We conducted an analysis of data from the Breast Cancer Survivorship Patient Navigator Virtual Learning Collaborative (VLC), a case-based, iterative, virtual training program designed to increase capacity of community-based patient navigators to support women diagnosed with breast cancer. Navigators participated in a 14-week practice-based curriculum focused on improving community support for breast cancer survivors. Each session included a brief lecture followed by a case presentation by a participant. Lecture topics include Breast Cancer 101, Psychosocial support, Treatment options, Clinical trials, Sexual Health, Palliative Care, Genetic Testing, and Trauma. All participants were asked to present at least one de-identified case for discussion, using an 55-item case presentation template. The template included data on patient demographics, diagnosis, treatment, and support. To encourage active learning, navigators were encouraged to present challenging cases for discussion focused on identifying solutions and providing peer support. This analysis focuses on the characteristics of patients presented by community navigators from January 2021 to May 2023.

A total of 92 de-identified patient cases were presented by 71 patient navigators and community health workers. (Table 1) The majority of patients were diagnosed within 12 months (62%), with early stage (Stages I-III) disease (78%), and were in active treatment or had not yet started treatment (67%). More than half of the cases had tumors that were HR+ (54%) and nearly half were HER2- (43%); 9% of cases were triple negative and 9% were triple positive. Tumor characteristics were not reported for 27% of cases. Individuals diagnosed with metastatic breast cancer (MBC) compared with those diagnosed with early stage disease were more likely to be Black (59% v 39%), single (56% v 31%), not currently employed (100% v 46%), younger (average age 52 v 55 years old) and insured through Medicaid (56% v 17%)

Individuals living with MBC relied more heavily on professional support compared to those diagnosed with early stage disease. The majority of MBC patients relied on the clinical care team (67%) and friends and family (67%) for support, with a large number also receiving support from faith-based organizations (56%), compared to those with early stage disease who relied on friends and family (90%) and the clinical care team (54%). Both groups relied on navigators (33% v 35%) and social workers (44% v 34%), while those with MBC relied more frequently on paid caregivers (44% v 3%), disability services (22% v 6%). The data indicates that individuals with MBC had more unmet needs, including practical support (55% v 33%) and disability (55% v 14%).

Supportive care needs vary considerably based on stage of diagnosis, while community-based supportive services are often designed to meet the needs of those diagnosed with early stage disease. Community-based survivorship navigators more readily engage with patients with early stage disease who are newly diagnosed or in active treatment. Individuals with MBC have fewer community-based resources and are less likely to connect with a community-based navigator. Data from our Breast Cancer Survivorship Patient Navigator VLC points to the potential to identify gaps in community-based survivorship care. Future research should focus on expanding the reach of community navigators and ensuring community-based support for patients across all stages.

Table 1 Demographics of Patients Presented at VLC

Table 1. Demographics of Patients Presented at VLC

Average Age	54 years old
Age Range	21-84 Years old
Race	
Black	36 39%
White	43 47%
Other	3 3%
Not reported	10 11%
Ethnicity	
Hispanic	27 29%
Non-Hispanic	65 71%
Marital Status	
Single	29 32%
Married	39 42%
Separated	3 3%
Divorced	6 7%
Widowed	10 11%
Other	5 5%
Work	
Yes	36 39%
No	54 59%
Unknown	2 2%
Type of work	
Full time	24 67%
Part time	9 25%
Other	3 8%
Insurance	
Employer	33 35%
Marketplace	4 4%
Medicare	19 20%
Medicaid	30 32%
Other	10 11%
Uninsured	10 11%

PO5-12-02

Landscape analysis of oncology nutrition research among patients being treated for breast cancer

Presenting Author(s) and Co-Author(s):

K. Robien. Milken Institute School of Public Health, George Washington University, United States

H. Wopat. Milken Institute School of Public Health, George Washington University, United States

The American Institute for Cancer Research/World Cancer Research Fund and the American Cancer Society regularly conduct systematic reviews on the evidence supporting nutrition interventions during cancer treatment. These reviews have found that the evidence to support clinical oncology nutrition practice guidelines is limited. It is unclear how many oncology nutrition studies are currently being conducted, especially among patients being treated for breast cancer. The goal of this project was to conduct a landscape analysis of nutrition research being conducted among breast cancer patients over the past 10 years. **Methods:** This analysis was part of a larger effort to describe the oncology nutrition research landscape for all cancer sites. Searches of ClinicalTrials.gov were performed on 1/8/2023 using the following search terms/combinations: “cancer AND nutrition”, “cancer nutrition”, “oncology AND nutrition”, “diet AND cancer”, “cancer, oncology, neoplasms, nutrition, diet”. Search results were downloaded as .csv files and uploaded to RStudio for merging and data cleaning (elimination of duplicates, and exclusion of studies registered in ClinicalTrials.gov before 1/1/2013 or after 12/31/2022). The resulting harmonized dataset was then uploaded to REDCap, and each entry was reviewed for eligibility by one of the authors. To be included in this landscape analysis, studies must have included data collection from patients who were actively receiving cancer treatment at the time of the study and the study had to be first posted to ClinicalTrials.gov between 1/1/2013 and 12/31/2022. Studies were excluded if they: 1) focused on the role of diet in primary cancer prevention, 2) focused on cancer survivors who had completed primary treatment for their cancers. Following eligibility review, the study datafile was returned to RStudio for further cleaning and analysis. **Results:** The initial ClinicalTrials.gov search identified 4,345 unique study listings. After review, 1,267 studies met the inclusion criteria, of which 132 (10.4%) studies were specific to breast cancer (117 intervention studies and 15 observational studies). Among breast cancer studies, reasons for exclusion were: study focused on diet/nutrition in the prevention of a primary cancer diagnosis (n=40), study participants had already completed their cancer treatment (n=128), study did not include a diet/nutrition intervention or assessment (n=31). The largest number of breast cancer specific studies were based in the United States (n=55, 41.6%), Italy (n=11, 8.3%), France (n=10, 7.6%) and Canada (n=9, 6.8%). Dietary supplement interventions were the most common type of intervention (n=50 studies, 42.7%), followed by behavior change interventions (n=22, 18.8%), diet in relation to a drug intervention (n=25, 21.4%), diet in relation to a device/procedure/radiation intervention (n=16, 14%), fasting/time-restricted feeding studies (n=13, 11.1%) and ketogenic diet interventions (n=3, 2.6%). Changes in weight or body composition (n=52, 39.4%), quality of life (n=45, 34.1%), adverse events (n=24, 18.2%), survival (n=20, 15.2%) and fatigue (n=17, 12.9%) were the most common outcome measures. Sixteen (12.1%) studies were supported by NIH funding and 9 (6.8%) studies were industry funded, although the majority (n=124, 93.9%) reported funding from “other” sources. Of the 41 studies that started between 2013-2017 (five years prior to the January 2023 ClinicalTrials.gov search), only 21 (51.2%) were listed as being “completed” and of those, only 7 were listed as “has results”. **Conclusion:** More research is needed to support evidence-based supportive

care guidelines for oncology nutrition interventions during breast cancer treatment. Efforts should be made to support researchers in completing studies and disseminating research findings.

PO5-12-03

Cardiovascular Toxicities in Breast Cancer Survivors

Presenting Author(s) and Co-Author(s):

V. Ayodele. UT Health Science Center San Antonio, United States

E. Sherry. UT Health Science Center San Antonio, United States

M. Mazo-Canola. Mays Cancer Center, San Antonio , Texas, United States

Background: Chemotherapy, despite its effectiveness, presents drawbacks in breast cancer patients due to its side effects. Fatigue, hair loss, nausea, and anemia are among the many symptoms associated with chemotherapy. Moreover, chemotherapy can lead to cardiovascular diseases, including cardiac arrhythmias, hypertension, heart failure, heart attacks, and cardiomyopathy, particularly with the use of anthracyclines and HER-2-targeted agents. Risk factors such as weight, age, race, comorbidities (e.g., obesity, diabetes, hyperlipidemia), and radiation exposure further increase these risks. Despite these potential complications, guidelines are just emerging aiming to prevent these cardiovascular complications in breast cancer patients. Untreated cardiovascular abnormalities can have long-term effects on breast cancer survivors. Our aim is to analyze the relationships between breast cancer treatment and cardiovascular abnormalities, examining associations with various factors, including race, BMI, and age in a majority Hispanic cohort of breast cancer survivors. Methods: retrospective, single institution study data from a total of 53 patients treated with chemotherapy with either anthracyclines and/ or HER 2 directed therapy with curative intent between 2018-2020. Our analysis included basic demographic information, menopausal status, breast cancer type, treatment types, use of cardio-protective medications, and cardiovascular effects (both pre-existing and developed during treatment). Results: Our sample of 50 women primarily comprised Hispanic individuals (73%), most of whom were postmenopausal (86%), with an average age of 63 years (range 35-86). Among the breast cancer types identified, 35 were hormone-positive, 8 were HER-2 positive, and 10 were triple negative. 72% of the patients received adjuvant hormonal therapy. 18% of the population received anthracycline-based treatment, 8% received Her 2 directed therapy and 2 % received Immune check point inhibitors . Radiation therapy was administered to 50% of the patients. The most prevalent cardiovascular disease observed was hypertension, affecting 62% of patients, followed by type 2 diabetes (38%), hyperlipidemia (34%), stroke (8%), and heart attack (6%). The predominant cardioprotective medications used were ACE inhibitors/ARBs (48%), followed by statins (46%), beta-blockers (20%), aspirin (16%), and GLP-1 agonists (14%). Conclusion: Our analysis revealed a high prevalence of cardiovascular conditions among breast cancer survivors treated with chemotherapy in a majority Hispanic cohort of patients. This population has been linked to higher risk of developing comorbidities such as diabetes, obesity and hypertension. Further analysis evaluating risk factors and implementation of treatment strategies to minimize adverse effects is needed in this population.

PO5-12-05

A Retrospective Study of the Rate of Cognitive Impairment and Influencing Factors during Postoperative Endocrine Therapy for Breast Cancer

Presenting Author(s) and Co-Author(s):

A. Murakami. Ehime University Hospital, Ehime, Japan, Japan

M. Aono. Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, United States

K. Utsunomiya. Matsuyama Red Cross Hospital, Matsuyama, Ehime, Japan

K. Okujima. Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, United States

K. Takemoto. Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, United States

M. Takaoka. Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, United States

E. Kusakabe. Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, United States

K. Taguchi. Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, United States

K. Nishiyama. Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, United States

Y. Kamei. Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, United States

Y. Takada. Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, United States

H. Tanimukai. Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, United States

Background Although cancer-related cognitive impairment (CRCI) has been gradually recognized, general cognitive function tests such as the MMSE are not sensitive enough to diagnose CRCI. There is also a lack of evidence on the incidence and its response. However, even mild cognitive impairment can have a significant impact on quality of life. In this study, we retrospectively analyzed the prevalence of cognitive impairment in patients undergoing endocrine therapy at our hospital and the factors influencing the symptoms. **Subjects** 349 patients who continued single-agent postoperative endocrine therapy for at least 6 months between January 1 and October 31, 2022, and who responded to the cognitive dysfunction questionnaire at least once. Data from the cognitive dysfunction items of the endocrine therapy questionnaire administered during the period were used to retrospectively examine the CRCI awareness rate and factors involved. **Results and Discussion** The patients who were aware of cognitive dysfunction was 170, or 49% of all patients, and univariate analysis showed that age was significantly higher in the group with CRCI, but there were no significant differences in type of endocrine therapy or history of chemotherapy between the groups with and without CRCI. Physical symptoms such as menopausal symptoms (hot flashes and sweats), arthralgia, myalgia, fatigue, depressed mood, and malaise were significantly more frequent in patients with CRCI, which could be considered side effects of endocrine therapy. Risk factors such as low cognitive reserve, low level of education, advanced age, race, depression, fatigue, and anxiety have been reported in the past, and in this study, fatigue, depressed mood, and malaise were

found significantly more frequently in patients with cognitive dysfunction. However, the diagnosis of depression and dementia may also be important. Non-pharmacological interventions, especially cognitive rehabilitation and exercise, are expected to be effective in improving symptoms, but there is no certain opinion yet. The limitation of this study is that it was a single-center, retrospective analysis. In addition, it was difficult to evaluate the results over time, including before the start of oral medication, so we are considering conducting a prospective data collection study so that comparisons can be made in the future. Conclusion: This study was a simple screening, based only on subjective symptoms. In recent years, postoperative endocrine therapy has been prolonged to 10 years, and there is a possibility to improve the quality of life of patients by recognizing the possibility of cognitive dysfunction in both providers and patients, and by taking measures that include multiple factors.

PO5-12-06

Minimization of treatment toxicity/side effects and their impact on quality of life (QoL) in patients (pts) with ER+/HER2- metastatic breast cancer (mBC)

Presenting Author(s) and Co-Author(s):

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

K. Shanahan. Metavivor Research and Support, Inc, Annapolis, MD, United States

T. Pluard. Saint Luke's Cancer Institute, University of Missouri, Kansas City, Missouri, United States

F. Chino. Memorial Sloan Kettering Cancer Center, New York, New York, United States

D. Trapani. European Institute of Oncology, IRCCS, University of Milano, Milan, Lombardia, Italy

D. Carroll. Sermonix Pharmaceuticals, United States

M. Kozlowski. Sermonix Pharmaceuticals, United States

E. Attias. Sermonix Pharmaceuticals, United States

N. Kuderer. Advanced Cancer Research Group, United States

Introduction: Treatment toxicity and side effects may be underreported (Basu Roy. J Thorac Oncol 2018;13:1815-17) and can negatively impact QoL. As such toxicities can influence pts' treatment decisions, we surveyed pts with ER+/HER2- mBC to better understand the impact and patient reporting accuracy of treatment toxicities/side effects.

Methods: The EQUALS 3 (ESR1 QUALity of Life Survey 3), 55-question survey was designed by the EQUALS Steering Committee, trialed by pt advocates, emailed to US subjects (Cure Media Group and authors' contacts), and posted to private BC Facebook and Twitter groups for 2 wks in June 2023. Eligible pts had ER+/HER2- mBC and treatment changes due to disease progression. Pts received a \$10 gift card at survey completion. Survey answers were descriptively summarized.

Results: 213 pts completed the survey. Most were < 60 yrs of age (77%), White (44%) or Hispanic/Latino (48%), peri-/postmenopausal (54%), and college-educated (71%); had income >\$50,000 (66%); lived in urban (51%)/rural areas (22%); and had therapy lines of 1st (8%), 2nd (36%), or 3rd+ (51%). Current mBC treatments were endocrine therapy (ET) ± targeted therapies (70%), antibody drug conjugate (8%), chemotherapy (11%), and other (10%). Most pts had a female oncologist (65%) who worked in an academic hospital (61%); 68% had >1 oncologist.

Surveyed pts reported toxicity concerns for side effects ranging from serious to nuisance. Side effects most frequently reported as extremely/moderately concerning were respiratory symptoms (51%), blood clots in lungs (49%) or heart/brain (47%), cognitive dysfunction (47%), infections (46%), nausea/vomiting (44%), cardiac adverse effects (44%), diarrhea (42%), gait instability (41%), fatigue (39%), joint pain (39%), hair loss (33%), or sexual dysfunction (27%).

Although 49% of pts felt comfortable speaking to their medical team (MT) about side effects, 62% reported having minimized side effects to their MT due to fears/concerns of being seen as a complainer (70%), dose reduction (66%), being taken off drug (65%), not accessing other

drugs with similar toxicities (61%), reduced efficacy with lower dose (59%), or coming off trial (47%). Almost half (47%) did not report treatment side effects, mostly due to fear of being seen as a complainer (63%), being taken off drug (57%), reduced efficacy with lower dose (51%), dose reduction (50%), not accessing other drugs (50%), or coming off trial (41%).

QoL was poor/very poor in 20% of pts and QoL was the most common (68%) important/very important factor for making a treatment decision based on risks. Most common side effects that negatively impacted QoL were sexual dysfunction (45%), joint pain (38%), vaginal atrophy/dryness (36%), fatigue (33%), bone pain (31%), and hair loss (26%). Toxicities/side effects also impacted pts' anxiety (49%), career (46%), marriage (42%), finances (32%), housework (30%), and relationships (19%).

Regret after taking a cancer medication due to side effects was reported by 46% of pts.

Conclusion: In this survey of pts with ER+/HER2- mBC on ET predominantly, many treatment side effects caused concern, not necessarily related to their seriousness, and most pts had minimized or hid side effects at some point due to fear of negative perceptions from their MT, reduced treatment efficacy, or clinical trial changes. Although QoL was overall good for most, 20% had poor QoL (largely impacted by sexual dysfunction, joint pain, and vaginal issues). Regret about toxicities was also common and should be explored. Provider awareness of pts' toxicity experience, fears, and impacts on daily lives opens the door for educational tools to improve MT communications for treatment decisions, informed consent, and more accurate toxicity reporting in clinical trials.

PO5-12-07

Analyzing Patient Experiences with Adjuvant Hormone Therapy for Early Breast Cancer Treatment via NLP/ML on Social Media: Symptoms and Their Mitigation

Presenting Author(s) and Co-Author(s):

S. Sreenivasan. AstraZeneca, United States

C. Fang. AstraZeneca, United States

E. Flood. AstraZeneca, United States

N. Markuzon. AstraZeneca, United States

J. Sze. AstraZeneca, United States

Understanding the early breast cancer (eBC) patient experience of disease and treatment is critical to addressing unmet patient needs, improving outcomes, and informing the next wave of drug development. Traditional approaches, such as interviews or focus group studies, are resource intensive and have limitations in reflecting the diverse experiences of patients with different disease characteristics, treatments, and sociodemographic backgrounds, and in detecting rare severe events that could potentially lead to therapy discontinuation.

To overcome these limitations, we have developed a semi-automated approach utilizing Natural Language Processing (NLP) and Machine Learning (ML) methods in application to public patient forums to extract patient insights. Specifically, we analyzed 500,000 anonymized posts from the BreastCancer.org forum, utilizing Transformer-based methods to identify posts related to eBC patient experiences treated with standard hormonal therapies (HT).

First, a novel ML-based model identified posts related to eBC adjuvant HT. For those, patient demographics, symptoms and their severity, and symptom management strategies such as exercise and yoga were subject to further analysis. Out of 362,074 relevant eBC posts, 32 symptoms and 9 impacts were significantly associated with at least one of the six hormonal therapies we considered. Hot flushes (relative risk [RR]: 6.70; 95% CI: 3.36–13.36), arthralgia (RR: 6.67; 95% CI: 3.53–12.59), weight increase (RR: 4.83; 95% CI: 3.20–7.28), mood swings (RR: 7.36; 95% CI: 5.75–9.42), insomnia (RR: 4.76; 95% CI: 3.14–7.22), and depression (RR: 3.05; 95% CI: 1.71–5.44) demonstrated the strongest associations. Severe headache, dizziness, back pain, and muscle spasms showed significant associations with ≥ 1 HT despite their low overall prevalence in eBC posts. Notably, posts contained a wide range of symptoms severity, including rarely seen symptoms in smaller patient pools, such as severe night hot flashes leading to treatment discontinuation.

Symptoms/impacts mentioned in association with exercise and yoga as a way for symptom mitigation included hot flashes, arthralgia, fatigue, anxiety, depression, and pain. Of those posts, 53.3% to 82.5% reported positive or neutral sentiments for exercise, and 22.2% to 100.0% for yoga. For posts specifically mentioning the management of side effects of HT, between 50.0% and 63.5% had a positive sentiment associated with exercise concerning each of the symptoms/impacts with a lower positive impact related to yoga (between 11.1% and 43.0% of posts). Posts discussing pain management and exercise included a higher proportion of negative feedback, versus positive sentiment for depression. Posts related to yoga as an HT symptom mitigation strategy had a higher prevalence of negative sentiments for anxiety and depression.

Our proposed ML/NLP-based approach to collecting patient feedback from publicly available

forums complements standard qualitative methods by enabling the scalable extraction of insights from hundreds of thousands of online conversations that could span a broad diversity of symptoms and well-being reflections. Furthermore, our findings suggest the potential value of informing clinical outcome assessment (COA) measurement for clinical trials, alone and in combination with standard qualitative research approaches to guide the next clinical development. Overall, our study highlights the significant potential of NLP and ML to address the critical need to better understand the eBC patient experience of disease and treatment to improve outcomes for patients.

PO5-12-08

QTc prolongation as Adverse Effect of CDK4/6 inhibitors: A systematic review and meta-analysis of randomized controlled trials

Presenting Author(s) and Co-Author(s):

B. Carvalho. Faculdade de Medicina de Barbacena, Lavras, Minas Gerais, Brazil

P. Cotta Abrahão Reis. Universidade Federal do Rio de Janeiro - UFRJ, United States

A. Marinho. Federal University of the State of Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil

A. Comini. A.C. Camargo Cancer Center, São Paulo, Brazil

D. Xavier. Universidade Federal do Para, United States

B. Mella S. Pessoa. Federal University of Amazonas, Manaus, Amazonas, Brazil

F. Batalini. Mayo Clinic, United States

Introduction: CDK4/6 inhibitors (CDK4/6i), such as abemaciclib, ribociclib, and palbociclib, have significantly improved outcomes for patients with ER+/HER2- breast cancer. Nevertheless, they differ among each other in terms of chemical, biological, and pharmacological features, as well as toxicity profiles. Ribociclib causes concentration-dependent increases in the QTc interval, particularly in combination with tamoxifen. However, the pathogenesis of ribociclib-induced QTc prolongation remains unclear. We aim to determine whether QTc prolongation is caused by CDK4/6i in general or if it is associated with ribociclib only.

Methods: We performed a systematic review and meta-analysis of randomized clinical trials (RCTs) to compare QTc prolongation in patients using CDK4/6i in combination with hormonal agents to patients that did not use CDK4/6i, including neoadjuvant, adjuvant, or metastatic scenarios in breast cancer. We searched Embase, PubMed and Cochrane Library databases from inception to June 2023. The outcomes evaluated were QTc prolongation of all grades. Statistical analysis was performed with R software version 2023.03.0+386.

Results: We included 14 RCTs comprising 16,013 patients in the quantitative analysis, of whom 8,585 underwent therapy with CDK4/6i, and one more paper was included only in the qualitative analysis due to not reporting the exact number of events of QTc prolongation. An increased risk of QTc prolongation was associated with the use of CDK4/6i (RR 2.32; 95% CI 1.67–3.23; $p=0.000001$; $I^2=46\%$). Subgroup analyses revealed a significant increase in the QTc interval for the ribociclib and palbociclib cohorts. The ribociclib subgroup showed a risk ratio of 3.07 (RR 3.07; 95% CI 2.17-4.36; $p<0.000001$; $I^2=21\%$) while the palbociclib subgroup had a risk ratio of 1.52 (RR 1.51; 95% CI 1.05-2.16; $p=0.025$, $I^2=0\%$).

Conclusion: Our findings suggest that QTc prolongation may be a common adverse effect of CDK4/6i, with ribociclib carrying greater risk. These results are important for guiding clinical decision-making, and further investigation is warranted to better understand the mechanisms and clinical implications of CDK4/6 i-induced QTc prolongation.

PO5-12-09

A Single-Arm Pilot Study of the Feasibility and Efficacy of Electro-Acupuncture in Subjects with Chemotherapy-Induced Peripheral Neuropathy

Presenting Author(s) and Co-Author(s):

N. Vobugari. Houston Methodist Hospital, United States

J. Liang. Houston Methodist Hospital, United States

L. Savage. Houston Methodist Hospital, United States

D. Jain. Houston Methodist Neal Cancer Center, Houston, Texas, United States

K. Sun. Houston Methodist Dr. Mary and Ron Neal Cancer Center, Houston, Texas, United States

H. Mai. Houston Methodist Hospital, United States

J. Chang. Houston Methodist Hospital, United States

M. Desai. Houston Methodist Hospital, United States

T. Patel. MD Anderson Cancer Center, United States

P. Niravath. Houston Methodist Hospital, Houston, Texas, United States

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a very common dose-limiting side effect of many cancer treatments. However, the optimal treatment for CIPN remains unclear. Electroacupuncture (EA) is a non-pharmacologic treatment that combines traditional acupuncture with electrical stimulation. EA is being examined for CIPN and has shown modest benefits. Design: This is a pilot, single-center, prospective, single-arm, non-blinded study. All subjects had residual grade ≥ 2 CIPN after having received curative intent chemotherapy for stage I-III breast cancer, completed at least 3 months prior to study enrollment. Patients received 10 sessions of electro-acupuncture, administered by a licensed professional, over the course of 7 weeks. A sub-group of patients also had baseline and post-treatment skin punch biopsies to assess intra-epithelial nerve density (IEND). The primary objective was to determine the feasibility of completing a 10-treatment EA program in this patient population. Feasibility was defined as ≥ 15 subjects completing ≥ 8 EA treatments. Secondary endpoints included neuropathic pain, as assessed by the Brief Pain Inventory-Short Form (BPI-SF), and change in the quality of life, as assessed by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) subscale. Results: Twenty eligible female subjects were included in the study, with a median age of 66.5 years (range 45-81 years old). All patients received taxane chemotherapy, with 15 (75%) patients receiving weekly paclitaxel, 4 (8%) patients receiving Taxotere every 3 weeks, and 1 (2%) patient received weekly abraxane. The duration between chemotherapy completion and EA treatment initiation ranged between 4-92 months, with a median of 29 months. Eight (40%) patients were taking gabapentin, 2 (10%) on duloxetine, 1 (5%) pregabalin, and 3 (15%) on NSAIDs before and during the study. The study met its primary endpoint of feasibility, with 18 of 20 (90%) patients completing 8 or more EA sessions. Pain level, as assessed by the worst pain score on BPI-SF, improved significantly from a mean of 6.3 to 3.7, 2 weeks after completion of EA treatments ($p = .0058$). FACT/GOG-NTX quality of life measurement, "I am bothered by side effects of my treatment" also significantly improved from a mean score of 2.1 to 0.8 ($p = .0177$). There were no major adverse events (AEs) related to EA. Nine mild AEs were noted among 6 (30%) patients; localized skin biopsy site infections: G1=3, G2=3, nonlocalized cellulitis G3=1, Fatigue G1-2 =2. The localized skin biopsy site infections led to the discontinuation of further skin biopsy procedures. [We will also present data on the IEND for the

nine patients who have paired before and after skin punch biopsies – this will be available at the time of the conference.] Conclusion: Electroacupuncture is a feasible treatment for CIPN. Furthermore, this pilot study did show a benefit for perceived pain and quality of life. Further studies will need to be conducted in regards to longevity of response. As larger studies in the future confirm the benefit of acupuncture, insurance payors are more likely to cover this important service.

PO5-12-10

Eyebrow and eyelash loss in breast cancer survivors

Presenting Author(s) and Co-Author(s):

S. Premji. Department of Oncology, Mayo Clinic, Rochester, Minnesota, United States

K. Ruddy. Mayo Clinic, Rochester, Minnesota, United States

N. Larson. Mayo Clinic, United States

C. Loprinzi. Department of Oncology, Mayo Clinic, United States

B. Dulmage. Department of Dermatology, Ohio State University, United States

m. lustberg. Yale Cancer Center, New Haven, Connecticut, United States

F. Couch. Mayo Clinic, Rochester, Minnesota, United States

J. Olson. Mayo Clinic, United States

E. Cathcart-Rake. Mayo Clinic, United States

Background: Eyebrow and eyelash loss, known as madarosis, can occur secondary to breast cancer-directed therapy. However, the incidence and predictors of this phenomenon are not well-known. The purpose of this study is to ascertain the proportion of breast cancer survivors who experience madarosis, potential contributing factors to eyebrow and eyelash loss, and associations between this symptom and mental health. Methods: Breast cancer survivors were invited to participate in an ongoing longitudinal cohort study, the Mayo Clinic Breast Disease Registry (MCBDR), after having been seen at least once for breast cancer at Mayo Clinic in Rochester, MN. Those who consented were mailed a survey approximately one year after diagnosis. Respondents were asked to report their degree of eyebrow and eyelash loss experienced since their diagnosis on a 4-point scale of "no loss" (0) to "complete loss" (3). The proportions of participants who reported eyebrow and eyelash loss were evaluated overall and according to treatment type by descriptive statistics. Relationships between eyebrow and eyelash loss and mental health scores collected using the PROMIS-10 project scales (ranging from 0-20), with the poorest mental health indicated by scores under 8, were explored. Results: 838 registry participants responded to the year 1 survey's alopecia questions. The median age of breast cancer survivors was 59.4 years (range 22-100 years). The majority were diagnosed at stage I-II (69%). 315 (37%) had received chemotherapy (+/- endocrine therapy), 415 (50%) had received endocrine therapy only, and 108 (13%) had received neither. Nearly half reported eyebrow loss (49%) or eyelash loss (49%). Eyebrow loss was reported by 89% of chemotherapy recipients, 27% of endocrine therapy only recipients, and 19% of those not treated with chemotherapy or endocrine therapy. 102 (32%) of those with chemotherapy-associated eyebrow loss reported that it was complete. Eyelash loss was reported by 274 (87%) of chemotherapy recipients, 112 (27%) of endocrine therapy only recipients, and 23 (21%) of those who received neither. Although no formal statistical testing was performed, there was a numerically higher proportion of patients with eyebrow and/or eyelash loss who reported poor mental health. Conclusions: Madarosis is a bothersome symptom in cancer survivors, particularly after chemotherapy. Future investigation into the incidence, predictors, and treatment of anti-neoplastic medication-related madarosis is needed.

Global mental health scores on PROMIS scale for eyebrow and eyelash loss

	<i>Eyebrow Loss</i>		<i>Eyelash Loss</i>	
Mental Health Score	Reported	Not Reported	Reported	Not Reported
5 to 8	11 (55%)	9 (45%)	12 (60%)	8 (40%)
9 to 12	84 (54%)	71 (47%)	83 (54%)	72 (46%)
13 to 16	200 (50%)	193 (49%)	202 (51%)	191 (49%)
17 to 20	106 (43%)	142 (57%)	100 (40%)	147 (60%)

PO5-12-11

Characterizing Symptom Alerts in Different Breast Cancer Regimens: A Remote Symptom Monitoring Study

Presenting Author(s) and Co-Author(s):

K. Khoury. O'Neal Comprehensive Cancer Center at the University of Alabama, Birmingham, Alabama, United States

N. Caston. The University of Alabama at Birmingham, United States

M. Patterson. UAB, United States

N. Holmes. UAB, United States

J. Seward. UAB, United States

E. Stringer-Reasor. University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, Alabama, United States

N. Jahan. University of Alabama at Birmingham, Birmingham, Alabama, United States

G. Rocque. University of Alabama at Birmingham, Birmingham, Alabama, United States

Introduction: Remote symptom monitoring is becoming more common in the management of patients on active cancer treatments. The patterns of symptoms and subsequent alerts for specific types of treatment administered as part of standard of care remains unknown. This study aims to characterize the frequencies and types of symptom alerts among breast cancer patients receiving neoadjuvant and adjuvant therapy. **Methods:** This secondary analysis used data from a hybrid type 2 randomized controlled trial testing the implementation of remote symptom monitoring. For our analysis, we included women with breast cancer receiving (neo)adjuvant therapy. Enrolled patients received remote symptom monitoring surveys within 30 days of treatment initiation at the University of Alabama at Birmingham from 06/2021 to 05/2023. Self-reported symptoms were recorded via weekly electronic surveys for six months. The weekly survey used the PRO-CTCAE measurement tool and patients report frequency, intensity, and interference of the following symptoms: constipation, decreased appetite, diarrhea, cough, insomnia, nausea/vomiting, neuropathy, pain, urinary problems. Symptom alert severity is categorized as either moderate or severe. Self-reported race and treatment regimen (within the first 60 days) were abstracted from the electronic medical record. Regimens were grouped into three categories 1) trastuzumab-containing, 2) any regimen with pembrolizumab, 3) chemotherapy without trastuzumab or pembrolizumab. Descriptive statistics were calculated using frequencies and percentages for categorical variables and medians and interquartile ranges (IQR) for categorical variables. **Results:** A total of 108 women with breast cancer were included in our analysis. Overall, 54% were of White race, 36.1% were of Black or African American race, and 1.85% were of Asian race. The median age was 54 years (IQR 41-65). Fifty-one percent were prescribed a chemotherapy regimen, 33% trastuzumab-based regimen, and 15% pembrolizumab-based regimen. Symptom alerts were addressed supportively or escalated with nursing and treating oncologist via direct communication with patients. A total of 1438 symptom alerts were triggered with 55% of surveys generating an alert. The most reported symptom alert was pain, accounting for 30% of all alerts. Additionally, of all symptom alerts, 70% were moderate and 30% severe, with similar distributions across regimens. Patients receiving pembrolizumab regimen most often reported moderate pain compared to the other two regimens (35% vs 22% vs 23%). However, severe pain was most often reported by those receiving chemotherapy at 46%, trastuzumab-based regimen at 40%, and pembrolizumab-based regimen at 31%. Furthermore, patients on trastuzumab-based regimens reported severe diarrhea most frequently (11%) compared to 3% & 2% for the other

two regimens. Discussion: Symptoms experienced during receipt of (neo)adjuvant breast cancer treatment are common, with the majority being moderate in nature. Differences in symptom profiles were observed across different treatment modalities, consistent with known side effect profiles. The higher prevalence of pain in patients receiving chemotherapy alone may be attributed to the use of growth factors in these regimens. Further exploration is warranted to investigate the use of supportive medications in managing these symptoms. Further evaluations are underway to evaluate how symptom alerts could potentially increase treatment adherence and decrease hospitalizations.

PO5-12-12

Implementation of a comprehensive monitoring protocol for the prevention and treatment of interstitial lung disease in patients undergoing treatment with trastuzumab deruxtecan

Presenting Author(s) and Co-Author(s):

H. Moore. Duke Cancer Institute, Durham, North Carolina, United States

K. Westbrook. Duke Cancer Institute, Duke University, United States

T. Bagwell. Mercer University, United States

S. Shofer. Duke University Hospital, United States

C. Anders. Duke Cancer Institute, Durham, North Carolina, United States

a. guisinger. Duke University, United States

O. White. Duke University Hospital, United States

S. Dent. Duke University, Durham, North Carolina, United States

Background: In the DESTINY-BREAST studies, Trastuzumab deruxtecan (T-DXd) demonstrated significant antitumor activity in heavily pretreated patients (pts) with HER2-positive and HER2-low advanced breast cancer (ABC). T-DXd is associated with an increased risk of interstitial lung disease (ILD), which occurs in 10-15% of patients with a 2.2% rate of fatal events. Increased monitoring for ILD within DESTINY-BREAST03 showed a reduction in grade 3-5 events. Patients with a history of clinically significant lung disease were excluded from this study, however this may not be reflective of the standard community patient population treated with T-DXd. There are currently no standardized monitoring protocols for ILD/pneumonitis for pts treated with T-DXd. We conducted a retrospective chart review to assess the benefit of implementing an ILD monitoring protocol in a cohort of patients receiving treatment with T-DXd at the Duke Cancer Institute. Methods: Patients with HER2-positive or HER2-low ABC who received \geq five cycles of T-DXd between Jan 1, 2020- April 30, 2022 were included. Imaging with CT chest ILD protocol and pulmonary function testing with diffusing capacity for carbon monoxide (DLCO) were performed at baseline prior to initiation of T-DXd, prior to cycle 3 and cycle 5 in conjunction with ILD chest CT and then every 6 weeks to monitor for ILD. DLCO was corrected for hemoglobin. Clinical symptoms including cough, shortness of breath, dyspnea, and new or worsening respiratory symptoms were recorded. For pts that experienced more than a 10% decrease in corrected DLCO (DLCOc), a pulmonology consult was recommended. DLCOc was reviewed in combination with chest imaging and clinical history to evaluate for ILD and guidance was provided for continuation or cessation of T-DXd. Results: A total of 33 patients with HER2-positive (N=27) and HER2-low (N=6) ABC were monitored as per the predefined ILD monitoring protocol. There were 5 confirmed cases of ILD/pneumonitis within the pt cohort. 16 patients (48%) experienced DLCOc decreases $>10\%$ warranting a pulmonology consult or further review. Upon further assessment, ILD/pneumonitis was ruled out based on chest imaging and/or asymptomatic presentation in 11 patients and therapy continued without treatment delay or discontinuation. There were 5 confirmed cases of ILD/pneumonitis within the patient cohort. 3 of the 5 patients diagnosed with ILD experienced DLCOc decreases $\geq 10\%$, while 2 of the 5 diagnosed patients had DLCOc changes of $< 10\%$ but had concern for ILD on ILD/chest CT and were diagnosed after pulmonology consult. Additional results to be presented at meeting. Conclusion: For patients receiving T-DXd, implementation of a comprehensive protocol to monitor and assess for ILD secondary to treatment may allow patients with suspected ILD to begin treatment sooner or prevent permanent discontinuation by excluding ILD diagnosis. While PFT monitoring can be helpful for

some patients to monitor for ILD, continuous PFT monitoring is not recommended for all patients given inconsistency. However, baseline PFTs prior to initiation and with suspected ILD in combination with imaging warrants further investigation. The use of a multidisciplinary team including pulmonologists experienced with T-DXd-induced ILD may assist in diagnosing or excluding ILD and allow for continuation of T-DXd therapy.

PO5-13-01

An App-Based Approach to Monitor Chemotherapy Symptoms

Presenting Author(s) and Co-Author(s):

O. Globus. Sheba Medical Center, Israel

T. Sella. Sheba Medical Center, Tel Aviv, Israel

A. Itay. Sheba Medical Center, Israel

T. Shapira. Sheba Medical Center, Israel

R. Gold. Sheba Medical Center, Israel

T. Modiano. Sheba Medical Center, Israel

C. Oedegaard. Sheba Medical Center, Israel

M. Krikli. Sheba Medical Center, Israel

M. Bakalenik-Gavry. Sheba Medical Center, Israel

B. Shaham. Sheba Medical Center, Israel

A. Galper. Sheba Medical Center, Israel

E. Gal-Yam. Breast Oncology Institute Sheba Medical Center, Ramat-Gan, Not Applicable, Israel

Introduction

Patient-Reported Outcome Measures (PROM's) are important tools that can enhance symptom management and patient quality of life in cancer treatment. Despite well-documented benefits, they are not often employed in routine care. This study aims to investigate the feasibility and acceptance of the integration of a dedicated mobile app for real-time symptom tracking and intervention using PROM's among patients undergoing neoadjuvant or adjuvant chemotherapy for breast cancer.

Methods

We developed a dedicated mobile app for tracking PROM's utilizing the NCI PRO-CTCAE to monitor 12 common chemotherapy-related symptoms. We aimed to evaluate patient acceptance and clinical feasibility of the app. Patient responses were directed to a personalized dashboard for designed for the clinical treatment team. We determined self-reported grade 3 or 4 vomiting, diarrhea, constipation, shortness of breath, cough, or peripheral neuropathy and grade 4 mucositis, nausea, or pain as symptoms severe enough to trigger an automatic alert requiring a phone call from our nursing staff for support. Each questionnaire generated up to 1 alert regardless of the number of severe symptoms. Symptomatic patients also received personalized automated instructions and video links for symptom management regardless of the severity of their symptoms. In response to staff feedback during the study, we added an additional assessment to determine whether patients with severe symptoms were interested in direct contact from the clinical staff when alerts were triggered. At baseline patients reported if they felt they were skillful at using smartphone apps. Quality of life, psychological and emotional health measures were collected at baseline, and weeks 6, 12, and 18. Categorical variable were described using percentages and compared using the chi squared test. Statistical analyses were performed by SPSS.

Results:

At the time of this analysis, 58 patients were recruited and found eligible for the study. All 58 patients self-reported as skilled with the use of smartphone apps. Eighteen patients (31%)

withdrew from the study after receiving at least one questionnaire and their data was included up to their point of withdrawal. The different chemotherapy regimens given in the study are shown in table 1. Out of 772 questionnaires sent, 404 were returned, resulting in a 52% completion rate. These 404 completed questionnaires generated 126 (31%) alerts. After including feedback on the interest of direct contact from our nursing staff to manage alarming symptoms, only 23/102 (22.5%) alerts required clinical contact. Twenty-one patients (36%) did not complete even a single questionnaire. For the 37 (64%) patients who completed at least 1 questionnaire the completion rate was 74%. There was no significant difference in the alert rate of completed questionnaires between patients receiving TCHP, TC-AC-Pembro, and AC-T (38%, 38%, 29% p=NS). TC triggered significantly less alerts than AC-T (11% vs 29% p=0.01).

Conclusion:

The interim results of our ongoing study highlight the potential of a mobile app in real-time monitoring of chemotherapy-related symptoms. Our results suggest symptom monitoring using a dedicated mobile app is both acceptable and feasible for both patients and clinical personnel. The digital approach also seems effective in triggering alerts for severe symptoms, facilitating timely intervention. However, most alerts did not necessitate direct clinical contact, underscoring the role these interventions may play in allowing for patient self-care. However, over a third of patients did not utilize the app at all, emphasizing the need for further research examining the factors influencing the utilization of this technology for symptom monitoring. As the study continues, we hope to gain insights that can simplify and improve patient and clinician interaction with this tool, potentially improving symptom management for adjuvant breast cancer.

Table 1 Chemotherapy Regimens

Protocol	DD-AC-T	TCHP	TC-AC-Pembro	TC	DD-AC-T weekly	TH	AC-THP	AC-TC
N (%)	14 (24%)	20 (35%)	11 (19%)	6 (10%)	3 (5%)	2 (3%)	1 (2%)	1 (2%)

DD AC-T dose dense doxorubicin cyclophosphamide paclitaxel, TCHP docetaxel carboplatin trastuzumab pertuzumab, TC-AC-Pembro paclitaxel carboplatin doxorubicin cyclophosphamide pembrolizumab, TC docetaxel cyclophosphamide, DD AC-T weekly dose dense doxorubicin cyclophosphamide paclitaxel weekly, TH paclitaxel trastuzumab, AC-THP doxorubicin cyclophosphamide paclitaxel trastuzumab pertuzumab, AC-TC doxorubicin cyclophosphamide paclitaxel carboplatin

PO5-13-02

BRCA mutational profiles of endocrine-resistant breast cancer

Presenting Author(s) and Co-Author(s):

E. Karlsson. Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, United States

C. Schagerholm. Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden, United States

S. Robertson. Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, United States

H. Toosi. Division of Computational Science and Technology, KTH Royal Institute of Technology and Science for Life Laboratory, United States

E. Sifakis. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden, United States

J. Hartman. Department of Oncology-Pathology, Karolinska, Institutet, Stockholm, Sweden; Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden, United States

Background

Around 75% of breast cancer (BC) patients have tumors expressing the treatment-predictive biomarker estrogen receptor α (ER) and are consequently offered endocrine therapy. One-third of these patients develop endocrine resistance, a majority with tumors that retain ER expression. For most cases, the resistance mechanism is still unknown, but mutational activity is a suggested mechanism. Germline BRCA mutations are well-known in BC and are found in approximately 23% of patients with triple-negative BC and in 5% of patients with ER+ BC. However, less is certain about the somatic variants, though studies have shown prevalences of around 3% in BC. This study aimed to examine the somatic BRCA mutational profiles of endocrine-resistant paired primary and relapse tumors.

Methods

A retrospective cohort of verified endocrine-resistant BC patients was collected at Karolinska University Hospital in Stockholm, Sweden. Patients diagnosed in 2008-2012 with an ER+ and human epidermal growth factor receptor 2 (HER2) negative primary tumor and a following ER+ and HER2- relapse tumor within five years of ongoing endocrine therapy were included (N=63). DNA was extracted from archived formalin-fixed paraffin-embedded relapse and primary tumor tissue and analyzed by panel sequencing. Tumor-free lymph nodes were used as germline normal samples.

Results

The analysis showed somatic BRCA mutational activity in 38.1% of the patients. Variants were present in 20.3% of primary tumors and 30.4% of relapse tumors. BRCA1 mutations were present in 11.9% of primary tumors and 21.4% of relapse tumors. BRCA2 variations were, in turn, seen in 11.9% of primary tumors and 14.3% of relapse tumors. The frequency of patients that had alterations in both the primary and relapse tumors was 3.2% for BRCA1 and BRCA2 respectively.

Conclusion

This study of a unique endocrine-resistant BC cohort shows a high presence and varying

distribution of somatic BRCA mutations in both primary and even higher in relapse tumors. These results suggest that mutational testing for possible further treatment decisions may be relevant for patients exhibiting endocrine resistance, especially in the advanced setting.

PO5-13-03

Early Detection of Breast Cancer using Targeted Plasma Metabolomic Profiling

Presenting Author(s) and Co-Author(s):

J. Haince. BIOMARK DIAGNOSTIC SOLUTIONS, Canada

L. Zhang. The Metabolomics Innovation Centre, United States

R. Bux. BIOMARK DIAGNOSTICS, United States

P. Tappia. Asper Clinical Research Institute, St. Boniface Hospital, United States

B. Ramjiawan. Asper Clinical Research Institute, St. Boniface Hospital, United States

D. Wishart. Department of Biological Sciences, University of Alberta, United States

A. Maksymiuk. Cancer Care Manitoba, United States

Background:

Breast cancer (BC) is the second leading cause of cancer death among women. Accordingly, early diagnosis is key to the successful treatment, management, and care of BC. Recent studies confirmed that plasma metabolites could be reliable cancer biomarkers, allowing for the development of a minimally invasive routine blood test that can be used for screening, as well as for monitoring disease evolution in patients. The exact metabolic pathways involved in early BC development remain unclear. Metabolomic profiling of women with BC may help to identify new biomarkers to predict breast cancer long before symptoms appear. The purpose of this study was to validate a plasma metabolomic biomarker panel for an improved risk assessment for early detection BC in 241 patients, and to understand the potential role and the relationship between BC subtypes and hormone receptor status.

Methods:

Our study included a total of 185 plasma samples from women with biopsy-confirmed BC and 56 plasma samples from healthy controls. A targeted, quantitative mass spectrometry (MS)-based metabolomics approach was used to analyze 138 metabolites in plasma samples using a combination of direct injection (DI) MS and reverse-phase high performance liquid chromatography (HPLC) tandem mass spectrometry (MS/MS). The sample set was split into a discovery set and validation set. Metabolite concentration data, clinical data, and hormones receptor status were used to determine optimal biomarker sets. The same biomarkers and regression models were used and assessed on the validation models. The area under the receiver operator characteristic curves (AUROC), sensitivities and specificities at selected cut off points were calculated for each subgroup.

Results:

A large proportion of BC patients were at an early stage, with 98 at stage I (53.0 %), 70 at stage II (37.8%), and 17 at stage III (9.2%). The BC patients were of all subtypes: 138 luminal A (76.2%), 23 luminal B (12.7%), 5 hormone receptor-negative/HER2-positive (2.8%), and 15 triples negative (8.3%). A feature selection was performed on the training set using Partial Least-Squares Discriminant Analysis (PLS-DA), and the top performing metabolites were identified as the most important in discriminating BC from healthy subjects. The impact of age was also investigated. Features with >80% missing values were removed. To predict BC, the best signature comprised 9 variables implicated in fatty acid metabolism, amino acid metabolism, polyamine biosynthesis and related signaling pathways. We further developed and validated a logistic regression with AUROC > 0.9 using these metabolites and other clinical data for detecting different stages and subtypes of BC.

Conclusion:

This study identified and validated a simple, high-performing, metabolite-based test for the early detection of BC. After confirmation in other independent cohort studies, our findings could provide the foundations for the development of a blood-based routine test for women at the highest risk for BC that is cost-effective, accurate and reliable. In addition, this approach could be used to complement other modalities especially for BC patients with dense breasts.

PO5-13-04

Breast Cancer Index (BCI) results from a HER2 low breast cancer community cohort of operable stage I-II hormone receptor positive (HR+) breast cancer

Presenting Author(s) and Co-Author(s):

M. Dolezal. Stanford Healthcare, Emeryville, California, United States

M. Pegram. Stanford School of Medicine, United States

Background

Hormone receptor positive (HR+) breast cancer (BC) traditionally included HER2-negative or HER2-positive classifications. The BCI test is a quantitative RNA profile assay applied to HR+ early-stage breast cancers from archival pretreatment surgical specimens. The BCI assay estimates the likelihood of distant recurrence (DR) during years 5-10 (prognostic result) and predicts extended endocrine therapy benefit (ETT)(i.e., BCI (H/I)-High, yes benefit) or no benefit (i.e., BCI (H/I)- Low) for patients who have completed 5 years of adjuvant endocrine therapy (AET).

Based on the Destiny Breast 04 trial, an antibody drug conjugate (ADC) anti-HER2 therapy was recently approved for treating metastatic HR+HER2 low BCs, which are currently defined as tumors with either HER2 immunohistochemical (IHC) staining of 1+ or IHC 2+ without HER2 gene amplification. Primary archival specimens were eligible for enrollment on the Destiny Breast 04 trial (35%). Quality control of IHC result categories is needed due to new clinical implications in the metastatic setting. To date, BCI results for tumors classified as HER2 low has not been reported.

Objectives

Determine the average BCI distant DR risk (prognostic result) and the proportion of tumors with BCI (H/I)-High, yes benefit versus BCI (H/I)-Low, no benefit (predictive result) from a small community-based retrospective study of pretreatment samples from a cohort of HER2 low, HR+ breast tumors.

Methods

Around completion of 5 years of AET, BCI testing was applied to 110 surgically excised archived stage I and 2 HR+ untreated tumors that were collected between 2017 and 2022. Specimens had paired HER2 local pathology IHC and in-situ hybridization (ISH) results.

Results

32 tumors were identified as HER2-low including 26 specimens with HER2 IHC 1+ results and six HER2 IHC 2+ tumors with non-amplified HER2 ISH results. Given this was a small exploratory analysis, statistical significance was deliberately not evaluated.

Prognostic Results: The average estimated DR risk during years 5-10 was 8% for tumors classified as HER2-low (Range 1.3-17.5%).

For 26/32 patients with HER2 IHC1+, the average DR risk was 7.4% (Range 1.3-17.5%).

For 6/32 patients with HER2 IHC 2+ and non-amplified HER2 ISH results, the average DR risk was 4.6% (Range 1.6-8.6%).

Predictive Results: Of the 32 HER2-low tumors, 15/32 (47%) were BCI (H/I)-High (yes benefit)

compared to 17/32 (53%) which were BCI (H/I)-Low (no benefit).

Conclusions

The prevalence of HER2 low tumors appears to be as high as 67% in reports to date. In this small series, the prevalence of HR+ HER2 low tumors was 29% (32/110). The average DR risk in these HR+ HER2 low cases was roughly 8% which represents a DR risk that is very similar to the average DR risk of 7.4% for HR+ HER2 negative tumors reported from one of the large BCI validation studies (TransATAC).

In this series of HER2 low BCs, the proportions of BCI (H/I)-High (yes benefit) and BCI (H/I)-Low (no benefit) tumors were 47% and 53%, compared with 46% and 54%, respectively, in three large BCI validation studies (Trans-aTTom, B42, IDEAL) for HER2 negative tumors.

Although this is a small retrospective series, these results suggest that HER2 low tumors are, by BCI testing, very similar to HER2 negative tumors in DR risk (prognostic results). Also, it appears that BCI (H/I)-High (yes benefit) and BCI (H/I)-Low (no benefit) proportions (predictive results) for HER2 low tumors appear similar to reported results for HER2 negative tumors.

Follow-up data from larger series are needed to determine if BCI testing is prognostic and predictive for HER-2 low BCs.

PO5-13-05

Comparison of whole exome, whole transcriptome genomic profiling and targeted sequencing with 50-gene panels

Presenting Author(s) and Co-Author(s):

S. Thakkar. Exact Sciences, United States

D. Hall. Exact Sciences, United States

J. Hoag. Exact Sciences, United States

C. Flannery. Exact Sciences, United States

N. Therala. Exact Sciences, United States

A. Tharayanil. Exact Sciences, United States

J. Ortendahl. Stratevi, United States

G. Carter. Exact Sciences, United States

G. Basu. Exact Sciences, United States

Introduction

Genomic profiling to identify targetable genomic alterations is the standard of care in the management of advanced cancers, including breast cancer (BC), and is recommended by ASCO provisional clinical guidelines. Genomic panels of ≤ 50 genes are generally less expensive than larger panels but may miss targetable alterations. This study compared a comprehensive tumor-normal whole-exome, whole-transcriptome panel to four 50-gene panels. In addition, for triple-negative BC (TNBC), the budget impact of using a comprehensive panel versus 50-gene panels was estimated.

Methods

Gene lists derived from three commercially available 50-gene panels (A, B and C) and a customized pan-cancer gene panel list (D) were used. The genes listed on the custom panel were chosen by medical experts. Samples from BC patients that underwent OncoExTra™ testing from May 2018 through March 2023 were included. The OncoExTra assay uses tumor-normal whole exome and whole transcriptome sequencing to detect somatic single base substitutions, indels, copy number alterations, gene fusions and alternative transcripts. In this analysis, the focus was actionable biomarkers, defined as those with associated FDA-approved targeted therapies in any cancer type, those that made patients eligible for an active clinical trial, or those with evidence in guidelines or the literature for possible matched therapies in any cancer. The frequencies of patients who would have been missed (no actionable alterations identified) using only the genes on each 50-gene panel were summarized. It was assumed that any alteration involving a listed gene would be detected, maximizing the potential utility of each panel. For TNBC, the budget impact of shifting the 20% of patients currently tested with 50-gene panels to OncoExTra testing was estimated using a previously published model.

Results

A total of 2161 BC patient samples were included. Across all samples, between 11.9% and 28.1% of patients would have been missed by restricting to only 50 genes (Table 1). The proportion of missed patients across panels was highest in TNBC and lowest in HER2+ cancers. Major drivers of missed patients included absence of FGF3/4/19 (A-D), MAP3K1 (A-D), BRCA1/2 (A, B, C), CCND1 (B, C, D), and PTEN (A, D). Across the four panels, patients were missed due to actionable alterations in 96 to 126 genes. Tumor mutational burden and

microsatellite instability, which are not reported in 50-gene panels, were high in 35 (1.6%) and 7 (0.3%) BC patient samples, respectively.

Within a 1-million-member plan, 44 TNBC patients would be eligible for testing. If all these patients were tested with OncoExtra rather than a 50-gene panel, the increase in per-member-per-month costs ranges from \$0.0104-0.0172, driven predominantly by increased matched therapy costs. Between two and five TNBC patients would be eligible to receive a different treatment with a comprehensive panel.

Conclusions

In BC, between 11.9% and 28.1% of patients with actionable alterations would have been missed by restricting analysis to the 50 genes found in these panels. Using a comprehensive profiling assay such as OncoExTra led to the identification of additional TNBC patients with actionable alterations at a minimal budget impact.

Table 1. BC patients (pts) with actionable alterations missed by each 50-gene panel. NS = subtype not specified.

Breast cancer subtype	Total (% of total) pts	Number (%) pts with actionable alterations missed by A	Number (%) pts with actionable alterations missed by B	Number (%) pts with actionable alterations missed by C	Number (%) pts with actionable alterations missed by D
All	2161 (100%)	542 (25.1%)	297 (13.7%)	258 (11.9%)	607 (28.1%)
HR+ HER2-	1413 (65.4%)	315 (22.3%)	257 (18.2%)	226 (16.0%)	396 (28.0%)
HER2+	347 (16.1%)	22 (6.3%)	8 (2.3%)	6 (1.7%)	23 (6.6%)
TNBC	306 (14.2%)	176 (57.5%)	11 (3.6%)	11 (3.6%)	158 (51.6%)
NS	95 (4.4%)	29 (30.5%)	21 (22.1%)	15 (15.8%)	30 (31.6%)

PO5-13-06

Classifying HER2-low breast cancer using a combination of ERBB2 mRNA expression and altered genes

Presenting Author(s) and Co-Author(s):

G. Basu. Exact Sciences, United States

N. Chennagiri. Exact Sciences, United States

T. Dogruluk. Exact Sciences, United States

D. Hall. Exact Sciences, United States

J. Hoag. Exact Sciences, United States

C. Flannery. Exact Sciences, United States

S. Thakkar. Exact Sciences, United States

M. Palomares. Exact Sciences, United States

F. Baehner. Exact Sciences, SAN FRANCISCO, California, United States

L. pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

Background

It has been recently demonstrated that some HER2-low, defined as immunohistochemistry (IHC) 1+ or 2+ with no gene amplification by FISH, breast cancer (BC) patients respond to trastuzumab deruxtecan (T-DXd). Results of the DAISY trial also suggested clinical activity with T-DXd in some of those classified as HER2-0 cancers by IHC, indicating an unmet need to better identify cancers that may truly respond to T-DXd. We compared ERBB2 (HER2) mRNA expression obtained from whole-transcriptome sequencing with IHC/FISH assignment of HER2 status. Furthermore, we constructed a classifier using ERBB2 expression and alterations in other genes as a proof of concept to illustrate classification of BC samples into HER2-0 versus HER2-low status.

Methods

We chose consecutive HR positive/HER2-negative BC samples that were submitted for OncoExTra™ testing between April 2020 and October 2022. The OncoExTra test uses tumor-normal whole exome and whole transcriptome sequencing to detect somatic single base substitutions, indels, copy number alterations, gene fusions and alternative transcripts. In addition, we investigated the expression profile of select genes for this analysis. We utilized OncoExTra data to examine the relationship between HER2 IHC status and gene expression, mutation and copy number profiles of selected genes, and built a classifier to predict HER2 status.

Results

A total of 279 BC samples were analyzed, including 106 HER2-IHC 0, 120 HER2-IHC 1+ and 53 HER2-IHC 2+. Of these, 273 were primary and 6 were metastatic samples. The distributions of patient age and tumor fraction were similar among these categories ($p=0.54$ and $p=0.41$, respectively; one-way ANOVA). ERBB2 expression differed among all three HER2-IHC categories and was lowest in HER2-0 and highest in HER2-2+ (HER2-0 vs HER2-1+, $p<0.001$; HER2-0 vs HER2-2+, $p<0.0001$; HER2-1+ vs HER2-2+, $p=0.011$; HER2-0 vs HER2-low, $p<0.0001$; Mann-Whitney U test in all comparisons). Five genes were mutated in more than 10% of samples: PIK3CA (45.5%), GATA3 (15.4%), CDH1 (12.5%), MAP3K1 (11.1%) and TP53 (10.8%). Mutations in two genes, GATA3 and PTEN, appeared to differ in frequency between

the HER2-0 and HER2-low categories (Table 1). We selected 4 genes with mutations, 2 genes with copy number changes, and expression from ERBB2, ESR1, CD274, HLA-A, HLA-B and HLA-C to train a logistic regression classifier to predict HER2 IHC status. The classifier was trained on 163 samples, hyperparameter tuning was done using 55 samples, and testing was performed on 61 samples. Preliminary results indicated that of the 28 HER2-IHC 0 samples in the test set, 17 (65%) were classified as HER2-low. Further development and evaluation of the classifier using a blinded testing set is currently in progress.

Conclusion

In this cohort of BC samples, ERBB2 mRNA expression was positively associated with HER2 protein IHC status. Additional studies are required to determine whether a classifier including ERBB2 mRNA expression could be used to identify patients for T-DXd therapy. The relative enrichment of PTEN alterations in HER2-IHC 0 samples suggests that mTOR /AKT inhibitors may sometimes be appropriate in patients who are not eligible for T-DXd therapy, and further investigation should be considered.

Gene	HER2-0 n=106 n (%)	HER2-1+ or 2+ n=173 n (%)	p- value*
<i>GATA3</i>	9 (8.5%)	34 (19.7%)	0.012
<i>PTEN</i>	10 (9.4%)	6 (3.5%)	0.038
<i>TP53</i>	16 (15.1%)	14 (8.1%)	0.06
<i>MAP3K1</i>	8 (7.5%)	23 (13.3%)	0.13
<i>BRCA2</i>	1 (0.9%)	8 (4.6%)	0.16
<i>ARID1A</i>	4 (3.8%)	12 (6.9%)	0.27
<i>CDH1</i>	16 (15.1%)	19 (11.0%)	0.31
<i>PIK3CA</i>	51 (48.1%)	76 (43.9%)	0.49
<i>AKT1</i>	6 (5.7%)	8 (4.6%)	0.70
<i>RUNX1</i>	5 (4.7%)	7 (4%)	0.77
<i>KMT2C</i>	8 (7.5%)	13 (7.5%)	0.99

*p-value was calculated using Fisher's Exact Test for *BRCA2* and *RUNX1* and using Chi-Squared Test for the other genes.

Table 1. Number (frequency) of altered genes by HER2 IHC status.

PO5-13-07

Prediction of recurrence in triple negative breast cancer patients after receiving neoadjuvant treatment using plasma metabolomics

Presenting Author(s) and Co-Author(s):

P. Sánchez-Rovira. Hospital Universitario de Jaén, Jaén, Spain, Andalucía, Spain

R. Urbano-Cubero. Hospital Universitario de Jaen, United States

A. Gamez Pozo. Molecular OncologyLab, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain, United States

C. González-Olmedo. Hospital Universitario de Jaen, United States

A. Cano-Jimenez. Hospital Universitario de Jaen, United States

A. Zapater- Moros. Hospital Universitario La Paz-IdiPAZ, United States

L. Díaz-Beltrán. Department of Experimental Biology, University of Jaén, United States

L. Trilla-Fuertes. Molecular OncologyLab, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain, United States

M. Díaz-Almirón. Hospital Universitario La Paz-IdiPAZ, United States

E. Espinosa. Hospital Universitario La Paz, Madrid. GEICAM Spanish Breast Cancer Group, Madrid, Spain, United States

P. Zamora. Hospital Universitario La Paz, Madrid, Spain, Madrid, Spain

J. Fresno Vara. Molecular OncologyLab, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain, United States

Background

Early-stage triple-negative breast cancer (TNBC) is usually treated with neoadjuvant chemotherapy (NADC), but prognosis remains poor compared with other BC subtypes. Unfortunately, less than 30% of BC patients achieve pathological complete response (pCR) to NADC and the overall survival of TNBC when cancer spreads is estimated at 10-13 months. Complete response is associated with improved progression-free and overall survival rates, but more accurate prognostic markers are needed. In this study, we assessed the prognostic value of blood circulating metabolites by using targeted-based metabolomics.

Methods

Patients received standard neoadjuvant chemotherapy with epirubicin plus cyclophosphamide followed by paclitaxel. Blood samples were obtained upon completion of chemotherapy and before surgery. Pathological response to treatment was recorded according to the Miller & Payne system, and categorized as partial (MP 1, 2, & 3) or complete response (MP 4 & 5). Blood samples were collected in EDTA tubes, centrifuged and plasma was stored at -80°C. After QC standard addition and methanol extraction of proteins, four fractions of the resulting extract were analysed: two by reverse-phase/UPLC-MS/MS methods with positive ion mode electrospray ionization (ESI), one by reverse phase/UPLC-MS/MS with negative ion mode ESI, and one by hydrophilic interaction liquid chromatography/UPLC-MS/MS by Metabolon using a Thermo Scientific Q-Exactive mass spectrometer with a heated electrospray ionization source and an Orbitrap mass analyser. Using Metabolon's hardware and software, raw data were extracted, identified, QC processed and quantified using the area under the curve (AUC). Identified compounds were compared with library entries of purified standards or recurrent unknown entities. The prognostic capacity of each metabolite was assessed using BRB ArrayTools. Selected metabolites were validated using a targeted approach using compound

standards as follows. Plasma samples were re-analysed by UPLC/MS using a Vanquish LC coupled to an Orbitrap Exploris 240 MS (Thermo Fisher Scientific) with positive and negative ionization mode ESI under polarity switching. Identification of compounds were performed by comparison of retention times (against in-house authentic standards), accurate mass (with an accepted deviation of 3ppm), and MS/MS spectra. These analyses were carried out by MS-Omics (Denmark).

Results

Twenty patients treated in the Medical Oncology Unit of the University Hospital of Jaén were recruited. Median age was 50 (31-76). Twelve patients obtained a pathological complete response. Median follow-up after surgery was 25 months. Seven patients eventually had distant metastases (2 in the lungs, 1 in the brain, 1 in the bones and 3 multi-site). Metabolon untargeted analysis identified and quantified 985 metabolites, 789 after xenobiotics exclusion. Survival analysis identified 16 metabolites related with distant relapse ($p < 0.05$). The ten metabolites with lower p-value were selected for targeted validation. Ms-Omics pipeline allowed absolute quantification of 5 metabolites, 3 of them showing high correlation ($R > 0.7$) between both measurements (targeted and untargeted). Validation of the prognostic value of the candidate metabolites is ongoing in a larger TNBC cohort.

Conclusions

Metabolomics is a useful tool for the detection of simply assessable and cost-effective prognostic biomarkers in TNBC. Easily monitoring the presence of minimal residual disease is worth to be settled up in the clinical practice for the most aggressive molecular subtype of breast cancer. In this work we have defined a set of metabolites that could predict distant relapse events in TNBC patients treated with neoadjuvant chemotherapy. Further analyses are being carried out to validate the prognostic value of the proposed candidate metabolites.

PO5-13-08

Impact of systemic inflammation markers in response to neoadjuvant pembrolizumab and chemotherapy in triple-negative breast cancer - a retrospective analysis

Presenting Author(s) and Co-Author(s):

M. Spotti. Research Department - Interdisciplinary Department for Patient Pathway Organization (DIOPP), Gustave Roussy Cancer Campus, Grand Paris, France, United States

E. Rassy. Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France, United States

A. Viansone. Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France, United States

F. Pham. Gustave Roussy, Département de Pharmacie Clinique, F-94805, VILLEJUIF France, United States

L. Rached. Gustave Roussy, Département d'Innovation Thérapeutique et d'Essais Précoces, F-94805, VILLEJUIF France, United States

B. Pistilli. Gustave Roussy, Villejuif, Not Applicable, France

C. Dutertre. Paris-Saclay University, Gustave Roussy, INSERM U981, PRISM Center, F-94805, VILLEJUIF France/Institut National de la Santé Et de la Recherche Médicale (INSERM) U1015, Equipe Labellisée—Ligue Nationale contre le Cancer, F-94805, VILLEJUIF France, United States

J. Ribeiro. Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France/Paris-Saclay University, Gustave Roussy, INSERM U981, PRISM Center, F-94805, VILLEJUIF France, United States

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment landscape for triple-negative breast cancer (TNBC). Systemic inflammation has been linked to cancer development and overall poor outcomes. Routine blood parameters have been investigated as potential inflammatory biomarkers in patients (pts) with various types of cancer, such as the derived NLR (neutrophils/leucocytes-neutrophils) ratio (dNLR).

A high dNLR has been associated with worse survival in several types of cancer. Specifically, it has been linked to lower pathologic complete response (pCR) rates after neoadjuvant chemotherapy (CTx). We investigated the association between systemic inflammation markers (dNLR, LIPI score and platelet-to-lymphocyte ratio [PLR]) and pCR in early TNBC pts treated with CTx + pembrolizumab (Pemb).

Methods: Retrospective analysis of pts with early TNBC treated with Pemb + CTx from April 2022 to March 2023. dNLR was estimated from analytical values of peripheral blood collected before treatment (baseline). dNLR was calculated as the ratio of the absolute neutrophil number to the difference between absolute total leukocyte and absolute neutrophil counts. Univariate and multivariate logistic regression analyses were used to explore the association of dNLR with main clinical characteristics and dNLR capability (distributed as a continuous variable, using median cut-off) to predict pCR.

Results: The study included 86 TNBC pts with a median age of 51 years (IQR: 42.2 – 56-7). Most pts had stage II disease (64%) and presented grade 3 tumours (n=66; 78.5%). HER2 low tumours represented 27% (n=23) of the cohort. Germline mutations were present in 20 pts (23%) with the following distribution: BRCA1 (n=14), BRCA 2 (n=5) and PALB2 (n=1). The

median stromal tumor infiltrating lymphocytes (TILs) was 20% (IQR: 10-30%). The median Ki67 was 70% (IQR:50%-80%). All pts received Pemb. The majority of pts received carboplatin plus paclitaxel, followed by EC90 (n=77 (90%), while 10% (n=9) did not receive anthracyclines.

Data concerning surgical outcomes was available in 80 pts. Pathological complete response rate was 61.2% (n=49). Pts achieving pCR presented significantly higher TILs ($p < 0.01$). Residual cancer burden (RCB) class (n=80) was distributed as follows: 0: 61% (n=49); I: 13% (n=10); II: 20% (n=16); III: 1% (n=1) and non-assigned: 5% (n=4). In pts with germline mutations (n=20), the pCR rate was 85% (n=17).

Median dNLR at baseline was 1.30 (interquartile range (IQR): 0.99 – 1.86). High baseline dNLR levels considered a continuous variable was associated with a higher likelihood of achieving a pCR in univariate (OR: 2.59; 95% CI: 1.01–6.6; p-value = 0.046) but not in multivariate (OR: 2.33; 95% CI: 0.85–6.33; p-value = 0.097) logistic regression analysis (adjusted for stage and histologic grade).

High baseline dNLR, defined by the median cut-off, was associated with an increased likelihood of achieving pCR in both univariate (OR: 3.85; 95% CI: 1.47–10.1; p-value = 0.006) and multivariate (OR: 3.72; 95% CI: 1.28–10.8; p-value = 0.016) logistic regression analysis (adjusted for stage and histologic grade).

Conclusion: In this real-life cohort of early TNBC pts treated with Pemb and CTx we found similar pCR rates (61.2%) to the ones reported in the KN522 trial. No association between PLR or LIPI score with pCR was evidenced. High baseline dNLR (assessed as a continuous variable or by the median cut-off) was associated with a higher likelihood of pCR in the univariate analysis. In the multivariate analysis, only high baseline dNLR defined by the median cut-off retained an association with pCR after stage and histologic grade adjustment. Despite several limitations, these exploratory data provide initial evidence of a potential association between dNLR values and independent prediction of pCR. Further research to assess the role of dNLR as a predictive marker for pCR in early TNBC pts treated with CTx + immunotherapy is needed.

PO5-13-09

Clinical usage of a CLIA accredited protein/phosphoprotein assay for breast cancer: Primary usage cases and significant findings in the HER2- setting.

Presenting Author(s) and Co-Author(s):

C. Mueller. Theralink Technologies, United States

B. Corgiat. Theralink Technologies, United States

E. Petricoin. George Mason University, United States

K. Sparks. Theralink Technologies, United States

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

C. Gawryletz. UCHHealth, Fort Collins, Colorado, United States

M. Schwartz. Comprehensive Cancer Centers of Nevada, United States

J. Davis. Theralink Technologies, Inc, United States

Clinical usage of a CLIA accredited protein/phosphoprotein assay for breast cancer: Primary usage cases and significant findings in the HER2- setting.

Mueller C, Corgiat B, Petricoin E, Sparks K, Gawryletz C, O'Shaughnessy J, Schwartz M, , Davis JB.

Background: A CLIA-accredited assay that measures the expression and/or activation levels of 32 clinically actionable protein and phosphoprotein analytes in clinical tissue biopsy samples was launched in January 2021. The current intended use population for the assay is for patients with late/advanced stage breast cancer wherein molecular profiling is being utilized for clinical decision making. Assessment of physician ordering practices, clinical use dynamics as well as protein/phosphoprotein actionability frequencies were determined for clinically actionable biomarkers.

Methods: A total of 219 cases have been processed to date, with mean turn-around time of 16.4 days. The assay utilizes laser capture microdissection to enrich tumor epithelium from FFPE core needle biopsy and resection material coupled to reverse phase protein array. Results for each of the 32 analytes are generated by comparing each patient to a reference population and reported both as a relative quartile and as a continuous percentile compared to the reference population (0-100%). For the purposes of this analysis, significant expression/activation cutpoints were set at the 40th percentile threshold.

Results: To date, clinicians have requested the test most frequently to identify potential therapeutic targets in patients with HER2-negative disease (84% of all tested patients, 36% were triple-negative). Despite the majority of cases being HER2-negative, we found that phosphorylated (p) HER2 (Y1248) was found to be activated in 17% of all HER2-negative cases and 19% of triple negative breast cancer cases (TNBC). pHER2 was concurrently activated with pHER3 (Y1289) in 15% (12/80) of TNBC cases and 13% (24/187) of all HER2-negative cases. pHER2 presented concurrently with pEGFR (Y1068 or T654) in 14% (11/80) of TNBC cases and 14% (26/187) of all HER2- cases. Expression of TROP2 was observed in 16% of HER2-negative patients including 11% of ER+/HER2- and 23% of TNBC cancers. MHCII expression, a recently described candidate predictive biomarker of anti-PDL1/PD1 response in TNBC, was found to be expressed in 29% of TNBC patients. Activation frequencies

of other clinically relevant drug targets in HER2-negative disease such AKT and mTOR pathway activation was also assessed. We found that pAKT (S473 and/or T308) was activated in 7% of ER+/HER2- cases and 14% of TNBC. Concurrent with AKT activation, at least one additional member of the AKT-mTOR pathway (mTORC1 (S2448), 4E-BP1 (S65), p70S6K (T389), or S6RP (S235/S236) was co-activated in 50% and 45% of ER+/HER2- and TNBC cancers respectively.

Conclusion: This initial assessment of a CLIA LDT protein/phosphoprotein assay utilized to date found that physicians most often order the test for advanced stage HER2-negative breast cancer. Activation/expression of clinically important protein drug targets with potential actionability in HER2-negative disease was observed in a significant number of cases and demonstrates the power of the assay to elucidate actionable targets for potential therapeutic intervention.

PO5-13-10

Determining tumor-driving cell signaling pathways in breast cancer: Support for targeted therapy selection.

Presenting Author(s) and Co-Author(s):

P. van de Wiel. InnoSIGN, Noord-Brabant, Netherlands

Y. Wesseling-Rozendaal. InnoSIGN, Netherlands

A. Pierik. InnoSIGN, Netherlands

D. van Strijp. InnoSIGN, Eindhoven, Netherlands

S. vermeer. InnoSIGN, Netherlands

F. Tashrifwala. Stamford Health, Connecticut, United States

J. Hartnett. Stamford Hospital, Connecticut, United States

R. Babkowski. Stamford Health, Connecticut, United States

S. Rose. Research Department, Stamford Hospital, Connecticut, United States

Introduction:

Success of therapeutic interventions largely rely on the pathological and biological characteristics of the tumor and varies due to the heterogeneous nature of breast cancers. Signal transduction pathways play an important role and are often used as target for specific therapies like hormone treatment, PI3K inhibitors etc. Immunohistochemistry (IHC) is currently the first assessment to divide tumors for subtyping and treatment and, especially in more advanced disease, mutation analyses are often used. Both IHC and mutation analyses only analyze a specific part of a signal transduction pathway and do not correlate well with outcome. Therefore, there is a need for new approaches to look at signaling pathways in cancer. We have developed a methodology that measures and quantifies signal transduction pathways (STPs) activities to reveal potential tumor-driving STPs to identify new options for targeted therapy in breast cancer.

Method:

Using the mRNA-based OncoSIGNal pathway activity profiling qPCR test (InnoSIGN), STP activities of 7 pathways (AR, ER, PI3K, MAPK, HH, TGF β and Notch) were measured and quantified on a scale from 0-100. By using a set of non-tumor epithelial breast tissue samples, a reference range for normal physiological pathway activity was defined. A threshold was set on the 95th percentile of this range. A pathway activity score above this threshold was considered to be high (activated). Using this methodology, 201 ER positive (based on IHC) and 64 triple negative FFPE breast tumor samples obtained from different study sites and commercial biobanks were analyzed, including samples from primary and metastatic lesions, to determine for each individual tumor its pathway activity profile and identify activated tumor-driving pathways.

Results:

In the 195 primary ER positive tumors, the ER pathway was found to be activated in 78% of the samples, even though all samples were strongly ER immunohistochemistry stain positive. In addition to ER pathway activation, occasionally other pathways were activated: PI3K in 37%, HH in 25%, MAPK in 19%, AR in 20%, TGF β in 6%, and Notch in 1%, of these samples.

Analysis of 27 metastatic samples of ER positive tumors revealed in only 63% an active ER

pathway. Additionally, more frequently PI3K pathway was observed in 70% of the samples. Other frequencies of pathway activation were: AR in 7% and MAPK in 4%, No Notch and TGF β activity was found in this cohort.

In 76 of the 78 triple negative tumors (TNBC) the ER pathway was inactive as expected. Remarkably, 2 samples appeared to have an activated ER pathway. An activated MAPK pathway was found in 50%, PI3K in 49%, HH in 18%, AR in 14%, TGF β in 5% and Notch in 3% of these TNBC tumors.

Conclusion:

Compared to ER positive primary tumors we observed in metastatic ER positive tumors less frequent activation of the ER and more frequent activation of the PI3K pathway, suggesting that the latter pathway is associated with a more aggressive tumor phenotype.

The triple negative subtype is characterized predominantly by activation of the PI3K, MAPK, AR and/or HH pathways, which may create new options for personalized targeted therapy of this subtype.

OncoSIGNAL can be used to determine the tumor driving signaling pathways in breast cancer patients, guiding selection of personalized targeted therapies.

PO5-13-11

Quantitative Assessment of HER2 Expression in Intraductal Neoplasms of the Breast

Presenting Author(s) and Co-Author(s):

N. Chan. Yale School of Medicine, New Haven, Connecticut, United States

h. Zhan. Yale University, United States

R. Khaimova. Alexion, AstraZeneca Rare Disease, United States

T. Aung. Yale University, New Haven, Connecticut, United States

C. Robbins. Yale, United States

P. Gaule. Yale University, United States

D. Rimm. Yale University, New Haven, Connecticut, United States

HER2 (ERBB2) is an established prognostic and predictive marker for patients with invasive breast cancer and used in HER2-targeted therapy. The clinical and biological significance of expression of HER2 protein in patients with intraductal neoplasms of the breast is not well characterized. In this study, we used our HS-HER2 (High Sensitivity-HER2) which is a CAP/CLIA certified laboratory derived test (LDT) using quantitative immunofluorescence (QIF). We evaluated HER2 expression in DCIS (ductal carcinoma in situ), LCIS (lobular carcinoma in situ) and benign lesions to correlate with their clinicopathologic characteristics. Thirty- eight cases of DCIS, and fourteen cases of LCIS and thirty benign cases were selected from the Yale Pathology department archives and 252 ROIs (regions of interest) were annotated by a board-certified pathologist. DCIS is classified according to the three-tier nuclear grading system: low, intermediate, and high-nuclear grade. LCIS is classified as PLCIS (pleomorphic variant) and CLCIS (classic LCIS) according to the WHO classification of breast tumors. Serial sections of FFPE tumor specimens were used to accurately quantify the HER2 expression by the HS-HER2 assay and the acquisition by QuPath v.04 with Qymia extension. According to the LOD (limit of detection, 3 amol/mm^2), LOQ (limit of quantification, 9 amol/mm^2) and LOL (limit of linearity, 23 amol/mm^2) of the optimized HS-HER2 assay as performed in our CLIA lab shows a broad range of HER2 expression in both DCIS and LCIS lesions, ranging from 0.7 amol/mm^2 to 111.4 amol/mm^2 in DCIS and 3.6 amol/mm^2 to 49.9 amol/mm^2 in LCIS. High grade DCIS lesions express higher average HER2 levels ($111.4 + 0.7 \text{ amol/mm}^2$) than combined low and intermediate grade DCIS ($77.9 + 1.9 \text{ amol/mm}^2$) with no significant difference between low/intermediate and high-grade DCIS. CLCIS lesions express higher average HER2 level ($49.9 + 3.6 \text{ amol/mm}^2$) than PLCIS ($35.1 + 5.4 \text{ amol/mm}^2$) but again this is not statistically significant. HER2 protein expression is relatively low in benign lesions ranging from 0.8 to 8.4 amol/mm^2 . Using the HS-HER2 assay, our results show quantitative level HER2 levels in DCIS and LCIS breast lesions. These findings may be important as HER2 targeted therapies that work in gene-unamplified cancer (HER2 conjugated ADCs) gain broader usage in the clinic.

PO5-13-12

Personalized circulating tumor DNA testing for recurrence detection and treatment response monitoring in patients with metastatic invasive lobular carcinoma

Presenting Author(s) and Co-Author(s):

S. Oesterreich. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

A. Tin. Natera, Inc., United States

S. Rivero-Hinojosa. Natera, Inc., United States

J. Fielder. Natera INC, United States

J. Ferguson. Natera, Inc, United States

E. Kalashnikova. Natera, San Carlos, California, United States

A. Rodriguez. Natera, United States

M. Liu. Natera, United States

A. LEE. UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, United States

Introduction

Metastatic invasive lobular carcinoma (mILC) presents unique challenges during treatment response monitoring. A higher frequency of metastases to the bone, gastrointestinal tract, uterus, meninges, ovary, and diffuse serosal involvement is observed in mILC. The challenge with mILC is that they can be difficult to detect clinically and radiographically, and consequently clinical progression can be difficult to determine with conventional imaging modalities like CT Scans, thus precluding many patients with mILC from enrolling into clinical trials. Therefore more accurate biomarkers are needed to better assess response to treatment in real time. In this study, we demonstrate the feasibility of longitudinal ctDNA testing for treatment response monitoring in patients with mILC.

Methods

In this real-world study, longitudinal plasma samples (n=219) from 60 patients with mILC, treated across 52 independent clinics between 7/22/21 and 6/15/23, were analyzed. A personalized, tumor-informed ctDNA assay (Signatera™ bespoke, mPCR-NGS assay) was used for detection and quantification of ctDNA in plasma samples.

Results

In this cohort, the median patient age at diagnosis of metastatic disease (baseline) was 62.9 years (range: 32.2-79.7). Of the 60 patients, 41 (68%) had ER+PR+HER2-, 7 (12%) ER+PR-HER2-, 4 (7%) ER+PR+HER2+, 2 (3%) ER+PR-HER2+, 1 (2%) triple negative breast cancer; receptor status was not available for 5 (8%) patients.

CDH1 (75%) and PIK3CA (42%) were observed to be the top two genes with somatic, nonsynonymous mutations. Mutations in TP53 and TBX3 were observed in 13% of patients, mutations in AKAP9, IGFN1, RBM26, and RFC3 in 10% of patients, and mutations in ESR1 in 6.7% of patients. At variant level, PIK3CA p.H1047R (22%) and RBM26 p.Q701Tfs*23 (10%) were the top two somatic variants identified. The most common CDH1 variant, p.Q23*, was found in 5% of the cases.

Of the 60 patients, 37 (61.7%) were ctDNA-positive at all time points while on treatment (chemotherapy/ endocrine therapy/ targeted therapy) with the first time point collected at a

median of 6.7 months (range: 2.5-2307 months) from baseline. Of these 37, imaging/biopsy results after baseline were available for 32 patients, 86% (27/32) of whom progressed. Thirty-two of 37 persistently ctDNA-positive patients had serial ctDNA measurements available, of which 14 (43%) had significant increase in ctDNA levels (average: 47-fold increase, standard deviation: 98) from first to last time points. At some point during their care ctDNA was detectable in all (n=51) patients with evidence of clinical progression.

Of the 60 patients, 14 (23.3%) were ctDNA-negative at all time points tested. None of the 14 persistently ctDNA-negative patients had evidence of disease recurrence or progression at the time of initial testing or throughout ctDNA monitoring. The first ctDNA time point was collected at a median of 33.1 months (range: 0.68-92 months) from baseline for these patients, a median of 3 time points was tested per patient (1-12).

Of the remaining 9/60 patients, 3 (33%) had sustained ctDNA clearance for a median of 46 days (range: 0-224 days) in response to treatment, and 2 (22%) were initially ctDNA-negative but turned positive 105 and 156 days later, indicating potential resistance to treatment and molecular progression. Additional 4/9 (44%) had ctDNA levels consistently low levels (average: 0.42 mean tumor molecules/mL) while on treatment for a median of 260 days (range: 217-442) and showed no evidence of progression.

Conclusions

ctDNA status and dynamics correlate well with clinical status of patients with mILC, as determined by conventional monitoring tools such as imaging and biopsy. Our results indicate that personalized, tumor-informed, longitudinal ctDNA testing may serve as a useful tool for detection of progression and monitoring treatment response in mILC patients.

PO5-14-01

Weight loss and omega-3 polyunsaturated fatty acid intervention in overweight and obese peri- and postmenopausal women with increased breast cancer risk modifies the gut microbiome and is associated with circulating biomarkers

Presenting Author(s) and Co-Author(s):

K. Cook. Wake Forest University School of Medicine, United States

E. Giles. University of Michigan, Ann Arbor, Michigan, United States

A. Kreuzjans. University of Kansas Medical Center, Kansas City, Kansas, United States

S. Umar. University of Kansas Medical Center, United States

C. Befort. University of Kansas Medical Center, United States

B. Kimler. University of Kansas Medical Center, Kansas City, Kansas, United States

S. Hursting. University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

C. Fabian. University of Kansas Cancer Center, Kansas City, Kansas, United States

Background: Obesity-associated gut microbiome dysbiosis is thought to increase risk for postmenopausal breast cancer through alteration of estrogen metabolism and an increase in pro-inflammatory microbe abundance. Many studies have reported an increase in the Firmicutes/Bacteroidetes phyla ratio as a biomarker of obesity and is associated with adverse metabolic outcomes. Marine omega-3 eicosapentaenoic (EPA) and docosahexaenoic (DHA) fatty acids are thought to have favorable metabolic and inflammation resolving properties resulting in reduced risk for several epithelial cancers. One possible mechanism is the effect of EPA and DHA on the gut microbiome. We assessed the effect of weight loss and/or omega-3 supplementation on the gut microbiome and circulating molecular breast cancer risk factors. Methods: 46 peri/postmenopausal overweight and obese women at increased risk for breast cancer were enrolled into a weight-loss intervention and after 2 weeks randomized to 3.25 g/day combined EPA and DHA or placebo (PMC8416797). Fecal samples were collected at 0, 2-weeks and 6-months, with matched fecal samples for all timepoints available for 26 patients. Fecal samples at 6-months were available for 34 patients. 12M read depth metagenomic sequencing was performed on DNA isolated from feces to determine shifts in the gut microbiome. Fasting and non-fasting blood was also collected for circulating biomarker analysis. Body composition by DXA scan were also performed at baseline and 6-month time points. Results: Mean baseline BMI was 32 kg/m². There was no significant difference between arms in age, baseline BMI, % body fat, or baseline Firmicutes/Bacteroidetes ratio. We identified gut microbiota species (*A. hadrus* and *P. faecium*) that correlated with metabolic parameters (% body fat, adiponectin/leptin ratio, and fasting insulin), species (*P. dorei* and *B. ovatus*) that correlated with estradiol levels, and mucin-degrading species (*D. formicigenerans* and *R. gnavus*) whose abundance correlated with inflammation (as measured by circulating monocyte-chemoattractant protein 1 (MCP-1)). Median 6-month weight change for all randomized subjects was -10% from baseline. Favorable change in the Firmicutes/Bacteroidetes ratio was associated both with the degree of weight loss and with omega-3 supplementation, although significant species modification differed between weight loss and omega-3 PUFA groups. Women with both >10% weight loss and omega-3 supplementation had a significantly reduced Firmicutes abundance and lower Firmicute/Bacteroidetes ratio than other groups. Species abundance shifts appear to differ between weight loss and omega-3 supplementation with 3 species modified by weight loss and 12 species shifted by omega-3 PUFA administration. Omega-3 PUFA supplementation significantly reduced proportional abundance of *Dorea*

formicigenerans, which was a microbe associated with inflammation. Conclusions: Omega-3 supplementation at 3.25 g/day compared to placebo had a greater net effect on changing the gut microbiome in overweight and obese women at increased risk for breast cancer undergoing a weight loss intervention. Change in the gut microbiome may serve as a useful response biomarker in Phase II prevention trials of omega-3 fatty acid and weight loss.

PO5-14-02

Diagnostic leukapheresis to increase CTC detection rate in breast cancer patients after 5 years of adjuvant endocrine treatment

Presenting Author(s) and Co-Author(s):

N. Verschoor. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

J. Kraan. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

J. Zuetenhorst. Department of Medical Oncology, Franciscus Gasthuis & Vlietland, Rotterdam/Schiedam, the Netherlands, United States

M. Vastbinder. Department of Medical Oncology, IJsselland Hospital, Capelle aan den IJssel, the Netherlands, United States

J. Drooger. Department of Internal Medicine, Breast Cancer Center South Holland South, Ikazia Hospital, Rotterdam, The Netherlands, United States

S. Sleijfer. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

S. Wilting. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, United States

J. Martens. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, Rotterdam, Zuid-Holland, Netherlands

A. Jager. Erasmus MC Cancer Institute, Rotterdam, The Netherlands, Rotterdam, Netherlands

Purpose: Patients with early hormone receptor positive, HER2 negative breast cancer have a risk of recurrence for up to 20 years after the initial diagnosis and is therefore treated with adjuvant endocrine treatment (ET) for 5 to 10 years. As a result there is a large proportion of patients that overtreated, hence, an urgent need for better biomarkers to guide treatment decisions. In previous research, it was shown that circulating tumor cells (CTCs) are detected in 5% of patient after 5 years of adjuvant treatment and that this indicated a 13-fold higher risk of recurrence, with a median lead time of 2.8 years. However, the sensitivity and specificity of the test were moderate. This could be caused by stochastic variation, given the low numbers of CTCs detected in 7.5 ml peripheral blood. We hypothesized that increasing the screening volume, increases the test statistics.

Methods: In this study, we investigated whether increasing the screening volume by diagnostic leukapheresis (DLA) can increase the detection rate of CTCs (CellSearch platform). With DLA, 5 liters of peripheral blood was screened, which in previous studies had shown to increase the CTC-yield per ml by 25-fold. To this end, we included early hormone receptor positive, HER2 negative breast cancer patients that were treated with ET for 4.5-5.5 years with no signs of disease recurrence. We compared the number of detected CTCs in the standard fraction of 7,5 mL peripheral blood (PB), to buffy coat (30 ml), to DLA sample (200 x 10⁹ white blood cells (WBC), equal to 25-50 mL PB) and to DLA after WBC depletion.

Results: Thirty two hormone receptor positive/HER2 negative breast cancer patients were included in this study after a median duration of ET of 60 months, of which 3 (9%) patients completed ET according to clinical guidelines and the remaining patients were still on treatment. Twenty eight patients (88%) had 1-3 positive lymph nodes at diagnosis, and 3 patients had 4-9 positive lymph nodes. The Clinical Treatment Score at 5 years (CTS5 score) was intermediate or high in 75%, and unknown in 19%, indicating a recurrence risk of >5% at years 5-10 after diagnosis. In none of the included patients, CTCs were detected in 7,5 ml PB, nor in any of the other tested blood volumes. To date, 2 patients have been diagnosed with

overt metastatic disease during follow-up. DLA was well tolerated and did not cause adverse events.

Conclusions: We conclude that DLA was unable to increase the detection rate of CTCs in hormone receptor positive, HER2 negative patients with early breast cancer being on treatment for a median duration of 5 years. Additional circulating tumor DNA analyses are planned.

PO5-14-03

Analytical Validation of the StemPrintER Assay in Patients with Breast Cancer

Presenting Author(s) and Co-Author(s):

C. Cronister. Oncocyte Corporation, United States

B. Schweitzer. Oncocyte Corporation, United States

H. Gilmore. University Hospitals Cleveland Medical Center, United States

T. Nielsen. Oncocyte, United States

Discussion: Breast cancer is the most common malignancy diagnosed amongst women, with more than two million new cases identified globally each year. Thus, considerable resources have been devoted to a better understanding of the disease and how to optimize outcomes for patients. Genetics and genomics have become part of routine care with the latter used to inform treatment planning for patients with ER+ breast cancer (ER+ BC). A multitude of assays may be used to determine the need for adjuvant chemotherapy but none of the current tests on the market are guideline-recommended for making decisions related to neoadjuvant chemotherapy, surgery, or radiation. The 24-gene StemPrintER assay was developed to measure the “stemness” of tumors, or how much a tumor behaves like stem cells, which could have important and novel implications for breast cancer treatment planning. The assay has been validated for predicting prognosis using formalin-fixed paraffin-embedded (FFPE) tissue blocks from several clinical cohorts, including TransATAC. The goal of current and future research will be to determine whether the assay can determine the ideal surgical intervention for ER+BC patients. Early in silico work demonstrated a trend toward this predictive capacity for the assay and suggests the assay may be able to identify the benefit of mastectomy versus quadrantectomy. Here, we report on the ability to set up and run the assay in our lab using synthetic oligonucleotides and archival tissue blocks.

Methods: Synthetic oligonucleotides and archival FFPE breast cancer tissue were used to set up and analytically validate the assay’s performance in two phases. The initial phase was intended to confirm the individual assay design performance by assessing linearity and precision and the ability to amplify RNA from FFPE, which confirmed compatibility with standard extraction methods. The second phase was intended to determine whether these methods could be implemented to reliably extract and amplify RNA from FFPE >10 years old (range: 10-14 years) in order to generate a StemPrintER score. The assay was run according to standard operating procedures for StemPrintER. Analyses were conducted Python 3.9.12.

Results: Two assay runs with duplicate samples for each run using a 7-point dilution series demonstrated linearity (coefficient of correlation, r^2) results ranging from 0.978 to 0.999 for each of the 24 genes in the assay. Amplification efficiency was between 100-101% for each gene. Using 14 FFPE samples from patients with triple-negative breast cancer, we demonstrated a consistent extraction yield of RNA from tumor blocks which produced amplification of each of the targets. Analysis of intra- and inter-run precision resulted in coefficients of variation (CV) ranging from 0.2-1.07% and inter-run CV’s ranging from 0.66%-5.56%. Utilizing FFPE >10 years old from ER+BC patients demonstrated that the lab could extract RNA from 100% of samples and amplify the material to obtain binary StemPrintER results.

Conclusion: These data demonstrate that StemPrintER can be run reliably on FFPE tissue up to 14 years old. In addition, our laboratory has demonstrated that assay results are highly linear

and reproducible. Additional studies are planned to build on preliminary surgical prediction data and determine whether the assay can meet the unmet need of identifying the ideal surgical intervention in patients with early-stage ER+/HER2- breast cancer.

PO5-14-04

FTIR Spectroscopy Analysis of Lipid Region: Distinguishing Breast Cancer from Benign Breast Diseases Using PCA-SVM

Presenting Author(s) and Co-Author(s):

J. Pereira. Federal University of Uberlandia, Uberlândia, Minas Gerais, Brazil

A. Faria. Federal University of Uberlândia, UFU, MG, Brazil, United States

I. Ferreira. Federal University of Uberlandia, United States

L. Santos. Federal University of Uberlândia, United States

D. Santos. Federal University of Uberlândia, United States

M. Maia. Faculty of Computing, Federal University of Uberlandia, United States

O. Costa. Brazilian Synchrotron Light Laboratory (LNLS), United States

R. Freitas. Brazilian Synchrotron Light Laboratory (LNLS), United States

C. Paiva. Barretos Cancer Hospital, Barretos, Brazil

Y. Maia. Federal University of Uberlândia, UFU, MG, Brazil, United States

Background: Breast cancer (BC) is the most diagnosed type worldwide, with 2.26 million new cases in 2020. Mammography is the preferred screening method, but it has limitations such as radiation exposure and low sensitivity in dense breasts. Therefore, there is a need for accurate diagnostic methods to detect breast cancer and distinguish benign conditions. **Objective:** This study aimed to develop an automated tool for the comparison of lipid spectral region in benign breast disease (BBD) and breast cancer (BC) to determine their potential diagnostic value using Fourier Transform Infrared Spectroscopy (ATR-FTIR).

Methods: This study was conducted at a Clinical Hospital in Uberlandia, MG, Brazil, after approval by the Human Research Ethics Committee of the Federal University of Uberlandia, and all subjects provided written informed consent. Women who went to the Clinical Hospital for breast surgery were invited to participate in the study as volunteers. After surgery and histopathological analysis, the tumors and lesions found were classified according to histological type, staging, and the status of ER, PR, and HER2 receptors. A total of 60 women participated in the study, of whom 27 had BBD, and 33 had BC. Spectra were measured in the wavenumber range of 4000 cm^{-1} to 650 cm^{-1} using an Agilent Cary 600 Series FTIR spectrometer coupled to an MCT detector. The air spectrum was used as a background before each sample analysis. The sample spectra were obtained in triplicate, with a spectral resolution of 4 cm^{-1} , and 128 scans were performed for each measurement. The infrared spectra were analyzed after undergoing preprocessing, which involved positive baseline rubberband normalization, normalization by minimum and maximum, and application of the second derivative. **Results:** The region of 3050-2800 cm^{-1} was able to differentiate BC from BBD using principal component analysis (PCA) followed by the support vector machine algorithm (PCA-SVM) with an accuracy of 80%, sensitivity of 88%, and specificity of 70%. This range corresponds to the vibration of lipids, and it is known that changes in the contents of biomolecules in the serum, an increase or decrease, can be related to the presence or absence of BC. The implementation of this approach in clinical practice may automate the diagnosis of BC, monitoring whether changes in therapy or interventions are necessary throughout the treatment. FTIR can potentially assist in clinical decision-making regarding follow-up or biopsy recommendations, avoiding unnecessary biopsies that are more invasive and expensive than blood collection, and which often cause significant anxiety to the patient even if the lesion is not highly suspicious. **Conclusion:** This study shows that it is possible to detect BC with good

accuracy through a minimally invasive, fast, and cost-effective method analyzing the lipid spectral region using principal component analysis (PCA) followed by the support vector machine algorithm (PCA-SVM).

PO5-14-05

Circulating tumor DNA fraction correlates with residual cancer burden post-neoadjuvant chemotherapy in triple negative breast cancer patients

Presenting Author(s) and Co-Author(s):

N. Shan. Yale Cancer Center, United States

B. Gould. Predicine, United States

K. Blenman. Yale University, United States

J. Foldi. Yale School of Medicine, United States

P. Du. Huidu Shanghai Medical Sciences Ltd., United States

F. Zhang. Predicine, United States

M. Walsh. Predicine, United States

L. pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

Background: Pathologic response after preoperative/neoadjuvant chemotherapy is a continuum that can range from no residual cancer to extensive disease. Viable cancers can shed tumor DNA into the blood and we hypothesized that plasma ctDNA levels can reflect pathologic response as continuum.

Patients and methods: Post-neoadjuvant plasma samples were obtained after completion of chemotherapy but before surgery from patients with stage I to III TNBC who received treatment with durvalumab concurrent with weekly nab-paclitaxel followed by dose dense doxorubicin/cyclophosphamide in a single arm neoadjuvant clinical trial (NCT02489448). Up to 3 mL of blood was collected into EDTA- and heparin- containing vacutainer tubes, and plasma cfDNA was extracted and twice purified in the lab at Predicine Inc. Pathologic response was quantified on a continuous scale using the Residual Cancer Burden (RCB) score, and also categorized as RCB-0 (complete pathologic response, n=21), -I (minimal residual cancer, n=7), -II (moderate residual cancer, n=13), and -III (extensive residual cancer, n=3). Median follow-up was 35 months (range 25-70 months). Tumor whole exome sequencing (WES) data was previously generated using HiSeq 4000 at the Yale Center for Genome Analysis (dbGaP: PRJNA558949). A personalized MRD panel of up to 60 personalized variants per patient was designed based on the tumor WES data, and ultra-deep next-generation sequencing (100,000X) of plasma cfDNA was performed using the PredicineBEACON assay for MRD detection by Predicine. CtDNA positivity (MRD) was defined as a weighted score equivalent to 2 or more tumor variants detected in the plasma. cfDNA tumor fraction was measured based on mutant allele fraction of observed variants. Adjusted tumor fraction could be confidently measured for 37 out of 44 patients that had enough confidently called personalized ctDNA variants. We compared tumor fraction versus RCB score as continuous variables, and also compared tumor fraction between RCB categories as ordinal variables. Invasive disease-free survival was examined by Kaplan-Meier analysis. Bioinformatic data analysis was performed using Graphpad Prism and R.

Results: 44 of 48 plasma samples yielded successful cfDNA generation and sequencing. Six patients (13.6%) were MRD positive. Among these 6 cases, 3 had RCB-0 response (14.3% of RCB 0 cases), 1 had RCB II response (7.7% of RCB II cases), and 2 had RCB III response (66.7% of RCB III cases). The median cfDNA tumor fraction of patients with pathological complete response to treatment (pCR) was significantly lower than patients with residual disease (RD) (0.06% vs. 0.3%, p=0.02). There was a positive correlation between RCB scores

and tumor fraction ($r= 0.45$, Spearman). Tumor fraction was more strongly correlated with later recurrence than a binary ctDNA positivity call. Tumor fraction was significantly higher in patients that later experienced local or metastatic recurrence ($n=8$) compared to those with no evidence of disease ($n=29$) (Wilcoxon test, $p=0.02$). Both ctDNA positive RCB III cases had metastatic recurrence while the remaining 4 ctDNA positive cases currently remain recurrence-free. Mutational genomic landscape of both tumor WES and plasma ctDNA samples identified hotspot mutations in 19 cancer-associated genes. Novel hot-spot mutations were observed in the plasma of two patients following treatment. TP53 mutations were highly prevalent in tissue and plasma, however no significant association of mutation of any gene with treatment response was detected.

Conclusions: PredicineBeacon MRD assay was successfully performed on 3 mL plasma samples collected using from EDTA and heparin-containing tubes. Tumor fraction correlated with residual disease, RCB score and disease recurrence.

PO5-14-06

Transcriptomics-based drug screening in 3D ex vivo patient-driven breast cancer model and patient biopsy for personalized therapy

Presenting Author(s) and Co-Author(s):

Y. Zhang. Swiss Federal Institute of Technology in Lausanne (EPFL), Lausanne, Vaud, Switzerland

C. Venturi Ronchi. Swiss Federal Institute of Technology Lausanne (EPFL), United States

G. Ambrosini. Swiss Federal Institute of Technology in Lausanne (EPFL), United States

Y. Liu. SOPHiA GENETICS, United States

P. Aouad. Hospital Ophthalmic Jules-Gonin, United States

D. Matvienko. Swiss Federal Institute of Technology in Lausanne (EPFL), United States

C. Merten. Swiss Federal Institute of Technology in Lausanne (EPFL), United States

C. Brisken. ISREC - Swiss Institute for Experimental Cancer Research, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, United States

Breast cancer is a leading cause of cancer-related mortality for women worldwide. Hormone receptor-positive (HR+) breast tumors, which represent 70% of all breast cancer cases, are treated with endocrine therapy. However, not all patients benefit from this treatment regimen because of patient-to-patient variation. Therefore, high throughput drug screening system is warranted to enable personalized medicine. Patient-derived organoids, which serve as a screening platform, lose their hormone receptors and response upon ex vivo culturing, and may not be adequate models for HR+ breast tumors. Moreover, unidentified biological components in the widely-used basement membrane matrix, Matrigel, result in high batch-to-batch variations and poor reproducibility in organoid cultures. Here, we propose a hydrogel-based 3D ex vivo model with defined structural and chemical properties to test hormone and drug sensitivity of HR+ breast tumors from patient-derived xenografts (PDXs) and patient tumor biopsies using microfluidics. Our data demonstrate the feasibility of this model to preserve cell proliferation and hormone receptor expression over 7 days. We also demonstrate that responses to hormones and FDA-approved drugs are faithfully maintained in this model. Finally, to establish a high throughput hormone and drug testing workflow with transcriptomic readout, we multiplexed barcoded- and drug-treated tumor samples in a single experiment with bulk RNA-sequencing. Our preliminary data demonstrate patient-specific responses to hormones and drugs that correspond to patient genetic mutation profiles, treatment history, disease stages and subtypes. This platform also enables testing of drugs in clinical trials that shows promising therapeutic outcomes for breast cancer, such as CDK4/6i, AKTi, PARPi, mTORi and their combination with endocrine therapy, thanks to the high throughput of the screening system and the low consumption of patient-derived or patient tissue. Given the capability of combining this physiologically-relevant 3D ex vivo model with RNA-seq for HR+ breast tumors, this platform holds potential for high throughput compound testing and transcriptomic profiling of patient biopsies for personalized medicine.

PO5-14-08

External Reproducibility of PD-L1 IHC 22C3 pharmDx on Breast Cancer Specimens at CPS \geq 1 and CPS \geq 10 Cutoffs

Presenting Author(s) and Co-Author(s):

L. Steiner. Agilent Technologies, Inc., Carpinteria, California, United States

J. Barreto. Agilent Technologies, Inc., Carp, California, United States

E. Olander. Agilent Technologies, Inc., Carpinteria, California, United States

D. Kell. Agilent Technologies, Inc., Carpinteria, California, United States

S. Tabuena-Frolli. Agilent Technologies, Inc., Carpinteria, California, United States

M. Polewski. Agilent Technologies, Inc., Carpinteria, California, United States

Title: External Reproducibility of PD-L1 IHC 22C3 pharmDx on Breast Cancer Specimens at CPS \geq 1 and CPS \geq 10 Cutoffs

Authors: Lori Steiner, Joseph Barreto, Emily Olander, Siena Tabuena-Frolli, Donna Kell, Monika Polewski*

*corresponding author

Institution: Agilent Technologies, Inc.

Background: PD-L1 IHC 22C3 pharmDx is an approved companion diagnostic for pembrolizumab treatment in triple-negative breast cancer (TNBC). Clinical evidence for pembrolizumab approval in TNBC was demonstrated by KEYNOTE-355 (NCT02819518), which investigated the clinical validity of PD-L1 IHC 22C3 pharmDx in identifying patients with PD-L1 expressing Combined Positive Score (CPS) \geq 10 in previously untreated locally recurrent unresectable or metastatic TNBC.¹ The role of immune checkpoint inhibitors for breast cancer as a whole is not as well defined as it is for TNBC. In this study, we show evidence of the reproducibility of PD-L1 IHC 22C3 pharmDx in PD-L1 expression determination in breast cancer specimens at the CPS \geq 1 and CPS \geq 10 cutoffs documenting robust assay performance in breast cancer.

Methods: A blinded, randomized study was conducted at three external sites using formalin-fixed, paraffin-embedded breast cancer specimens. Reproducibility of PD-L1 IHC 22C3 pharmDx was assessed at the inter-site, intra-site/inter-day, inter-observer, and intra-observer endpoints at the CPS \geq 1 and CPS \geq 10 cutoffs. To assess inter-site and intra-site reproducibility, five replicate sets of pre-qualified unstained specimens were stained and evaluated at each of the three external sites. To assess inter-observer and intra-observer reproducibility, one set of pre-stained specimens was evaluated three times by each of three external pathologists. Negative percent agreement (NPA), positive percent agreement (PPA), and overall percent agreement (OA), based on comparisons to consensus diagnostic outcome, were computed with corresponding two-sided 95% percentile bootstrap confidence intervals. Acceptance criteria required at least 85.0% for the lower-bound (LB) of the two-sided 95% confidence interval (CI) on NPA, PPA, and OA for all endpoints.

Results: All but one endpoint in the external reproducibility study met pre-determined acceptance criteria. Both the inter- and intra-site reproducibility endpoints had 95% CI LB

values of 98.8% for NPA, 95.9% for PPA, and 97.9% OA at the CPS \geq 1 cutoff. At the CPS \geq 10 cutoff, the inter-site reproducibility endpoint had 95% CI LB values of 88.0% for NPA, 87.1% for PPA, and 89.5% OA, and the intra-site reproducibility endpoint had 95% CI LB values of 96.7% for NPA, 92.2% for PPA, and 95.6% OA. The inter-observer reproducibility endpoint had 95% CI LB values of 95.3% for NPA, 92.3% for PPA, and 94.7% OA at the CPS \geq 1 cutoff. At the CPS \geq 10 cutoff, the inter-observer reproducibility endpoint had 95% CI LB values of 84.9% for NPA, 86.8% for PPA, and 87.3% OA. The intra-observer reproducibility endpoint had 95% CI LB values of 97.0% for NPA, 95.0% for PPA, and 96.6% OA at the CPS \geq 1 cutoff. At the CPS \geq 10 cutoff, the intra-observer reproducibility endpoint had 95% CI LB values of 92.2% for NPA, 89.2% for PPA, and 91.7% OA.

Conclusions: Acceptance criteria were met for all endpoints in the breast cancer external reproducibility study of PD-L1 IHC 22C3 pharmDx at the CPS \geq 1 and CPS \geq 10 cutoffs, except for inter-observer at the CPS \geq 10 cutoff, which had a 95% CI LB value of 84.9% for NPA.

References:

1. Cortes, J.; Rugo, H.S.; Cescon, D.W.; et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. *N Engl J Med* 387;3, July 21, 2022.

PO5-14-09

Does transcriptome based DEPTH2 score reflect intratumor heterogeneity in breast cancer patients?

Presenting Author(s) and Co-Author(s):

K. Chida. Department of Surgical Oncology, Roswell Park Comprehensive Cancer Center, United States

R. Wu. Roswell Park Comprehensive Cancer Center, United States

A. Roy. Roswell Park Comprehensive Cancer Center, Amherst, New York, United States

T. Ishikawa. Tokyo Medical University, United States

K. Takabe. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

Background: Intratumor heterogeneity (ITH) refers to the presence of distinct cancer cell populations with different clones within a single tumor mass. Tumors with high ITH are more prone to progression, exhibit resistance to therapies, and are associated with an unfavorable prognosis. Therefore, evaluation of ITH is anticipated to serve as a breakthrough biomarker for prognosis and treatment strategies. Several computational algorithms have been proposed to quantify ITH. However, with the exception of DEPTH2, all of these algorithms require both DNA and RNA-sequence data from the same tumor, which can be challenging. In this study, we investigated whether DEPTH2 which solely analyzes RNA-sequence data, accurately reflects the biological characteristics of ITH.

Methods: We analyzed clinicopathological and gene expression data from a total of 6573 breast cancer patients from several large independent cohorts: METABRIC (n = 1903), GSE96058 (n = 3273), GSE21974 (n = 57), GSE28844 (n = 61), GSE87455 (n = 153), GSE180280 (n = 57), and The Cancer Genome Atlas (TCGA, n = 1069).

Results: DEPTH2 score was high in Triple Negative Breast Cancer (TNBC) subtype ($p < 0.001$), but no consistent correlation was observed with lymph node or distal metastasis. Higher DEPTH2 score was associated with cell proliferation, as evidenced by higher Nottingham histological grade and Ki67 gene expression (both $p < 0.001$). In agreement, high DEPTH2 tumors enriched all cell proliferation-related Hallmark gene sets such as E2F targets, G2M checkpoint, MYC targets v1 and v2, and Mitotic Spindle (FDR < 0.25). Additionally, high DEPTH2 tumors exhibited reduced immune cell infiltrations, such as CD8, CD4, Th1, Th2, B cells, and macrophages, and increased infiltrations of stromal cells, such as adipocytes, fibroblasts, blood and lymphatic endothelial cells (all $p < 0.05$). In TCGA cohort, DEPTH2 score exhibited a similar trend to intratumoral heterogeneity, homologous recombination deficiency, fraction altered, silent and nonsilent mutations, as well as SNV and Indel neoantigens. However, the Pearson's correlation coefficient was very weak ($p < 0.05$). DEPTH2 score decreased in the GSE21974 and GSE87455 cohorts after neoadjuvant chemotherapy (NAC), whereas no change was observed in the GSE28844 and GSE180280 cohorts. DEPTH2 high tumors showed a lower rate of pathologic complete response (pCR) after NAC in estrogen receptor (ER)+HER2- subtype across all cohorts, however, opposite pattern was observed in the HER2+ and TNBC subtypes in all cohorts. Lastly, high DEPTH2 score was associated with lower disease free and overall survival in METABRIC and GSE96058 ($p < 0.05$), but not in the TCGA cohort.

Conclusions: Our findings suggest that DEPTH2 score may not completely capture the biological characteristics associated with intratumor heterogeneity.

PO5-14-10

Dynamics and prognostic value of subtype specific TROP2 expression in matched pair samples of primary (PBC) and metastatic breast cancer (MBC) tissues

Presenting Author(s) and Co-Author(s):

T. Deutsch. Heidelberg University Hospital, Germany

R. Wirtz. STRATIFYER Molecular Pathology GmbH, Germany, Germany

S. Stefanovic. Mannheim University Hospital, Germany

A. Hartkopf. Tuebingen University Hospital, Germany

H. Sinn. Pathologie, Universitätsklinikum, Heidelberg, Germany

A. Schneeweiss. National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

M. Wallwiener. Heidelberg University Hospital, Germany

Background: The genotype and phenotype of breast cancer may change during disease progression. This is of particular interest in the advent of targeted treatment addressing extracellular targets such as TROP2, which serves as chemotherapy carrier rather than being required for tumor cell survival. In addition, technical issues may affect biomarker assessment when comparing primary breast cancer (PBC) tissues with biopsies of metastatic breast cancer (MBC) tissues at distant sites. Here we analyzed TROP2 expression on mRNA level by RT-qPCR in primary tumor and metastatic tissues on basis of molecular subtyping to determine subtype specificity and target gene stability / dynamics.

Methods: The tumor bank of a single institution was screened for paraffin-embedded pairs of PBC and MBC tissue samples and a total of 34 matched PBC and MBC pairs were retrieved. RNA was extracted using a bead-based extraction method (RNXtract® IVD kits, Cerca Biotech). Multiplex RT-qPCR was performed using TaqMan® based primer probe sets for ESR1/PGR/ERBB2 and MKI67 (MammaTyper® IVD kits, Cerca Biotech) as well as TROP2 (TargetTyper RUO kits, STRATIFYER Molecular Pathology GmbH). Correlation analysis, Scatter Plots, Partitioning tests and Kaplan Meier analysis were performed using the SAS JMP® 9.0.0 software.

Results: Samples from 34 patients with MBC and PBC were available. Positivity of PBC RT-qPCR for ESR1, PGR and HER2 was 78%, 70% and 3%. The overall agreement between matched primary and metastatic lesions 90%, 70% and 100% for RT-qPCR of ESR1, PGR and HER2. Median expression of TROP2 was 2 fold lower in metastatic tissues compared to matched primary tumor tissues, while the lower quartile of mRNA expression dropped 4 fold. In primary tumor tissues TROP2 expression was significantly associated with PGR and HER2 expression (Spearman $r=0.5284$ $p=0.0013$ and $r=0.3950$ $p=0.0208$; respectively), while no significant association was found for ESR1 and MKI67. In contrast, no significant association with neither PGR nor HER2 was found (Spearman $r=0.0461$ $p=0.8041$ and $r=0.0461$ $p=0.7955$; respectively), while TROP2 trended to be associated with MKI67 in metastatic lesions (Spearman $r=0.3247$ $p=0.0610$). In line with the strong positive association of TROP2 with PGR in primary tumor tissues, elevated TROP2 levels were associated with substantially longer median distant metastasis free survival of 72 months, while TROP2 negative tumors exhibited a median DDFS of only 24 months ($p=0,0091$). In contrast, no prognostic value for TROP2 mRNA level could be determined from metastatic lesions and determining the time from initial metastasis until death.

Conclusion: In this selected matched pair, metastatic cohort, TROP2 mRNA in primary tumors is strongly associated with luminal type of breast cancer expressing higher levels of PGR mRNA, while no such correlation was found in matched metastatic tissues. Moreover, TROP2 is significantly downregulated in metastatic lesions. As TROP2 is expressed in luminal tumors, it may serve as a valuable target for luminal tumors of higher progression risk. However, TROP2 expression is unstable and requires careful decision making on actual biopsies rather than archival tissue samples.

PO5-14-11

Leveraging a pharmacokinetic/pharmacodynamic (PK/PD) model to guide dose optimization of palbociclib (palbo) in combination with vepdegestrant

Presenting Author(s) and Co-Author(s):

B. Jermain. Pfizer Inc., United States

D. Yang. Pfizer Inc., La Jolla, California, United States

W. Tan. Pfizer Inc., La Jolla, California, United States

J. Perkins-Smith. Pfizer.Inc, United States

J. Hoffman. Pfizer Inc., United States

J. Williams. Pfizer Inc., United States

Background: Vepdegestrant is a potent, selective, orally bioavailable PROteolysis TArgeting Chimeric (PROTAC) estrogen receptor (ER) degrader. A phase 3 study will evaluate the combination of vepdegestrant and palbo in participants with ER+, human epidermal growth factor receptor negative (HER2[-]) advanced/metastatic breast cancer (NCT05909397). The recommended starting dose of palbo is 125 mg once daily for 3 weeks followed by 1 week off treatment for each 28-day cycle in combination with aromatase inhibitors or fulvestrant.¹ Neutropenia is the most frequently reported adverse event for patients receiving palbo in clinical trials.¹ When co-administered with vepdegestrant in a phase 1b cohort of the first-in-human phase 1/2 study (NCT04072952), higher rates of medically manageable neutropenia and increased palbo concentrations were observed compared with historical studies of palbo administered with letrozole or fulvestrant.¹ Reduced starting doses of palbo (100 mg, 75 mg) are planned to mitigate increased rates of Grade 4 neutropenia while maintaining similar palbo exposure when combined with vepdegestrant. The analysis objective was to leverage a PK/PD model to simulate palbo exposure and neutropenia taking into consideration the dose modification and management for hematologic toxicities provided in the palbo prescribing information.¹ Methods: A Monte-Carlo simulation platform² was utilized to monitor absolute neutrophil count (ANC) in 1000 patients with weekly monitoring over 4 cycles (112 days) of palbo administration. Simulated ANC was determined using a semi-mechanistic model of chemotherapy-induced myelosuppression as previously described.³ Palbo dose modification methods included both dose hold and reduction based on an individual's ANC and thresholds for Grade 3 (< 1000 mm³) or Grade 4 (< 500 mm³) neutropenia. Simulated neutropenia and exposures from palbo starting doses of 100 mg and 75 mg in the presence of a 25%, 49%, and 67% increase in typical exposure were compared to a palbo starting dose of 125 mg in the absence of increased exposure (historical reference). Average concentration is calculated as the cumulative area under the curve divided by the simulation duration. Results: After a 4-cycle simulation, the 100 mg starting dose of palbo simulated across varying levels of increased exposure resulted in similar Grade 4 neutropenia incidence and average concentration compared to the reference simulation (< 12% difference). The 75 mg starting dose of palbo simulated across varying levels of increased exposure resulted in lower Grade 4 neutropenia incidence as well as lower average concentration compared to the reference simulation (Table 1). Conclusion: The PK/PD model simulation allows for relative comparison of Grade 4 neutropenia incidence and average palbo concentration between the planned reduced starting doses of palbo in the context of increased exposure relative to standard palbo dosing, i.e., without vepdegestrant. This simulation indicates a reduced dose of palbo (100 mg) in combination with vepdegestrant produces similar incidence of Grade 4 neutropenia and

comparable average palbo concentration compared to historical reference providing additional support for the study lead-in of NCT05909397.

Citations:

1. IBRANCE® (Palbociclib) [Package Insert]. New York, US: Pfizer, Inc.
2. Jermain et al. ACOP13 2023.
3. Friberg et al. J Clin Oncol 2002.

Table 1. 4-cycle simulation results comparing reduced starting doses of palbociclib in the presence of increased typical exposure to a reference standard palbociclib dosing in the absence of increased exposure

Palbociclib Starting Dose (mg)	Relative increase in palbociclib exposure (%)	Relative change in Grade 4 neutropenia incidence (%)	Relative change in average palbociclib concentration (%)
100	25	-9	-7.8
	49	5.6	2.6
	67	11.8	9.3
75	25	-42.4	-31.7
	49	-31.3	-23.8
	67	-25.7	-19

PO5-15-01

Prospective Biomarker Assessment of Cardiotoxicity Among Ethnically Diverse Women with Early Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Jahangier. Advocate Aurora Health, United States

R. Qamar. Advocate Aurora Health, United States

M. Singh. Aurora research Institute, Milwaukee, Wisconsin, United States

V. Thohan. Mission Health, United States

J. Weese. Advocate Aurora Health, United States

B. Khandheria. Advocate Health, United States

A. Kamke-Jordan. Advocate Aurora Research Institute, United States

Prospective Biomarker Assessment of Cardiotoxicity Among Ethnically Diverse Women with Early Breast Cancer

Shahzaad K Jahangier, MD, Vinay Thohan, MD, Maharaj Singh, PhD, James Weese, MD, Bijoy Khandheria, MD, Anna Kamke-Jordan MS, Rubina Qamar, MD

Background: Approximately 4.1 million women in the United States are living with breast cancer¹. Cardiac dysfunction is a significant adverse effect of commonly used breast cancer therapies like doxorubicin (D) and trastuzumab (T). The cardiotoxicity (CTox) associated with these agents manifests as a reduction in left ventricular ejection fraction (LVEF) with or without signs and symptoms of heart failure.

Purpose: The objective of this study is to evaluate serum cardiac and inflammatory biomarkers over time and their association with CTox development.

Methods: A total of 133 newly diagnosed stage I-III invasive breast cancer patients were enrolled in a prospective clinical trial (2013-2017) and received standard of care T and/or D based systemic therapy. They underwent serial echocardiograms every 6 months for two years and then based on clinical need for a total of six years. CTox was defined as a >10% drop in LVEF, and/or LVEF < 50%.

Biomarker data was collected at baseline, 12 and 24 months and included both cardiac biomarkers (Troponin-I, TN-I and amino terminal B-type natriuretic peptide, NT-proBNP) and measures of inflammation (C-reactive protein, CRP). Of the 32 with CTox patients, 15 had adequate serum samples and were matched with 15 patients without CTox (N=30), controlling for age, race, and treatment regimen prior to serum sample analysis.

Results: The mean LVEF at baseline was similar between CTox and non-CTox patients (64% vs 62%, p=0.342). However, over the course of 12 and 24 months, CTox patients experienced a statistically significant decrease in LVEF compared to their baseline values (55% and 56%, respectively, p < 0.001).

At baseline, CTox patients had higher CRP levels compared to non-CTox (13.4 mg/L vs 3.35 mg/L), however this difference did not reach statistical significance (P >0.05). Although this difference seemed to narrow at 12 months (3.88 mg/L vs 1.52 mg/L, p< 0.05) and 24 months

(6.85 mg/L vs 2.36 mg/L, $p < 0.05$), CTox patients consistently had higher mean CRP levels.

Mean TN-I levels increased at both 12 and 24 months compared to baseline (CTox 1.13 ng/L, 7.13 ng/L, 4.13 ng/L vs non-CTox 0.800 ng/L, 8.13 ng/L, 4.60 ng/L, $p < 0.05$) but there were no significant differences between the two groups ($p > 0.05$). While baseline NT-proBNP levels did not differ significantly between the CTox and non-CTox patients, there were statistically significant increases in CTox patients at 12 and 24 months (205 pg/mL vs 74 pg/mL, and 200 pg/mL vs 96 pg/mL, $p < 0.01$, respectively).

Conclusion: In a well characterized, diverse, matched subset of patients with early breast cancer who were prospectively followed with serial echocardiograms, distinct biomarker patterns were observed. Measures of inflammation (CRP) at baseline were different and these changes appeared to diminish over time. While the cardiac biomarker TN-I appeared to increase in both +CTox and -CTox group over time, only those with differential NT-proBNP elevations were associated with cardiotoxicity.

¹Lisa Gallicchio, PhD and others, Estimation of the Number of Individuals Living With Metastatic Cancer in the United States, JNCI: Journal of the National Cancer Institute, Volume 114, Issue 11, November 2022, Pages 1476–1483

PO5-15-02

Integration of synonymous mutations and variants of unknown significance for basal and longitudinal characterization of metastatic breast cancer by circulating tumor DNA

Presenting Author(s) and Co-Author(s):

E. Molteni. Department of Medicine, University of Udine, Italy/Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA, United States

C. REDUZZI. Weill Cornell Medicine, United States

A. Davis. Washington University in St Louis School of Medicine, United States

L. Foffano. Department of Medicine, University of Udine, United States

A. Medford. Massachusetts General Hospital Cancer Center / Dana Farber Cancer Institute, United States

K. Clifton. Washington University in St Louis School of Medicine, United States

W. Hensing. Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA., United States

M. Velimirovic. Cleveland Clinic, United States

A. Shah. Northwestern University, United States

L. Munoz Arcos. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, New York, United States

C. Dai. MGH Cancer Center, United States

J. Keenan. Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Boston, MA 02114, USA., United States

E. Denault. Massachusetts General Hospital, United States

W. Gradishar. Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, United States

G. Damante. Institute of Human Genetics, University of Udine, United States

A. Behdad. Pathology and Laboratory medicine, Cleveland Clinic, United States

L. Gerratana. Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

F. Puglisi. National Cancer Institute, Centro di Riferimento Oncologico (CRO), IRCCS, United States

C. Ma. Washington University in St. Louis, St. Louis, Missouri, United States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

M. Cristofanilli. Weill Cornell Medicine, United States

Background: Despite how commonly synonymous mutations (SYN) and unknown significance (VUS) are detected in tissue and circulating tumor DNA (ctDNA) next-generation sequencing (NGS), the potential for these somatic changes to impact personalized approaches in metastatic breast cancer (MBC) is unclear. Emerging evidence suggests that SYN mutations may play a role in cancer biology through changes in mRNA stability, splicing, and gene expression. The aim of this study was to characterize SYN and VUS in a large multicenter consortium and to analyze their interplay with pathogenic variants (PATH).

Methods: The study retrospectively analyzed a multi-institutional cohort comprising 1189 patients with MBC characterized for ctDNA using NGS (Guardant360™, Guardant Health) before treatment start (BL) and at disease progression (PD). Pathway classification was defined based on prior research (Sanchez-Vega F et al, Cell. 2018). Single Nucleotide Variations (SNVs) were annotated for oncogenicity (OncoKB) and protein domain (UniProtKB). Associations between clinical characteristics and pathway classifications for SYN and VUS were explored by multinomial logistic regression; survival was tested through Cox regression in terms of overall survival (OS).

Results: Hormone-receptor positive (HR+)/HER2 negative (luminal-like) was the most represented subtype (68.7%) followed by HER2-positive (14.6%), and triple-negative (TNBC) (16.7%). PATH were mainly detected in the TP53 DNA binding domain, ESR1 ligand binding domain, helical and catalytic domains of PIK3CA, SYN in the ligand binding domain of ESR1, MET Sema, KIT protein kinase domain, and FGFR1 Ig-like C2-type 1. In contrast, VUS were mainly found in the ESR1 ligand binding domain, MET Sema, ATM PI3K/PI4K catalytic domain, DDR2 Protein kinase and PIK3CA C2 PI3K-type. Analyzing pathways, after multivariable multinomial logistic regression, RAS SYN, PI3K and ESR PATH were significantly associated with HER2+ MBC (respectively RRR=4.14, P=0.046; RRR = 0.474, P < 0.001 and RRR = 0.306, P < 0.001). TNBC was associated with PATH PI3K (RRR = 0.366, P < 0.001), PATH P53 (RRR = 4.71, P < 0.001) and PATH RAS (RRR = 0.362, P = 0.026, 95% CI 0.147 - 0.888). In luminal-like MBC, a significant impact on OS was observed for SYN P53 (HR = 2.53, P = 0.008) and PATH ER (HR = 1.54, P < 0.001), PATH P53 (HR = 1.56, P < 0.001), PATH cell-cycle (HR = 1.64, P = 0.0299), and PATH RAS (HR = 1.62, P = 0.010). An impact on OS was observed in TNBC for SYN cell-cycle (HR = 5.41, P = 0.006), VUS ESR (HR = 2.87, P = 0.018), PATH P53 (HR = 1.84, P = 0.012) and PATH cell-cycle (HR = 5.07, P < 0.001). VUS MYC (HR = 38.5, P = 0.001) and PATH PI3K3 (HR = 2.32, P = 0.022) were significant among HER2 positive. Differences in SYN, VUS and PATH alterations were then compared between baseline and progressive disease. While a significant increase in mutant allele frequency (MAF) was observed for PATH (P=0.0010) and VUS (P=0.0152) at PD, no differences were highlighted for SYN (P=0.8362).

Conclusions: In our cohort we characterized the MBC for PATH, VUS and SYN utilizing the ctDNA. In this study, considering the complex genomic landscape of MBC, we demonstrated that both SYN and VUS mutations had an impact on the survival outcome. Therefore, further analysis to validate the prognostic and predictive role of SYN and VUS, with or without PATH mutations, are needed to better characterize and monitoring of MBC through ctDNA. Moreover, functional studies are needed to better understand their role in the nuanced biology of MBC.

PO5-15-03

Neutrophil-lymphocyte ratio and absolute lymphocyte count, inflammatory markers, may predict lymph node metastasis in elderly patients with operable breast cancer

Presenting Author(s) and Co-Author(s):

E. Tokuda. Department of Medical Oncology, Fukushima Medical University, United States

M. Morita. Division of Endocrine & Breast Surgery, Kyoto Prefectural University of Medicine, United States

A. Shimomura. Department of Breast and Medical Oncology, National Center For Global Health And Medicine, Tokyo, Japan

Y. Horimoto. Department of Breast Oncology, Juntendo University, United States

Y. Kawamura. Dept. of Breast and Medical Oncology, National Center for Global Health and Medicine, United States

Y. Ishizuka. Department of Breast Oncology, Juntendo University, United States

K. Sekine. Medical Oncology Center, Saitama City Hospital, United States

S. Obayashi. Department of General Surgical Science, Gunma University, United States

Y. Kojima. National Cancer Center Hospital, United States

T. Higuchi. Breast Surgery Unit, Japanese Red Cross Saitama Hospital, United States

Background: Blood-derived systemic inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and absolute lymphocyte count (ALC) have been demonstrated as predictive markers of recurrence and prognosis in several malignancies. Increased chronic inflammation with aging has been reported to be involved in cancer cells and their microenvironment. Several studies have also reported a close relationship between inflammatory markers and cancer grade and prognosis in the elderly. In this study, we retrospectively examined the relationship between lymphocyte-related inflammatory markers and prognosis in elderly breast cancer patients. **Method:** We included 602 patients diagnosed with primary invasive breast cancer at 8 institutions between 2008 and 2013, all of whom were older than 70 years old and had undergone breast cancer surgery. Preoperative blood collection data were used to analyze the relationship between NLR, PLR, LMR, ALC and clinicopathological data including recurrence. **Results:** The pathological stages of the 602 patients were Stage I: 275, Stage II: 276, and Stage III: 51, with median NLR, PLR, LMR, and ALC values of 2.21, 134.51, 6.76, and 1840, respectively. The mean age of the patients was 75.3 years. The median follow-up was 72.8 months. 76 patients relapsed, and the mean time to relapse was 42.7 months. Lymphocyte-associated inflammatory markers and Li Sheng pathological characteristics showed no significant differences in stage, presence or absence of recurrence, or form of recurrence, but lymph node metastasis on surgical pathology showed significant differences between cases with and without lymph node metastasis in NLR and ALC ($P < 0.05$). **Conclusions:** LMR and ALC were considered useful biomarkers that can be easily measured to predict lymph node metastasis in operable elderly breast cancer

PO5-15-04

MammaPrint index predicts neoadjuvant chemosensitivity in patients with HR+HER2-early-stage breast cancer in the real-world evidence FLEX study

Presenting Author(s) and Co-Author(s):

J. O'Shaughnessy. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas, United States

L. pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

C. Graham. Emory University, United States

P. Whitworth. Nashville Breast Center, United States

P. Beitsch. Dallas Surgical Group, United States

C. Osborne. Baylor Charles A. Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, Texas, United States

R. Rahman. Texas Tech University Health Sciences Center, United States

A. Menicucci. Agendia Inc, United States

W. Audeh. Agendia Inc., United States

F. Investigators' Group. Agendia, United States

Background: Neoadjuvant chemotherapy (NCT) yields low pathologic complete response (pCR, ypT0/is ypN0) rates in hormone receptor positive (HR+), HER2- early-stage breast cancer (ESBC). Genomic signatures may predict chemosensitivity and treatment benefit better than receptor status based clinical subtyping. The 70-gene expression signature, MammaPrint (MP), classifies patients with ESBC as having a High or Low Risk of distant recurrence. In the NBRST and ISPY2 trials, further stratification of MammaPrint High Risk into High 1 (H1) or High 2 (H2) showed significantly higher pCR rates to NCT or targeted agents in MP H2 cancers compared to MP H1 tumors. We evaluated MammaPrint H1 and H2 status as a biomarker for neoadjuvant chemosensitivity in patients with HR+HER2- ESBC enrolled in the real-world evidence FLEX study.

Methods: FLEX (NCT03053193) is an ongoing prospective, observational trial that has currently enrolled 12,328 patients with ESBC who were tested with MammaPrint as standard of care, with or without molecular subtyping signature, Blueprint (BP), and consented to clinically annotated full genome data collection (data locked Feb. 2023). Patients with HR+HER2-, MP High Risk tumors who received NCT (majority received AC-T) and had pCR data available were included in this analysis (n = 214). Patients were stratified into MP H1 (index 0.000 to -0.569) and H2 (index -0.570 to -1.000) groups. BP classified MP High Risk tumors into Luminal B-, HER2-, or Basal-Type. Differences in clinical characteristics and pCR rates between H1 and H2 tumors was assessed by Chi-Squared test and two-sided proportional z-test, respectively. The association between MP H1 and H2, BP subtype, and pCR was assessed using logistic regression and was adjusted for age, race, grade, T stage, N stage, and NCT regimen.

Results: MammaPrint classified 142 (66%) cancers as H1 and 72 (34%) as H2 tumors. Age, menopausal status, race, tumor stage, and lymph node status were comparable between both groups. Although most H2 tumors (78%) were Grade 3, only 59% of all Grade 3 tumors were H2. Nearly all (98%) H1 tumors were Luminal B whereas for H2 tumors, 51% were Luminal B and 49% were Basal by BP classification. pCR rate was significantly higher in H2 tumors (29.2%) compared to H1 tumors (6.3%, p < 0.01) (Table). Basal-Type, H2 tumors (n=35)

exhibited the highest pCR rate of 37.1%. Among BP Luminal B tumors, those with MP H2 tumors had a significantly higher pCR rate (21.6%) vs. MP H1 tumors (5.8%, $p = 0.003$). Multivariate analysis revealed MP H2 (OR=4.91, $p=0.003$) and BP Basal-Type (OR=3.54, $p=0.03$) were significantly associated with likelihood of pCR, whereas clinical variables were not associated with pCR.

Conclusion: These data demonstrate MammaPrint and Blueprint utility to predict the likelihood of achieving pCR after NCT in HR+HER2- ESBC. Although both MP High Risk groups exhibit chemosensitivity, High 2 tumors have higher chemosensitivity than High 1 tumors. MP High 2 status can be utilized to identify ER+ patients who are the most likely to experience pathologic downstaging and pCR after NCT. Also, patients with High 2 tumors treated with PD-L1 or PARP inhibitors in the ISPY2 trial exhibited significantly higher pCR rates than those observed for High 2 tumors treated with NCT alone. These data suggest that for patients with MP High 2 tumors, neoadjuvant use of chemotherapy is appropriate and these patients may further benefit from the addition of targeted agents to standard NCT.

Table: Distribution of pCR rates among MammaPrint H1 and H2 and Blueprint molecular subgroups

pCR rate	MP High 1 n = 142	MP High 2 n = 72
All patients n = 214	9/142 (6.3%)	21/72 (29.2%)
Patients with Luminal B-Type tumors n = 176	8/139 (5.8%)	8/37 (21.6%)
Patients with Basal-Type tumors n = 38	1/3 (33.3%)	13/35 (37.1%)

Data presented as # of patients with pCR/(total # patients in subgroup) and as percentage

PO5-15-05

Clinical and genomic landscape of ERBB2 and ERBB3 mutated breast cancer

Presenting Author(s) and Co-Author(s):

- N. Bilani. Icahn School of Medicine at Mount Sinai Morningside-West, United States
J. Tao. New York Presbyterian-Weill Cornell, New York, NY, USA, United States
A. Safonov. Memorial Sloan Kettering Cancer Center, New York, United States
D. Casey. University of North Carolina at Chapel Hill, United States
J. Drago. Memorial Sloan Kettering Cancer Center, New York, New York, United States
M. Ahmed. Memorial Sloan Kettering Cancer Center, United States
B. Acevedo. Memorial Sloan Kettering Cancer Center, United States
K. Jhaveri. Memorial Sloan Kettering Cancer Center, New York, New York, United States
J. Reis-Filho. AstraZeneca, Gaithersburg, Maryland, United States
M. Robson. Memorial Sloan Kettering Cancer Center, New York, United States
E. Toska. Johns Hopkins University School of Medicine, Baltimore, Maryland, United States
A. Hanker. UT Southwestern Medical Center, Dallas, Texas, United States
C. Arteaga. UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, Texas, United States
S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States
H. Wen. Memorial Sloan Kettering Cancer Center, United States
P. Razavi. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Our understanding of tumorigenesis in ERBB2 (HER2) non-amplified breast cancer has recently evolved through genome sequencing efforts identifying somatic mutations in ERBB2 and its ERBB3 coreceptor (ERBB2/3). These alterations result in upregulation of HER2 activity and have been implicated in resistance to certain targeted therapies. To develop efficacious therapeutic strategies in this context, further delineation of the clinical and genomic landscape of ERBB2/3-mutated (ERBB2/3-mut) breast cancers is paramount. **Methods:** Patients (pts) with breast cancer who underwent tumor and normal tissue sequencing using the MSK-IMPACT assay between April 2015 to August 2019 were surveyed in this analysis. We performed gene enrichment analyses to assess the frequency, type and pattern of ERBB2/3-mut, and compared demographics and clinicopathologic characteristics of this cohort with those of pts with ERBB2/3-wild-type (wt) tumors. The landscape of co-occurring and mutually exclusive genomic alterations in oncogenic (as per OncoKB) ERBB2/3-mut vs. ERBB2/3-wt was studied in the context of receptor status. Finally, we investigated the association between ERBB2/3-mut status and clinical outcomes in HR+/HER2- pts. Progression free survival (PFS) on first line CDK4/6 inhibitors and endocrine therapy (CDK4/6i-ET) was assessed utilizing Cox proportional hazard models adjusted for endocrine therapy partner. **Results:** Of 4,458 evaluable pts with breast cancer, 260 were ERBB2/3-mut (ERBB2 n=182, 4.1%; ERBB3 n=90, 2.0%, with both ERBB2/3 n=12, 0.27%). A total of 368 ERBB2/3 alterations were identified in 321 samples, of which 324 were SNVs (88.0%) and 44 indels (12.0%). Of the 256 ERBB2-mut, 185 (72.3%) were pathogenic variants (PVs), with the most frequent alterations being L755S (28.6%), V777L (13.5%), G778_P780dup (10.3%) and S310F (12.4%). Of the 112 ERBB3-mut, 53 (47.3%) were PVs; E928G (47.3%) and G284R (11.3%) were the most common. ERBB2/3-mut tumors were enriched in lobular (n=72, 13.3%) over ductal histology (n=164, 4.6%; Odds ratio [OR]:

3.15, 95% confidence interval [CI]: 2.31–4.25; $p=8.2 \times 10^{-13}$). When duplicates from each category were excluded, ERBB2/3 variants were more prevalent in metastatic tumors (n=165, 7.3%) compared to primaries (n=119, 4.7%; OR: 1.61, 95% CI: 1.25–2.06, $p=0.0001$). A similar trend was observed in the HR+/HER2- subgroup (metastatic: 6.7% vs. primary: 4.3%; OR: 1.61, 95% CI: 1.12–2.2, $p=0.0024$). In the HR+/HER2- subgroup (n=3,039), ERBB2-mut (4.0%, PVs: 3.1%) were significantly co-altered ($q < 0.1$) with CDH1, TBX3, ERBB3, RUNX1, CBF, MAP3K1, FOXA1 and NF1 and mutually exclusive with GATA3. In the HER2+ subgroup (n=640), ERBB2-mut (7.2%, PVs: 4.7%) were significantly co-altered with CDH1, TBX3, and CDKN2A/B. In the TNBC cohort (n=779), ERBB2-mut (2.3%, PVs: 1.7%) were mutually exclusive with TP53, and co-altered with PIK3CA, ARID1A, MAP3K1, CBF, and CDH1. Overall, the ERBB3-mut were co-altered with ERBB2, CDH1, and CBF. In HR+/HER2- pts with tumor sequencing performed prior to receiving first-line CDK4/6i-ET (n=468), PFS for ERBB2/3-mut (n=23) was not significantly different than ERBB2/3-wt (hazard ratio: 1.19, 95% CI: 0.75–1.90, $p=0.46$). Conclusion: Here we describe the clinical and genomic characteristics of a large cohort of ERBB2/3-mut breast cancers. We identify a notable enrichment of ERBB2/3-mut in lobular histology and metastatic tumors and tendency for co-alteration with CDH1 and multiple transcription factors reflecting the unique biology of ERBB2/3-mut breast cancers. Further analyses on an expanded cohort (n >6000 pts), including outcomes on HER2-directed antibody-drug conjugates (T-DXd) and targeted therapies such as PI3K inhibitors, will be presented at the 2023 SABCS Annual Meeting.

PO5-15-06

NVIGEN X® Comprehensive Liquid Biopsy for Sensitive ctDNA, Circulating Tumor Cells (CTC), and Protein Detection in Breast Cancer: Next-Generation Sequencing, Patient Case Studies, and Clinical Implications

Presenting Author(s) and Co-Author(s):

A. Fu. NVIGEN Inc., United States

M. Ton. NVIGEN Inc., United States

K. Wang. NVIGEN Inc., United States

W. Gu. NVIGEN Inc., United States

H. Jin. NVIGEN Inc., United States

N. Shaikh. Stanford University, United States

S. Madan. Stanford University, United States

S. Perepa. Stanford University, United States

T. Li. UC Davis Medical Center, United States

M. Liu. Natera, Austin, Texas, United States

H. Parsons. Dana Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States

G. Sledge. Stanford University, Stanford, California, United States

F. Riaz. Stanford University, United States

Background Breast cancer (BC) represents the most prevalent cancer and is a leading cause of cancer related mortality among women worldwide. Despite notable therapeutic advancements, concern for metastatic recurrence remains a significant challenge. Liquid biopsy has emerged as a promising method for monitoring cancer treatment efficacy and disease progression. However, existing technologies predominantly focus on ctDNA, and their clinical utility is hindered by limited detection sensitivity and accuracy. To address these challenges, NVIGEN has developed NVIGEN X® comprehensive liquid biopsy, a novel minimally invasive approach that integrates ctDNA, CTC, and protein biomarkers. This comprehensive method could enable longitudinal monitoring of tumor dynamics, offering valuable insights into cancer biology, treatment responses, and emerging therapeutic targets. Here, we showcase compelling patient case studies, and the potential clinical implications of our technology for an exciting and evolving field in cancer diagnostics. Method Patients with advanced breast cancer were prospectively identified and consented. 10mL blood per timepoint was collected in Streck tubes. ctDNA, CTC and proteins were captured from a single tube of blood using NVIGEN magnetic nanoparticles according to established protocols. Following DNA extraction, ctDNA and CTC samples underwent NVIGEN's highly sensitive sample workflow, optimized for NGS data accuracy and efficiency, employing hybridization capture with a 180 gene customizable cancer panel. Sequenced data were processed with NVIGEN's proprietary high-sensitivity data analysis pipeline. Gene alterations identified from both ctDNA and CTC samples were analyzed and integrated to provide a comprehensive view of the tumor profile. Protein biomarkers of interest were detected using NVIGEN's on-beads ELISA assay. Correlation analysis was performed to examine the relationship between the detected gene alterations, protein biomarkers, ctDNA/CTC data, and clinicopathologic features. Treatment response and identification of potential new treatment targets were evaluated based on the integrated analysis of ctDNA, CTC, protein biomarkers, and patient information. Result We collected 94

blood samples from 85 patients. Here we will present data from initial 36 patient samples. Of these 36 patients, 18 were tested with ctDNA/protein biomarkers (duo assays), and 18 were tested with ctDNA/CTC/protein biomarkers (trio assays). Comparison between duo and trio samples revealed that trio samples provided 2.5 times the number of detected variants compared to duo samples, with the median of variant numbers in duo assays being 52 (range 22-442), and in trio assays being 130 (range 73-703). Over 50% of the detected variants fell within the 0.1-0.5% variant allele frequency (VAF) range (number 2599) with total variant number being 5123. Several patient case studies were conducted using serial blood samples. These case studies revealed notable patterns of important gene alterations, such as ESR1, ERBB2 and PIK3CA, and demonstrated trends in the presence of these genes in ctDNA, CTC, or their coexistence. Protein biomarker information was correlated with ctDNA, CTC NGS data, and patient clinical status. **Conclusions** The analysis of the presented data from 36 patient samples with advanced breast cancer highlight the clinical relevance and potential significance of utilizing ctDNA, CTC and protein biomarkers in monitoring disease dynamics, treatment response, and guiding personalized treatment approaches. Our results suggest that individual protein biomarker analysis may be crucial in supporting personalized diagnostics and enabling more effective personalized medicine strategies.

PO5-15-07

Integrative proteomics, phosphoproteomics, and RNA profiling revealed novel timeline-dependent vulnerabilities in HER2-positive breast cancer.

Presenting Author(s) and Co-Author(s):

C. Wei. City of Hope Medical Center, United States

L. Yang. City of Hope Medical Center, United States

K. Mansfield. TGen, United States

J. Liu. City of Hope Medical Center, United States

R. Sharma. TGen, United States

R. Rockne. Beckman Research Institute, United States

R. Pillai. City of Hope National Medical Center, United States

P. Pirrotte. TGen/City of Hope Medical center, United States

J. Mortimer. City of Hope, Duarte, California, United States

Background: Most personalized breast cancer therapies leverage biomarkers identified in the pre-treatment setting. They do not always reflect the dynamic nature of early indicators of treatment response/resistance. Herein, we have a unique cohort of newly diagnosed HER2-positive breast tumors treated with a single low dose of trastuzumab (50mg), and the corresponding residual tumors that did not achieve pathologic complete response (pCR) to HER2-targeted neoadjuvant therapy. We hypothesize that integrative molecular profiling with proteomics and transcriptomics of these breast tumors could reveal novel time-course dependent contributors of therapy response and resistance. **Method:** This correlative biomarker study was a secondary objective of a parent study that evaluated 64uc-DOTA-trastuzumab PET imaging to predict response to trastuzumab and pertuzumab-based neoadjuvant therapy in HER2-positive breast cancer patients. Eighteen newly diagnosed breast cancer patients were enrolled, and pCR was achieved in 13 patients (72%). This correlative biomarker study was performed on breast tumors collected within 72 hours following administering a low dose trastuzumab (50mg) to the subjects prior to imaging and neoadjuvant therapy. Deep expression proteomics and phosphoproteomics data acquisition were performed on a Thermo Orbitrap Eclipse mass spectrometer. RNA profiling was performed using Nanostring breast cancer profiler. **Results:** Our multi-omic approach identified increased abundance or activity in the pCR group on the following ($p < 0.05$): Her2 protein and ERBB2 transcript levels, increased phosphorylation of ERBB2 (T1052), increase in Golgi trafficking activities, posttranslational modification with protein glycosylation, and lipid biosynthesis. Interestingly, compared to the non-pCR group, the pCR group showed lower activity level in ERBB2's downstream pathways, such as MAPK, SRC, and PI3K. In the non-pCR group, the residual tumor showed decrease in the following ($p < 0.05$): Golgi trafficking, glycosylation, antigen processing, and Her2 protein and phosphorylation (T1166). The pCR group had a negative enrichment for SGK1, a kinase which mediates PI3K pathway independently of AKT. SGK1 abundance was highest in residual tumors following neoadjuvant therapy. **Conclusion:** Using integrative proteomic and RNA profiling, we identified several in-vivo biological perturbations following administration of low dose trastuzumab. Increased Her2 abundance and ERBB2 transcript levels are associated with pCR, in keeping with previous reports of known pCR predictors. Decreased abundance of ERBB's downstream signaling proteins in the pCR group suggests that early treatment response to trastuzumab may be a predictor of pCR. Our integrative approach identified other dynamic biomarkers. For example,

compared to non-pCR group, Golgi trafficking is more active in pCR group tumors, and lowest in residual tumors following neoadjuvant therapy. This suggests that novel Golgi-targeting agents may be best utilized in neoadjuvant setting. Further, we identified SGK1 may be an important kinase for mediating therapy resistance early in treatment course, since its level is higher in non-pCR group following early exposure to trastuzumab compared to pCR group, with highest level detected in the residual tumors. These findings warrant orthogonal validation using in-vitro functional assays.

PO5-15-08

Role of next-generation sequencing testing in metastatic breast cancer

Presenting Author(s) and Co-Author(s):

K. Wani. Henry Ford Health, United States

M. Godbole. Henry Ford Cancer Institute, Henry Ford Health System, Detroit, Michigan, United States

B. Jacob. Henry Ford Health, United States

K. Springer. Henry Ford Health System, Detroit, Michigan, United States

V. Dabak. Henry Ford Cancer Institute, Henry Ford Health System, Detroit, Michigan, United States

Background: With recent advances in therapy, patients with metastatic breast cancer have been living longer. Treatment has previously largely depended on the subtypes of breast cancer (ER/PR positive, HER2 positive, triple negative). In recent years, testing metastatic breast cancer samples for somatic and germline mutations has revealed additional therapeutic targets which could help patients further than standard therapeutic options. Recent evidence has demonstrated that targeted therapy may offer an advantage in overall survival in patients with metastatic breast cancer. However, data regarding the use of targeted therapy is still sparse and its overall impact on metastatic breast cancer patients needs to be further investigated. We wanted to study genomic testing in such patients and see how often it leads to new therapy recommendations beyond standard of care as we move towards the era of precision medicine.

Methods: Patients who were diagnosed with metastatic breast cancer between 2015-2020 were screened and a total of 193 patients were identified. Baseline characteristics, treatment/outcome and NGS testing information was collected. Univariate two group comparisons were performed using t-tests for continuous variables, and using chi-square, or Fisher's tests if cell counts were < 5 for categorical variables. Survival analysis for progression free survival (PFS) and overall survival (OS) were done using log rank tests.

Results: Out of 193 patients, the majority (189) were female. There were 121 (62.7%) White patients, 69 (35.8%) Black patients, and 3 (1.6%) patients that were another race. 30.6 % of patients received next-generation sequencing (NGS) testing, 68.4% of patients did not, and 1% were unknown. Patients that received NGS testing were on average younger than those that did not receive NGS testing (53.24 years old vs 65.17 years old, respectively). Patients that received NGS testing were more likely to be premenopausal ($p < .0001$). Patients without NGS testing were more likely to die than those with NGS testing ($p=.0327$). There were no statistically significant differences observed in percentage of patients getting NGS testing done and whether patients were triple negative, HER2 positive with hormone receptor positive or negative, and HER2 negative with hormone receptor positive. As the year of metastatic breast cancer diagnosis advanced from 2015-2020, a high percentage of patients received NGS testing (i.e. 20% diagnosed in 2015 received NGS testing, whereas 50% diagnosed in 2020 received NGS testing). As the number of years between diagnosis and last follow-up increased, the probability of progression decreased for patients that had NGS testing done. Patients with NGS testing did better than those without NGS testing, but patients with no treatment change had the lowest probability of progression.

Conclusion: On average, only 30% of patients are receiving NGS testing, however it is being

done more often in recent years than ever before. There is a clear progression free survival benefit seen in patients who received NGS testing. It is interesting to note that those who did not receive any changes in treatment based on NGS testing have the lowest probability of progression, but overall survival was not different for any of the different groups studied. This could be related to the low number of patients with NGS testing in our analysis. Further studies are warranted to understand this association.

Summary of NGS testing data in various demographic categories

	No NGS testing (N=132)	NGS testing (N=59)	P-value
Age			<.0001
N	132	59	
Mean (SD)	65.17 (11.80)	53.24 (13.47)	
Median (IQR)	65.00 (56.00, 73.00)	52.00 (40.00, 63.00)	
Gender, n (%)			0.6877
Female	130 (98.5%)	57 (96.6%)	
Male	2 (1.5%)	2 (3.4%)	
Race, n (%)			0.2450
Black	53 (40.2%)	15 (25.4%)	
Other	1 (0.8%)	2 (3.4%)	
White	78 (59.1%)	42 (71.2%)	
Menopausal Status, n (%)			<.0001
Postmenopausal	118 (91.5%)	37 (64.9%)	
Premenopausal	11 (8.5%)	20 (35.1%)	
Missing	3	2	
Status, n (%)			0.0327
Alive	33 (25.8%)	21 (36.2%)	
Dead	95 (74.2%)	37 (63.8%)	
Missing	4	1	

There was a statistically significant difference in whether NGS testing was obtained or not and age, menopausal status and current status. There was no statistically significant difference in whether NGS testing was obtained or not and gender or race.

PO5-15-09

DNA damage induced necroptosis predicts response to radioimmunotherapy

Presenting Author(s) and Co-Author(s):

A. Goddard. University of North Carolina, North Carolina, United States

Q. wang. University of North Carolina, United States

M. Cho. University of North Carolina, United States

L. Lerner. University of North Carolina, United States

G. Gupta. University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

Background: More than half of all cancer patients receive radiotherapy (RT) during their cancer experience. DNA damage induced by RT can initiate a pro-inflammatory immune response within the tumor microenvironment (TME), yet this response is not uniformly observed across all tumors. Mre11 is one of the first responders to double stranded breaks and coordinates the DNA damage response. Recent work in our lab reveals that Mre11 is required for cGAS mediated detection of cytoplasmic DNA, in turn activating STING to engage the type I interferon signaling pathway, downstream of which can activate ZBP1/RIPK3/MLKL mediated necroptosis. The purpose of this study is to determine if expression of the necroptotic pathway may predict whether breast tumors benefit from RT to overcome ICI resistance and induce systemic anti-tumor immunity in the form of an abscopal response. Methods: Four Trp53^{-/-} Balb/c breast cancer syngeneic allograft models with low tumor mutational burden and resistance to dual ICI (anti-PD1 and anti-CTLA4, BioXcell) were used. Mice were implanted with bilateral tumors and randomly divided into four treatment cohorts: untreated, RT, ICI, or RT+ICI, where RT (8Gyx3) was administered to one tumor. Two lines exhibited abscopal responses to RT+ICI (i.e., "abscopal models"), whereas the other two did not (i.e., "non-abscopal models"). To identify gene expression patterns associated with abscopal responding breast tumors, we performed spatial transcriptomic analysis of tumors 10 days after initiating treatment using the GeoMx whole transcriptome assay targeting panCK⁺ tumor cells and tumor adjacent CD45⁺ immune cells (N >5 for each treatment group and tumor type). Unsupervised hierarchical clustering was performed to identify gene expression patterns across areas of interest. Genes selectively induced by RT+ICI in abscopal models that were not induced in non-abscopal models were identified using two-tailed t-test and FDR correction for multiple testing (FDR < 5%). DeSEQ2 and GSEA analysis were performed using publicly available mouse gene sets (Broad Institute). Results: The TME in untreated tumors in the abscopal models demonstrate upregulation in the B cell survival pathway and apoptotic pathways compared to untreated tumors in non-abscopal models. Hierarchical clustering of immune related genes in CD45⁺ segments of RT+ICI treated tumors exhibiting an abscopal response revealed a global shift in gene expression profiles after treatment. GSEA analysis of CD45⁺ segments from abscopal models shows that RT+ICI treatment results in enrichment of the interferon mediated signaling pathway including interferon alpha (p < 0.0001), interferon beta (p < 0.0001), type II interferon response (p < 0.0001), and antigen processing and presentation (p < 0.0001). In tumor cells of breast cancers demonstrating the abscopal response, Isg15 and Zbp1 are highly induced by RT+ICI. The necroptotic pathway, including Zbp1, Ripk3, and Mlkl, are significantly higher expressed in the panCK⁺ tumors known to demonstrate the abscopal response. Conclusion: Breast cancer models with an abscopal response to RT+ICI demonstrate higher expression of Isg15 and Zbp1, both of which are involved in secreted inflammatory signaling. The TME in these models have increased interferon signaling and antigen presentation in response to RT+ICI. The role of DNA damage induced necroptosis in generating an abscopal

response in breast cancer warrants further investigation as a potential biomarker for response to RT+ICI combination therapy.

PO5-15-10

Plasticity marker FOXC1 expression accurately predicts efficacy of Adjuvant Tamoxifen + Chemotherapy in reducing all-cause mortality in ER+LN- Breast Cancer: Validation in the SCAN-B Prospective Study (NCT02306096)

Presenting Author(s) and Co-Author(s):

P. Ray. Private Practice, Evanston, Illinois, United States

T. Ray. Onconostic Technologies, Inc., United States

C. Taylor. USC, United States

R. Husa. Onconostic Technologies, Inc., United States

INTRODUCTION: Despite the development and validation of multimarker gene panels like OncotypeDx[®], MammaPrint[®] and EndoPredict[®], an affordable and globally accessible biomarker approach that can predict increased risk of all-cause mortality in patients diagnosed with ER+LN- breast cancer, as well as the efficacy of adjuvant endocrine + chemotherapy in mitigating such elevated risk, continues to be an unmet medical need. Lack of such a pragmatic solution continues to be the cause of preventable recurrent/metastatic disease in patients diagnosed with ER+LN- breast cancer in resource-challenged settings around the world. We hypothesized that a predictive biomarker strategy that measures expression of the plasticity marker FOXC1, in combination with clinical parameters like tumor size (TS) and tumor grade (TG), may offer equivalent results to that of the above multimarker gene panels at a significantly lower economic cost without compromising accuracy of prediction results.

METHODS: Pre-treatment tumor RNA data obtained from a training cohort (compendium of gene expression microarray datasets, n=2857) and a single large validation cohort (SCAN-B Prospective Multicenter Observational Study, n=3520) for patients diagnosed with ER+LN- breast cancer were analyzed for FOXC1 expression, tumor size (TS) and tumor grade (TG) and correlated with Recurrence-Free Survival (RFS) and Overall Survival (OS). Optimized biomarker cutoff values based on model area-under-curve were leave-one-out cross validated and Risk-of-Recurrence (ROR) prediction algorithm derived utilizing the (compendium) training dataset. The unmodified strategy was then validated in the independent (SCAN-B) validation dataset.

RESULTS: A predetermined High ROR score calculated using FOXC1 expression, TS and TG (trained using the compendium dataset) predicted efficacy of adjuvant endocrine + chemotherapy over that of adjuvant endocrine therapy alone in ER+LN- patients in terms of statistically significant reduction in all-cause mortality at 8-years post-diagnosis in the SCAN-B validation dataset (4.66% vs 24.06%, n=326, OR=6.48, 95%CI [2.97-14.11], p< 0.0001).

OncotypeDx[®] (5.7% vs 14.4%, n=762, OR=2.79, 95%CI [1.37-5.67], p=0.002),

MammaPrint[®] (5.1% vs 18.4%, n=665, OR= 95%CI [2.04-8.43], p< 0.0001) and

Endopredict[®] (4.8% vs 15.2%, n=923, OR=3.58 95%CI [1.78-7.21], p=0.0002) were

also statistically significant predictors of the same.

CONCLUSION: Pre-treatment tumor FOXC1 mRNA or protein expression (assessed using qRT-PCR or routine immunohistochemistry (IHC), respectively, when combined with TS and TG presents a unique and economical alternative solution to multimarker gene panel tests like OncotypeDx[®], MammaPrint[®] or Endopredict[®], for guiding therapy of patients diagnosed with ER+LN- breast cancer in resource challenged settings. Such an approach to identify elevated

risk of recurrence in patients diagnosed with ER+LN- breast cancer and prevent the same by guiding adjuvant endocrine + chemotherapy decisions, could help to extend recurrence-free and overall survival. Such an approach merits testing in real world ER+LN- patient cohorts in resource-challenged settings to help support implementation of this FOXC1-driven predictive biomarker strategy in the clinic.

PO5-15-11

A Novel Biosignature to Predict Radiation Therapy Response in Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Surgery

Presenting Author(s) and Co-Author(s):

T. Bremer. PreludeDx, United States

K. Mittal. PreludeDx, United States

C. Shah. Cleveland Clinic, Ohio, United States

F. Vicini. GenesisCare, United States

S. Shivers. PreludeDx, St Johns, Florida, United States

C. Wadsten. Dept of Surgery, Sundsvall Hospital, Sundsvall, Sweden

Introduction: Radiation therapy (RT) is a standard component of treatment for most patients with early-stage, hormone receptor-positive, invasive breast cancer (BC) following breast-conserving surgery (BCS). RT recommendations are primarily based on clinicopathologic (CP) factors, such as tumor size, nodal status, and histological grade. While these factors provide prognostic information, their ability to accurately identify patients at a higher risk of ipsilateral breast recurrence (IBR) or those who will significantly benefit from RT is unclear. Therefore, incorporation of additional predictive markers beyond CP factors is warranted and there remains a need to refine the selection criteria for patients who will derive the greatest benefit from RT. In this study, we aimed to explore the role of immune and metabolic signaling axes as potential predictive markers for RT response in hormone receptor-positive breast cancer patients. **Methods:** A cohort of 939 women from Sweden were diagnosed with BC between 1987 and 2004. A subset of 471 patients was diagnosed with T1-T2N0M0 BC and underwent BCS with negative margins. Patients were treated with BCS plus/minus RT (median dose 50Gy) based upon physician preference. Biomarkers were assayed in formalin-fixed paraffin-embedded tissue micro arrays using multiplex immunofluorescence and multi-spectral imaging in a CLIA lab (Laguna Hills, CA). Immune and metabolic axes were defined employing biomarkers and used to classify patients into three risk groups: 1) Low Risk (lower baseline risk and no RT benefit), 2) Elevated Risk (higher baseline risk and significant RT benefit), and 3) Residual Risk (higher baseline risk and suboptimal RT benefit). Risk groups were analyzed for IBR rate using Kaplan-Meier and Cox proportional hazards analyses. Risk group prognosis and RT prediction was assessed for RT-risk group interaction in multivariable analysis, adjusting for CP factors. **Results:** Among the patients with complete biomarker data, 261 were hormone receptor-positive, and had a median follow-up of 140 months. Median age was 62 years (28-88 years), and median tumor size was 1.1 cm (0.1-4 cm). Some patients (21%) received endocrine therapy (ET), and most (76%) received RT, with 79% of patients who received ET also receiving RT. In the overall population, RT following BCS was associated with a reduction in HR for recurrence (HR=0.3, 95%CI [0.1, 0.5], p< 0.001). Patients classified as Low Risk (41%) did not have a significant benefit from RT (HR=0.9, 95%CI [0.1, 8.3], p=0.95) in multivariable analysis adjusted for CP factors. For patients who were classified as Elevated Risk (31%), multivariable analysis showed a higher IBR rate without RT (HR=5.7, 95%CI [1.3, 25.1], p< 0.021) relative to the Low Risk group who had a significant benefit from RT (HR=0.1, 95%CI [0.02, 0.2], p< 0.001). Patients classified into the Residual Risk group (28%) had no significant reduction from RT (HR=0.7, 95%CI [0.2, 2.0], p=0.61). However, in multivariable analysis adjusted for CP factors, patients treated with RT in the Residual Risk group had higher IBR rates (HR=3.7, 95%CI [1.6, 8.7], p=0.0026) compared to RT-treated patients in other risk groups. The biosignature was predictive for RT benefit in multivariable analysis adjusted for CP

factors (p-interaction < 0.001). Conclusions: The biosignature used in this study demonstrated the potential to identify patients who may derive limited benefit from RT, allowing for tailored therapeutic approaches. These findings underscore the importance of individualized treatment decisions based on risk stratification. Further clinical validation and refinement of risk stratification strategies are warranted to optimize outcomes in hormone receptor-positive, BC patients undergoing BCS.

PO5-15-12

Spatial immune correlates of response to eribulin and pembrolizumab in metastatic triple negative breast cancer (mTNBC) on the ENHANCE1 trial

Presenting Author(s) and Co-Author(s):

M. Kearney. Saint Luke's Cancer Specialists-South, United States

H. Guo. Columbia University Irving Medical Center, United States

R. Vanguri. Children's Hospital of Philadelphia, United States

Q. Wang. Columbia University Irving Medical Center, United States

E. Connolly. Columbia University Irving Medical Center, New York, New York, United States

Background: PD-L1 is the only approved biomarker for pembrolizumab in metastatic breast cancer for response to combination chemo-immunotherapy. As it is not predictive of response in all cases, additional biomarkers are needed. Previously we have demonstrated that stromal tumor infiltrating lymphocytes (sTILs) are associated with response to therapy in patients treated with front-line combination chemoimmunotherapy on the ENHANCE-1 study with eribulin and pembrolizumab. However, sTILs was not predictive of response in patients treated with prior lines of chemotherapy in the metastatic setting. We used multiplexed immunofluorescence on whole slide images to characterize associations between specific immune populations and outcomes in patients treated prospectively on the ENHANCE-1 study. Methods: ENHANCE-1 was a single arm phase Ib/II trial which evaluated the efficacy and safety of eribulin and pembrolizumab in 167 patients (pts) with mTNBC who had received 0-2 prior lines of therapy (66 pts in the first line setting [stratum 1] and 101 pts with 1-2 prior lines of therapy [stratum 2]). 138 patient samples were evaluable for our study: 58 samples from stratum 1 and 80 samples from stratum 2. Objective response rate (ORR) was defined as percentage of pts with either complete response (CR) or partial response (PR) by RECIST 1.1. The ORR was 25.8% in stratum 1 and 22.5% in stratum 2 for the 138 patients analyzed. We utilized whole tissue sections and quantitative multiplexed immunofluorescence (qmIF) stained with: CD4, FoxP3, CD8, CD56 and pancytokeratin to characterize T-cells, NK cells and tumor cells. Halo (Indica labs) was used to segment and threshold cells for positive markers as well as to identify tumor and stromal tissue areas. Results: We found that the ratio of CD8+ to CD4+FoxP3+ T-cells were associated with response, irrespective of stratum ($p=0.005$). As biopsies were not required immediately prior to enrollment on ENHANCE-1, we also evaluated samples based on prior number of treatments since biopsy to enrollment. We found that only 58/138 patient samples evaluated were obtained without intervening treatment: 35 out of 58 from stratum 1 and 12 out of 80 from stratum 2. When samples were evaluated by stratum and the timing of tissue acquisition we found the ratio of CD8+ to CD4+FoxP3+ T-cells was more significantly associated with response (< 0.001) in patients whose sample were collected prior to enrollment, regardless of patient stratum. The ratio was not predictive in samples taken prior to treatments before enrollment. In addition, we found stromal and intratumoral CD8+ T-cell density is associated with response ($p=0.02$ and $p=0.03$ respectively) across both stratum. We did not find any significant changes assessed by qmIF in patient samples which had intervening treatment between sample collection and enrollment onto ENHANCE-1 trial. Conclusion: In this population of patients with mTNBC treated prospectively with eribulin and pembrolizumab, we find that a higher ratio of CD8+ to CD4+FoxP3+ T-cells and stromal and intratumoral CD8+ T-cell density is associated with response in patients with biopsy samples obtained prior to enrollment without intervening treatments after sample collection. The tumor microenvironment on patient samples obtained before one or more lines of therapy prior to enrollment on study

are not predictive of response to treatment. Further characterization of the TME via quantitative immunofluorescence is ongoing. This study was funded by Eisai

PO5-16-01

Clinicogenomic analysis reveals genomic associations of brain metastatic tropism in breast cancer.

Presenting Author(s) and Co-Author(s):

A. Safonov. Memorial Sloan Kettering Cancer Center, New York, United States

D. Smith. Memorial Sloan Kettering Cancer Center, United States

E. Ferraro. Memorial Sloan Kettering Cancer Center/Breast Medicine Service, New York City, New York, United States

J. Shen. Memorial Sloan Kettering Cancer Center, United States

I. Khatri. The Warren Alpert Medical School of Brown University, United States

R. Kumar. University of Miami, United States

J. An. Memorial Sloan Kettering Cancer Center, United States

M. Robson. Memorial Sloan Kettering Cancer Center, New York, United States

S. Chandarlapaty. Memorial Sloan Cancer Center, New York, New York, United States

A. Boire. Memorial Sloan Kettering Cancer Center, United States

N. Schultz. Memorial Sloan Kettering Cancer Center, United States

N. Moss. Memorial Sloan Kettering Cancer Center, New York, New York, United States

L. Pike. Memorial Sloan Kettering Cancer Center, United States

P. Razavi. Memorial Sloan Kettering Cancer Center, New York, New York, United States

Introduction: Recent progress in imaging and therapeutics has led to improvements in the treatment of advanced breast cancer. However, the incidence of brain metastasis (BM) in breast cancer is increasing and continues to be associated with poor prognosis and significant morbidity. Herein, we describe genomic enrichments associated with brain tropism from a large institutional clinico-genomic cohort. **Methods:** Patients who underwent tumor and matched normal sequencing utilizing hybridization-capture based targeted exonic sequencing (MSK-IMPACT) from April 2014 to March 2023 were included in this analysis; this cohort included 6,377 samples from 5,135 patients. We analyzed genomic data to inform the full spectrum of somatic and germline mutations, copy number changes and structural variants enriched in samples in resected BM specimens (n = 179), compared to primary tumors (n = 2980), stratified by receptor status. Enrichment analysis was conducted using a Fisher exact test for each respective receptor status. Similar analyses were conducted between extracranial metastatic (ECM) sites (n = 3186) and primary tumors, to differentiate the unique genomic features driving the emergence of BM as compared to general metastatic propensity. Multiple hypothesis testing was performed using Benjamini-Hochberg. Further genomic analysis, including allele specific copy number changes and mutational signatures will be reported at the 2023 SABCS meeting. **Results:** Oncogenic alterations in several genes were found to be enriched in BM samples compared to primary tumor, with an odds ratio exceeding that of the corresponding ECM comparison. For example, in the HR+/HER2- subset (4329 samples from 3476 patients), pathogenic variants in the following genes were enriched in BM: Primary analysis: NF1 (OR 6.4 [2.9 – 13.7], q = 0.001, 15.5% of BM), MYC (OR 3.9 [2.0 – 7.4], q = 0.001, 24.4% of BM), AGO2 (5.2 [2.4 – 10.9], q = 0.002, 15.5% of BM), CDKN2A (OR 3.9 [1.6 – 9.4], q = 0.06, 10.3% of BM), ERBB2 (OR 3.6 [1.5 – 8.6], q = 0.06, 10.3% of BM), RB1 (OR 4.2 [1.5 – 11.4], q = 0.06, 8.6% of BM), TP53 (OR 2.0 [1.1 – 3.5], q = 0.07, 40% of BM). In contrast, ESR1 variants were enriched in BM: Primary (OR 14.0 [6.7 – 28.2], but at the same level as ECM: Primary (OR

12.3 [8.7 – 17.7]). When considering HER2+ tumors (919 samples from 739 patients), only NKX.3 was enriched in the BM:Primary comparison (OR 11.5 [3.2 – 42.3], $q = 0.004$, 11.6% of BM). Although no TNBC samples met significance thresholds after adjustment for multiple hypothesis testing, CDH1, NTRK1, EGFR, and TP53 emerged as putatively significant. Conclusions: In a large cohort of genomically-profiled breast cancer samples, we find recurrent involvement of genes involved in cell cycle regulation (RB1, CDKN2A, TP53); these have been found to be enriched in brain metastases from other cancer types and are implicated in resistance to common lineage-directed therapies. Our approach also uncovered several targets for which therapies are actively in development (ERBB2, MYC). Further study of genomic evolution of breast cancer in the context of brain metastasis and therapeutic resistance will uncover conserved site-specific genomic changes and will identify novel, rational therapeutic targets.

PO5-16-02

Investigating survivin as a novel target for immunotherapy in diverse breast cancer patients

Presenting Author(s) and Co-Author(s):

A. Hamilton. UNC Lineberger, United States

Q. Wang. University of North Carolina at Chapel Hill, United States

S. Soppe. University of North Carolina at Chapel Hill, United States

M. Troester. UNC-Chapel Hill, United States

Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States

Background: The BIRC5 gene encodes survivin, a tumor-specific antigen associated with aggressive tumor features, Black race and poor prognosis in breast cancer (BC). Recent studies have shown that anti-survivin vaccines stimulate a strong anti-tumor immune response in multiple tumor types. However, the relationship between BIRC5/survivin and immune response in BC is poorly understood, particularly among diverse patients. In this analysis, we sought to investigate the relationship between BIRC5/survivin and the BC immune microenvironment across clinical tumor features and RNA-based risk scores for genomic instability. **Methods:** We leveraged the Carolina Breast Cancer Study (CBCS), a large population-based study that oversampled young (≤ 50 years) and Black women with invasive BC. NanoString mRNA expression profiling was used to evaluate breast tumor expression for 10 major immune cell types, adaptive and innate immune response, TP53 and homologous recombination deficiency (HRD) pathways, and BIRC5/survivin from 1952 BC patients, including 1,030 (53%) Black and 922 (47%) non-Black women from the CBCS, with additional comparison in The Cancer genome Atlas (TCGA) ($n=1,095$ breast tumors). BIRC5 was evaluated both as a continuous and categorical variable, using the third expression quartile as a cut point for BIRC5-high, with the lower three quartiles categorized as BIRC5-low. We used generalized linear models to estimate beta values and adjusted p-values as the measure of association between BIRC5 status and immune-related expression in strata defined by estrogen receptor (ER) status, tumor stage, TP53 and HRD status. All analyses were adjusted for multiple comparisons with the Benjamini-Hochberg procedure. **Results:** In an analysis of continuous BIRC5 expression and global classes of immune response, BIRC5 mRNA expression was highest among tumors with an adaptive-enriched immune class ($p < 0.001$) in both CBCS and TCGA. However, when investigating immune gene expression according to BIRC5 status (i.e., BIRC5-high relative to BIRC5-low), multivariate differential expression analysis revealed significantly decreased immune cell-related expression scores among BIRC5-high tumors relative to BIRC5-low, and this relationship persisted in analysis stratified on stage (I/II vs III/IV), ER status, TP53 and HRD status. Across all strata, the strongest relationship between BIRC5-high and the immune microenvironment was observed for adaptive immune response (Beta: -0.14; $p=0.005$), with decreased immune gene expression related to B cells (Beta: -0.16; $p=0.01$), T cells (Beta: -0.14; $p=0.007$), Cytotoxic cells (Beta: -0.14; $p=0.005$), and PD-L1 (Beta: -0.15; $p=0.005$), relative to BIRC5-low. **Conclusion:** High BIRC5/survivin expression is associated with decreased immune-related gene expression in both ER-positive and ER-negative disease, and across all tumor stages. Anti-survivin therapies may be beneficial for boosting immune response in breast tumors with low immunogenicity, offering promise for BC subtypes previously ineligible for immunotherapy.

PO5-16-03

RT LAMP assay for the subtyping of breast cancer

Presenting Author(s) and Co-Author(s):

I. Lee. Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital, United States

B. Kang. Kyungpook National University Chilgok Hospital, United States

J. Lee. Department of Breast & Thyroid Surgery, Kyungpook National University Chilgok Hospital, United States

J. JUNG. Department of Breast & Thyroid Surgery, Kyungpook National University Chilgok Hospital, United States

H. PARK. Department of Breast & Thyroid Surgery, Kyungpook National University Chilgok Hospital, United States

N. PARK. Department of Pathology, Kyungpook National University Chilgok Hospital, United States

J. PARK. Department of Pathology, Kyungpook National University Chilgok Hospital, United States

E. KIM. Kyungpook National University Chilgok Hospital, United States

J. KANG. Kyungpook National University Chilgok Hospital, United States

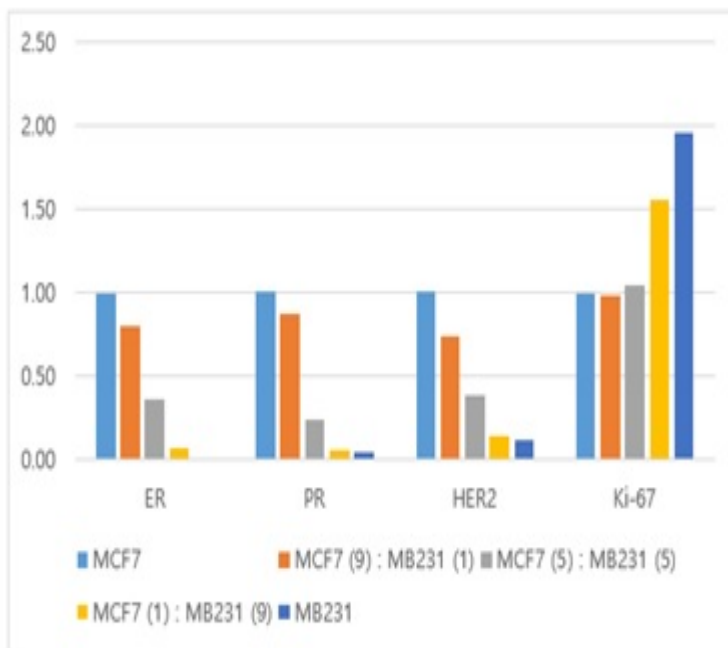
Y. Chae. Department of Oncology/Hematology, Kyungpook National University, Chilgok Hospital, Daegu, Republic of Korea, Republic of Korea

S. Lee. Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital, United States

Introduction Our previous study showed that direct reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay can be employed as a substitute in order to detect tumor involvement of lymph nodes within breast cancer patients. In this research, we aimed to investigate the potential applicability of RT-LAMP for the classification of breast cancer subtype. **Method** Breast Cancer Cell line RNA extraction Total RNA from the cell lines was isolated from cultured cells using RNAiso Plus (TaKaRa, Shiga, Japan) according to the manufacturer's instructions; MCF10A, MCF7, T47D, BT474, SKBR3, MB468, HCC1806, MB231 Primer design For the Primer design, ER, PR, HER2, Ki 67, CK7 and GATA were targeted. LAMP primers targeted at ER were created between exons 5 and 6, PR were created between exons 6 and 7, HER2 were created between exons 17 and 18, KI67 were created between exons 2 and 3, CK7 were created between exons 5 and 6, and GATA3 were created between exons 2 and 3 utilizing Primer Explorer V4 (<http://primereplorer.jp/elamp4.00/index.html>). RT-LAMP assays RT-LAMP assays were carried out within a 25 μ L reaction which included 12.5 μ L of 2 \times reaction buffer, 2 μ L of each primer, 1 μ L of enzyme mixture (16U Bst DNA polymerase and 120U M-MLV reverse transcriptase) 8 μ L of DEPC-treated water, and 2 μ L of the template RNA. DEPC-treated water was also employed for purposes of a negative control. The reaction mixture was conducted within qRT-PCR. Results ER, PR, HER2, Ki-67, CK7, GATA3 expression level were checked for each breast cancer cell line using RT-LAMP. The luminal cell line exhibited elevated levels of ER and PR expression, while the her2 cell line demonstrated a high level of expression for her2. In the RT LAMP assay, there is a direct correlation between shorter detection time and higher expression levels of the substance. Specifically, in the luminal type, ER/PR was detected within a timeframe of 10 to 12 seconds, while HER2 was detected within a timeframe of 15 to 16 seconds. The expression levels of ER, PR, and HER2 were

compared between MCF7 (luminal A) and MDA-MB-231 (TNBC) cell lines. RT-LAMP was performed to examine the RNA expression levels, while RT-PCR was applied to confirm the cDNA expression levels. MCF7 and MDA-MB-231 were mixed at 1:9, 5:5 and 9:1 ratios, respectively, and the difference in ER/PR/HER2 expression level was confirmed (Table1, Figure1). The presence of ER was detected in the MCF7 cell line at 14.44 minutes, and PR was observed at 18.84 minutes. HER2 was detected at a similar time (approximately 15 minutes) in both the MCF7 and MB 231 cell lines. Conclusion This study demonstrated that ER, PR, and HER2 can be quantified using RT-LAMP. Ongoing experiments are being conducted to classify breast cancer using the RT-LAMP method, aiming to enhance sensitivity in the quantification of ER, PR, and HER2. Additionally, new primers are being developed specifically for HER2 detection. RT-LAMP offers the advantages of being a point-of-care test that can be conducted on-site and reducing the discrepancies between pathologists.

RT PCR



PO5-16-04

Tissue-informed personalized MRD detection assay may outperform tumor-informed fixed panel strategy in Triple Negative Breast Cancer (TNBC)

Presenting Author(s) and Co-Author(s):

S. Li. Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

W. Gao. GenePlus-Beijing, United States

N. Fu. GenePlus-Beijing, United States

W. Cao. GenePlus-Beijing, United States

X. Zeng. GenePlus-Beijing, United States

X. Du. GenePlus-Beijing, United States

Q. Liu. Sun Yat-sen Memorial Hospital, Sun Yat-sen University, United States

Background: Minimal residual disease (MRD) detection by ctDNA analysis enables identifying patients with high recurrence risk and refining risk stratification to guide treatment selection precisely, which may improve patient survival or avoid overtreatment. We previously developed a 1021-gene fixed panel MRD detection assay, MNavigator V1, demonstrating high prognostic evaluation value in various solid tumors, including lung cancer, colorectal cancer, and esophageal carcinoma, and relevant research results have been published. Recently, the assay upgraded to MNavigator V2, a customized patient-specific panel strategy to ultra-deep sequencing, with higher clinical performance and more economical. Here, we head-to-head compared the performance of MNavigator V1 with V2, using the same collection of blood samples from TNBC patients. Methods: The retrospective study recruited 48 patients diagnosed with stage II-III TNBC with adequate samples (NCT04501523/NCT04803539). Five patients in the cohort received neoadjuvant therapy (Noad-group), and the standard treatment regimen of the remaining 43 patients was adjuvant therapy (ad-group) after surgery. The surgical tumor tissue of all these patients was collected. Peripheral blood samples were collected at various time points, baseline samples before neoadjuvant therapy, 7-day after neoadjuvant therapy, 1-month postoperative, 7-day after adjuvant therapy, and subsequent every 3~6 months follow-up. The personalized, tumor-informed MRD detection approach MNavigator V2 started by identifying somatic mutation of the resected tumor with a 1021-gene panel covering 1.6Mb of the human genome. Then, a customized panel consisting of up to 20 top-ranked patient-specific somatic variants was designed. After that, unique molecular identifiers (UMI) based 100,000X ultra-deep next-generation sequencing on plasma samples was conducted by adopting the mix panel of the patient-specific panel and a 5kb breast cancer universal core panel. MNavigator V1 assay, a fixed panel assay also applied the same off-the-shelf 1021-genes panel with a sequencing depth of 10,000X to detect MRD of blood samples. Results: Until May 2023, the median follow-up time of 660 days, and 8 patients were recurrence confirmed by CT imaging. The median tracked tissue-informed mutations was 7 (2~18). In this study, the screening time point was defined as the combined MRD status of the blood samples collected before and after neoadjuvant therapy, and 1-month post-surgery for the Noad-group, as for the ad-group, the time point referred to 1-month post-surgery and post-adjuvant therapy. If any one of these time nodes' MRD was positive, the screening period MRD was positive. During the screening period, MNavigator V1 and V2 accurately predicted 6/8 (75.0%) recurrence. MRD-positive status was associated with a worse prognosis, compared to the MRD-negative population, with hazard ratios of 9.0 and 19.9 for V1 and V2 assay, respectively. The longitudinal MRD evaluation yield a higher sensitivity of 7/8 (87.5%) for recurrence prediction with MNavigator V2 at a median lead time of 104 days, whereas the V1

assay predicted 6/8 (75.0%) at 94 days, and the hazard ratio was 40.4 vs 8.5. In one brain-only metastasis patient, MRD was undetectable, which may be due to the limitation of the blood-brain barrier. For recurrence-free patients with 1 year of follow-up, 92.5% (37/40) were MRD-negative with MNavigator V2 assay. These three patients who detected MRD-positive after surgery, ctDNA cleared after adjuvant therapy, and persistently negative during follow-up, may benefit from treatment. Conclusion: Based on the patient-specific tumor mutation profile, the personalized MRD detection assay achieved better clinical performance than the fixed panel strategy.

PO5-16-05

Integrating Circulating Tumor Cells (CTCs) and Cell-free DNA (cfDNA) Signatures for Monitoring Treatment Response in Stage III/IV Inflammatory Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Addanki. MD Anderson Cancer Center, United States

S. Meas. MD Anderson Cancer Center, United States

V. Sarli. MD Anderson Cancer Center, United States

A. Almosa. MD Anderson Cancer Center, United States

W. Woodward. UT MD Anderson Cancer Center, Houston, Texas, United States

D. Roy. MD Anderson Cancer Center, United States

A. Lucci. MD Anderson Cancer Center, Houston, Texas, United States

Background: Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer, comprising only between 1-5% of all breast cancer cases in the United States. Despite its low incidence, IBC accounts for 10% of breast cancer-related deaths and is often diagnosed with metastasis, resulting in shorter survival compared to non-IBC cases. The 5-year relative survival rate for all stages of IBC is 39%, dropping to 19% for patients with distant metastasis. Liquid biopsy-based biomarkers have emerged as potential analytes for predicting prognosis and monitoring response to therapies in IBC patients. We explored the prognostic role of liquid biopsy encompassing both CTCs and cfDNA in the blood of patients with stage III/IV IBC and their clinical outcomes. Methods: CTC and cfDNA analysis was performed on 90 blood samples from 47 patients with stage III and IV IBC. Samples were collected before (pre-treatment, n=43) initiation and after (post-treatment, n=47) completion of neoadjuvant chemotherapy. CTCs were enriched and enumerated using the CellSearch® platform (Menarini-Silicon Biosystems). CfDNA was extracted from plasma using MagMax™ Cell-Free Total Nucleic Acid Isolation Kit (Applied Biosystems™) and quantified using the Qubit™ dsDNA High Sensitivity kit (Invitrogen™). Differences in cfDNA concentrations were used to plot a receiver operating characteristic (ROC) curve which was then used to determine Area Under the Curve (AUC) and a cfDNA cut-off point. ROC cut-off was calculated based on Youden Index J. Survival analysis was performed by the Kaplan-Meier estimator and Cox regression models. P-values were measured using the Student t-test. Results: Prior to neoadjuvant treatment, CTC was detected in 51% of patient samples, and the median cfDNA concentration was 5.87 ng/mL (range 0.95-24.11 ng/mL). After completion of neoadjuvant treatment, CTC was detected in 25% of patient samples, and the median cfDNA concentration was 11.19 ng/mL (range 3.41-88.13 ng/mL). The cut-off points determined for pre-treatment and post-treatment cfDNA concentration was >4.2 ng/mL and >9.5 ng/mL respectively. At pre-treatment, CTC detection and cfDNA concentration >4.2 ng/mL were independently associated with disease relapse (P=0.007, 0.016, respectively). The combination of CTC detection and cfDNA concentration >4.2 ng/mL was significantly associated with disease relapse (P=0.0004), decreased relapse free survival (RFS, P=0.005) and overall survival (OS, P=0.007). At the post-neoadjuvant treatment time point, the combination of CTC detection and cfDNA concentration >9.5 ng/mL was significantly associated with relapse regardless of pCR status (P=0.02). Conclusion: The combined presence of CTCs and elevated cfDNA concentrations in patients with stage III/IV IBC after completion of neoadjuvant chemotherapy was associated with disease relapse regardless of pCR status. A combination of elevated cfDNA and CTC detection signatures after completion of neoadjuvant chemotherapy may be useful for risk stratification and adjuvant systemic therapy planning.

PO5-16-06

Prophylactic Neurokinin-1 Receptor Antagonist Use Pre- and Post- Choosing Wisely Initiative among Women with Breast Cancer

Presenting Author(s) and Co-Author(s):

S. Kamat. University of Rhode Island, United States

B. Brown. University of Rhode Island, United States

S. Cohen. University of Rhode Island, United States

A. Vyas. University of Rhode Island, United States

Objective: In April 2012, the American Society of Clinical Oncology (ASCO) issued recommendations as a part of the Choosing Wisely (CW) campaign with the aim to identify the areas of low-value utilization. One of the CW recommendations is not to use expensive antiemetics, specifically Neurokinin-1 Receptor Antagonist (NK1-RA) for patients initiating low or moderate emetic risk chemotherapy. The purpose of this study was to determine the impact of CW on prophylactic NK1-RA use among women with breast cancer.

Methods: Using Optum's de-identified Clinformatics® Data Mart Database for 2010 to 2018, a retrospective cohort study was conducted for women aged ≥ 18 years with breast cancer with at least one newly initiated claim for low/minimal/moderate emetic risk chemotherapy ($n = 25,549$). All approved antiemetics - aprepitant, fosaprepitant, rolapitant, and netupitant/palonosetron) were included. An interrupted time series using a segmented regression model was used to assess the effect of CW on the prophylactic NK1-RA use.

Results: The prophylactic use of NK1-RAs among patients with breast cancer receiving low/minimal/moderate emetic risk chemotherapy decreased from 11.1% pre-CW to 7.7% post-CW. Segmented regression analysis showed that there was a significant increase of 0.11 per 100 patients per quarter in the use of prophylactic NK1-RAs prior to CW recommendation. However, immediately after the CW (occurred in Q42013), there was a significant decline in prophylactic NK1-RA use by 1.03 per 100 patients in Q22014. For the time after intervention, there was a significant decline in NK1-RA use by 0.37 per 100 patients per quarter in the post-CW period compared to the pre-CW period ($p < 0.05$).

Conclusion: This study highlights a significant but modest decline in the inappropriate use of prophylactic NK1-RAs after the implementation of CW antiemetic recommendation. Continued statewide or local educational efforts for dissemination of CW recommendations are needed to facilitate appropriate prophylactic use of NK1-RAs.

Adjusted* Interrupted Time Series Segmented Regression Analysis of Prophylactic NK1-RA use among women with breast cancer before and after the Choosing Wisely initiative

Table 1: Adjusted* Interrupted Time Series Segmented Regression Analysis of Prophylactic NK1-RA use among women with breast cancer before and after the Choosing Wisely initiative.

	Beta estimates	95% CI	p-value
Intercept-NR1-RA use at time zero (β_0)	10.30	10.24 to 10.43	< 0.0001
Pre-Choosing Wisely trend (β_1)	0.11	0.10 to 0.12	< 0.0001
Level change after Choosing Wisely initiative (β_2)	-1.03	-0.93 to -1.13	< 0.0001
Trend change after Choosing Wisely initiative (β_3)	-0.37	-0.36 to -0.38	< 0.0001

*Adjusted for insurance, health plan type, age, comorbidity, and emetic risk

PO5-16-07

Unveiling the Landscape of PD-L1 Expression and Tumor-Infiltrating Lymphocyte Subtypes in Advanced Triple-Negative Breast Cancer

Presenting Author(s) and Co-Author(s):

A. dos Santos. Brazilian National Cancer Institute, Rio de Janeiro, Brazil

J. da Silva. Brazilian National Cancer Institute, Rio de Janeiro, Brazil

L. De Albuquerque. Brazilian National Cancer Institute, Rio de Janeiro, Brazil

A. Araújo Neto. Brazilian National Cancer Institute, Rio de Janeiro, Brazil

C. Silva. Brazilian National Cancer Institute, Rio de Janeiro, Brazil

L. Cerva. Brazilian National Cancer Institute, Piaui, Brazil

I. Small. Brazilian National Cancer Institute, Rio de Janeiro, Brazil

C. Marcelino. MSD Brazil, Sao Paulo, Brazil

P. Batista. MSD Brazil, Santa Catarina, Brazil

M. Rego. MSD Brazil, Sao Paulo, Brazil

M. Borba. MSD Brazil, Sao Paulo, Brazil

L. de Albuquerque. Brazilian National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil

Background: Triple-negative breast cancer (TNBC) is known for its aggressive behavior with poor survival outcomes. Influenced by different expression levels of Programmed Death-Ligand 1 (PD-L1) and several subtypes of tumor-infiltrating lymphocytes (TILs), tumor microenvironment (TME) plays a crucial role in TNBC response to treatment and progression.

Objective: To assess the prevalence and prognostic role of PD-L1 expression in advanced TNBC, defined as unresectable stage III or stage IV disease, in patients treated with a standard cytotoxic chemotherapy regimen. TILs composition was also evaluated as an exploratory objective.

Methods: The internal database of the Brazilian National Cancer Institute was queried out for women diagnosed and treated with advanced TNBC from January 2018 to December 2022. Formalin-fixed paraffin-embedded samples of a maximum of four years old were analyzed. PD-L1 expression using 22C3 pharmDX assay was estimated through combined positive score (CPS) dichotomization (CPS < 10 vs. CPS ≥ 10). Tissue microarrays comprising the samples of biopsies were subjected to immunohistochemistry, targeting specific markers including CD3, CD4, CD8, CD56, CD68, CD117, FOXP3, PD-1, the immune cell profiles were carefully examined and their correlation with the PD-L1 CPS was determined.

Results: A total of 150 patients were included. The expression of PD-L1 was undetermined in 2 cases. The median age was 51.5 years (IQR 41.8-60.2) and 20.9% of the cases had CPS ≥ 10. Most patients were < 65 years (73.0%), were postmenopausal (56.8%) and belonged to non-white ethnicity (70.3%). Postmenopausal women predominated in the CPS ≥ 10 subgroup (74.2%) (Table 1). No significant differences in demographic characteristics and clinicopathological variables were observed based on PD-L1 subgroups, 117 patients (79.1%) had CPS < 10, with 91 (77.8%) being de novo stage IV metastatic disease. CD3+ (p=0.037), CD4+ (p=0.005) and CD8+ (p=0.001) TILs had higher expression in tumors with PD-L1 CPS ≥ 10 (Table 2). According to the treatment received, almost half of the patients only received first-line chemotherapy (47%), as the following second line was applied to 28.8% of

the total group. The third and fourth lines were administered in 12.9% and 9.1% of patients, respectively. Only 2 patients went through five palliative chemotherapy lines, and only one received up to 6 treatment lines. Between the subgroups CPS \geq 10 versus CPS< 10 no statistically significant differences were observed in the median progression-free survival (PFS) (5.1 vs. 5.0 months, p=0.89) and overall survival (OS) (8.7 vs. 8.8 months, p=0.6).

Conclusion: This study offers insights into the expression patterns of PD-L1 and TILs subtypes in advanced TNBC cases in Brazil. PD-L1 CPS did not influence survival outcomes for this cohort of patients treated with cytotoxic chemotherapy only. The composition of TILs subtypes within the TME appears to vary based on PD-L1 CPS.

Table 1. Advanced TNBC population characteristic by CPS (Nf148).

Characteristics		CPS<10 N (%)	CPS \geq 10 N (%)	Total N (%)	p
Age	Total [Median (IQR)]	49.0 (41.0 to 61.0)	54.0 (45.5 to 59.5)	51.5 (41.8 to 60.2)	0.546
	Non-elderly	85 (72.6)	23 (74.2)	108 (73.0)	1.000
	Elderly (Age>65)	32 (27.4)	8 (25.8)	40 (27.0)	
Ethnicity	White	35 (29.9)	9 (29.0)	44 (29.7)	1.000
	Non-white	82 (70.1)	22 (71.0)	104 (70.3)	
Menopausal status	Premenopausal	42 (35.9)	7 (22.6)	49 (33.1)	0.072
	Perimenopausal	14 (12.0)	1 (3.2)	15 (10.1)	
	Postmenopausal	61 (52.1)	23 (74.2)	84 (56.8)	

Table 2. Tumor Infiltrating Lymphocytes characterization (CD3, CD4, CD8, CD56, CD68, CD 117, FOXP3 and PD-1) and its correlation with CPS status.

Immunohistochemistry markers	Total N (%)	Missing N	CPS<10 Median (IQR)	CPS \geq 10 Median (IQR)	Total Median (IQR)	p
CD3 expression	142 (95.9)	6	5.0 (1.0 to 20.0)	10.0 (4.0 to 35.0)	5.0 (1.0 to 27.5)	0.037
CD4 expression	142 (95.9)	6	5.0 (1.0 to 20.0)	20.0 (5.0 to 60.0)	10.0 (1.0 to 30.0)	0.005
CD8 expression	145 (98.0)	3	5.0 (1.0 to 15.0)	20.0 (5.0 to 50.0)	5.0 (1.0 to 20.0)	0.001
CD56 expression	145 (98.0)	3	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.883
CD68 expression	143 (96.6)	5	7.5 (1.0 to 40.0)	20.0 (1.0 to 30.0)	10.0 (1.0 to 40.0)	0.894
CD117 expression	145 (98.0)	3	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.683
FOXP3 expression	145 (98.0)	3	0.0 (0.0 to 2.0)	3.0 (0.0 to 10.0)	0.0 (0.0 to 3.0)	0.014
PD-1 expression	125 (84.5)	23	0.0 (0.0 to 1.0)	1.0 (0.2 to 13.8)	1.0 (0.0 to 1.0)	0.003

PO5-16-08

Breast cancer in men: 15 years of experience in an oncology reference center in northern Mexico.

Presenting Author(s) and Co-Author(s):

F. Peña. Centro Universitario Contra el Cáncer, Hospital Universitario, Universidad Autónoma de Nuevo León, Monterrey, Nuevo Leon, Mexico

J. Martínez-Moyano. Oncology Service, Centro Universitario Contra el Cáncer, Hospital Universitario "Dr. José Eleuterio González", Faculty of Medicine, Universidad Autónoma de Nuevo León., Nuevo Leon, Mexico

F. Alvarado-Villarreal. Centro Universitario Contra el Cáncer, Hospital Universitario, Universidad Autónoma de Nuevo León, United States

C. Salazar-Mejía. Centro Universitario Contra el Cáncer, Hospital Universitario, Universidad Autónoma de Nuevo León, United States

D. Hernández-Barajas. Centro Universitario Contra el Cáncer, Hospital Universitario, Universidad Autónoma de Nuevo León, United States

O. Vidal-Gutiérrez. Oncology Service, Centro Universitario Contra el Cáncer, Hospital Universitario "Dr. José Eleuterio González", Faculty of Medicine, Universidad Autónoma de Nuevo León., Nuevo Leon, Mexico

Background

Breast cancer in men accounts for about 1% of all breast cancers. Classic risk factors include increasing age, a family history of cancer, and mutations in predisposing genes. The alteration of the estrogen-androgen ratio has been as involved in the genesis of this cancer due to its increased risk in conditions such as liver dysfunction, obesity, marijuana use, thyroid disease, Klinefelter's syndrome, hormonal therapies, orchitis, cryptorchidism, and testicular damage.

Purpose

Hereby we aim to update the analysis of the published demographic, clinical and treatment-related characteristics of this disease in our center including the last 15 years, as well as newly identified relevant variables that will serve as the basis for awareness and screening programmes for our population.

Methods

We performed a retrospective observational analysis of the medical records of men diagnosed with breast cancer that were treated in "Centro Universitario Contra el Cáncer" between January 2007 and December 2022. A total of seventeen cases of male breast cancer were included in the analysis.

The variables included are age at diagnosis, body mass index, comorbidities, cigarette and alcohol use, method of diagnosis, histological type / grade, clinical stage, estrogen, progesterone, and human epidermal growth factor receptor-2 (HER2) receptor status, and treatment received. We also looked at the dates of symptom onset, diagnosis, and treatment to determine the intervals between these events. SPSS v25 software was used for data analysis. The Shapiro-Wilk test was employed to determine the normality of the variables. Variables with a normal distribution were described with median and interquartile range for the 25th and 75th percentiles. Categorical variables were expressed as absolute numbers and percentages.

Results

Although we found some similarities between the characteristics of our population and those reported in the American and European series, there were many significant differences.

Mean age at diagnosis was 62.9 (± 11.7) years, 5.5 years earlier than the reported age of 68.4 years.

In terms of risk factors, our population was twice as likely to report a family history of cancer as the American series (41% vs. 15-20%). Overweight and obesity together accounted for 76.5% followed by alcohol consumption in 70.6% and cigarette smoking in 47.1% of patients. Diabetes mellitus and systemic arterial hypertension were present in 70% of our population. These entities are known to alter the estrogen-androgen ratio.

The initial symptom in 88.2% of patients was a retroareolar tumor. The mean time from symptom onset to cancer diagnosis was 14.4 months.

Estrogen and/or progesterone receptor status was positive in 82.3%. HER2 overexpression was not found. 17.6% of the cancers were classified as triple negative in contrast to the 0.3% reported in other series.

Regarding treatment, 88.3% underwent upfront surgery, of which 76% were modified radical mastectomies. Axillary node dissection was performed in 86.6% of the cases and sentinel node biopsy in the rest. Seventy-six percent of patients received chemotherapy and radiotherapy in the adjuvant setting. Tamoxifen was the most common drug of choice (87.5%) in the patients considered as candidates for hormonal therapy

Conclusions

This study updates the results previously reported from our center with additional information that enabled new important conclusions to be drawn about our population. These findings provide the basis for a better understanding of this disease, which is necessary to establish public policies and recommendations to reduce the negative impact of this type of cancer.

Keywords: Breast cancer, men, male, Mexico, Latin America

Demographic and Clinical Characteristics of the Patients

Table 1. Demographic and Clinical Characteristics of the Patients		
Characteristic		n (%)
Median Age – yr	62.9	
Cigarette smoking – no. (%)		8 (47.1)
Alcohol consumption – no. (%)		12 (70.6)
BMI – no. (%)	Normal	4 (23.5)
	Overweight	8 (47.1)
	Obesity	5 (29.4)
T – no. (%)	1	1 (5.9)
	2	12 (70.6)
	3	2 (11.8)
	4	2 (11.8)
N – no. (%)	0	9 (52.9)
	1	4 (23.5)
	2	3 (17.6)
	3	1 (5.9)
M – no. (%)	0	15 (88.2)
	1	2 (11.8)
Clinical Stage – no. (%)	I	2 (11.8)
	II	11 (64.7)
	III	2 (11.8)
	IV	2 (11.8)
Tumoral Grade – no. (%)	1	2 (11.8)
	2	10 (58.8)
	3	5 (29.4)
Estrogen receptors – no. (%)	Positive	11 (64.7)
	Negative	5 (29.4)
	Unknown	1 (5.9)
Progesterone receptors – no. (%)	Positive	11 (64.7)
	Negative	5 (29.4)
	Unknown	1 (5.9)
HER2 – no. (%)	Negative	15 (88.2)
	Unknown	2 (11.8)
Immunophenotype	Luminal A	11 (64.7)
	Luminal B	3 (17.6)
	Triple negative	3 (17.6)
Chemotherapy	None	3 (17.6)
	Adjuvant	13 (76.4)

Demographic and Clinical Characteristics of the Patients

PO5-16-09

Associations of age, body mass index, diabetes and hypertension with relative dose intensity among women receiving anthracycline- and/or taxane-based chemotherapy for invasive breast cancer

Presenting Author(s) and Co-Author(s):

H. Wopat. George Washington University Department of Exercise Science and Applied Nutrition, United States

A. Aldous. George Washington University Department of Biostatistics and Bioinformatics, United States

A. Ciarleglio. George Washington University Department of Biostatistics and Bioinformatics, United States

K. Anderson. George Washington University Cancer Center, United States

K. Robien. Milken Institute School of Public Health, George Washington University, United States

Research suggests that medical comorbidity is associated with reduced relative dose intensity (RDI) in patients receiving chemotherapy for treatment of breast cancer. We aimed to determine factors associated with RDI of specific chemotherapy drugs in anthracycline- and/or taxane-based regimens.

Women with a diagnosis of lymph node positive, invasive breast cancer who received neoadjuvant or adjuvant chemotherapy with either doxorubicin (DOX) + paclitaxel (PAC) or docetaxel (DOCE)-containing regimens at a single center from 2012 to 2019 were included in this retrospective study. Age, race, comorbidities, height, weight, and chemotherapy regimen and dose were abstracted from the electronic health record. BMI was calculated using height and weight measured in clinic at the time initial chemotherapy orders were written and categorized according to US national guidelines (18.5 to < 25, 25 to < 30, and >30kg/m²). Presence of diabetes (DM) and hypertension (HTN) at time of diagnosis were determined by chart review. The oncologists' initial chemotherapy orders (dose and duration) were used as the basis for RDI calculations. Cumulative actual dose received and duration of treatment were compared to planned dose and duration for individual chemotherapy drug and by regimen (DOX+PAC vs. DOCE). Associations between patient characteristics and RDI were evaluated in bivariate and multivariable analyses.

A total of 230 women met the inclusion criteria, with 125 receiving a DOX+PAC regimen and 105 receiving a DOCE-based regimen. A higher percentage of women on DOX+PAC received >85% RDI compared to women receiving DOCE (80.8% vs 67.6%). Women aged 65+ years had lower median RDI [IQR] for DOCE than younger women (0.83 [0.67 - 0.98] vs 0.94 [0.84 - 1.00], p = 0.04), and a lower percentage in the older group received >85% RDI (35.3% vs 73.9%, p < 0.01). Median RDIs of PAC and DOX+PAC were lower for Black women than for White and Asian women (PAC: 0.91 [0.75 - 1.00] vs 1.00 [0.89 - 1.00], p = 0.02, DOX+PAC: 0.92 [0.87-0.99] vs. 0.97 [0.91-1.00], p = 0.03), and the percent of Black women receiving >85% RDI of PAC was also lower (55.3% vs 77.6%, p = 0.01). BMI category was associated with median RDI for PAC (p = 0.03) and DOX+PAC (p = 0.01), with women in the >30kg/m² category having the lowest median RDIs and PAC RDI >85% (p < 0.01). Median RDI of DOX+PAC was lower for women with DM (0.89 [0.84-0.92] vs. 0.96 [0.88-1.00], p = 0.03), and a lower percentage of women with DM received DOX RDI >85% compared to women without DM

(66.7% vs 91.6%, $p < 0.01$). Median RDI was lower among women with HTN compared to women without for PAC (0.85 [0.73 - 1.00] vs 0.98 [0.83 - 1.00], $p = 0.01$) and DOX+PAC (0.91 [0.84 - 0.97] vs 0.97 [0.90 - 1.00], $p = 0.01$), and a lower percentage of women with HTN received >85% RDI for PAC (50.0% vs 73.3%, $p = 0.01$). Multiple logistic regression models adjusted for age (continuous), race, BMI (continuous), DM, and HTN had modestly improved predictive value compared to null models (McFadden's $R^2 = 0.10$ to 0.19); each year of increased age was associated with lower odds of RDI > 85% for DOX (OR [95% confidence interval] 0.91 [0.84-0.97], $p = < 0.01$), DOX+PAC (0.95 [0.90-0.99], $p = 0.02$), and DOCE (0.93 [0.88-0.97], $p < 0.01$), and DM with lower odds for DOX (0.26 [0.07-0.95], $p = 0.04$).

Our findings of associations between increasing age, Black race, BMI, DM, and HTN and reduced RDI are consistent with prior research and present new data regarding associations between medical comorbidities and individual components of chemotherapy regimens.

PO5-16-10

The efficacy of novel antibody-drug-conjugates on brain metastases in metastatic breast cancer patients – a multicenter real-world analysis

Presenting Author(s) and Co-Author(s):

- D. Dannehl. Department of Women's Health, University Hospital Tuebingen, Germany
H. Schäffler. Department for Gynecology and Obstetrics, Ulm University, United States
T. Engler. Department of Women's Health, Tuebingen University, United States
L. Volmer. Department of Women's Health, Tuebingen University, United States
A. Estler. Diagnostic and Interventional Neuroradiology, Tuebingen University, United States
I. Popp. Department of Radiology, Freiburg University, United States
S. Lorenz. Department of Radiology, Ulm University, United States
E. Grischke. Universitäts-Frauenklinik Tübingen, Eberhard Karls University, Tübingen, Germany
M. Hahn. Universitätsklinikum Tübingen, United States
G. Tabatabai. Department of Neurology & Interdisciplinary Neuro-Oncology, University Hospital Tübingen, United States
I. Juhasz-Böss. Department for Gynecology and Obstetrics, Freiburg University, United States
W. Janni. Department Gynecology and Obstetrics, University of Ulm, Ulm, Baden-Württemberg, Germany
S. Brucker. Research Institute for Women's Health, University of Tuebingen, Tuebingen, Germany, United States
F. Taran. Department for Gynecology and Obstetrics, Freiburg University, United States
A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

15 – 30% of all patients with metastatic breast cancer (MBC) develop brain metastases (BMs). Treatment of BMs include radiation therapy and surgical resection while systemic treatment is challenging and prospective evidence for the treatment of active brain metastases is restricted to the small molecule Tucatinib. Recently, the antibody-drug-conjugates (ADCs) Sacituzumab-Govitecan (SG) and Trastuzumab-Deruxtecan (T-DXd) have shown to be highly effective in the treatment of triple-negative (SG), HER2-positive (T-DXd) and HR+/HER2- (SG and, in case of HER2-low-expression, T-DxD) MBC. However, there is only limited data, whether these macromolecules are also effective in patients with BMs. We therefore aimed to examine the efficacy of SG and T-DXd in patients with stable and active BMs in a multicenter real-world analysis. Female patients with stable or active BMs who were treated with either SG or T-DXd at the breast centers of Tuebingen University, Ulm University or Freiburg University in Germany before June 30, 2023 were included into this analysis. Data cut-off for this analysis was July 10, 2023. BMs were classified as active if they were newly diagnosed and did not require local treatment or if they were progressing and did not require local treatment. Preexisting BMs without intracranial disease progression or preexisting/newly diagnosed BMs that had been treated by surgery and/or radiotherapy directly prior to SG/T-DXd therapy were considered as stable. All patients underwent baseline magnetic resonance imaging (MRI) of the brain and received follow-up MRIs at least every three months. Growth dynamics of BMs were assessed by board certified neuroradiologists. Intracranial disease control rate (icDCR) was defined as the percentage of patients with at least intracranial stable disease at the first follow-up MRI. Intracranial progression-free survival (icPFS) was determined as the period between the first

application of SG or T-DXd and intracranial disease progression or treatment cessation due to the patients' will or the onset of intolerable toxicity. If ADC treatment was discontinued due to extracranial disease progression albeit at least stable intracranial disease patients were censored. Overall survival (OS) was defined as the period between the first application of SG or T-DXd and death. In total, 26 patients were included with a median of two prior therapy lines in the metastatic setting (range 2 – 15). 10 (38%) and 14 (54%) patients received SG and T-DXd, respectively. 2/26 (8%) patients receiving SG were consecutively subjected to T-DXd treatment. SG was applied to 12/12 patients (100%) due to triple-negative MBC and 12/16 patients (75%) treated with T-DXd were HER2-positive. The remaining 4/16 patients (25%) treated with T-DXd showed HER2 low tumor biology. 5/12 (42%) and 8/16 (50%) patients treated with SG or T-DXd had active BMs at treatment initiation. The icDCR was 33% (95% CI: 5% - 61%) / 81% (95% CI: 62% - 100%) for all patients treated with SG/T-DXd and 40% (95% CI: 0% - 88%) / 75% (95% CI: 43% - 100%) in case of active BMs. After a median follow-up of 7.2 months, 10/12 (83.3%) patients treated with SG and 4/16 (25%) patients subjected to T-DXd had discontinued treatment. Median icPFS was 3.1 months (95% CI: 0.4 – 5.8 months) for SG and not reached for T-DXd. 7/12 (58%) patients treated with SG and 4/16 patients (25%) treated with T-DXd died until data cut-off. Median OS was 7.2 months (95% CI: 3.0 – 11.4 months) for patients treated with SG and not reached for patients treated with T-DXd. SG and T-DXd showed promising clinical activity in both, stable and active cerebral breast cancer metastasis. Updated PFS and OS data will be reported at the meeting.

PO5-16-11

Novel antibody-drug-conjugates in clinical routine: adherence, efficacy and tolerability - real-world data from German breast centers

Presenting Author(s) and Co-Author(s):

H. Schäffler. Department for Gynecology and Obstetrics, Ulm University, United States

D. Dannehl. Department of Women's Health, University Hospital Tuebingen, Germany

K. Veselinovic. Breast Center, University Hospital Ulm, Department of Women's Health, Ulm, Baden-Wuerttemberg, Germany

F. Mergel. University hospital Ulm, Department for obstetrics and gynecology, Ulm, Baden-Wuerttemberg, Germany

K. Pfister. University hospital Ulm, Department for obstetrics and gynecology, United States

B. Rack. Department of Obstetrics and Gynecology, University Hospital Ulm, Germany

V. Fink. University hospital Ulm, Ulm, Baden-Wuerttemberg, Germany

E. Leinert. Breast Center, University Hospital Ulm, Department of Women's Health, Ulm, United States

L. Volmer. Department of Women's Health, Tuebingen University, United States

T. Engler. Department of Women's Health, Tuebingen University, United States

S. Brucker. Research Institute for Women's Health, University of Tuebingen, Tuebingen, Germany, United States

W. Janni. Department Gynecology and Obstetrics, University of Ulm, Ulm, Baden-Wuerttemberg, Germany

A. Hartkopf. Women's Clinic, University Clinics Tuebingen, Tuebingen, Germany

The third-generation antibody-drug conjugates, Trastuzumab-Deruxtecan (T-DXd) and Sacituzumab Govitecan (SG), have been approved for the treatment of metastatic breast carcinoma in various subtypes and therapeutic settings based on compelling Phase III study data. (DESTINY-Breast03 (T-DXd; HER2-positive), DESTINY-Breast04 (T-DXd; HER2-low), ASCENT (SG; triple-negative), and TROPiCS-02 (SG; HR+/HER2-negative). The aim of this retrospective study conducted at two major German Breast centers was to evaluate the tolerability, adherence, and efficacy of both substances in the real-world setting. All patients treated outside of clinical trials with T-DXd or SG at the Department of Gynecology and Obstetrics, Ulm University Hospital and the Department of Women's Health, Tuebingen University Hospital between November 2020 and May 2023 were included in this retrospective analysis. Seventy-five patients were included [T-DXd: 46; SG: 29]. The mean duration of therapy was 5.4 months [T-DXd: 6.2; SG: 4.2]. The real-world cohort was more heavily pretreated than the corresponding study cohorts, with a mean of 4.2 systemic therapies in the metastatic setting prior to T-DXd therapy and 3.6 systemic therapies prior to SG therapy. The administered cumulative dose on average was 87.9% [T-DXd: 94%; SG: 79%] of the theoretical full dose or 95.3% [T-DXd: 98%; SG: 92%] when considering dose reductions that occurred. Hematotoxicities of CTC $\geq 3^\circ$ occurred in 11% of patients treated with T-DXd and in 41% of patients treated with SG. Neutropenia was the predominant severe hematotoxicity (CTC \geq III $^\circ$) observed during SG therapy, occurring in 38% of patients. The occurrence of neutropenia during SG therapy was reduced with primary prophylactic administration of Granulocyte-Colony Stimulating Factor (GCSF), with a rate of 29% (21/29) of patients experiencing neutropenia \geq CTC-III $^\circ$, compared to 63% (8/29) without primary prophylactic GCSF. Therapy-associated

pneumonitis under T-DXd occurred in 5 out of the 46 included patients and was successfully treated with corticosteroids in all cases (CTC II° in 4 cases, CTC III° in 1 case). The median progression-free survival (PFS) from initial administration was 7.7 months under T-DXd [HER2-positive: 9.0; HER2-low: 6.1], and 4.8 months under SG [TNBC 4.8; HR+/HER2-negative: 2.8]. The median overall survival from initial administration was 27.1 months under T-DXd [HER2-positive: 27.1; HER2-low: not reached], and 11.9 months under SG therapy [TNBC: 11.0, HR+/HER2-negative: not reached]. This analysis provides evidence of the efficacy and tolerability of T-DXd and SG in a heterogeneous and heavily pretreated cohort in a real-world setting. However, a conclusive assessment of progression-free survival (PFS) and overall survival (OS) is not feasible yet, as a substantial number of patients are still under treatment. Updated PFS and OS data, with a specific focus on the therapy indication, will be presented at the meeting.

PO5-16-12

EFFICACY AND TOLERABILITY OF METRONOMIC CHEMOTHERAPY (mChT) WITH CYCLOPHOSPHAMIDE, METHOTREXATE AND CAPECITABINE (CMX) IN PATIENTS WITH HEAVILY PRETREATED ADVANCED BREAST CANCER. RESULTS FROM A MULTICENTER RETROSPECTIVE STUDY.

Presenting Author(s) and Co-Author(s):

C. Saavedra. Hospital Universitario Ramón y Cajal, Madrid (Spain), United States

M. Gion. Hospital Universitario Ramón y Cajal, United States

A. Cortés. Hospital Universitario Ramón y Cajal, Madrid (Spain); ONCARE, United States

P. Cortez. IOB Institute of Oncology, Madrid, Spain, United States

L. Garrigós. International Breast Cancer Center (IBCC), Quiron Group, Barcelona, Spain.
Hospital Universitari Dexeus, Barcelona, Spain

J. Pérez-García. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US., Catalonia, Spain

G. Antonarelli. European Institute of Oncology IRCCS, Milan, Italy, United States

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

BACKGROUND

mChT consists on the administration of repetitive, low doses of chemotherapy drugs and represents an attractive and active therapeutic strategy in cancer patients. Beyond the traditional cytotoxic effect of each drug on tumor cells, mChT seems to play a role in the modulation of angiogenesis and immune-regulation. mChT has demonstrated promising clinical activity and low toxicity in patients with advanced breast cancer (ABC). The aim of this study is to describe the safety and efficacy of CMX in a retrospective cohort of heavily pretreated HER2-negative ABC patients.

METHODS

This is a multicenter, retrospective study that included patients with HER2-negative ABC who received treatment with CMX (capecitabine 500 mg thrice daily, methotrexate 2.5 mg twice a week, and cyclophosphamide 50 mg daily). Demographic data, tumor characteristics, previous therapies, efficacy, and toxicity of the CMX treatment were collected. Statistical analyses were performed with Stata v.14. For standard summary statistics, mean and range for continuous data and relative and absolute frequencies for categorical data were used while for survival analysis Kaplan Meier approach was employed.

RESULTS

A total of 25 patients from 4 centers in Spain treated between October 2016 and February 2023 were included in this analysis. Median age was 63 years (range: 37-87), 68% had visceral disease, and 48% had triple-negative tumors. All patients previously received a median of 5 prior lines of systemic therapy in the metastatic setting and 80% of patients had been treated with capecitabine, most of them in the metastatic scenario with a median treatment duration of 6.2 months. Dose reductions were necessary in 5 patients and 1 patient discontinued treatment due to toxicity. No grade 3-4 hand-foot syndrome or diarrhea were reported. Objective response rate was 20.8% and disease control rate was 54.2%. Median progression-free

survival was 6.1 months (95% confidence interval [CI] 95%; 4.3 - 12.4) and median overall survival was 12.3 months (95% CI; 6.8 - 24.7). Neither the number of previous lines of treatment nor the prior use of capecitabine showed a negative impact on the efficacy of CMX.

CONCLUSIONS

CMX is an effective and well-tolerated scheme of mChT and may represent an adequate treatment option for patients with heavily pretreated HER2-negative ABC, including those patients that previously received capecitabine as single agent. These encouraging data warrant further investigation.

PO5-17-01

Pre-treatment tumor infiltrating lymphocytes are associated with higher likelihood of pathologic complete response among black women with TNBC receiving neoadjuvant chemoimmunotherapy

Presenting Author(s) and Co-Author(s):

S. Wood. Emory University, Decatur, Georgia, United States

J. Lee. Emory University, United States

Y. Gao. Emory University, United States

X. Li. Emory University, United States

J. Meisel. Winship Cancer Institute, Atlanta, Georgia, United States

Background: High risk, early-stage triple negative breast cancer (TNBC) is a heterogeneous disease that is associated with early recurrence and high mortality, particularly among black women as compared to their white counterparts. Pathologic complete response (pCR) to neoadjuvant chemotherapy (NACT) is a strong predictor of long-term disease-free survival in TNBC, and the KEYNOTE-522 trial demonstrated that the addition of immunotherapy (pembrolizumab) to NACT resulted in a higher likelihood of pathologic complete response (pCR) in high-risk early-stage TNBC. Following these findings, the standard of care has been to administer the K522 regimen (K522R) in the neoadjuvant setting for patients with high risk early-stage TNBC. However, our understanding of the clinical and tumor characteristics to prognosticate response to K522 are lacking, and additional real-world data is needed to better understand if these variables differ among race.

Methods: We evaluated 76 patients who were treated with the K522R at our institution. There were slides available from 29 patients' pre-treatment biopsies for pathology review. In the available slides, tumor infiltrating lymphocytes (TIL) were evaluated as the percentage of lymphocytes in the stroma within the tumor area. For the remaining cases that did not have available slides, these variables were retrieved from pathology reports and patients' charts. Patient characteristics including age, race and body mass index (BMI) were acquired via retrospective chart review. These clinicopathologic variables were correlated with pCR, which was defined by the absence of invasive carcinoma in the breast and axillary lymph nodes at the time of surgery. Binary logistic regression analysis was performed to correlate the above variables with pCR versus residual disease (RD).

Results: Seventy-six pre-treatment biopsy specimens treated with the K522R were evaluated. The patient population spanned a broad spectrum of age, body habitus, and race, with mean age 55, mean BMI 28.3, and predominantly black (over 60 percent) population. At the time of analysis, 64 of the 76 patients had completed the K522R and subsequently undergone surgery at our institution. Of the 64 patients who had undergone definitive surgery, 31 (48.4%) achieved pCR. In univariate analysis, pre-treatment TIL was significantly associated with attainment of pCR, with TIL of 28.5% (\pm 19.1) in patients who achieved pCR versus 9.73% (\pm 9.40) in those who had RD (95% CI 1.03-1.21, $p=0.014^*$). When TIL was further stratified by race, mean percentage of TIL was significantly higher among black women who achieved pCR (27.5% \pm 4.7) compared to black women with RD (12.2% \pm 3.05) (95% CI 0.021 – 0.197, $p=0.016^*$). Additionally, mean percentage of TIL was higher overall among black women when compared to the white patients in our cohort, though this finding was not statistically significant ($p=0.252$).

Conclusion: Our real-world data demonstrates high levels of pre-treatment TIL are significantly

associated with achievement of pCR in patients with TNBC treated with the K522 regimen. When TIL was further stratified by race, black patients were found to have higher TIL than white patients. Within the black population, a statistically significant difference in TIL percentage was found in those achieving pCR compared to those with RD. It is well understood that black women often have poorer breast cancer outcomes than white women, and our finding of higher TIL percentage among this population, along with the significant association between TIL and attainment of pCR with chemoimmunotherapy, could have important implications for optimization of therapy. Further exploration of this phenomenon in larger, diverse breast cancer populations is warranted.

PO5-17-02

Triple-negative breast cancer as an untraceable tumor compared to other immunohistochemical subtypes: a cross-sectional study

Presenting Author(s) and Co-Author(s):

M. Silva. Universidade Federal de São Paulo - Unifesp, United States

A. Nazário. Universidade Federal de São Paulo, United States

V. Sanvido. Universidade Federal de São Paulo/ Hospital do Coração (Hcor), United States

Objective: To compare the form of presentation at diagnosis of triple negative breast tumors with other immunohistochemical subtypes, in relation to clinical examination or imaging examination. **Methods:** This is a cross sectional study that evaluated data related to the presentation of breast carcinomas at diagnosis (clinical examination or screening imaging examination findings), immunohistochemical subtype, histological grade and tumor size, in diagnosed and referred patients. for the Mastology service at Hospital São Paulo – Unifesp, in São Paulo – Brazil, in the period between 2012 and 2021, by analyzing data from the medical records of these patients. **Results:** Among the 699 invasive carcinomas diagnosed, 246 patients were diagnosed with luminal profile A (35.2%), 257 luminal B (36.8%), 58 luminal B HER-2+ (8.3%), 26 HER-2 enriched (3.7%) and 112 triple negative (16%). Triple negative carcinomas had a higher rate of diagnosis by clinical examination (86.6%), 6.65 times more likely to be diagnosed by clinical examination than luminal A, in addition to having a larger lesion. The triple negative and HER-2 enriched subtypes presented the worst scenarios of clinical stage at diagnosis. Among the tumors diagnosed by screening examination, those belonging to the luminal A were associated with nodules seen on imaging (in 45.1%) and the subtypes luminal B and luminal B HER-2+ with the appearance of microcalcifications. There were no cases of triple negatives involving microcalcifications in our sample. Asymmetries were more common in images of luminal B HER-2+ tumors. In the multivariate analysis, it was observed that only the histological grade and the Ki-67 value are related to the form of diagnosis. Tumors with histological grade 2 or 3 are more likely to be diagnosed by clinical examination and not be traceable in relation to histological grade 1. As for Ki-67, its increase of 1 percentage point leads to an increase of 1.3% in the chance finding on physical examination. There was no correlation of hormone receptors and HER-2 with the chance of the tumor not being screenable. **Conclusions:** triple negative subtype breast carcinomas present a higher risk of diagnosis by clinical examination compared to other immunohistochemical subtypes and, therefore, tend not to be traceable. Parameters such as high Ki-67 and histological grade correlate with this trend.

PO5-17-03

Relative Dose Intensity and Protraction of Neoadjuvant Chemotherapy in Early-Stage and Locally Advanced Breast Cancer: A collaborative multicenter analysis in Colombia

Presenting Author(s) and Co-Author(s):

A. Murillo. Institute of Cancer Carlos Ardila Lulle, Fundación Santa Fe de Bogotá, United States

A. Acevedo. Internal Medicine Department, Fundación Santa Fe de Bogotá -Faculty of Medicine, Universidad del Bosque - Alprocrates Think Tank, OxLER Lab, United States

S. Betancur. Alprocrates Think Tank, OxLER Lab, United States

M. Borrás-Osorio. Fundación Cardioinfantil, Bogota, Distrito Capital de Bogota, Colombia

I. Munevar. Fundación Cardioinfantil / Hospital Militar Central, Bogota, Distrito Capital de Bogota, Colombia

W. Mantilla. Luis Carlos Sarmiento Angulo Cancer Treatment and Research Center CTIC, United States

L. Pino. Institute of Cancer Carlos Ardila Lulle, Fundación Santa Fe de Bogotá - Alprocrates Think Tank, OxLER Lab -, United States

Introduction: Breast cancer (BC) is the most frequent neoplasm in Colombia. In contrast to high-income countries, the expected 5-year overall survival (OS) remains below 80% over the last years. Neoadjuvant chemotherapy (NACT) has reduced the risk of relapse and death by achieving higher pathological complete response (ypCR) rates, but delays and dose reductions could impact prognosis negatively. We have previously reported the outcomes of NACT from a real-world multicenter historical cohort of Colombian early and locally advanced BC patients. We aimed to analyze NACT Relative Dose Intensity (RDI) and protraction data as related to clinical outcomes in the same cohort. **Methods:** We performed a secondary analysis of the primary database of 312 BC patients treated with NACT where ypCR rate was 34.6%, with 88.2% 5-year OS. We considered RDI and protraction as independent variables for the same outcomes. The RDI was estimated using the Hrynuik method, and protraction was defined as the difference between planned and actual completion time for the NACT exceeding 7 days from standard 21-day cycles. Chemotherapy regimens are based on the National Hematology and Oncology Association (ACHO) guidelines. We excluded cases with missing or conflicting data. Univariate, and bivariate analysis, and partition survival trees were performed to examine variable interactions. **Results:** From the original cohort of 312 patients, 47 and 7 additional patients were excluded due to missing protraction and RDI data, respectively; the final analysis included 261 and 254 patients, respectively. The average days to complete planned chemotherapy cycles were 154,4 (SD 32,29 days). 203 patients (77,8%), 26 patients (10%), and 11 patients (4,2%) received complete 8,7 and 6 NACT cycles, respectively. Overall, 175 patients (67%) had protracted chemotherapy cycles, being highest in the 7-cycle subgroup (77%). 169 patients (66,5%) had a dose intensity over 85% and 90 patients (35.43%) achieved an RDI of 100% or more. The mean RDI for the cohort was 79,8% (SD 19,91%) and it differed according to expression profile subgroups in decreasing order as follows: HER2 pure 98,85% (SD 19,59%), Luminal A 96,03% (SD 21,28%), Triple Negative 97,81% (SD 19,73%), Luminal B HER+ and HER2- being lowest with 90,43% (SD 19,47%) and 87,75% (SD 23,22%), respectively. Neither NACT RDI nor protraction was associated significantly with ypCR, conservative surgery, or all-cause OS. Although statistically not-significant, sensitivity analysis through different RDI thresholds (20%-100%) demonstrated improved discriminatory capacity over ypCR for RDI \geq 85%. **Conclusion:** On average, NACT-RDI greater than 85% was observed in Colombian patients with early and locally advanced BC similar to other cohorts.

However, it was not associated with ypCR, conservative surgery, or OS. Also, NACT protraction beyond 7 days did not adversely affect clinical outcomes. However, this conclusion is limited due to the retrospective nature and loss of real-world data. Adverse events and their impact on RDI were not analyzed either. Further research is warranted to understand RDI's impact on clinical outcomes, and a large-scale trial is proposed to validate these findings.

PO5-17-04

Tolerability of pertuzumab in older adults with HER2 positive breast cancer: A single institution experience

Presenting Author(s) and Co-Author(s):

N. Williams. The Ohio State University Comprehensive Cancer Center, United States

A. Warmbier. Scribe American, United States

D. Doto. The Ohio State University, United States

M. Palettas. The Ohio State University Wexner Medical Center, United States

J. Stephens. The Ohio State University Comprehensive Cancer Center, United States

D. Quiroga. The Ohio State University Comprehensive Cancer Center, United States

K. Johnson. The Ohio State University Comprehensive Cancer Center, United States

A. Pariser. The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

M. Cherian. The Ohio State University Comprehensive Cancer Center, Dublin, Ohio, United States

S. Sardesai. The Ohio State University Comprehensive Cancer Center, United States

D. Stover. Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

M. Gatti-Mays. The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

R. Wesolowski. James Cancer Hospital and the Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States

B. Ramaswamy. Ohio State University Comprehensive Cancer Center, United States

Background: Tumor HER2 over-expression occurs in 10 to 15% of older adults with breast cancer (BC). Combination HER2-directed therapy (pertuzumab and trastuzumab) with chemotherapy (CT) is the standard treatment for early and advanced HER2-positive bc. However, a study of more than 1,300 Medicare beneficiaries showed that about half of patients (pts) aged 65 or older with stage I to III HER2 positive bc did not receive trastuzumab-based therapy. This is likely due to concern for tolerability as older women remain underrepresented in clinical trials of breast cancer making it difficult to extrapolate tolerability of these agents in these patients. In the Neosphere and TRYPHAENA studies, the mean age of pts were 49.8 and 50.6 years, respectively. We examined the real-world tolerability of pertuzumab in combination with trastuzumab and systemic ct in women over the age of 65 with HER2 positive bc. Methods: An IRB approved retrospective review of medical records was conducted evaluating pts over the age of 65 with early or advanced HER2 positive bc treated at The Ohio State University Comprehensive Cancer center from January 1, 2015 to May ,1 2020. Descriptive statistics (means, standard deviations, medians and ranges for continuous variables and frequencies and percents for categorical variables) were used to summarize disease and patient characteristics for pts enrolled in this study and treated with pertuzumab. The total number of planned and completed cycles of treatment as well as the number of treatment delays and dose reductions were also summarized using frequencies and percentages. The same descriptive statistics were used to summarize the number of grade II or IV toxicities and pathologic complete response (pCR) in the neoadjuvant setting. Results: A total of 71 pts met inclusion criteria. Mean age was 76 years (SD 4.1). Of these pts, 62 had stage I-III disease and 9 had

metastatic disease. Additionally, 68% (48/71) had estrogen positive (ER) disease whereas 32% (23/71) had ER negative disease. Neoadjuvant systemic therapy was provided to 81% (50/62) of non-metastatic pts and 19% (12/62) received adjuvant therapy. The median number of completed neoadjuvant cycles (ct plus trastuzumab and pertuzumab) was 5.4 (SD 1.5). Among those who received pertuzumab with systemic ct in the neoadjuvant setting, 46% (23/50) of pts achieved a pCR (56% for ER negative disease and 41% for ER positive disease) The median number of completed adjuvant cycles (ct plus trastuzumab and pertuzumab) was 4.9 (SD 2.0). Pts with stage I to III disease completed a mean of 8.6 (SD 5.0) targeted therapy cycles (pertuzumab/trastuzumab). Pts with metastatic disease had a median of 5.7 (SD 1.0) cycles of ct plus trastuzumab and pertuzumab and received a mean of 34.4 (SD 36.0) cycles of maintenance pertuzumab. Treatment delay by 7 or more days occurred in 11% (8/71) of pts whereas 25% (18/71) of pts discontinued pertuzumab early. Pertuzumab termination occurred due to toxicity in 44% (8/18), metastasis in 11% (2/18), and other causes in 44% (8/18) of cases. For toxicities, 2% (1/51) of patients reported grade 3 pain, 25% (2/8) reported grade 3 fatigue, and 12% reported grade 4 diarrhea (1/8) (Table 1). Conclusions: Our study showed that pertuzumab was well tolerated in older pts with bc in the real-world setting. However, 25 % of pts still discontinued pertuzumab early which illustrates the importance of identifying pts who are at higher risk for toxicities prior to starting treatment.

Table 1

Did the patient experience any of the following Grade 1-4 toxicities during pertuzumab treatment?	
Nausea	63% (45/71)
Vomiting	37% (26/71)
Anorexia	77% (55/71)
Constipation	54% (38/71)
Neuropathy	77% (55/71)
Depression	66% (47/71)
Mucositis	49% (35/71)
Dyspnea	62% (44/71)
Pain	72% (51/71)
Fever	7% (5/71)
Edema	51% (36/71)
Rash	46% (33/71)
Hand Foot Syndrome	32% (23/71)

Reported adverse events in patients age 65 and older receiving pertuzumab

PO5-17-05

Recommendations of a panel of experts from the Brazilian Society of Mastology on breast and axilla clipping: when, how and for whom?

Presenting Author(s) and Co-Author(s):

H. Couto. Brazilian Mastology Society, Belo Horizonte, Minas Gerais, Brazil

A. Hassan. Brazilian Mastology Society, Rio de Janeiro, Rio de Janeiro, Brazil

D. Steinmacher. UniCesumar, Maringá, Parana, Brazil

E. Pessoa. UNESP - Botucatu, Botucatu, Sao Paulo, Brazil

E. Millen. Oncoclinicas, United States

F. Zerwes. PUC-RS, United States

F. Pimentel Cavalcante. Hospital Geral Fortaleza (HGF), United States

G. Tosello. Instituto do Cancer Oeste Paulista (inCOP), PRESIDENTE PRUDENTE, Sao Paulo, Brazil

G. Badan. Santa Casa de São Paulo, São PAulo, Sao Paulo, Brazil

J. Francisco. Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, Sao Paulo, Brazil

L. Soares. Federal University of Goiás, Seoul, Brazil

L. Budel. Universidade Federal do Paraná, Curitiba, Sao Paulo, Brazil

L. Chala. Grupo Fleury Medicina e Saúde, São Paulo, Sao Paulo, Brazil

R. Fernandes. Perola Byington Hospital, United States

R. Freitas-Junior. Federal University of Goias & Araujo Jorge Cancer Hospital, Goiânia, Goias, Brazil

V. Oliveira. Santa Casa de São Paulo, São PAulo, Sao Paulo, Brazil

V. Budel. Universidade Federal do Parana, Curitiba, Parana, Brazil

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

Background: The precise location of the tumor site is essential for obtaining free margins and success of surgical treatment, reducing the rates of reoperation and local recurrences. Neoadjuvant chemotherapy (NAC) is a challenge for preoperative tumor localization, due to the different patterns of locoregional response, limitations related to imaging methods, and the possibility of a pathological complete response (pCR). In addition, there are several divergent approaches regarding preoperative axillary evaluation, lymph node marking methods and approaches when facing cN1. Thus, the knowledge and attitudes of the affiliated members of the Brazilian Society of Mastology (SBM) regarding breast and axilla marking were evaluated and a consensus regarding management and treatment was reached.

Methods: This is an online survey conducted between June and December 2022. All 1.742 active mastologists affiliated to SBM were anonymously invited to participate in the study. The online form contained 28 objective questions, of which 22 were formulated on a Likert scale. These questions addressed several relevant aspects related to breast and axilla marking in the neoadjuvant setting. Responses that reached 70% agreement were considered consensual. Statistical analysis was performed using the SPSS program. Post hoc analysis was performed when appropriate and, in all analyses, the significance level of $p < 0.05$ was adopted.

Results: A total of 468 mastologists answered the questionnaire (26.8%), with a predominance of professionals aged between 40-49 years (32.1%), male (50.4%), and residents of state capitals (63.9%). Most professionals were board-certified (84.8%), 87.7% for more than five years. The indication of tumor marking in the breast prior to NAC was consensual (96.4%) and the metal clip was the preferred method (69.7%). If available, the US-visible clip is preferred (86.5%). With respect to the marking of the breast and axilla prior to NAC, 93.3% of the mastologists considered relevant issues related to the techniques and materials. There was no consensus regarding the indication of pre-NAC histologically positive lymph node marking (49.8% disagree and 42.8% agree), however there was consensus that the clinical and imaging evaluation is insufficient for staging the axilla as N1 (71.6 %). The contraindication of breast and node marking in T4b tumors (71.2%) was consensual. There was consensus on the indication of sentinel lymph node biopsy (SLNB) for initially cN1 (92.3%) or cN2 (72.7%) tumors that became cN0 after NAC, with 67.5% opting for dual staining with technetium and patent blue. There was also consensus on the indication of axillary lymphadenectomy (89%) after NAC when double marking with technetium and patent blue for SLNB is not available. In addition, 41.0% of mastologists perform axillary lymphadenectomy when less than three lymph nodes are found in the SLNB. Among the 28 questions, consensus was reached on only 11 (39.3%); with some consensus variations according to age group, sex, geographic location of residence, place of professional activity (public or private), and professional experience.

Conclusion: The indication of pre-NAC breast marking is consensual among Brazilian mastologists, although axillary nodal marking is not. There is a great divergence of attitudes among Brazilian surgeons in relation to the many issues related to pre-NAC breast and axilla marking, indicating the need to establish continuing education programs on the subject.

PO5-17-06

Prevalence of BRCA Mutations: A Predictive Model in a High-Risk Population of BC Patients at a Tertiary Care Center

Presenting Author(s) and Co-Author(s):

K. Suleman. King Faisal Specialist Hospital and Research Center, Riyadh, Ar Riyad, Saudi Arabia

K. Al-Khatib. King Faisal Specialist Hospital & Research Center, United States

E. Haque. College of Medicine, Alfaisal University, United States

T. El Hassan. King Faisal Specialist Hospital & Research Center, United States

A. Al suwaidan. King Faisal Specialist Hospital & Research Center, United States

S. Alaklabi. King Faisal Specialist Hospital & Research Center, RIYADH, Saudi Arabia

T. Twegieri. King Faisal Specialist Hospital and Research Center, Saudi Arabia

A. AlSayed. King Faisal Specialist Hospital and Research Center, Saudi Arabia

D. Ajarim. King Faisal Specialist Hospital and Research Center, Saudi Arabia

M. Al Zahrani. King Faisal Specialist Hospital & Research Center, United States

S. Akhtar. King Faisal Specialist Hospital & Research Center, United States

O. Al Malik. King Faisal Specialist Hospital & Research Center, United States

A. Al Hefdhi. King Faisal Specialist Hospital & Research Center, United States

W. Khayal. King Faisal Specialist Hospital & Research Center, United States

S. Al Zughaihi. King Faisal Specialist Hospital & Research Center, United States

A. Tulbah. King Faisal Specialist Hospital & Research Center, United States

Background: Breast cancer (BC) is a prevalent cancer in Saudi Arabia, with the majority of cases being sporadic. However, 25-30% of cases are associated with hereditary factors. Germline BRCA mutations are the most common mutations linked to hereditary BC predisposition syndromes, with a reported frequency of up to 11% in Saudi Arabia. Methods: This retrospective cohort study was conducted at a single institution in Saudi Arabia. Medical records of BC cases were reviewed where BRCA testing was performed, typically in patients with triple negative BC, hormone-positive (HR+) BC in younger premenopausal patients under the age of 45, or those with a personal or family history of BC. Patients meeting these criteria were diagnosed and treated at a tertiary care center in Saudi Arabia, between 2018 and 2021. The association between BRCA positivity and proposed risk factors was evaluated using chi-square analysis. Multivariate analysis was performed using logistic regression to assess the association between independent significant risk factors and BRCA+. Results: 482 cases of breast cancer were reviewed, with 412 testing negative for mutations and an overall BRCA positivity rate of 13.7%. Among BRCA positive patients, 62% had a positive family history (p-value < 0.001), and they tended to be younger, with a median age of 38 compared to BRCA negative patients with a median age of 42 (p-value = 0.01). Of the 469 female patients, 62 (13%) were BRCA positive, and of the 12 male patients, 3 (25%) were BRCA positive. Among the BRCA positive patients, 73% had BRCA1 mutations, and 26% had BRCA2 mutations. No patients with lobular BC tested positive for BRCA mutations. The odds ratio for BRCA positivity in triple negative BC was 3.6 (95% CI 2.1-6.2, p-value < 0.001). The odds ratio for BRCA positivity in HR+ cases was 2.5 (95% CI 1.4-4.2, p-value = 0.001). In HR+ cases, 4.6% had BRCA1 mutations, and 5% had BRCA2 mutations. In ER- cases, 20% had BRCA1 mutations,

and 1.2% had BRCA2 mutations. Multivariate analysis revealed that increasing the age of diagnosis by one year reduced the chance of having BRCA positivity by 5% (p-value = 0.009). Having a positive family history increased the risk of BRCA positivity with an OR of 8 (95% CI 4-15.8, p-value < 0.001), and triple negative BC increased the risk of BRCA positivity with an OR of 4.1 (CI 2.2-7.5, p-value < 0.001). The model performance was evaluated using an AUC of 0.80. Conclusion: This study highlights the high prevalence of BRCA mutations in a high-risk population of BC patients. The proposed predictive model identified younger age, triple negativity, and a positive family history as independent predictors, with an AUC of 0.8. The study's predictive model suggest that these factors may be useful in identifying patients who are at increased risk of carrying BRCA mutations and could benefit from genetic counseling and testing.

PO5-17-07

MUCINOUS BREAST CARCINOMA: REAL WORLD DATA IN A REFERENCE CENTER IN SÃO PAULO

Presenting Author(s) and Co-Author(s):

M. Fleury De Figueiredo. Womens' Health Hospital, São Paulo, Brazil, São Paulo, Sao Paulo, Brazil

A. MATTAR. HOSPITAL PEROLA BYINGTON, São Paulo, Sao Paulo, Brazil

F. Cavagna. Womens' Health Hospital, São Paulo, Brazil, United States

A. Minatel da Silva. Womens' Health Hospital, São Paulo, Brazil, United States

R. nadai. Womens' Health Hospital, São Paulo, Brazil, United States

J. Medeiros de Oliveira. Womens' Health Hospital, São Paulo, Brazil, United States

L. Fleury de Figueiredo. Pará's State University (Belém-PA, Brazil), United States

BACKGROUND: Mucinous breast carcinoma (MC) is a subtype of invasive carcinoma that corresponds to 1 to 6% of all types of breast cancer. It occurs when the mucinous component accounts for more than 50% of the tumor producing extracellular mucin in large scale. Mucin is a complex carbohydrate engaged in processes such as epithelial differentiation, adhesion modulation and cell signaling. Along with other special types of breast neoplasia, MC appears to have a unique behavior and, since it's low amount of cases, a detailed clinical evaluation has been difficult. **OBJECTIVES:** To describe the profile of patients with breast MC that were treated in a reference center in São Paulo, Brazil as well as evaluate its management and outcomes. **METHODS:** A descriptive longitudinal observation study conducted at São Paulo's Women's Health Reference Center - Hospital da Mulher from July 2022 to January 2023, based on 192 medical records of patients diagnosed with MC from 2003 to 2018. **RESULTS:** 192 patient's records were included. The age range was 31-93 years, out of which 74,3% of the patients were older than 50 when diagnosed. 48,7% identified as white and 43,7% showed earlier diagnoses of systemic hypertension. The time range between diagnosis and first treatment was 4,5 months. Out of the histopathological features, the nuclear grade was 3 in 69 patients (34,6% of the cases), and histological grade 1 in 52,7%. About pathological staging, the size of the tumors went from 0,5 to 9,5 cm, with an average of $\pm 4,7$ cm, the majority of them showed positive ER (89,4%), negative PR (85%), and were negative for Her-2 (76%). Greater number of patients (92,4%) went through both clinical and surgical treatment. Only 15 (7,5%) had isolated clinical treatment. 31% of the patients received systemic chemotherapy treatment, 25% of those were neoadjuvant. 81,9% of patients received aromatase inhibitor and only 17% radiotherapy. Distant metastasis were diagnosed in 27 patients (13,5%) and the local recurrence was observed in 15,3%. Out of distant metastasis, pulmonary type was more prevalent, registered in 45,7% of patients, followed by osseous (22,88%) and hepatic (14,2%). 33 patients (16,5%) progressed to death, however, the specific cause was not determined. **CONCLUSION:** MC is a rare subtype of breast cancer, more prevalent in post-menopausal and white women. Frequently shows low histological grade and positive hormonal receptors, which reinforces the idea of a indolent behavior. The treatment is mostly surgical, with adjuvance if necessary. Metastasis are infrequent and knowing the profile of patients with MC, as well as it's behavior, allows the better management when facing this diagnosis.

PO5-17-08

Real world outcomes of neoadjuvant chemotherapy in ER-positive/PR-positive, HER2-negative breast cancer

Presenting Author(s) and Co-Author(s):

M. Kurian. St. Elizabeth Cancer Center, United States

M. Trybula. University Hospitals/Seidman Cancer Center, United States

K. Patell. University Hospitals/Seidman Cancer Center, United States

G. Guzik. University Hospitals, United States

S. Margevicius. Case Comprehensive Cancer Center, United States

P. Fu. Case Western Reserve University, Department of Population and Quantitative Health Sciences, United States

A. Montero. UH/Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA, United States

J. Martin. University Hospitals/Seidman Cancer Center, Cleveland, Ohio, United States

Background:

Neoadjuvant chemotherapy is utilized to downstage locally-advanced estrogen receptor-positive (ER+)/progesterone receptor-positive (PR+), HER2-negative breast cancer despite modest pathological complete response (pCR) rates. The two most commonly utilized regimens include docetaxel plus cyclophosphamide (TC) or dose-dense doxorubicin and cyclophosphamide followed by paclitaxel (ddAC-T). Given few head-to-head comparisons of neoadjuvant TC with ddAC-T in this population, we performed a real world data analysis.

Methods:

148 patients with ER+/PR+, HER2-negative breast cancer were included in the analysis. The patients were divided into two groups based on the neoadjuvant chemotherapy regimen used (TC vs ddAC-T) and the clinical responses to chemotherapy were categorized as complete, partial, no response/stable, or progressive disease. We examined the differences or associations in demographics, clinical characteristics, overall survival (OS), and invasive disease-free survival (IDFS) between TC and ddAC-T neoadjuvant chemotherapy. pCR was defined as the absence of invasive carcinoma in breast and lymph nodes (ypT0/ypTis and ypN0). Partial response was defined as a decrease in either or both T and/or N stage, compared to pre-treatment evaluation; no response was defined as no change in either T or N categories; and progressive disease was defined as an increase in either the T or N staging at time of pathologic evaluation.

Results:

The median age of participants was 55 years (range 28-78 years). 67% had clinical stage II disease, while 26% had stage III. 130 participants received neoadjuvant ddAC-T while 18 participants received TC. The ddAC-T group had 7% patients who achieved a pCR and 37% with a partial response, compared to the TC group with 0% of patients with a pCR and 33% with a partial response. The TC group had a higher rate of progressive disease, compared to the ddAC-T group (67% versus 20%). On univariate analysis, the choice of neoadjuvant chemotherapy was not predictive of pathologic response ($p = 0.3864$). As expected, premenopausal status was associated with a higher likelihood of a pathologic response with an odds ratio of 2.917 (95% CI: 1.465-5.809). On multivariate analysis, chemotherapy regimen was not predictive of pathologic response ($p = 0.6047$), after controlling the effects of age and

menopausal status. No significant difference was noted in OS or IDFS at 24 and 48 months between the ddAC-T and TC groups. On multivariate analysis, controlling for BMI, ER, PR, race, and ECOG performance status, the choice of chemotherapy was not predictive of IDFS. Non-white participants appeared to have inferior IDFS (HR = 2.956, 95% CI: 1.208, 7.238, p-value = 0.0177).

Conclusion:

In this single-center retrospective analysis, we show real world outcomes of the use of neoadjuvant chemotherapy regimens among patients with ER+/PR+, HER2-negative breast cancer. Both ddAC-T and TC had low pCR rates, 5.98% and 0%, respectively. However, there was no statistical difference between IDFS or OS when comparing the two chemotherapy regimens. More data are needed to optimize neoadjuvant treatment in this patient population and to determine whether anthracyclines can be avoided.

Pathologic responses

Factor	Univariate Analysis		Multivariable Analysis	
	OR (95 %CI)	p-value	OR (95 %CI)	p-value
Chemotherapy (TC vs. AC-T)	0.632 (0.223, 1.787)	0.3864	0.753 (0.258, 2.202)	0.6047
Age	0.973 (0.941, 1.001)	0.0604	1.016 (0.971, 1.063)	0.4959
Race (Black/Asian/Other) vs. White	0.611 (0.254, 1.469)	0.2712		
BMI	0.984 (0.945, 1.024)	0.4168		
CMI Index	0.842 (0.650, 1.089)	0.19		
ER				
>80 % vs. ≤80%	0.352 (0.084, 1.465)	0.1513		
PR				
20-80% vs. <20%	0.989 (0.374, 2.619)	0.9045		
>80 % vs. <20%	1.077 (0.465, 2.492)	0.8124		
Menopausal status (Pre vs. Post)	2.917 (1.465, 5.809)	0.0023	3.794 (1.288, 11.173)	0.0155
ECOG				
≥1 vs. 0	0.593 (0.285, 1.235)	0.1624		
Adjuvant bisphosphonates used (Yes vs. No)	1.163 (0.571, 2.367)	0.6776		
Axillary Dissection (Yes vs. No)	0.861 (0.357, 2.076)	0.739		
Stage				
Stage 2 vs. Stage 1	3.763 (0.774, 18.297)	0.1279		
Stage 3 vs. Stage 1	3.375 (0.634, 17.964)	0.2949		
T-stage				
T2 vs. (T0/T1)	2.898 (1.247, 6.731)	0.0547		
T3 vs. (T0/T1)	2.231 (0.880, 5.657)	0.4816		
N-stage				
N1 vs N0	0.901 (0.331, 2.447)	0.6051		
(N2/N3) vs. N0	1.250 (0.289, 5.407)	0.6626		

The results (summarized by odds ratio (OR) and its 95% CI) from logistic regression on the pathological responses (complete and partial).

PO5-17-09

Event-free survival in HER2-low vs HER2-zero breast cancer patients submitted to neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

G. Sartori. Federal University of Rio Grande do Sul, Porto Alegre, Brazil, Rio Grande do Sul, Brazil

S. Ramalho. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

L. Roberto da Silva. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

T. Reinert. Oncoclinicas, Porto Alegre, Brazil

M. Lopes Da Rosa. Post Graduation Program of Medical Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, United States

G. Morais Tavares. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

V. Vasconcelos. caism-UNICAMP, Sao Paulo, Brazil

H. Mantovani. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

A. Ribeiro Da Silva Cabello. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

G. Coelho. Grupo Diagnose Patologia e Biologia Molecular, Caxias do Sul, Rio Grande do Sul, Brazil, United States

J. Mandelli. Grupo Diagnose Patologia e Biologia Molecular, Caxias do Sul, Rio Grande do Sul, Brazil, United States

F. Zaffaroni. Faro Stat Solutions, Porto Alegre, Brazil, United States

C. Cabello. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

M. Silveira Graudenz. Faculty of Medical Sciences, Department of Pathology, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, United States

Background: Breast cancer (BC) with low expression of HER2 (HER2-low) might constitute a group of tumors with unique clinical and biological characteristics. However, the prognostic impact of HER2-low status vs HER2-zero in terms of pathological complete response (pCR) and event-free survival (EFS) after neoadjuvant chemotherapy (NACT) remains controversial. The aim of this study was to evaluate pCR and EFS rates in HER2-low vs HER2-zero early BC patients treated with NACT. Methods: In this cross-sectional study, we analyzed 565 consecutive patients with HER2-low and HER2-zero early BC submitted to neoadjuvant therapy from 2017 to 2021 in a single academic center. Patients with biopsy-confirmed stage I-III BC, with HER2-low or HER2-zero status, submitted to locoregional therapy after NACT were included. Clinical and pathological characteristics, pathological response, treatment protocol and RFS were analyzed and considered for statistical analysis. HER2-low was defined by IHC 1+, or 2+ ISH non-amplified; HER2-zero was defined by IHC 0. Pathological response was determined locally, and pCR defined as the absence of residual invasive disease with or

without ductal carcinoma in situ in the breast and axilla. EFS was defined as the time from diagnosis to distant recurrence, a second primary, or death from any cause, whichever occurred first. Results: 441 patients were included in the analysis, 236 (53.5%) patients with HER2-low tumors, and 205 (46.5%) with HER2-zero tumors. Overall, 279 (63.3%) were estrogen receptor (ER)-positive tumors, and 162 (36.5%) were ER-negative tumors. Among ER-positive tumors, 166 (59.5%) had HER2-low status, and 113 (40.5%) were HER2-zero. For the ER-negative subgroup, the corresponding rates were 70 (43.2%) and 92 (56.8%), respectively. Most patients had stage II-III BC (423/441; 96%), and 20.2% (89/441) had high nodal tumor burden. Many patients received anthracycline- and taxane-based NACT (425/441; 96.4%), and over 90% (148/162; 91.3%) of ER-negative patients received a platinum agent. The overall pCR rate were 18.1%. Among ER+ tumors, pCR rates were 6.4%, 6.0%, and 7.0% in the overall, HER2-low and HER2-zero tumors, respectively. In ER- tumors, the corresponding pCR rates were 38.3%, 35.7, and 40.2%, respectively. The differences in pCR rates between HER2-low and HER2-zero tumors were not statistically significant (ER-positive, $p=0.724$; ER-negative, $p=0.559$). After a median follow-up of 42 months, 90 EFS events occurred. In the HER2-low group there were 56 (23.7%) EFS events, and 34 (16.6%) EFS events in the HER2-zero (HR 1.19; 95% CI 0.77-1.82; $p=0.427$). Among 279 patients in the ER-positive group there were 48 events, 32 in the HER2-low subgroup and 16 in the HER2-zero group (HR 1.16; 95% CI 0.64-2.13; $p=0.622$). Among 162 ER-negative tumors there were 42 events, 24 in the HER2-low subgroup, and 18 in the HER2-zero subgroup (HR 1.56; 95% CI 0.84-2.88; $p=0.158$). NACT discontinuation occurred in 86 patients (ER-positive: 45, 16.1%; ER-negative: 41, 25.3%), mainly due to toxicity (anthracycline-taxane: 10.0%; platinum: 11.7%). Disease progression during NACT were reported in 6.8% (30/441) of patients. Conclusions: Our results show similar pCR rates and RFS among HER2-low and HER2-zero early BC patients after standard NACT, which are consistent with the current literature. Despite the predictive role of low HER2 expression in selecting patients for novel antibody-drug conjugates (ADCs) therapy, its prognostic value could not be confirmed.

PO5-17-10

PERFORMANCE AND OUTCOMES OF THE 70-GENES SIGNATURE (MAMMAPRINT™) IN A POPULATION WITH MIDDLE INCOME – REAL WORLD STUDY (AGEMA-BRA)

Presenting Author(s) and Co-Author(s):

F. Mansani. UNIVERSIDADE ESTADUAL DE PONTA GROSSA, Ponta Grossa, Parana, Brazil
R. Freitas-Junior. Federal University of Goiás & Araujo Jorge Cancer Hospital, Goiânia, Goiás, Brazil

INTRODUCTION – Breast cancer remains the most frequent tumor in the female population and the fourth in mortality in the world population (GLOBOCAN 2020). With the aim of reducing mortality and at the same time de-escalating treatment, avoiding overtreatment, individualized therapy is increasingly being applied. The genomic signature of 70-genes, when stratifying patients into high and low risk of relapse, makes it possible to withdraw part of the cases of high clinical risk from chemotherapy treatment. However, the MINDACT study, which validated this signature, was carried out only in the European population, with no data on performance and outcomes in other populations with greater miscegenation.

OBJECTIVE – To study the performance and outcomes of the 70-gene genomic signature (MammaPrint™) in a Brazilian population with a high ethnic miscegenation.

METHODOLOGY – A retrospective cohort study was conducted in 953 women with breast cancer at high clinical risk, who underwent genomic analysis with the 70-gene platform (MammaPrint™), from January 2016 to December 2020. For the statistical evaluation, a descriptive analysis of the data with absolute and relative frequencies of the variables was performed. To verify the association between qualitative variables, the chi-square test was used. All analyzes were performed in the R 4.1.0 environment (R Core Team, 2021). Study approved by the Research Ethics Committee of the State University of Ponta Grossa (PR) - (CAAE: 12194219.4.0000.0105).

RESULTS – The analysis of 955 cases from the AGEMABRA cohort (all at high clinical risk) showed 546 cases (57.2%) with low genomic risk and 409 cases (42.8%) with high genomic risk to MammaPrint™ (MP); when compared with data from the MINDACT study (46.2% low risk and 53.8% high risk) a significant difference was observed in the distribution for high and low risk in the two populations ($p < 0.001$). After excluding patients with missing data, 409 cases of low- and high-risk MP were studied. The variables regarding age group, tumor diameter, number of affected lymph nodes, hormone receptors and HER2 overexpression showed no significant difference; within this same analysis, the tumor grade showed a higher incidence of grade 1 in the population with low genomic risk (6.6%) compared to high risk (2.9%) and grade 3 in high risk (13%) compared to low risk (5%) with $p < 0.001$ (table 1). With an average follow-up of 40 months, the DMFS (disease metastatic free survival) found was 97.2%, being 97.8% for low risk and 96.2% for high risk ($p = 0.54$). All patients with high-risk MP who progressed had used adjuvant chemotherapy, and all patients with low-risk MP who relapsed received only endocrine therapy. When compared to the MINDACT population, the AGEMA-BRA has more elderly patients, and smaller tumors with a lower histological grade ($p = < 0.001$).

CONCLUSION – The analysis of the Brazilian population submitted to the 70-gene genomic signature showed a greater proportional number of tumors with low genomic risk than in the test approval study, favoring its application with the aim of de-escalating systemic treatment in

this population. Despite the low rate of disease progression in the AGEMA-BRA study, probably determined by the population with the best prognosis disease and the short follow-up, recurrence was similar in the high and low genomic risk groups, demonstrating the adequate selection of systemic therapy following the results of the MP. An increase in the sample size and longer follow-up are necessary to confirm the results found.

Table 1. Characteristics of patients and tumor according to risk (AGEMA-BRA)

Variable	High clinical risk and low genomic risk (n= 546)		High clinical risk and low genomic risk (n= 409)		p-valor*	
	N	%col	N	%col		
Age	< 35	13	2,4	15	3,7	0,311
	35 - 49	143	26,2	119	29,1	
	50 - 70	302	55,3	204	49,9	
	>70	49	9	32	7,8	
	not available	39	7,1	39	9,5	
Tumor size	<1 cm	14	2,6	13	3,2	0,058
	1-2 cm	91	16,7	70	17,1	
	>2-5 cm	69	12,6	65	15,9	
	> 5cm	8	1,5	0	0	
	not available	364	66,7	261	63,8	
Tumor grade	1	36	6,6	12	2,9	<0,001
	2	118	21,6	83	20,3	
	3	27	5	53	13	
	not available	365	66,9	261	63,8	
Positive lymph nodes	0	96	17,6	91	22,3	0,119
	1	66	12,1	39	9,5	
	2	14	2,6	10	2,4	
	3	2	0,4	4	1	
	≥4	1	0,2	4	1	
Hormonal receptor	not available	367	67,2	261	63,8	0,389
	Positive	260	47,6	209	51,1	
	Negative	0	0	2	0,5	
HER2	Not available	286	52,4	198	48,41	0,248
	Positivo	1	0,2	4	1	
	Negativo	249	45,6	196	47,9	
	not available	296	54,2	209	51,1	
Subtipo clínico-patológico	Luminal HER2-negative	249	45,6	196	47,9	0,248
	Luminal HER2-positive	1	0,2	3	0,7	
	Nonluminal HER2-positive	0	0	1	0,2	
	Triple negative	0	0	0	0	
	Not available	296	54,2	209	51,1	

*Chi square test; N= absolute frequency; %col= relative frequency.

PO5-17-11

STRATIFICATION OF HIGH GENOMIC RISK IN THE GENETIC SIGNATURE OF 70 GENES (MAMMAPRINT™) IN REAL WORLD ANALYSIS (AGEMA-BRA).

Presenting Author(s) and Co-Author(s):

F. Mansani. UNIVERSIDADE ESTADUAL DE PONTA GROSSA, Ponta Grossa, Parana, Brazil
R. Freitas-Junior. Federal University of Goiás & Araujo Jorge Cancer Hospital, Goiânia, Goiás, Brazil

INTRODUCTION – Although genetic signatures for breast cancer are used to de-escalate chemotherapy treatment, around half of the patients, according to several analyses, present high genomic risk and are conducted in the same way, regardless of the risk score found. The stratification into high risk 1 and high risk 2, proposed in the ISKY-2 cohort, sought to verify the possibility of selecting women with breast cancer who need to escalate the systemic treatment according to the score measured by the MammaPrint™ (MP). **OBJECTIVE** – To evaluate the outcomes of the AGEMA-BRA cohort population (Mammaprint™ genetic signature in the Brazilian population), analyzing the characteristics and behavior of patients stratified into high risk 1 (H1) and high risk 2 (H2) by the 70-gene genetic signature. **METHODOLOGY** – Retrospective study in the AGEMA-BRA cohort with high clinical and genomic risk. They were divided into high risk 1 (H1) with MP score between 0 and > -0.57 and high risk 2 (H2) with MP score ≤ -0.57 ; analyzing the epidemiological, anatomopathological, immunohistochemical (IHC) profiles and outcomes in the two populations. For the statistical evaluation, a descriptive analysis of the data with absolute and relative frequencies of the variables was performed. To verify the association between qualitative variables, the chi-square test was used. All analyzes were performed in the R 4.1.0 environment (R Core Team, 2021). The AGEMA-BRA study was approved by the ethics and research committee of the State University of Ponta Grossa (CAAE: 12194219.4.0000.0105). **RESULTS** – The AGEMA-BRA cohort comprises 953 patients with high clinical risk luminal breast cancer, of which 407 (42.7%) are at high genomic risk. After excluding cases that did not contain the necessary information, 176 records were analyzed, with an average follow-up of 40 months. The age group, tumor diameter and number of affected lymph nodes were similar. Statistical significance was observed when evaluating the histological grade where grade 3 was more frequent in cases with the highest risk MP score (H2) with 60% of the records ($p = 0.039$) (Table 1). As for the IHC analysis, the positivity of estrogen and progesterone receptors, and HER2 did not show statistical significance in the comparison between H1 and H2. In the Ki67 analysis, the comparison with expression $>20\%$ was more frequent in population H2 (76.4%) compared to H1 (48.2%) with $p = 0.002$. Metastasis-free survival (DMFS) was 96.4% for H1 and 95% for H2 ($p = 0.269$). **CONCLUSIONS** – The dichotomization of cases with MP score at high risk H1 and high risk H2 in the AGEMA-BRA cohort showed no difference in DMFS, inferring that this classification does not help in the management of these patients. The sample size and short follow-up for a disease that relapses later may have interfered with the result. More robust analysis of these two populations needs to be performed to confirm the presented data.

TABLE 1 - Profile of high genomic risk AGEMA-BRA

	HIGH RISK	HIGH RISK H1	HIGH RISK H2	p. valor
Patients (N)	407	347	60	
Age at diagnosis (years)	54,4	54,8	54,4	
Age	N = 370 (42,19%)	N = 317 (85,7%)	N= 53 (14,3%)	
<35	15 (3,7%)	14 (4,4%)	1 (1,9%)	<i>p. = 0,169</i>
35 - <50	119 (29,1%)	96 (30,4%)	23 (43,4%)	
50 - 70	204 (49,9%)	177 (55,7%)	27 (50,9)	
>70	32 (7,8)	30 (9,5%)	2 (3,8%)	
Tumor (T)				
T1a/b	12 (8,2%)	11 (8,6%)	1 (5%)	<i>p. = 0,782</i>
T1c	70 (47,6%)	61 (48,1%)	9 (45%)	
T2	65 (44,2%)	55 (43,3%)	10 (50%)	
T3	0 (0%)	0 (0%)	0 (0%)	
T4	0 (0%)	0 (0%)	0 (0%)	
Tumor grade				
1	12 (8,3%)	12 (9,5%)	0 (0%)	<i>p. = 0,039</i>
2	81 (55,8%)	73 (57,9%)	8 (40%)	
3	52 (35,9%)	41 (32,6%)	12 (60%)	
Positive lymph node				
0	91 (61,6%)	74 (57,9%)	17 (85,0%)	<i>p. =0.133</i>
1	39 (26,3%)	37 (28,9%)	2 (10,0%)	
2	10 (6,7%)	10 (7,8%)	0 (0%)	
3	4 (2,7%)	3 (2,3%)	1 (5,0%)	
≥4	4 (2,7%)	4 (3,1%)	0 (0%)	

PO5-17-12

Impact of HER2-low status on axillary response and surgical management after neoadjuvant chemotherapy in early breast cancer

Presenting Author(s) and Co-Author(s):

L. Roberto da Silva. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

G. Sartori. Federal University of Rio Grande do Sul, Porto Alegre, Brazil, Rio Grande do Sul, Brazil

S. Ramalho. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

T. Reinert. Oncoclinicas, Porto Alegre, Brazil

M. Lopes Da Rosa. Post Graduation Program of Medical Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, United States

G. Morais Tavares. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

H. Mantovani. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

V. Vasconcelos. caism-UNICAMP, Sao Paulo, Brazil

A. Ribeiro Da Silva Cabello. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

G. Coelho. Grupo Diagnose Patologia e Biologia Molecular, Caxias do Sul, Rio Grande do Sul, Brazil, United States

J. Mandelli. Grupo Diagnose Patologia e Biologia Molecular, Caxias do Sul, Rio Grande do Sul, Brazil, United States

F. Zaffaroni. Faro Stat Solutions, Porto Alegre, Brazil, United States

C. Barrios. Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Rio Grande do Sul, Brazil

M. Silveira Graudenz. Faculty of Medical Sciences, Department of Pathology, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, United States

C. Cabello. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil, United States

Background: Breast cancer (BC) with low expression of HER2 (HER2-low) might constitute a group of tumors with unique clinical and biological characteristics. Little is known about axillary downstaging and nodal surgical outcomes in HER2-low BC after neoadjuvant chemotherapy (NACT). The aim of this study was to evaluate axillary response and surgical management of the axilla in HER2-low BC patients submitted to NACT. Methods: In this cross-sectional single center study, we consecutively included all patients diagnosed with early HER2-negative BC between 2017 to 2021 that were treated with NACT. Patients must have biopsy-confirmed stage II-III BC, submitted to breast surgery after NACT. Clinical and pathological response in the axilla, type of axillary surgery, and surgical outcomes data were collected. HER2-low was defined by IHC score 1+, or 2+ ISH non-amplified; HER2-zero was defined by IHC score 0. Pathological response was determined locally. Results: At diagnosis, 291 patients had clinically involved axillary nodes (cN1: 69.4%; cN2: 25.1%; cN3: 5.5%). Among 136 patients eligible for SLN biopsy after NACT, 77 (26.5%) had pathologically negative SLN. Of those submitted to

upfront axillary dissection (n=154), 52 (33.7%) had pN0 disease. In total, 129 (44.3%) patients with clinically involved axillary lymph nodes at diagnosis were converted to cN0 after NACT. There was no difference in the rate of axillary downstaging between HER2-low and HER2-zero tumors, 17.8% vs 26.5%, respectively (p=0.0026). 236 patients were submitted to sentinel lymph node biopsy (SLN), of whom 214 (81.4%) with blue dye-only, 40 (15.2%) with radioactive isotope, and 7 (2.7%) with dual tracer. SLN detection failure were reported for 12 patients (0.046%). Mean number of lymph nodes retrieved were 2.7. Most patients had a negative SLN biopsy (180/263; 68.4%), of whom 91 (50.6%) were HER2-low and 89 (49.4%) were HER2-zero. Positive SLN biopsy were reported in 83 patients (isolated tumor cells: 20.5%; micrometastasis: 24.1%; macrometastasis: 55.4%), with capsular extravasation in 25.3%. A positive SLN biopsy occurred in 61.4% of patients with HER2-low tumors, and in 38.5% of patients with HER2-zero tumors. Among patients with a positive SLN biopsy (n=83), 67 were submitted to axillary dissection, of whom 39 (58.2%) had no additional nodes involved (HER2-low: 61.5%; HER2-zero: 38.4%). Considering N0 tumors at diagnosis, 127 patients were submitted to SNL, and only 18.9% had a positive result (HER2-low: 66.6%; HER2-zero: 33.3%). In the subgroup of initially cN+ disease, 136 (46.7%) underwent SLN biopsy, with 59 (43.4%) with a positive result (HER2-low: 59.3%; HER2-zero: 40.7%). Conclusions: Our results showed that HER2-low BC patients had a statistically significant lower frequency of axillary downstaging after NACT. More than 40% of patients with cN+ at diagnosis were downstaged to cN0 and were submitted to SNL biopsy. Axillary dissection were avoided in roughly 25% of patients with cN+ BC at initial staging.

PO5-18-01

Cancer Detection Rate Meta-Analysis Comparison of Contemporary Dense-Breast Supplemental Screening Modalities

Presenting Author(s) and Co-Author(s):

M. Tornai. Duke University, Durham, North Carolina, United States

J. Hugg. SmartBreast Corp, Texas, United States

B. Patt. SmartBreast Corp, California, United States

C. Chen. University of Chicago, United States

E. Santos. SmartBreast Corp, California, United States

A. Erkanli. Duke University Hospital, United States

S. Morrison. Duke University, United States

M. Covington. University of Utah, Utah, United States

We performed a meta-analysis of the cancer detection rates from 24 published reports in dense breasts for all contemporary and FDA-approved imaging modalities (DM, DBT, U/S, CEM, MBI, MRI) available for supplemental breast cancer screening. This information is critical to the 40% of women with BIRADS categorized dense breasts (C,D) receiving breast cancer screening. In the paper an analysis of the net lives saved using a benefit-to-risk comparison of the ionizing imaging modalities (DM, DBT and MBI) is also presented and the safety of each technique is described. Note that it is well accepted that carcinogenic risk associated with ionizing radiation doses of < 100 mSv are considered too small to be detected or altogether non-existent. Recently, with FDA's federal MQSA requirements changing to mandate notification of women's dense-breast status (C,D), awareness has grown substantially about the dismal cancer detection performances of DM, DBT and U/S which degrades substantially with increasing breast density. Additionally, this May 2023, federal legislation was introduced in congress. The Find It Early Act (HR3086), should it become law in 2024, will require that healthcare payors cover costs for supplemental screening of women with dense breasts. Knowing and understanding the arsenal of the highest performing imaging modalities (based on cancer detection rates (CDR), Sensitivity, Specificity, NPV) is critically important for all patients and physicians caring for them. The volume of women qualifying for supplemental breast screening is expected to be managed by existing and growing numbers of all the best performing available technologies and approaches. Since the analysis is based on numerous others' clinical trials of CDRs evaluating the various modalities in millions of women, this comprehensive analysis presents a level playing field for comparison. The top-three high performing imaging modalities (CEM, MBI, MRI) should be used to increase the number of early-stage cancers found in order to substantially decrease mortality, decrease patient trauma, decrease procedures, and decrease costs per cancer detected, all at overall benefit to the patients, the hospitals, the payors and provide long-term benefits to society.

Summary of Relative Cancer Detection Rates (per 1,000 women) in Dense-Breast Supplemental Screening

Modality (X)	n (DM)	#Ca (DM)	n (+X)	#Ca (+X)	CDR (DM)	CDR (+X)	Ratio CDR(+X)/CDR(DM)	Ratio Norm CDR(+X)	ICDR (+X)	Incremental Norm CDR(+X)	# Studies
DM	1,180,489	4,734			4.0		1.00	4.0	0.0	4.0	21
+DBT	635,781	2,869	429,959	2,594	4.5	6.0	1.34	5.4	1.5	5.5	8
+UIS	484,267	1,582	484,267	2,716	3.3	5.6	1.72	6.9	2.3	6.3	4
+CEM	2,215	12	2,215	32	5.4	14.4	2.67	10.7	9.0	13.0	2
+MBI	11,239	36	11,239	125	3.2	11.1	3.47	13.9	7.9	11.9	7
+MRI	46,987	235	17,377	308	5.0	17.7	3.54	14.2	12.7	16.7	7

Results of multiple pairwise meta-analyses comparing various modalities (Digital Breast Tomosynthesis; Ultrasound; Contrast Enhanced Mammography; Molecular Breast Imaging; Magnetic Resonance Imaging) to Digital Mammography. “X” represents the second supplemental screening modality compared to DM. “+X” means the combination of DM+X. Two normalizations are compared: “CDR Ratio model” and “Incremental CDR model.”

Net Lives Saved by Ionizing Radiation Imaging Modalities per Age Decade

BENEFIT	40-49 yo	50-59 yo	60-69 yo	70-79 yo
DM	127	124	119	102
DBT	174	171	163	140
MBI	423	415	397	342
DM + MBI	474	466	446	384
RISK				
DM	10	5	2	1
DBT	12	6	3	1
MBI	82	73	58	37
DM + MBI	92	78	61	38
NET LIVES SAVED				
DM	117	119	117	101
DBT	162	165	160	139
MBI	341	342	339	305
DM + MBI	382	388	385	346

PO5-18-02

A Population-Based Analysis of the Impact of Omission of Anthracyclines in the Neoadjuvant Setting on the Risk of Mortality

Presenting Author(s) and Co-Author(s):

D. Giffoni M. M. Mata. London Regional Cancer Program, Western University, London, Ontario, Canada

R. Sutradhar. Institute for Clinical Evaluative Sciences, United States

M. Castelo. University of Toronto, United States

L. Nguyen. Institute for Clinical Evaluative Sciences, United States

D. Rodin. University Health Network - Princess Margaret Cancer Centre, United States

E. Hahn. Princess Margaret Cancer Centre, United States

O. Fatiregun. University of Toronto, United States

C. Fong. Institute for Clinical Evaluative Sciences, United States

S. Trebinjac. Sunnybrook Health Sciences Center, United States

A. Eisen. Sunnybrook Health Sciences Center, United States

L. Paszat. Institute for Clinical Evaluative Sciences, United States

K. Jerzak. Sunnybrook Health Sciences Centre, United States

E. Rakovitch. Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Background Most patients with high-risk non-metastatic breast cancer are treated with neoadjuvant chemotherapy (NAC), which includes the administration of anthracyclines. The omission of anthracyclines was shown to be associated with excellent outcomes in selected patients. However, the extent to which anthracyclines are omitted among a population of women treated with NAC and its impact on mortality remain unclear. **Objective** To investigate the extent to which anthracyclines are omitted among a population of patients with invasive breast cancer treated with NAC and to examine the impact of non-anthracycline NAC on risks of breast cancer-specific and all-cause mortality. **Methods** We performed a retrospective population-based cohort analysis using patient-level health administrative data. The cohort includes women aged ≥ 18 years with stage I – III invasive breast cancer diagnosed between January 2012 and December 2020, treated with NAC and surgery. Patients were excluded if they received $< 50\%$ of the planned chemotherapy regimen, had bilateral breast cancer and/or a previous malignancy. The exposure of interest was anthracycline versus non-anthracycline NAC regimen. The primary and secondary endpoints were breast cancer-specific mortality and overall (all-cause) mortality. Multivariable Cox proportional hazards models adjusted by propensity score, and clinical/pathologic variables including a measure of comorbidity was performed to examine impact of omission of anthracyclines on outcomes. Cumulative incidence curves were generated to calculate the 5-year cumulative incidence of breast cancer and all-cause mortality for the whole cohort and in subset analyses, stratified by stage and receptor subtype. **Results** The cohort includes 4,180 women. Median follow was 62 months (IQR 44-85) and median age was 51 years (IQR 43-60). Most patients had low co-morbidities (96.0%), Stage II (44.1%) or Stage III (47.7%) disease, underwent mastectomy (72.6%), had axillary node dissection (64.4%) and received post-operative radiotherapy (88.8%). 279 (6.7%) individuals were treated with a non-anthracycline NAC and 3,901 (93.3 %) received an anthracycline NAC. Women who received non-anthracycline NAC were older (median 62 years vs. 50 years; $p < 0.001$), more likely to have stage I-II disease (77.0% vs. 51.3%; $p < 0.001$), and

more likely to have triple-negative breast cancer (TNBC) (14.0% vs. 24.4%; $p < 0.001$) than those who received anthracyclines. On propensity adjusted multivariable analysis, factors associated with an increased risk of BC mortality include Stage III (HR 9.3, 95%CI 4.5 - 19.2, $p < 0.0001$) or stage II at presentation (HR 2.57 95% CI 1.24, 5.34, $p = .01$) (ref: stage I) or triple negative subtype (HR 3.7 95% CI 3.03, 4.51, $p < .0001$) (ref: hormone positive/HER2-). There was no significant difference in the relative risks of BC death (HR 0.8, 95% CI 0.5-1.27) or all-cause mortality (HR 0.85, 95% CI 0.60-1.21) for patients selected for treatment without anthracyclines compared to those treated with anthracyclines. Overall, among individuals selected for treatment without or with anthracycline NAC there was no significant difference in the 5-year cumulative incidence of BC (15.4% vs 10.5%, $P = .05$) or all-cause mortality (16.4% vs 11.9%, $P = .07$). However, the 5-year cumulative incidence of BC specific death (31.8% vs 16.5%, $p = .03$) and 5-year cumulative incidence of all-cause death (31.8% vs. 18.2%, $p = .06$) was higher among 420 women with HER2+ Stage III breast cancer who received non-anthracycline versus anthracycline-based chemotherapy. No difference was observed for other subgroups. Conclusions The omission of anthracyclines in NAC for individuals with stage III HER2+ breast cancer was associated with higher cumulative risks of breast cancer and all-cause mortality but no difference was observed for other subgroups. Further research is warranted to better understand in whom anthracyclines can be safely omitted.

PO5-18-03

A Randomized Controlled Trial to Evaluate the Safety and Efficacy of 1 cm versus 2 cm resection margins in Phyllodes Tumours of the Breast - An Exploratory Study

Presenting Author(s) and Co-Author(s):

V. Rajgopal. All India Institute of Medical Sciences, New Delhi India, United States

A. Dhar. AIIMS, New Delhi, New Delhi, Delhi, India

K. Kataria. Aiiims New Delhi, United States

P. Ranjan. AIIMS New Delhi, United States

A. SRIVASTAVA. Subharti Institute of Cancer Management and Research, MEERUT, Uttar Pradesh, India

Introduction Phyllodes tumors are rare fibroepithelial tumors constituting 0.3-1% of breast tumors. It presents as a rapidly growing breast lump, with a bosselated surface and overlying shiny stretched skin with dilated prominent veins. Diagnosis is made by mammography and ultrasonography and tissue diagnosis is made by core needle biopsy. The tumor is known for its propensity to grow rapidly within the mesenchymal elements of breast tissue, and to locally recur. Surgery with adequate margins of excision has been known to prevent local recurrence. Phyllodes tumors have inspired much debate among surgeons, regarding the extent of margins during resection. These margins have been defined clearly for carcinoma of the breast (no ink on tumor) but the same consensus has not been reached for Phyllodes tumor.

We carried out the world's first randomized trial to settle the debate to compare the effects of a 1cm margin with that of a 2 cm margin, aiming to arrive at a consensus on the appropriate surgical margin to prevent re-excision and recurrences. We also aimed to compare cosmetic outcomes both subjectively and objectively between the 2 arms. **Materials and Methods** We carried out a prospective exploratory randomized control trial on patients with suspected phyllodes tumors of the breast from July 2020 to January 2022. After establishing diagnosis, and obtaining informed consent, patients were randomized to either of the 2 arms, to undergo resection with a 1cm vs a 2 cm margin. Intraoperatively, the margin of the tumor was delineated by ultrasound for maximum accuracy. The incision made was deepened through the breast and pectoralis major muscle at a distance of exactly 1 cm or 2 cm from the tumor edge. The entire mass was excised en bloc with a 3 dimensional clearance from all sides. If the tumor was found infiltrating the underlying muscle (e.g Pectoralis major muscle, Serratus anterior), a full thickness section of the muscle was also excised with the specimen. The patients were followed up every 3 months with clinical examination and ultrasonography (followed by core needle biopsy for any suspicious mass), for a period of 12-18 months, to evaluate for recurrence. Cosmesis was evaluated by a 5-point Likert scale evaluated by the patient and the surgeon, and objectively using Breast Retraction Assessment and Nipple Deviation. **Results** We analysed the results of 41 patients who underwent surgery for Phyllodes tumor of the breast. All patients had negative margins after surgery. The mean margin distance (SD) in the 1 cm arm was 0.69 (0.20) cm and 1.83 (0.67) cm in the 2 cm arm. which was statistically significant between the groups. On the follow up ultrasound examination at 12 months, 1 patient (5.3%) was found to have a locoregional recurrence, but this was not statistically significant. There was no statistically significant difference in cosmesis between the arms. **Conclusions** We achieved our primary objective of histologically negative margins in all patients within both the groups. However, due to the limited number of patients recruited in the study, and due to the short duration of follow-up, we are not able to report significance in terms of recurrences between the 2 groups, to advocate for one over the other. The practice in our unit

has been the 2 cm margin, as it offers good oncological outcomes and is definitely safe. Given that cosmetic outcomes were comparable in both arms, one can be assured that a 2 cm margin does not offer worse cosmesis compared to a 1 cm margin. However, our study at this point in time, establishes non inferiority of a 1 cm margin. There have been no randomized control trials conducted in world literature to influence guidelines and clinical practice regarding the ideal margin resection for phyllodes tumor. Our study would be the first of its kind, and is a novel concept not yet conducted for phyllodes tumor. We will continue this trial for years to come, and hope to generate level I data, with increased patient enrolment and a longer duration of follow up.

PO5-18-04

Effect of Digoxin on clusters of circulating tumor cells in patients with metastatic breast cancer (DICCT)

Presenting Author(s) and Co-Author(s):

M. Vetter. Cancer Center Baselland, Liestal, Basel-Landschaft, Switzerland

B. Ngyuen-Sträuli. Department of Gynecology, University Hospital Zurich, University of Zurich, United States

I. Krol. Department of Biology, Institute of Molecular Health Sciences, Swiss Federal Institute of Technology (ETH) Zurich, United States

A. Ring. Department of Medical Oncology and Hematology, University Hospital Zurich, University of Zurich, United States

A. Kohler. Center of Oncology and Hematology, Medical University Clinic, Kantonsspital Baselland, United States

F. Castro-Giner. Department of Biology, Institute of Molecular Health Sciences, Swiss Federal Institute of Technology (ETH) Zurich, United States

M. Vogel. Department of Gynecology and Gynecologic Oncology, University Hospital Basel, University of Basel, United States

C. Grasic Kuhar. Institute of Oncology Ljubljana, Ljubljana, Slovenia

F. Schwab. Department of Gynecology and Gynecologic Oncology, University Hospital Basel, University of Basel, United States

V. Heinzelmann-Schwarz. Department of Gynecology and Gynecologic Oncology, University Hospital Basel, University of Basel, United States

G. Kuster Pfister. Department of Cardiology, University Hospital Basel, University of Basel, United States

W. Weber. Breast Center, University Hospital of Basel, Basel-Stadt, Switzerland

C. Kurzeder. Breast Center, University Hospital of Basel, Basel, Switzerland, Basel-Stadt, Switzerland

N. Aceto. Department of Biology, Institute of Molecular Health Sciences, Swiss Federal Institute of Technology (ETH) Zurich, United States

Authors: Marcus Vetter^{1,*}, Bich Doan Nguyen-Sträuli^{2,3,*}, Ilona Krol^{3,*}, Alexander Ring^{3,4,*}, Angela Kohler⁵, Francesc Castro-Giner³, Maren Vogel⁶, Cvetka Grašič Kuhar⁶, Fabienne Schwab⁶, Viola Heinzelmann-Schwarz⁶, Gabriela Kuster Pfister⁷, Walter Paul Weber⁸, Christian Kurzeder^{6,#}, Nicola Aceto^{3,#}

* Co-first authors

Co-last authors

Background: The presence of circulating tumor cell (CTC) clusters is associated with tumor progression and with a bad prognosis in various cancer types^{1,2}. In breast cancer, a pre-clinical model demonstrated that Na/K-ATPase inhibitors such as digoxin could dissolve CTC clusters and reduce metastasis³. DICCT is a single-arm, therapeutic exploratory phase I study aimed to examine whether digoxin can disrupt CTC clusters in metastatic breast cancer patients (NCT03928210).

Material and methods: Metastatic breast cancer patients in whom clusters of CTCs have been detected were eligible. Patients with concomitant heart disease were excluded. After progressive disease in any line of therapy, a window of opportunity before initiation of subsequent systemic therapy was used to administer digoxin treatment for seven (7) days. For CTC detection, blood samples were processed with the FDA-cleared Parsortix system (ANGLE plc, UK). Captured CTCs were stained for EPCAM, HER2, EGFR (positive CTC selection) and CD45 (exclusion marker). To gain insight into the cluster-dissolution ability of digoxin, the primary endpoint was size of CTC clusters (i.e. number of cells within each cluster) under digoxin therapy. The cumulative effect of digoxin treatment on the primary endpoint was assessed by a linear regression model.

Results: Nine (9) patients with CTC clusters detected at baseline were enrolled. A target level of digoxin above 0.7 ng/ml could be confirmed at day 7 for all patients. For quantitative and qualitative analysis of CTC clusters, 5.5 to 27 ml of blood were analyzed at baseline, at day 0 pre-treatment, and post 2 hours, 3 days and 7 days of digoxin treatment. The average cluster size ranged between 2 and 11.8 cells (median 2.9) considering all samples from all patients. Digoxin treatment reduced cluster size in 8 patients (88.9%) to different extents, and the proportion of CTC cluster over single CTCs was also reduced in 6 patients (66.7%). The effect of digoxin was evident in both homotypic (cancer cells only) and heterotypic (aggregates of CTCs and white blood cells) clusters. The treatment was well tolerated, and no adverse events related to the study treatment occurred. All patients completed the treatment according to the protocol.

Conclusion: DICCT provides the first-in-human proof-of-principle that digoxin induces a partial dissolution of CTC clusters in patients with metastatic breast cancer at drug levels that are safe and well tolerated. Conceptualization of follow-up trials including Na/K-ATPase inhibitors and patient outcome endpoints are underway.

References:

1. Ring A, Nguyen-Strauli BD, Wicki A, Aceto N. Biology, vulnerabilities and clinical applications of circulating tumour cells. *Nat Rev Cancer* 2022;1-17. DOI: 10.1038/s41568-022-00536-4.
2. Schuster E, Taftaf R, Reduzzi C, Albert MK, Romero-Calvo I, Liu H. Better together: circulating tumor cell clustering in metastatic cancer. *Trends Cancer* 2021;7(11):1020-1032. DOI: 10.1016/j.trecan.2021.07.001.
3. Gkountela S, Castro-Giner F, Szczerba BM, et al. Circulating Tumor Cell Clustering Shapes DNA Methylation to Enable Metastasis Seeding. *Cell* 2019;176(1-2):98-112 e14. DOI: 10.1016/j.cell.2018.11.046.

PO5-18-05

Assessment of the Potential of Photon mini-GRID Therapy for Pre-operative Partial Breast Cancer Treatment

Presenting Author(s) and Co-Author(s):

A. Corvino. Institute Curie, Université Paris-Saclay, Orsay, France

T. Schneider. Université Paris-Saclay, United States

J. Vu-Bezin. Institut Gustave Roussy, United States

Y. Kirova. Institut Curie, Paris, Ile-de-France, France

Y. Prezado. Institute Curie, United States

Purpose

We propose a new spatially fractionated radiation therapy (SFRT) technique, called mini-GRID therapy, to reduce normal tissue toxicities in pre-operative partial breast cancer radiotherapy. Mini-GRID therapy, an optimized implementation of GRID therapy, utilizes very narrow beams (widths ~ 1-2 mm) which significantly increase normal tissue tolerances. The concept, proposed by our team in 2017 [1], has been successfully implemented at Hospital de Santiago de Compostela (Spain) showing excellent results in terms of brain toxicity reduction [2]. Profiting from this remarkable increase in tolerance, this study aims to evaluate the feasibility and efficacy of photon mini-GRID therapy for pre-operative partial breast cancer treatment.

Methods

Ten unbiased clinical cases were selected for the study, comparing photon mini-GRID therapy with conventional broad beam radiotherapy. Monte Carlo simulations (TOPAS v.3.6) were performed based on the mini-GRID therapy implementation (megavoltage X-rays, Varian flattening-filter-free LINAC) realized at the University Hospital in Santiago de Compostela. A mean dose of 24 Gy was delivered in the PTV using three photon mini-GRID arrays with mini beams of approximately 1.8x1.8 mm² at the isocenter. The study aimed to achieve better tumor coverage than conventional pre-operative radiotherapy while ensuring comparable skin toxicity. Valley doses, determining tissue-sparing effects, were compared against organs-at-risk (OARs) tolerance limits.

Results

The mini-GRID therapy treatments ensured partial tumor coverage and met the dose tolerance limits for all the considered OARs, the most challenging of all being the skin [3]. Peak-to-valley dose ratio (PVDR) in the skin was higher than 3.5 for all the considered patients. Compared to standard radiotherapy (SRT) plans, mini-GRID therapy significantly reduced mean doses to the lungs, heart, and chest wall in the studied cases.

Conclusion

In this proof-of-concept study, we evaluated photon mini-GRID therapy with megavoltage X-rays as an alternative treatment approach for pre-operative partial breast cancer irradiation, demonstrating its feasibility and straightforward implementation. Because of its high skin and normal tissue-sparing capacities, photon mini-GRID therapy has great potential to improve pre-operative treatment outcomes. Complementary studies and clinical validation are needed to fully establish the optimal protocols and assess long-term effects, but the results encourage the integration of photon mini-GRID therapy as a promising modality for breast cancer therapy.

References

[1] Martínez-Rovira I et al., Dose evaluation of Grid Therapy using a 6 MV flattening filter-free (FFF) photon beam: A Monte Carlo study. *Med Phys*, 2017.

[2] Sanchez-Garcia M et al., Implementation and dosimetry of an optimized spatially fractionated radiation therapy technique at a clinical medical accelerator. *Physica Medica: European Journal of Medical Physics*, 2022.

[3] QUANTEC 2010, Quantitative analyses of normal tissue effects in the clinic *Int. J. Radiat. Oncol. Biol. Phys.* 76 S1–160.

PO5-18-06

On-going phase 1A clinical trial of A01, a chimerized monoclonal antibody to Progranulin/Glycoprotein 88 (GP88) in patients with advanced malignancy.

Presenting Author(s) and Co-Author(s):

K. Tkaczuk. University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA, United States

P. Rosenblatt. University of Maryland School of Medicine, United States

R. Mehra. University of Maryland School of Medicine, Baltimore, Maryland, United States

K. Scilla. University of Maryland School of Medicine, Baltimore, Maryland, United States

N. Tait. University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, Maryland, United States

B. Yue. A&G Pharmaceutical, Columbia, Maryland, United States

G. Serrero. A&G Pharmaceutical Inc, Columbia, Maryland, United States

Progranulin (PGRN/GP88) is an 88 kDa glycoprotein characterized by seven and a half double cysteine rich repeats which is the largest member of the granulin-epithelin protein family. PGRN/GP88 has been demonstrated as a biological driver of tumorigenesis, survival, and drug resistance in several cancers including breast cancer (BC), lung prostate, ovarian and digestive cancers. PGRN/GP88 tissue expression is an independent prognostic factor of recurrence in breast, lung cancers while elevated serum PGRN/GP88 level in metastatic breast, lung, ovarian and prostate cancer patients. Elevated PGRN/GP88 levels are associated with poor outcomes such as progression and shortened survival. An anti-human PGRN/GP88 monoclonal antibody able to inhibit the the in vitro and in vivo action of human PGRN/GP88 has been developed, chimerized and expressed in CHO cells. All IND enabling activities including pharmacology, GMP manufacturing, formulation and GLP toxicology studies have been conducted. The IND application has been filed and cleared by the Food and Drug Administration. A first-in-human, first-in-class phase 1 safety and efficacy clinical study of AG01 in patients with solid tumors and advanced disease with special focus on patients with breast, lung and ovarian cancers has been initiated and is on-going at the University of Maryland Greenebaum Cancer Center. The trial is registered as NCT05627960 to clinicaltrials.gov site. The presentation will provide an update on the number of patients enrolled in this on-going phase 1A trial.

Supported by grants R44CA162629 and R44CA224718 from the National Cancer Institute to GS.

PO5-18-07

A Humanized Monoclonal Antibody to Secreted Frizzled-Related Protein 2 Inhibits TNBC Lung Metastases

Presenting Author(s) and Co-Author(s):

L. Hsu. MUSC, United States

P. Nasarre. Medical University of South Carolina, United States

J. Siegel. Medical University of South Carolina, United States

E. Hilliard. Medical University of South Carolina, United States

R. Mukherjee. Medical University of South Carolina, United States

N. Klauber-Demore. Medical University of South Carolina, United States

Introduction: A promising novel target for breast cancer is secreted frizzled-related protein 2 (SFRP2). SFRP2 protects tumors against apoptosis, promotes T-cell exhaustion, and induces angiogenesis. SFRP2 is expressed in breast cancer but has not been specifically evaluated in triple negative breast cancer. We previously developed a humanized monoclonal antibody to SFRP2, (hSFRP2 mAb) that inhibits primary breast cancer growth in mice without toxicity. The purpose of this study is to establish the presence of SFRP2 in human TNBC, evaluate the efficacy of hSFRP2 mAb in metastatic TNBC in vivo, and in a cell line resistant to chemotherapy.

Methods: Immunohistochemistry (IHC) with SFRP2 antibody on a human TNBC tissue microarray (TMA) containing 88 FFPE cores. After IHC with primary antibody to SFRP2, the TMA was scanned and staining intensity was quantified using spatial analysis. Results for SFRP2 staining were analyzed as previously described for analyses of estrogen and progesterone receptor positivity; categories are: 0-absence of staining; low positive (0-10%), and positive >10%. Development of a doxorubicin (dox)-resistant cell line and induction of apoptosis with hSFRP2 mAb. MDA-MB-231 cells were treated with 4nM dox and increased 2nM at a time until the cells were resistant to 10µM dox after 12 months. WT and dox-resistant cells were treated for 4 hours with either hSFRP2 mAb (10uM,) or IgG control (10uM) (n=6). Apoptosis was detected with Promokine Apoptosis/Necrosis/Healthy cells kit. Cells were imaged using the EVOS FLc and counted using Imagej software. Differences between treated and control were compared with two-tailed T-test. hSFRP2 mAb treatment of mice with metastatic TNBC. PY8119 and E0771 TNBC murine cells ($5 \times 10^5/100 \mu\text{L}$) were injected iv into 6–8-week-old C57BL/6 female mice. The next day the mice were treated with IgG1 control 8 mg/kg iv or hSFRP2 mAb 8 mg/kg iv every 3 days. After four weeks, the lungs were resected, and surface metastases were counted. Differences between treated and control were compared with Poisson distributions. FFPE sections of lungs were stained with ApopTag kit. Three metastases per lung were counted at 20 X, and the difference between IgG1 and hSFRP2 mAb groups compared with two-tailed T-test.

Results: SFRP2 protein is present in human TNBC. Out of 88 cores, 83 cores (94%) were positive, 4 cores (4.5%) were minimally positive, and 1 core (1.1%) was negative for SFRP2. Development of a doxorubicin (dox)-resistant cell line and induction of apoptosis with hSFRP2 mAb treatment in vitro. The number of apoptotic cells in IgG1 control-treated MDA-MB-231 cells was 11.5 ± 3.7 , and 76.6 ± 5.0 for hSFRP2 mAb-treated tumors ($p < 0.001$, $n=9$). The mean number of apoptotic MDA-MB-231 dox-resistant cells in IgG1 control was 16.7 ± 6.0 , and 68.4 ± 6.4 for hSFRP2 mAb-treated tumors, ($p < 0.001$, $n=9$). hSFRP2 mAb inhibits the growth of metastatic TNBC in vivo and increases apoptosis. For E0771, the number of surface metastases was 8.9 ± 2.8 in the IgG1 control group and 4.9 ± 1.1 in the hSFRP2 mAb treated

group ($p < 0.05$, $n=15$). The number of apoptotic cells/ HPF was 9.8 ± 1.8 for the IgG1 control group and 21.0 ± 4.6 for the hSFRP2 mAb group ($n=15$, $p < .01$). For Py8119 tumors there were 6.4 ± 1.0 metastases in the IgG1 control group and 3.6 ± 0.9 in the hSFRP2 mAb group ($p < 0.05$, $n=11$). The number of apoptotic cells/HPF was 6 ± 1.8 for the IgG1 control group and 14 ± 1.3 for the hSFRP2 mAb group ($n=10$, $p < 0.001$).

Conclusions: SFRP2 protein is abundantly expressed in human TNBC. A humanized monoclonal antibody to SFRP2 reduces TNBC lung metastases growth in two in vivo models and increases tumor apoptosis. TNBC resistant to doxorubicin remains sensitive to apoptosis induced by the hSFRP2 mAb.

PO5-18-09

Anthracycline-free neoadjuvant therapy with nab-paclitaxel and carboplatin in non-luminal breast cancer: a single-arm phase II trial

Presenting Author(s) and Co-Author(s):

D. Liu. Department of Breast and Thyroid Surgery, Shanghai General Hospital, Shanghai JiaoTong University School of Medicine, United States

L. Zhu. Department of Breast and Thyroid Surgery, Shanghai General Hospital, Shanghai JiaoTong University School of Medicine, United States

J. Wu. Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, United States

W. Wang. Shanghai General Hospital, United States

S. Ding. Shanghai General Hospital, United States

Background

Anthracycline and taxane-based chemotherapy are the corner stone of neoadjuvant therapy in early breast cancer. Anthracycline-free regimens have been addressed widely because of cardiac toxicity especially in HER2-positive breast cancer when combining trastuzumab and pertuzumab. Aim of this trial was to assess the efficacy and safety of nab-paclitaxel combined with carboplatin in the neoadjuvant therapy of non-luminal breast cancer.

Methods

The Neopath trial was a prospective, single-arm phase II trial conducted in Comprehensive Breast Health Center, Ruijin Hospital between April 2019 and October 2021. Patients who had cT2-4NanyM0 or cTanyN1-3M0 triple negative breast cancer (TNBC) or HER2-positive breast cancer were enrolled. Patients were treated with neoadjuvant nab-paclitaxel (100 mg/m²) and carboplatin (area under the curve 2) on days 1, 8, and 15, for four 4-week cycles. Concurrent trastuzumab at 2 mg/kg (loading dose 4 mg/kg) and pertuzumab 420 mg (loading dose 840 mg) were given in patients with HER2-positive tumors. Surgery was performed after 4-6 cycles of neoadjuvant therapy. Trastuzumab and pertuzumab after surgery was continued every 3 weeks for a total duration of 1 year. The primary endpoint was pathological complete response (pCR) rate, defined as no invasive tumor in breast and axillary lymph nodes (ypT0/Tis N0) after neoadjuvant therapy. Secondary endpoints were pCR rate in predefined subgroups, pCR (ypT0 N0), objective response rate (ORR); event-free survival (EFS), breast conservation rate and toxicity.

Results

A total of 106 patients were enrolled in the study and 99 of them proceeded to surgery. The pCR (ypT0/is N0) rate was 41.41% in total, 33.78% in TNBC and 64.00% in HER2-positive breast cancer. Proportion of patients achieving pCR (ypT0 N0) was 38.38% in total, 31.08% in TNBC and 60.00% in HER2-positive tumors. In the ITT population, 93 patients were event-free at a median follow-up of 24 months, while 5 in TNBC group and 1 in HER2-positive group had relapse or distant metastasis. EFS in patients achieving pCR was higher than patients without pCR (HR=7.328, 95%CI=1.453-36.96, p=0.0158). ORR was 72.49% in total, 67.12% in TNBC and 88.00% in HER2-positive breast cancer. Total breast conservation rate was 10.1% and 12.2% in TNBC, 4.0% in HER2-positive subgroup. The most frequent grade 3 or higher adverse events were neutropenia (57%), vomiting (11%) and thrombocytopenia (8%).

Conclusion

Neoadjuvant anthracycline-free regimen of nab-paclitaxel combined with carboplatin in non-luminal breast cancer was an effective and well-tolerated regimen.

PO5-18-10

Omission of SLNB in triple-negative and HER2-positive breast cancer patients with radiologic and pathologic complete response in the breast after NAST: a single-arm, prospective surgical trial (EUBREAST-01 trial, GBG 104)

Presenting Author(s) and Co-Author(s):

- T. Reimer. Breast Center, University of Rostock, Rostock, Germany
- B. Gerber. Universitätsfrauenklinik am Klinikum Südstadt Rostock, United States
- T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany
- N. Bangemann. Breast Center, United States
- A. Kleine-Tebbe. Breast Center, United States
- A. Stefek. Johanniter-Krankenhaus Genthin-Stendal, Germany, United States
- U. Doerste. Albertinen-KH Hamburg, Germany
- C. Hammerle. Breast Center, United States
- O. Hoffmann. University Hospital Essen, Germany
- A. Hein. Klinikum Esslingen, Germany
- I. Rubio. Clínica Universidad de Navarra, Madrid, Spain, United States
- F. Peintinger. Univ.Prof. Priv.Doiz. Dr. Florentia Peintinger, Austria
- K. Mehta. German Breast Group, Germany
- S. Loibl. German Breast Group, Germany
- E. Botteri. Cancer Registry Norway, United States
- O. Gentilini. San Raffaele Hospital Milan, Italy

Background: Currently, axillary surgery for breast cancer is considered a staging procedure that does not seem to influence breast cancer mortality since the risk of developing metastasis depends mainly on the biological behavior of the primary (seed-and-soil model). Based on this, postsurgical therapy should be considered based on biological tumor characteristics. Retrospective data of cancer registry trials showed a strong correlation between breast pathologic complete response (pCR) and nodal pCR depending on intrinsic subtypes. Improvements in systemic treatments for breast cancer have increased the rates of pCR in patients receiving neoadjuvant systemic therapy (NAST), offering the opportunity to decrease, and perhaps eliminate, surgery in patients who have a pCR. Trial design: The EUBREAST network designed a clinical trial (NCT04101851) in which only patients with the highest likelihood of having a pCR after NAST (triple-negative or HER2-positive breast cancer) will be included, and type of surgery will be defined according to the response to NAST rather than on the classical T and N status at presentation. In the ongoing trial, axillary surgery will be eliminated (no axillary sentinel lymph node biopsy [SLNB]) for initially clinical node-negative (cN0) patients with radiologic complete remission (rCR) and a breast pCR (ypT0/ypTis) as determined in the lumpectomy specimen. The trial design is a multicenter single-arm study with a limited number of patients (N=440 as the screening population with an expected 80% pCR-rate) which might give practice-changing results in a short period, sparing the time and the costs of a randomized comparison. Patients will be recruited in European countries (Austria, Germany, Italy, and Spain) over 48 months. Inclusion criteria: -Written informed consent - Histologically confirmed unilateral primary invasive carcinoma of the breast (core biopsy). Multifocal or multicentric tumors are allowed if breast-conserving surgery (BCS) is planned. -

Age at diagnosis at least 18 years -imaging techniques with estimated tumor stage between cT1-T3 before NAST -triple-negative (TNBC) or HER2-positive invasive breast cancer -TNBC is defined by: ER-negative (< 10% positive cells in IHC) and PgR-negative (< 10% positive cells in IHC), HER2-negative -clinically and sonographically tumor-free axilla before core biopsy (cN0/iN0) -in cases with cN0 and iN+, a negative core biopsy or fine-needle aspiration biopsy of the sonographically suspected lymph node is required -no evidence for distant metastasis (M0) -standard NAST with rCR -planned BCS with postoperative external whole-breast irradiation (conventional fractionation or hypofractionation) Primary objective: 3-year rate of axillary recurrence-free survival (ARFS) after BCS Statistics: The calculated total case number for per-protocol analysis is N=350, and the expected total number of screened patients is N=440. The assumption for acceptable 3-year ARFS $\geq 98.5\%$ in the experimental arm is based on previous study findings. Timelines: -First patient in: January 2021 -Last patient in: December 2024 - Primary outcome analysis: Q1/2027 Current accrual: In June 2023, 255 patients were recruited; the majority of them in Germany. Contact: Prof. Dr. Toralf Reimer (eubreast-01@kliniksued-rostock.de), study chair Dr. Oreste D. Gentilini (gentilini.oreste@hsr.it), study co-chair Funding by Else Kroener-Fresenius Foundation, German Society of Senology, University of Rostock (Germany), and San Raffaele Hospital (Milan, Italy).

PO5-18-11

Use of DiviTum®TKa as a biomarker assay for CDK4/6 inhibitor medication compliance and drug-drug interaction assessment in ER/PR positive metastatic breast cancer

Presenting Author(s) and Co-Author(s):

M. Rozenblit. Yale Cancer Center, New Haven, Connecticut, United States

A. Kahn. Yale Cancer Center, Yale University, United States

G. Gong. Yale University, United States

A. Williams. Biovica International AB, United States

L. puszta. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

Background: CDK4/6 inhibitor (CDK4/6i) with endocrine therapy (ET) is standard first line (1L) treatment for metastatic hormone positive (ER/PR+) HER2- negative breast cancer (mBC). Some patients have progression free survival (PFS) of 2 years or more whereas some patients have very short PFS on these medications. Thymidine kinase is a biomarker that reflects cell proliferation. DiviTum®TKa is an assay that was cleared by the FDA in July 2022 based on data that showed that thymidine kinase activity (TKa) value of < 250 DiviTum units (DuA) is associated with the decreased likelihood of disease progression within 30 days or 60 days post testing. The purpose of this study is to assess the use of TKa as a biomarker for identifying potential medical compliance issues and drug-drug interactions (DDI) in patients on CDK4/6i and to evaluate whether counseling and optimization of concurrent medications will lead to lower TKa levels in subsequent treatment cycles and possibly longer PFS. Trial design: This is a pilot study to assess whether TKa can serve as a biomarker to identify patients with a suboptimal reduction in tumor cell proliferation caused by a potential CDK4/6i compliance or DDI issue. We will also assess whether correction of the issue can improve suppression of TKa levels in ER/PR+ mBC patients on 1L CDK4/6i and ET. For screening, we are utilizing a novel automated real-time data driven cohort identification system designed by Dr. Guannan Gong at Yale. Patients will be treated and monitored as per standard of care. An aliquot of serum obtained during routine blood draws will be sent to a CLIA-certified Biovica lab for TKa testing. TKa results will be returned in real time. Patients with a detectable TKa baseline level (above 145 DuA), followed by a sustained TKa level (>145 DuA) at cycle 1 D15 and D28 will be assessed for medication compliance and DDI. TKa levels will be repeated at subsequent standard of care blood draws to assess if the intervention affected TKa levels. Patients will be followed for 2 years. Eligibility criteria: Participants must have ER+ mBC and starting 1L CDK4/6i + ET and be previously CDK4/6i -naïve. Specific aims: Primary objective: to estimate the rate of improvement in CDK4/6i response (change in TKa levels) after counseling for medication compliance and adjustment of potential deleterious DDIs. Secondary objectives: 1) estimate the rate of sub-optimal CDK 4/6i response in cycle 1 of treatment. 2) Compare clinical benefit rate (CBR) in patients with sub-optimal and optimal CDK4/6i response after both cycles 1 and cycle 3. 3) Compare PFS in patients with sub-optimal and optimal CDK 4/6i response after both cycles 1 and cycle 3. 4) Assess CDK4/6i response via TKa levels upon CDK4/6i dose reductions or changes in CDK4/6i regimens. 5) Compare CDK4/6i response profiles across the three CDK 4/6i among different patients and within the same patients if CDK4/6i is changed throughout treatment course. 6) Correlate TKa levels with tumor marker levels. 7) Assess plasma concentrations of CDK4/6i in patients with suboptimal TKa levels. Statistical methods: For binary endpoints measured at a given time point, we will estimate the two-sided 95% exact CI using Clopper-Pearson method. With a sample size of 120 patients, assuming 20% drop out rate, we predict that about 15% of patients will have suboptimal CDK4/6i response, estimating a 95% CI of 0.086-0.235 in the first cycle. Comparisons between paired outcomes will be

completed using the paired t-test or Wilcoxon signed-rank test for continuous parameters of interest, or McNemar's Chi-square test for categorical parameters of interest. Time to event endpoints will be estimated using Kaplan-Meier method. Present accrual and target accrual: This trial has just been activated. Target accrual is 120 patients. Contact information for people with a specific interest in the trial: Mariya.Rozenblit@yale.edu

PO5-18-12

Can we cure de novo oligometastatic stage IV HER2+ breast cancer with multimodality therapy? (CHLOE)

Presenting Author(s) and Co-Author(s):

M. Rozenblit. Yale Cancer Center, New Haven, Connecticut, United States

N. Wiesendanger. Yale University, United States

K. Shanahan. Metavivor Research and Support, United States

C. Hodgdon. GRASP - Guiding Researchers & Advocates To Scientific Partnerships, Baltimore, Maryland, United States

P. Gershkovich. Yale University, United States

M. Golshan. Yale School of medicine, Yale cancer center, United States

M. Moran. Yale, United States

m. lustberg. Yale Cancer Center, New Haven, Connecticut, United States

L. pusztai. Yale School of Medicine, Cancer Center, New Haven, Connecticut, United States

Background: The current standard of care is to treat all patients with metastatic breast cancer with palliative intent, regardless of extent of disease. However, in real world practice patients with oligometastatic disease are sometimes treated with surgery and/or radiation/ablation in combination with systemic therapy to render them as having no evidence of disease. Previous randomized clinical trials have not shown a benefit to adding surgery or radiation in metastatic breast cancer, however, these trials had a small number of HER2+ patients. HER2+ patients are uniquely responsive to combination of chemotherapy and targeted HER2 therapy and therefore may have different outcomes with a multimodality approach. The goal of this project is to use a novel, user friendly, on-line clinical study platform that registers patients and enables follow-up data collection to test the hypothesis that de novo stage IV oligometastatic HER2+ patients treated with multimodality therapy may result in improved long-term distant metastasis free survival and overall survival.

Trial design: This is a prospective, nationwide registry study that will enroll newly diagnosed (de novo) oligometastatic (operationally defined by local tumor boards as disease where all metastatic lesions can be ablated) HER2+ breast cancer. A secure online portal has been created by the Yale IT team in accordance with HIPPA and cybersecurity guidelines. Data will be directly entered into the online portal by participating investigators and information regarding what treatment the patient received, if they completed treatment, and survival data will be collected. All treatment decisions will be at the discretion of the treating provider.

Eligibility criteria: Patients with de novo oligometastatic HER2+ breast cancer in whom local treatment of all metastatic sites by either surgery, radiation, or ablative techniques is feasible as determined by multidisciplinary discussion or local tumor board.

Specific aims: Primary: To estimate the 3 year distant metastasis free survival in patients with de novo oligometastatic HER2+ breast cancer treated with a multi-modality treatment plan. Secondary: To estimate 3 year overall survival and to monitor QOL.

Statistical methods: The major analysis will occur after at least 3 years following the last subject's enrollment in a cohort, to ensure that the objective of distant metastasis free survival

at 3 years will be analyzed. It will include: tabulation of all cases entered, number and location of metastases, if treatment plan was implemented, compliance rate of treatment delivery, observed results with respect to the primary endpoint. Kaplan-Meier estimates will be presented for the analysis of survival endpoints together with a summary of associated statistics (median survival time if reached, landmark survival rate estimates and estimates for every 6 months thereafter if applicable), including the corresponding two-sided 95% confidence intervals. The 95% exact Clopper Pearson confidence intervals will be presented for binary endpoints. Paired t-test or Wilcoxon signed rank test will be used to assess the difference of continuous variables measured at different time points. The secondary clinical outcome is overall survival at 3 years, defined as the percentage of patients without an event at the 3-year follow-up time point measured from the study registration date. An event is considered death from any cause. OS time will be measured from the date of randomization to the date of first OS failure or last follow-up. OS will be estimated by the Kaplan-Meier method with OS failure defined as: death from any cause.

Present accrual and target accrual: 4/42 patients

Contact information for people with a specific interest in the trial: Mariya.Rozenblit@yale.edu
<https://chloe.yalepathways.org>

PO5-19-01

The HER2-RADiCAL study (Response ADaptive CAre pLan) – Tailoring treatment for HER2 positive early breast cancer

Presenting Author(s) and Co-Author(s):

- I. Macpherson. University of Glasgow - Institute of Cancer Sciences, United Kingdom
- S. McIntosh. Queen's University Belfast, United States
- L. Kilburn. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom
- H. Tovey. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom
- L. Moretti. Clinical Trials & Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom
- K. Goddard. The Institute of Cancer Research, United Kingdom
- I. Bhattacharya. Cambridge University Hospitals NHS Foundation Trust, United States
- C. Boyd. Belfast Health & Social Care Trust, United States
- C. Kirwan. The University of Manchester, United States
- C. O'Brien. The Christie NHS Foundation Trust, Manchester, UK, Manchester, United Kingdom
- D. Wheatley. Royal Cornwall Hospitals NHS Trust, Truro, England, United States
- J. Glendenning. Kent Oncology Centre, East Kent, Canterbury, England, United Kingdom
- M. MacKenzie. Independent Cancer Patients' Voice, United States
- H. Stobart. Independent Cancer Patients' Voice, United States
- C. Snowdon. Clinical Trials & Statistics Unit, The Institute of Cancer Research, London, United Kingdom, United States
- A. Wardley. Outreach Research & Innovation Group Ltd, Manchester, England, United Kingdom
- A. Shaaban. Queen Elizabeth Hospital, Birmingham, United States
- P. Hall. University of Edinburgh, Edinburgh, United Kingdom
- D. Cameron. The University of Edinburgh, Edinburgh Cancer Research, EDINBURGH, Scotland, United Kingdom
- J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

Background The presence or absence of residual disease following neoadjuvant systemic anti-cancer therapy (neoSACT) for HER2-positive early breast cancer (HER2+ EBC) provides powerful prognostic information. Pathological complete response (pCR) following neoSACT, particularly in patients with earlier clinical TNM stage at diagnosis, identifies a population with excellent survival outcomes in whom the balance of toxicity associated with the current treatment pathway may be disproportionate to absolute clinical benefit. Aims >HER2-RADiCAL seeks to reduce the treatment burden and healthcare costs of treating HER2+ EBC by testing the hypothesis that pCR can be used as a functional response biomarker to select patients who can safely receive less systemic therapy with minimal/no loss of efficacy. Trial design and eligibility criteria HER2-RADiCAL is a response-directed interventional cohort/threshold-crossing design study embedded within a real-world data-driven clinical pathway model.

Patients with ER-positive or negative HER2+ EBC with cT1N1 or cT2N0-1 stage at diagnosis are eligible after completion of standard of care neoSACT and locally determined pCR (ypT0/Tis ypN0). Patients with pathological features consistent with previous malignant involvement in >4 nodes are not eligible. Adjuvant trastuzumab +/- pertuzumab may have continued prior to study entry provided no more than 9 cycles of trastuzumab are received. After registration all participants receive a total of 9 cycles of trastuzumab including those administered prior to study entry. Participants receive no further pertuzumab and no adjuvant chemotherapy. Adjuvant endocrine therapy and radiotherapy are given as per standard of care. Central pathology review of pCR status will be conducted in a subset of cases. A Study Within a Trial (SWAT) will explore identification of factors influencing patient decision-making for participation in studies of response-adapted treatment. Statistical methods The primary endpoint is relapse-free interval. Recruitment of 720 participants over 3.5 years will provide 90% power to exclude an event rate >6.5% at 3 years (expected event rate ≤4%). Secondary endpoints include relapse-free survival, invasive breast cancer-free survival, invasive disease-free survival, distant recurrence-free interval, breast cancer-free interval, overall survival, treatment pathway adherence and cost-effectiveness. An interventional cohort is preferred to a randomised non-inferiority trial based on the known event rate in this population which is sufficiently low such that any deviation from this expected event rate would indicate failure of the reduced therapy strategy. Real-world data driven clinical pathway model Health economic modelling will compare the protocol-driven study cohort with two comparator pathways: a non-response adapted maximum therapy pathway (the standard clinical pathway prior to the study) and a real-world representative pathway derived from anonymised data for all patients treated for HER2+ EBC within the UK NHS. Patient and public involvement Our PPI partners continue to shape this research, holding key roles as trial management group members, overseeing progress of the study, contributing to protocol amendment development, and design and implementation of the SWAT. Current status The first patient was enrolled in December 2021. At 10th July 2023, 25 research sites have opened with 39 participants recruited. Site opening continues with a minimum target of 40. Responding to continued use of anthracycline-based regimens in UK practice, eligibility criteria have recently been extended to permit entry of patients who have received anthracycline-containing neoSACT. For further information contact her2radical-icrctsu@icr.ac.uk.

PO5-19-02

I-PREPARE: International Prospective REgistry on Pre-pectorAl breast Reconstruction (EUBREAST 11R-NCT 05817175)

Presenting Author(s) and Co-Author(s):

R. Di Micco. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), Italy

M. Banyś-Paluchowski. Department of Obstetrics and Gynecology, Asklepios Hospital Barmbek, Hamburg, Germany

M. Cardoso. Breast Unit, Champalimaud Research and Clinical Centre, Champalimaud Foundation (Lisbon, Portugal); Faculdade de Medicina da Universidade de Lisboa (Lisbon, Portugal), United States

J. de Boniface. Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, and Department of Surgery, Capio St. Göran's Hospital, Stockholm, Stockholms Lan, Sweden

B. Gulluoglu. Marmara University School of Medicine, Department of Surgery, Istanbul, Turkey

O. Kaidar-Person. Breast Cancer Radiation Therapy Unit, Sheba Medical Center (Ramat Gan, Israel); Sackler School of Medicine, Tel-Aviv University (Tel-Aviv, Israel), United States

T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany

M. Nava. Breast unit, Valduce Hospital, Como, Italy; G.Re.T.A. Foundation, Milan, Italy, United States

P. Poortmans. Department of Radiation Oncology, Iridium Netwerk and University of Antwerp, Belgium, United States

S. Potter. Bristol Medical School, United States

N. Rotmensz. Breast Surgery Unit, San Raffaele University and Research Hospital (Milan, Italy), United States

T. Spanic. Europa Donna Slovenia, Slovenia

M. Thill. Agaplesion Markus Krankenhaus, 60431 Frankfurt a.M., Hessen, Germany

L. Travado. Champalimaud Clinical & Research Center, Champalimaud Foundation, Lisbon, Portugal, United States

W. Weber. Breast Center, University Hospital of Basel, Basel-Stadt, Switzerland

O. Gentilini. Breast Surgery Unit, San Raffaele University Hospital, Milan, Italy

Background: Despite the progressive de-escalation of breast cancer (BC) surgery, mastectomy rates remain around 30-40%. Furthermore, up to 1/3 of BC patients undergo a contralateral risk-reducing mastectomy and around 40% of mutation carriers choose a bilateral intervention. To date, immediate breast reconstruction (IBR) with implants is the most commonly performed reconstructive procedure. After an initial experience with implants in subcutaneous positioning under the mastectomy flap in the seventies, this technique was abandoned due to a high rate of implant loss (28%), flap necrosis (13.5%) and capsular contracture (56%). For this reason, the positioning of the implant under the pectoralis major has become the standard of care. However, over time surgical techniques and implants have improved, resulting in decreasing implant loss, flap necrosis and capsular contracture rates. Moreover, biological/synthetic meshes have been used to cover the implant placed over the pectoralis major, thus avoiding to mobilize the muscle with some benefits in terms of reduced complications (no animation

deformity, no chronic pain, no loss of muscular function), patients' wellbeing, postoperative pain and recovery. Additionally, recent literature reported encouraging results with polyurethane breast implants in pre-pectoral positioning without any kind of implant coverage. Although these procedures are considered safe they were not evaluated in prospective randomized trials. In 2019 a joint consensus on pre-pectoral breast reconstruction (PBR) clearly recommended to properly audit the results in terms of surgical complications and patient-reported outcomes. Based on these premises the EUBREAST (European Breast Cancer Research Association of Surgical Trialists, www.eubreast.org) study group decided to launch a prospective international cohort study aimed at comparatively evaluating data on different surgical techniques of PBR with or without PMRT. Therefore, we will prospectively evaluate the utilization of PBR, including surgical, oncological, aesthetic and patients' satisfaction and quality of life outcomes related to each type of surgical technique and the interaction with post-mastectomy radiation therapy (PMRT).

Eligibility criteria:

- Female patients age ≥ 18 years
- Signed informed consent
- Patients undergoing mono/bilateral therapeutic mastectomy and immediate PBR

Exclusion criteria

- Patients not suitable for surgical treatment
- Patients undergoing subpectoral reconstruction, reconstruction with tissue expander or autologous IBR

Specific aims: The primary endpoint is implant-loss at 3 months defined as the unplanned removal or loss of the implant, as a result of infection or any other complication

Secondary endpoints are infection, re-admission and re-operation rates, quality of life evaluated through BREASTQ Breast Reconstruction Module and EQ-5D-5L questionnaires on an App for patients before and after breast reconstruction at 6, 12, 24 months, early onset complication at 3 months, late-onset complications at 6, 12, 24 months, further surgery at 24 months, time to adjuvant therapy.

Tertiary endpoints are further surgery, loco-regional recurrence, disease free survival, breast cancer specific survival, distant-disease free survival, overall survival, development of seroma/breast implant-associated anaplastic cell lymphoma.

Statistics: We will use a single-arm design to assess the surgical safety of PBR through implant loss rate at 3 months which is expected to be $\leq 9\%$ based on previous literature; 12% or greater will be regarded as unacceptably high. The assessment will be based on 1,112 patients. For this sample size calculation, power was set to 90%, and the two-sided alpha was set to 0.05.

Allowing for a 10% loss to follow-up at 3 months, we aim at recruiting 1,236 patients. Accrual has not started yet.

Funding: EUBREAST ETS Italy

Contact: Oreste Davide Gentilini: gentilini@eubreast.org

PO5-19-03

1st-in-human CAR T targets MUC1 transmembrane cleavage product

Presenting Author(s) and Co-Author(s):

C. Bamdad. Minerva Biotechnologies, Waltham, Massachusetts, United States

J. Mortimer. City of Hope, Duarte, California, United States

Y. Yuan. Cedars-Sinai Cancer, Los Angeles, California, United States

J. Specht. Fred Hutch Cancer Center, University of Washington, Seattle, WA, United States

B. Smaghe. Minerva Biotechnologies, United States

S. Chi-Min Lin. City of Hope, United States

A. Stewart. Minerva Biotechnologies, United States

D. Walkley. Minerva Biotechnologies, United States

M. Carter. Minerva Biotechnologies, United States

T. Synold. City of Hope, United States

V. Parekh. City of Hope, United States

K. Yi. Minerva Biotechnologies, United States

J. Nash. Minerva Biotechnologies, United States

M. Nash. Minerva Biotechnologies, United States

Q. Liu-Michael. City of Hope, United States

S. Hamilton. City of Hope, United States

S. Forman. City of Hope, United States

Background: huMNC2-CAR44 and huMNC2-CAR22 are autologous CAR T cell therapies under study in an ongoing 1st-in-human trial for metastatic breast cancers (NCT04020575), being performed at City of Hope. Both CARs are targeted to the tumor by an antibody, huMNC2, that recognizes a cryptic binding site on MUC1*, which is the transmembrane cleavage product of MUC1. The antibody binds to an epitope that is only unmasked when MUC1 is cleaved to MUC1* by enzymes in the tumor microenvironment. huMNC2 strongly reacts with over 90% of breast cancers. No therapeutic that targets MUC1* had ever been tested in humans before this trial. We note that neither 5E5 nor antibodies that bind to a MUC1 “heterodimer” recognize MUC1*.

Eight patients have already been treated with huMNC2-CAR44. The next 8 patients will be treated with huMNC2-CAR22 to enable comparison and inform decision as to which CAR to bring forward for completion of Phase 1 and entry into Phase 2. huMNC2-CAR22 differs from huMNC2-CAR44 in that it is resistant to exhaustion. CAR22 achieves greater in vivo persistence due to Sadelain’s “1XX” mutations of Tyr to Phe in 2 of the 3 ITAMs, which prevent Tyr phosphorylation and signaling, leaving signaling through ITAM 1 alone.

Trial Design: Dose escalation or de-escalation is tested in cohorts of 3 patients each using standard “3+3” dose-finding, with the starting dose of 3.3×10^5 CAR+ T cells/kg up to a maximum of 1.0×10^7 CAR+ T cells/kg. Patients receive cyclophosphamide ($300 \text{ mg/m}^2/\text{day}$) and fludarabine ($30 \text{ mg/m}^2/\text{day}$) for 3 days prior to CAR T cell infusion. Safety will be evaluated by CTCAE version 5.0 and Lee criteria. Anti-tumor activity will be assessed by imaging studies completed between 1 and 3 months after huMNC2-CAR T cell infusion for determination of response by RECIST 1.1 or by FDG PET modified PERCIST for patients with predominant

bone disease.

Inclusion Criteria: Patients with confirmed diagnosis of breast cancer, with documented ER, PR, and HER2 status per ASCO/CAP guidelines. Patients with MUC1* expression of at least 30% by IHC. Patients must have received standard metastatic systemic therapy per NCCN guidelines which are known to confer benefit. No maximum on number of prior treatments.

Patients must have received at least 2 or 3 prior lines of chemotherapy in the metastatic setting.

Exclusion Criteria: Patients requiring >15 mg of prednisone per day or immunosuppressives; patients with major organ dysfunction; Serum creatinine > 2 mg/dL; Bilirubin \geq 1.5 mg/dL; AST/ALT \geq 2.5 x upper limit normal; 3x upper limit for patients with known liver metastasis; significant pulmonary dysfunction; significant cardiovascular abnormalities; ANC < 1000/mm³.

Primary Objectives: To determine the safety and maximally tolerated cell dose (MTD) and recommended phase 2 cell dose (RP2D) of ex vivo expanded autologous huMNC2-CAR T cells for patients with advanced MUC1* positive breast cancer using CTCAE version 5.0 and Lee criteria.

Secondary: Determine duration of in vivo persistence and phenotype of adoptively transferred huMNC2-CAR T cells. Determine antitumor activity by RECIST 1.1. Determine MTD/RP2D.

Contact: City of Hope Comprehensive Cancer Center

Joanne Mortimer, MD

1-800-826-4673

Minerva18625@coh.org

PO5-19-04

EVOLVE: An Ambispective, Patient-Centered, Real-World Early-Stage Breast Cancer Study in the United States

Presenting Author(s) and Co-Author(s):

H. Friedler. PicnicHealth, United States

M. Tierney. PicnicHealth, United States

M. Baker. PicnicHealth, United States

G. Hanson. PicnicHealth, United States

J. Briceno. AstraZeneca, United States

K. Smith. Johns Hopkins University School of Medicine, United States

M. Baber. AstraZeneca, United States

K. Glover. AstraZeneca, United States

X. Xu. AstraZeneca, United States

K. Ryan. AstraZeneca, United States

Z. Segunmaru. AstraZeneca, United States

C. Lam. AstraZeneca, Maryland, United States

m. lustberg. Yale Cancer Center, New Haven, Connecticut, United States

N. Henry. University of Michigan Medical School, United States

R. Greenup. Yale School of Medicine, New Haven, Connecticut, United States

M. Chavez. UT MD Anderson Cancer Center, Houston, Texas, United States

J. Unger. Fred Hutchinson Cancer Center, United States

A. Ho. Duke Cancer Center, United States

D. Collyar. Patient Advocates in Research, United States

Background: While survival for patients with early breast cancer (eBC) has greatly improved with earlier detection and modern treatments, the risk of recurrence and long-term/late treatment-related adverse events (AEs) remain concerns for many patients. Contemporary real-world data are needed to understand current diagnostic pathways, treatment patterns and toxicities, quality of life, and patient experience to better characterize eBC care and knowledge gaps and establish important hypotheses to test in prospective trials, with the ultimate goal to improve both treatment and outcomes for patients with eBC.

Study design: PicnicHealth and AstraZeneca are collaborating to build a real-world observational eBC cohort composed of de-identified medical records data supplemented with patient-reported outcomes (PROs), including patient-reported social determinants of health (SDoH). Patients recruited from multiple channels, such as digital marketing and community partnerships, will consent to participate and sign HIPAA authorization for PicnicHealth to collect their medical records from all providers and sites of care in the United States. All available retrospective medical records in any format will be retrieved, and records will continue to be collected for patients prospectively following enrollment. Disease-specific information will be abstracted using PicnicHealth's human-in-the-loop machine learning abstraction platform. Patients will have access to their records in the form of a searchable and shareable digital timeline. Additional data, including but not limited to symptoms, quality of life and treatment

experience will be collected through surveys. The first patient was enrolled in May 2023. Patients will be followed for ≥ 8 years or until withdrawal or death, whichever occurs first.

Eligibility criteria: Patients with stage I-III breast cancer diagnosed ≤ 3 years before enrollment, who onboard to the PicnicHealth platform, consent to participate, sign HIPAA authorization for medical record collection, and provide ≥ 1 provider/care site for record retrieval will be included in the cohort.

Specific aims: The cohort aims to generate contemporary real-world data relevant to understanding demographic and clinical characteristics, SDoH, diagnostic/testing pathways, treatment patterns, and clinical outcomes, including AEs and AE management. Specifically, demographic and SDoH differences in management, outcomes, and the patient experience during and following eBC diagnosis and treatment will be evaluated. The cohort design and the data collected will evolve as the eBC landscape evolves to continuously address new research questions around diagnosis, management, outcomes, and patient experience.

Statistical methods: The demographics, SDoH, clinical characteristics, treatments, healthcare resource utilization, eBC outcomes, such as recurrence and progression, and patient experience will be summarized for the cohort overall and by pre-determined subgroups using descriptive statistics. Additional analyses include, but are not limited to, evaluating the impact of key exposures, such as SDoH, on treatment and diagnostic pathways, treatment compliance, clinical outcomes, and PROs. All analyses will be prespecified in study-specific statistical analysis plans.

Present accrual and target accrual: At least 3,000 patients will be enrolled in the PicnicHealth eBC Cohort. As of July 2023, 843 patients have onboarded to the PicnicHealth platform and will be screened for eligibility into the eBC registry cohort.

Contact information for people with a specific interest in the study: For additional information, please contact breastcancer@picnichealth.com.

PO5-19-05

A Phase II Trial of Stereotactic Body Radiation Therapy and Fluoroestradiol Positron Emission Tomography in Patients with Oligoprogressive Estrogen Receptor Positive Metastatic Breast Cancer

Presenting Author(s) and Co-Author(s):

J. Bazan. City of Hope Comprehensive Cancer Center, Duarate, California, United States

J. Mortimer. City of Hope, Duarte, California, United States

Y. Li. City of Hope Comprehensive Cancer Center, United States

Background: The term oligoprogression (OP) refers to a clinical scenario in which patients with diffuse metastatic disease on systemic therapy have a limited number of metastases that have progressed or are new whereas the majority of metastases are stable or improved. OP disease is increasingly being encountered in clinical practice due to improvements in systemic therapy. Treating OP disease with local ablative therapies may therefore prolong the time to more diffuse progression necessitating a change in systemic therapy and may therefore lead to improved overall survival in these patients. Only one study has evaluated the role of SBRT in patients with OP MBC. This trial accrued 47 patients with OP MBC, with 2/3 having triple negative disease. There was no difference in PFS between patients that received SBRT versus those that did not (4.2 months vs. 4.4 months, $p=0.2$). Whether ablative therapies are beneficial in subtypes of breast cancer that have many effective systemic therapies available, such as ER+ breast cancer, remains an open question and an unmet clinical need. Design: Phase II study for patients with OP ER+ MBC (1-4 new and/or progressing metastatic lesions). Eligible patients will receive stereotactic body radiation therapy (SBRT) to the OP lesions. SBRT will be delivered to each lesion in 3-5 fractions. Each patient's systemic therapy regimen will be held during study therapy and will resume upon completion of study therapy. Patients will then be restaged at 12 weeks post-SBSRT. Patients that have at least stable disease at that time point will continue on their systemic therapy and then be re-staged 12 weeks later (24 weeks after SBRT). This study will also study the role of ER-targeted positron emission tomography (PET) imaging with ^{18}F -Fluoro- $^{17}\beta$ -Fluoroestradiol (FES) in the OP ER+ patient population with FES PET scans obtained at baseline, and at each of the 2 follow-up imaging timepoints. A key secondary hypothesis is that the use of FES PET in addition to standard imaging at baseline and in follow-up will help confirm patients have OP disease and will help assess for new lesions on subsequent restaging. Eligibility: Key inclusion criteria: age ≥ 18 yo; histologically confirmed ER+/HER2- metastatic breast cancer; the presence of metastatic breast cancer at the time of study entry with progression in 1-4 lesions (including new lesions); SBRT must be feasible for all progressing lesions. Key Exclusion Criteria: >2 lines of systemic therapy for metastatic disease; intracranial disease progression Objective: To determine whether using SBRT to treat OP lesions allows ER+ breast cancer patients to continue on their current systemic therapy for at least 24 weeks post SBRT. Objective: To assess whether FES-PET increases the number of lesions found prior to SBRT; To determine the impact of SBRT on patient quality of life; time to next line systemic therapy; PFS Statistical Methods Simon 2 stage optimal design with $\alpha=0.05$ and $1-\beta=0.80$. The null hypothesis is that the proportion of patients that remain on their original systemic therapy ≥ 24 weeks (2 restaging scans) post-treatment is 20%. The alternative hypothesis is that the proportion of patients that remain on their original systemic therapy after 2 restaging scans is 50%. In stage 1, 8 patients that proceed to SBRT will be enrolled. The study will be terminated if only 0 or 1 subjects remain on original systemic therapy after 2 restaging scans. However, if ≥ 2 patients remain on original systemic therapy after 2 restaging, then an additional 10 patients would be enrolled for a total of 18 patients. The null hypothesis

will be rejected if ≥ 6 patients remain on their original systemic therapy after 2 restaging scans.
Contact Information: Jose G. Bazan (jbazan@coh.org) Funding Source: City of Hope
Comprehensive Cancer Center

PO5-19-07

A Single Arm Phase 2 Study of Peri-Operative Immune Checkpoint Inhibition and Cryoablation in Women With Hormone Receptor-Negative, HER2-Negative Early Stage/Resectable Breast Cancer

Presenting Author(s) and Co-Author(s):

- H. McArthur. UT Southwestern, Dallas, Texas, United States
- E. Comen. MSKCC, United States
- Y. Bryce. MSKCC, United States
- S. Solomon. MSKCC, United States
- S. Reddy. UT Southwestern Medical Center, Dallas, Texas, United States
- I. Chan. University of Texas Southwestern Medical Center, United States
- B. Dogan. UT Southwestern Medical Center, Dallas, Texas, United States
- D. Klemow. University of Texas Southwestern Medical Center, United States
- N. Unni. University of Texas Southwestern Medical Center, Dallas, Texas, United States
- J. Santos Leal. Oncoclínicas, Salvador, Brazil
- C. Martinez. Cedars-Sinai Medical Center, United States
- R. Basho. The Lawrence J. Ellison Institute for Transformative Medicine, Los Angeles, USA, Los Angeles, California, United States
- D. Park. Cedars-Sinai Medical Center, United States
- P. McAndrew. Cedars-Sinai Medical Center, United States
- B. Larkin. Cedars-Sinai Medical Center, United States
- D. Page. Robert W. Franz Cancer Research Center and Alliance, Portland, Oregon, United States
- W. Mills. Cedars-Sinai Medical Center, United States
- S. Mellinger. Providence Cancer Institute, Portland, Oregon, United States
- N. Fredrich. Providence, United States
- N. Moxon. Providence Cancer Institute, Portland, Oregon, United States
- L. Currie. Providence, United States
- M. Carter. University of Texas Southwestern Medical Center, United States
- M. Ramos. UTSW, United States
- S. Rice. Oncotherapeutics, United States
- S. Patil. Lerner Research Institute, United States
- M. Gatti-Mays. The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States
- L. Norton. Memorial Sloan Kettering Cancer Center, United States

Background: Triple negative breast cancer (TNBC) is a biologically distinct subtype with a high risk of early relapse. Patients not achieving a pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) have a 3-year event free survival (EFS) of < 60%. Approximately 1/3 of patients receiving NAC with pembrolizumab-mediated immune therapy will not achieve a pCR and of those, approximately 1/3 will experience a recurrence within 3 years.

Physical disruption of tumors with local strategies such as cryoablation (cryo) induces inflammation and releases antigens that can activate tumor-specific immune responses. The combination of cryo with immune checkpoint inhibition (ICI) has been shown to induce tumor regression and prevented tumor re-challenge in pre-clinical models. Clinical studies have also demonstrated that the combination of pre-operative cryo with ICI is safe in women with operable, early-stage breast cancer and generates intra-tumoral and systemic immune responses (NCT01502592, NCT02833233). This multi-center, single arm, phase 2 study is currently evaluating the impact of cryo with standard-of-care pembrolizumab (pembro) in women with residual TNBC after taxane-based NAC, a group at high risk of early relapse (NCT03546686). Methods: Eligible women are ≥ 18 y, with ER < 10%, PR < 10%, HER2 negative (per ASCO/CAP definition), ≥ 1.0 cm, residual operable disease after taxane-based NAC. Pts undergo percutaneous, image-guided cryo with concurrent research core biopsy 7-10 days prior to surgery and receive peri-operative pembro per standard-of-care. Adjuvant capecitabine or olaparib is recommended for all patients per local standard-of-care. Patients are stratified by NAC platinum administration, NAC anthracycline administration, and clinical nodal status (positive versus negative). The primary endpoint is 3-year Event Free Survival (EFS). Secondary endpoints include Invasive Disease-Free Survival (IDFS), Distant Disease-Free Survival (DDFS), overall survival (OS) and safety. Exploratory correlative studies will be performed on tumor and serum to characterize the immunologic impact of the intervention and to explore predictors of efficacy and toxicity. Funding sources: Conquer Cancer Foundation, Breast Cancer Research Foundation, Boston Scientific

PO5-19-08

**Neoadjuvant HER2-targeted Therapy +/- Immunotherapy with Pembrolizumab (neoHIP):
An Open Label Randomized Phase II Trial**

Presenting Author(s) and Co-Author(s):

H. McArthur. UT Southwestern, Dallas, Texas, United States

J. Santos Leal. Oncoclínicas, Salvador, Brazil

I. Chan. University of Texas Southwestern Medical Center, United States

N. Unni. University of Texas Southwestern Medical Center, Dallas, Texas, United States

S. Shiao. Cedars-Sinai Medical Center, United States

J. Gruber. University of Texas Southwestern Medical Center, United States

S. Syed. University of Texas Southwestern Medical Center, United States

N. Peswani. University of Texas Southwestern Medical Center, United States

N. Sadeghi. University of Texas Southwestern Medical Center, Dallas, Texas, United States

G. Delgado. UTSW, United States

D. Klemow. University of Texas Southwestern Medical Center, United States

R. Basho. The Lawrence J. Ellison Institute for Transformative Medicine, Los Angeles, USA,
Los Angeles, California, United States

M. Carter. University of Texas Southwestern Medical Center, United States

M. Badran. UTSW, United States

N. Qureshi. UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER SIMMONS
CANCER CENTER, Dallas, Texas, United States

J. Curtin. UTSW, United States

J. Weese. UTSW, United States

S. Rice. Oncotherapeutics, United States

M. Phillips. Cedars-Sinai Medical Center, United States

D. Chan. Cedars-Sinai Medical Center, United States

H. Hool. Cedars-Sinai Medical Center, United States

D. Park. Cedars-Sinai Medical Center, United States

M. El-Masry. Cedars-Sinai Medical Center, United States

P. McAndrew. Cedars-Sinai Medical Center, United States

S. Sikaria. Cedars-Sinai Medical Center, United States

L. Spring. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United
States

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United
States

M. Tighiourt. Cedars-Sinai Medical Center, United States

F. Dadmanesh. Cedars-Sinai Medical Center, United States

A. Giuliano. Cedars-Sinai Medical Center, United States

K. Sanchez. New Mexico Cancer Center, United States

D. Page. Robert W. Franz Cancer Research Center and Alliance, Portland, Oregon, United States

Background: Immune checkpoint inhibition (ICI) is synergistic with HER2-directed therapy in pre-clinical models. Clinically, pembrolizumab (K)-mediated ICI plus HER2-directed therapy with trastuzumab (H) was safe and demonstrated modest activity in H-resistant HER2-positive (HER2+) metastatic breast cancer. Because ICI may confer more robust activity when administered earlier in the course of disease, H and K administered in the curative-intent, treatment-naive setting may allow for de-escalation of cytotoxics; confer life-long, tumor-specific immunity; and ultimately, improve cure rates. Moreover, the synergy of H and K with paclitaxel (T) may overcome the need for dual HER2-blockade with H plus pertuzumab (P). In this randomized, multicenter, phase II, open-label trial the efficacy and safety of neoadjuvant THP vs THP-K vs TH-K are explored. Methods: Patients (pts) ≥ 18 y with previously untreated, stage II-III, HER2+ breast cancer are being randomized and stratified by clinical nodal status (positive vs. negative) and hormone receptor status (positive vs. negative). In arm A, pts receive T at 80mg/m² weekly for 12 weeks, H at 8mg/Kg (loading dose) and then 6mg/Kg every 3 weeks x 3 doses, P at 840 mg (loading dose) and then 420mg/Kg every 3 weeks x 3 doses (THP). In arm B, pts receive THP plus K at 200mg every 3 weeks x 4 doses (THP-K). In arm C, pts receive TH-K. After enrollment of 22 pts to arm C, a prespecified interim efficacy analysis was conducted, and enrollment to this arm was subsequently terminated. Enrollment to the other arms continues with 32/58 pts enrolled to arm A and 33/58 pts enrolled to arm B as of 2/14/2023. Definitive surgery is 3-6 weeks after the last dose. After surgery, pts are treated per the treating physician's discretion per local clinical standard. The primary end point is pathologic complete response (pCR) rate in the breast and axilla (ypT0/Tis ypN0). Secondary end points include pCR rate by ypT0ypN0 and ypT0/Tis, residual cancer burden index, event free survival, breast conserving surgery rate, safety and overall survival. Exploratory correlative studies will characterize potential immune biomarkers predictive of efficacy and/or toxicity. Funding sources: BCRF, Merck

NCT03747120

PO5-19-09

Trial in progress: A prospective randomized, controlled study to evaluate device efficacy for cutting and/or coagulation of tissue during mastectomy procedures.

Presenting Author(s) and Co-Author(s):

J. Montalvan. Baylor College of Medicine, Texas, United States

I. Marin. Baylor College of Medicine, United States

L. Healy. Baylor College of Medicine, United States

M. Riojas-Barrett. Baylor College of Medicine, United States

M. Bajomo. Baylor College of Medicine, United States

E. Bonefas. Baylor College of Medicine, United States

A. Thompson. Baylor College of Medicine, Houston, Texas, United States

M. Maricevich. Baylor College of Medicine, Houston, Texas, United States

S. Winocour. Baylor College of Medicine, United States

S. Carter. Baylor College of Medicine, United States

Background/Purpose: The ConMed HelixAR Electrosurgical Generator with Argon Beam Coagulation Technology (CHEST) trial aims to focus on patients undergoing mastectomy, either unilateral or bilateral, with immediate breast reconstruction including breast implants, tissue expander placement, or autologous flap. The study design follows the standard of care procedure with device efficacy being measured between two devices regularly used in the operative setting: the HelixAR Electrosurgical Generator (HEG) and the Conventional Electrosurgical Coagulation (CEC) systems. The need for safe alternative surgical tools is increasing as the number of women needing surgical treatment increases. Allowing for the test and comparison of these standardized devices gives an extent to the advantages of using one over the other. To evaluate the device effectiveness between the HelixAR Electrosurgical Generator and Conventional Electrosurgical Coagulation systems for cutting and/or coagulation of tissue during mastectomy and reconstruction surgery, we report the implementation in a randomized clinical trial. The study is powered to show superiority of the HEG to the CEC as it relates to the primary objective of time from post-mastectomy to hemostasis. The HEG is designed to deliver argon gas and high frequency electrical current compared to the CEC delivering high frequency electrical current only. The primary efficacy measure is the time it takes from post-mastectomy to hemostasis with the secondary effectiveness endpoints being infection, drain duration, total drain output, blood loss and device related adverse events. The study hypothesizes that the time for post-mastectomy hemostasis is significantly less for the HEG than the CEC. Additional hypotheses include overall less device related adverse events, lower blood loss, and reduced operative time in favor of the HEG.

Methods: This is a prospective 1:1 randomized controlled study of the HEG versus the CEC for patients undergoing a mastectomy with reconstruction procedure. 82 patients will be enrolled and distributed in two arms of 41 patients with a primary objective to assess the device efficacy for cutting and coagulation. The subject population includes patients with breast cancer or high risk from genetic mutations and/or family history. Exclusion factors include known history of bleeding diathesis or coagulopathy, advanced refusal of blood transfusion, active systemic or cutaneous infection or inflammation. The enrolled patients will be followed for 2 months post-operatively.

Results: The study is open with 53/82 (65%) patients enrolled at the time of the abstract submission. Of those, 26 subjects were randomized to the CEC and 27 to the HEG. 27 subjects have experienced an adverse or serious adverse event including bruising, infections, and wound dehiscence, none determined to be related to the device use. For the study, analysis will focus on the primary endpoint comparing post-mastectomy procedure time to hemostasis between the two devices.

Conclusion: The CHEST trial demonstrates the feasibility of conducting a randomized controlled trial at a single center in a complex operative setting comparing two surgical modalities. The testing of these surgical devices provides rationale for the implementation of safe and regulated clinical trials. While both devices are FDA approved and regularly used, the standardization of device efficacy is becoming more prevalent as new innovations get introduced into the surgical setting.

PO5-19-10

First oncological outcomes of HypoG-01: a UNICANCER phase III trial comparing loco-regional hypo vs normo fractionated radiation therapy in early breast cancer patients

Presenting Author(s) and Co-Author(s):

S. Rivera. Gustave Roussy, villejuif, United States

E. Karamouza. Gustave Roussy, Bureau Biostatistique and Epidémiologie, F-94805, VILLEJUIF France/Oncostat U1018, Inserm, Université Paris-Saclay, Ligue Contre le Cancer, F-94805, VILLEJUIF France, United States

Y. Kirova. Institut Curie, Paris, Ile-de-France, France

S. Racadot. Centre Léon Bérard, Lyon, France, United States

M. Benchalal. Centre Eugène Marquis, Rennes, France, United States

J. Clavier. ICANS - Institut de cancérologie Strasbourg Europe, Strasbourg, France, United States

c. charra-brunaud. Institut de Cancérologie de Lorraine, vandoeuvre les nancy, France

M. Chand-Fouche. Département de radiothérapie, Centre Antoine Lacassagne, Nice, France, United States

D. Argo-Leignel. Hôpital du Scorff, Lorient, France, United States

K. Peignaux. Centre Régional De Lutte Contre Le Cancer Georges-François Leclerc C.G.F.L, Dijon, France, United States

A. Benyoucef. Centre Henri Becquerel, Rouen, France, United States

D. Pasquier. Centre Oscar Lambret, Lille, France, United States

P. Guilbert. Institut Godinot, United States

J. Blanchecotte. Institut de Cancérologie de l'Ouest (ICO) - Site d'Angers, Angers, France, United States

A. Tallet. Paoli-Calmettes Institute, Marseille (France), United States

A. Petit. Institut Bergonié, United States

G. Bernadou. CORT37, Chambray-lès-Tours, France, United States

X. Zasadny. Site Chénieux - Polyclinique de Limoges, Limoges, France, United States

C. Lemanski. ICM - Montpellier, Montpellier, France, United States

J. Fourquet. C.H. de Lens, Lens, France, United States

E. Malaurie. C.H. Intercommunal Créteil, Créteil, France, United States

H. Kouto. Centre Galilée, Lille, France, United States

C. Massabeau. Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France, United States

A. Henni. Institut de cancerologie des haut de France, Beuvry, France, United States

P. Regnault. Clinique Bordeaux Tivoli-Ducos, Bordeaux, France, United States

A. Belliere. Centre Jean Perrin, Clermont-Ferrand, France, United States

Y. Belkacemi. Henri Mondor University Hospital, France

M. Le Blanc-Onfroy. Institut de Cancérologie de l'Ouest, ICO - René Gauducheau, Nantes, France, United States

J. Geffrelot. Centre Francois Baclesse, United States
J. Prevost. Centre Pierre Curie, Beuvry, France, United States
M. Bergeaud. UNICANCER, Unistrad, Paris, France, United States
A. Lamrani-Ghaouti. UNICANCER, Unistrad, Paris, France, United States
A. Ruffier. Centre Jean Bernard - Clinique Victor Hugo - Institut inter-régional de Cancérologie (ILC) - CCS, 64 Rue de Degré, 72000 Le Mans, France, United States
N. bonnet. UNICANCER, United States
S. wong. APHM, United States
C. Rossier. Clinique de Genolier, United States
T. Brion. Institut Curie, United States
P. Maroun. nstitut de Radiothérapie du Sud de l'Oise, United States
c. Petit. Institut Paoli Calmette, United States
G. Auzac. Gustave Roussy, United States
S. Michiels. Gustave Roussy, Villejuif, France, United States

Objective

Normofractionated (NF) radiation therapy (RT) is still standard for loco-regional early breast cancer (EBC) in many countries. HypoG-01, a UNICANCER, non-inferiority, open-label, multicenter, randomized phase III trial (NCT03127995), conducted in parallel with the DBCG Skagen trial 1 (NCT02384733), evaluated hypofractionated (HF) RT with 40 Gy/15 fr (2.67 Gy/fr) versus NF RT 50 Gy/25 fr (2.0 Gy/fr). This is the first report of oncological outcomes, secondary endpoints of the trial.

Methods

Patients (pts) ≥ 18 years old were operated for T1-3, N0-3, M0 breast cancer. All pts received nodal and thoracic wall or breast RT. Tumor-bed boost (sequential or simultaneous) and nodal levels treated were decided according to local guidelines. Target volumes were delineated according to the ESTRO consensus. RT technique was left at the investigator's discretion. Stratification factors included treating center, type of surgery, number of positive nodes and body mass index. The primary endpoint, reported previously, was time to occurrence of arm lymphedema. Oncological outcomes included locoregional relapse free survival (LRFS), invasive disease-free survival (IDFS), distant disease-free survival (DDFS), breast cancer specific survival (BCSS) and overall survival (OS) as defined per DATECAN guidelines. All time to cancer related endpoints were defined as starting from the date of randomization until the event. The primary statistic test was stratified one-sided logrank test: 5% significance level in per-protocol population (PPP) with a pre-specified non-inferiority margin of 1.545. Stratified Cox model was used for calculating hazard ratios of oncological outcomes.

Results

In total, 1265 pts were randomized to HF versus NF RT from Sep 2016 to Mar 2020 with 1221 in the PPP (HF group 614 pts (50.3%); NF group 607 (49.7%)), 5 consent withdrawn and 39 major deviations. Median age was 58 years (range 23-91), surgery included mastectomy (501 pts; 45%) and axillary clearance (921 pts; 82.8%). Sequential (67.8%) or simultaneous integrated (32.2%) tumor-bed boost was used in 596 pts (48.8%). With a median follow-up for OS in PP analysis of 3.8 years (95% CI 3.3 to 3.9), HF was non-inferior to NF RT in terms of lymphedema (HR=1.07; 90% CI 0.86-1.34, non-inferiority p=0.003). Table 1 reports the hazard ratio and 3-year survival rates for the oncological endpoints LRFS, IDFS, DDFS, BCCS and OS. There was no sign of disadvantage for any of these endpoints comparing HF to NF.

Additional analyses will be presented at the meeting.

Conclusion

Moderately HF loco-regional RT is non-inferior to NF RT in terms of lymphedema risk in EBC and does not show a disadvantage in terms of LRFS, IDFS, DDFS, BCCS and OS with a median follow-up of 3.8 years. Together with the Skagen 1 trial, this study provides level 1A evidence supporting the use of 40 Gy/15 fr for loco-regional radiation therapy in EBC with respect to arm lymphedema risk;

Table 1: Oncological outcomes according to treatment arm in the per protocol analysis

Per-protocol analysis (n=1221)	N events	Hazard ratio (HF vs NF)	3y survival HF	3y survival NF
LRFS	81	0.50 [0.29 ; 0.88]	95.6% [93.6 ; 97.0]	93.1% [90.8 ; 94.9]
IDFS	140	0.55 [0.27 ; 1.13]	91.1% [88.5 ; 93.2]	88.6% [85.7 ; 90.9]
DDFS	102	0.46 [0.24 ; 0.88]	94.0% [91.8 ; 95.7]	91.5% [88.9 ; 93.5]
BCCS	49	0.43 [0.23 ; 0.81]	97.6% [96.0 ; 98.6]	95.8% [93.9 ; 97.2]
OS	68	0.48 [0.28 ; 0.82]	96.6% [94.8 ; 97.8]	94.2% [91.9 ; 95.8]

HF: Moderately hypofractionated radiation therapy; NF: Normofractionated radiation therapy; n:number of patients; N: number of events

PO5-19-11

A novel portable breast cancer screening method - initial institutional experience

Presenting Author(s) and Co-Author(s):

M. Riojas-Barrett. Baylor College of Medicine, United States

J. Montalvan. Baylor College of Medicine, Texas, United States

M. Bajomo. Baylor College of Medicine, United States

I. Marin. Baylor College of Medicine, United States

Q. Dang Nguyen. Baylor College of Medicine, United States

K. Sepulveda. Baylor College of Medicine, Texas, United States

E. Bonefas. Baylor College of Medicine, United States

A. Thompson. Baylor College of Medicine, Houston, Texas, United States

S. Carter. Baylor College of Medicine, United States

Background: Breast ultrasound (US) is a remarkable supplementary tool alongside mammography and magnetic resonance imaging (MRI) for the detection of breast lesions. US imaging is a fast, reliable method to identify and localize breast pathology. Innovative technologies that aim to timely identification and prompt diagnosis of suspicious lesions in breast cancer screening remain a clinical need. ATUSA is a B-type rechargeable US, shaped as a wearable device. It uses a linear array of transducers with water acting as a coupling medium that recreates a 3-dimensional image of the scanned breast. The ATUSA portability makes this device a practical breast screening method during a healthcare office visit. We report the initial feasibility of ATUSA to detect breast lesions in an outpatient setting from a trial in progress. Methodology: Interim prospective data from 35 female patients presenting with a mass of equal or greater than 1 cm in size, with a baseline handheld US image and pathology reports that evidenced a cancer diagnosis or a lesion suspicious of malignancy. Breast cancer types included invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS) and invasive lobular carcinoma (ILC), invasive mammary carcinoma (IMC) with mixed ductal and lobular features and atypical lobular hyperplasia (ALH). ATUSA and baseline handheld reference US images were cross-referenced from June 2022 to June 2023. Basic demographics, clinical characteristics, mammogram and/or MRI, and pathology reports were included in the analysis. Patients were followed up for a 30-day period to note occurrence of any adverse event (AE). Institutional Review Board (IRB) approved this study (protocol H-42616). Results: The 35 patients had a mean age of 57 years (range: 25 – 79), mean BMI 29.6 kg/m² (range: 18.1 – 49.3). Mammographic breast density was fibroglandular tissue 15 (42.8%), followed by heterogeneously dense (HD) 13 (3.7%), mixed HD and fibroglandular 1 (2.8%), mildly dense 1 (2.8%), extremely dense 2 (5.7%), and extremely fatty 1 (2.8%). Breast sizes were 1 (2.8 %) A cup, 11 (31.4%) B cups, 1 (2.8%) B – C cups, 5 (14.2%) C cups, 1 (2.8%) C – D cups, 13 (37.1%) D cups, and 3 (8.5%) DD cups. The 35 scanned lesions had a diagnosis (compared with final resected pathology) classified as IDC 18 (51.4 %), DCIS 2 (5.7 %), mixed IDC and DCIS 6 (17.1 %), ILC 3 (8.5 %), IMC with mixed features 2 (5.7 %), IMC with DCIS 1 (2.8 %), ALH 1 (2.8 %), and 2 (5.7 %) benign masses. ATUSA successfully identified 17/35 (48.5 %) lesions from this group as malignant, from which 4 were hard to distinguish due to shadowing artifact and 3 were underestimated in size. A total of 15 (42.8 %) malignant lesions were missed by ATUSA. No AEs related to the ATUSA device were reported. Conclusion: The ATUSA provides the means to produce a good quality US image during a clinic visit or where a facility lacks conventional US imaging. When compared to the handheld US, ATUSA can be

safely used in the outpatient setting without the need of trained specialists but requires further development and testing to match conventional breast imaging.

Table 1. Basic clinical characteristics & demographics

Sample size	n= 35	Percentage (%)
Race		
Asian	2	5.7
Black or African American	9	25.7
Caucasian	23	65.7
Other (Hispanic)	1	2.8
Ethnicity		
Hispanic or Latino	6	17.1
Not Hispanic or Latino	26	74.2
Other (English/Irish (1), Kikuyu (1), Asian (1))	3	8.5
Menopausal status		
Pre-menopausal	11	31.4
Peri-menopausal	0	0
Post-menopausal	24	68.5
Breast tissue characteristics		
Heterogeneously dense	13	3.7
Heterogeneously dense w/ fibroglandular tissue	1	2.8
Mildly dense	1	2.8
Extremely dense	2	5.7
Fibroglandular density	15	42.8
Entirely fatty	1	2.8
Unknown	2	2.8
Breast size (A – DD cup)		
Cup A	1	2.8
Cup B	11	31.4
Cup B - C	1	2.8
Cup C	5	14.2
Cup C- D	1	2.8
Cup D	13	37.1
Cup DD	3	8.5

PO5-19-12

Innovative Trial Design: ARTIDIS Nanomechanical Generated Measurements for Early Breast Lesions (ANGEL) - Multicentre Study

Presenting Author(s) and Co-Author(s):

K. Sepulveda. Baylor College of Medicine, United States

A. Roark. Baylor College of Medicine, United States

S. Dhamne. Baylor College of Medicine, United States

C. Nagi. Baylor College of Medicine, United States

I. Marin. Baylor College of Medicine, United States

I. Tabish. Baylor College of Medicine, United States

S. Hilsenbeck. Baylor College of Medicine, United States

S. Nizzero. Houston Methodist Research Institute, Houston, Texas, United States

M. Gachechiladze. Artidis, United States

T. Appenzeller. Artidis, United States

M. Loparic. Artidis, United States

M. Plodinec. Artidis, United States

A. Thompson. Baylor College of Medicine, Houston, Texas, United States

Background: The diagnosis of breast cancer based on histopathology of core needle biopsies and the delineation into breast cancer subtypes to drive clinical treatment decisions can be time consuming and cause patient (and clinician) anxiety. Alternative, near patient, approaches to conventional diagnostic pathways would be desirable to drive diagnostic and therapeutic planning. This study harnesses the novel concept of evaluating diagnostic cores for nanomechanical features at the time of core biopsy. Clinical manifestations of disease are often accompanied by biomechanical alterations at sub-/cellular, extracellular, tissue and organ level. Mechanical properties of cancer cells and their microenvironment play a critical role in cancer invasion, progression, and immune cell infiltration. Ultrastructural (sub-) cellular alterations (nanoscale level), including the remodulation and alteration of cellular cytoskeleton dynamics, contribute to altered mechanical state of cancer cells, and lead to increased deformability and motility of soft cancer cells to overcome stromal barrier, and spread into the adjacent tissues and distant sites in the body. This results in a direct mechanistic correlation between nanomechanical properties and clinical outcome in cancer tissues. The ARTIDIS Nanomechanical Generated measurements for Early Lesions (ANGEL) Study will prospectively evaluate the efficacy of the ARTIDIS system as an aid to diagnosis, as well as subtyping breast cancer and predicting clinical outcomes based on tissue nanomechanics, particularly in the context of neoadjuvant therapy (NAT).

Methods: The study seeks to validate the predictive power of the nanomechanical signature, a unique tissue biomarker reflecting the tissue phenotype, by comparing it to standard histological assessment. A projected cohort of 2,705 patients will be enrolled, from diverse ethnic and socioeconomic backgrounds, with benign or malignant breast conditions undergoing diagnostic core biopsy. A single core biopsy (gauge agnostic) is placed in a cassette and subjected to thousands of mechanical measurements at the “nano” scale over a period of 1-3 hours. The ARTIDIS technology builds upon the Atomic Force Microscopy platform to non-disruptively detect up to 17 different nanomechanical parameters in soft tissues with a subcellular

resolution. The same core biopsy can then undergo fixation and conventional histopathological analyses for comparison with the final pathology. The primary aim is to confirm the potential of the ARTIDIS system in diagnosis (benign vs malignant) and secondarily address whether the nanomechanical signature can differentiate subtypes of breast cancer, associate with clinical outcome, and guide treatment decisions. Particularly, we will investigate ARTIDIS potential as a predictor of treatment response for patients receiving NAT.

Results: The multicenter ANGEL study is a prospective investigation that builds upon previous clinical data from the NANO study at the University Hospital Basel (Switzerland) and is designed to demonstrate the power of using a nanomechanical signature to evaluate breast biopsies within a routine clinical setting in a multicenter setting. The data will be used to develop ARTIDIS as an aid to diagnosis, as well as NEO Match test applications to predict and guide response to NAT.

Conclusion: This study presents the first of its kind as a direct prospective, multi-center based clinical translation of the Physics of Cancer findings into clinical settings. This innovative trial design allows the prospective development of ARTIDIS as an aid to diagnosis and NAT outcome prediction and therapy guidance applications.

PO5-20-01

SENTINOT2- Use of superparamagnetic iron oxide tracer to avoid unnecessary sentinel lymph node biopsies

Presenting Author(s) and Co-Author(s):

M. Bajomo. Baylor College of Medicine, United States

I. Marin. Baylor College of Medicine, United States

J. Montalvan. Baylor College of Medicine, Texas, United States

M. Riojas-Barrett. Baylor College of Medicine, United States

L. Healy. Baylor College of Medicine, United States

E. Bonefas. Baylor College of Medicine, United States

S. Carter. Baylor College of Medicine, United States

A. Thompson. Baylor College of Medicine, Houston, Texas, United States

Background/Purpose: The use of superparamagnetic nanoparticles of iron oxide tracers (Magtrace) and electromagnetometers (SentiMag) for the detection of sentinel lymph nodes (SLN) during breast cancer surgery has been demonstrated to be noninferior to traditional radioisotope (RI) and blue dye detection, with additional safety benefits. Previous work has shown that transcutaneous detection of SLN with Magtrace/Sentimag is possible for over 30 days. Because of the safety, efficacy, and long detection window of Magtrace, we aim to investigate the use of Magtrace to prevent unnecessary SLN biopsies (SLNB) in breast cancer surgery. SLNB are commonly performed during breast conserving surgeries (BCS) or mastectomy for patients with a preoperative diagnosis of ductal carcinoma in-situ (DCIS). Because metastasis is not expected in patients diagnosed with DCIS, SLNB may be unnecessary and potentially harmful. However, in 15-25% of cases, unexpected invasive carcinoma is found during the post-surgical histopathological analysis of the resected breast tissue. For these cases, if SLNB are forgone during the initial surgery, SLNB during a second (delayed) procedure is the usual standard of care to evaluate SLN for metastasis. However, potential changes to lymphatic drainage following the initial resection may affect tracer localization to SLN. Consequently, we aim to compare SLN detection rates during delayed SLNB with Magtrace administered prior to initial BCS or mastectomy and subsequent RI tracer administered prior to delayed SLNB.

Methods: SENTINOT2 is an ongoing international trial with BCM as the sole US site. For eligible patients with a preoperative diagnosis of DCIS, Magtrace will be administered prior to BCS or mastectomy. If invasive carcinoma is found from the post-surgical histopathological analysis, patients will receive delayed SLNB within 4 weeks of their initial surgery. Prior to delayed SLNB, patients will be randomized into two groups differing in the order of modality used for SLN detection (Magtrace or RI). Subjects with the following conditions will be excluded from the study: hypersensitivity to Magtrace, iron overload disease, pregnancy, and lactation. The total expected accrual for this study is 538 subjects globally and 50 subjects at BCM.

Results: Currently, 19 patients have been enrolled in SENTINOT2. The subject population is 11% Asian, 26% Black/African American, and 47% Caucasian with non-Hispanic ethnicity. 5% of subjects identified as Hispanic Caucasian and 11% of subjects declined to report their race or ethnicity. 79% of patients had mastectomies, while 21% had BCS. After post-surgical histopathological analysis, 21% (4/19) patients were determined to have invasive carcinoma and received delayed SLNB. 50% (2/4) of these patients were randomized to have Magtrace as

their first SLN detection modality (Mag-RI) while the other 50% (2/4) had RI as their first SLN detection modality (RI-Mag). Table 1 shows comparable SLN detection rates between Magtrace and RI for patients who received delayed SLNB. Only 1/4 patients showed SLN metastasis. For this patient, the positive SLN was successfully detected by both modalities.

Conclusion: Magtrace has shown potential in delayed SLN detection and the use of Magtrace has prevented 79% (15/19) of enrolled patients from receiving unnecessary SLNB.

Table 1. Number of Lymph Nodes (LN) Detected by Magtrace/Radioisotope, Biopsied and Positive for Metastasis

Subject	Magtrace LN	Radioisotope LN	Biopsied LN	Positive LN
1 (RI-Mag)	3	4	4	1
2 (RI-Mag)	2	1	2	0
3 (Mag-RI)	0	0	21	0
4 (Mag-RI)	1	1	1	0

PO5-20-02

Secondary BRain metastases prevention after Isolated intracranial progression on trastuzumab/pertuzumab or T-DM1 in pts with aDvanced human epidermal Growth factor receptor 2+ brEast cancer with addition of Tucatinib (BRIDGET)

Presenting Author(s) and Co-Author(s):

S. Sammons. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

A. Van Swearingen. Duke Center for Brain and Spine Metastasis, United States

L. Noteware. Duke Cancer Center, United States

N. Bagegni. Washington University in St Louis School of Medicine, United States

K. Moulton. Duke University, United States

S. Threatt. Duke University, United States

D. Jagers. Duke University, United States

S. Shea. Duke University, United States

E. Lipp. Duke University, United States

E. Riley. Duke University, United States

S. Jung. Duke University, United States

G. Broadwater. Duke University, United States

M. Ross. VCU Health System, Henrico, Virginia, United States

K. Strickland. Novant Health Cancer Institute, Charlotte, NC, United States

S. Beyer. The Ohio State University Comprehensive Cancer Center, United States

A. Conlin. Providence Cancer Institute, United States

A. Morikawa. University of Michigan, United States

R. Murthy. MD ANDERSON CANCER CENTER, Houston, Texas, United States

C. Anders. Duke Cancer Institute, Durham, North Carolina, United States

Background: Despite treatment with trastuzumab-based therapy, up to half of patients with HER2+ advanced/metastatic breast cancer (MBC) will develop brain metastases (BrM). First-line therapy for advanced HER2+ MBC remains a taxane, trastuzumab, pertuzumab (TP) which demonstrates poor brain permeability. Isolated brain relapse with stable or absent extracranial disease remains a clinical problem in both the adjuvant (Untch et al., ESMO 2019 Congress) and metastatic settings (Noteware et al., Breast Cancer Res Treat. 2023). Current guidelines recommend continuing current systemic therapy in the setting of first isolated brain relapse following local therapy. Tucatinib, a brain-penetrable HER2-targeting tyrosine kinase inhibitor, when added to trastuzumab and capecitabine improves intracranial progression free survival (PFS) and overall survival (OS) in patients with stable or active HER2+ BrMs. We hypothesize that adding tucatinib to TP or T-DM1 in patients with HER2+ MBC with isolated brain relapse or progression could delay or prevent the development of further intracranial lesions and improve OS. Methods: BRIDGET (NCT05323955) is a single arm, phase II, multicenter study of tucatinib added to TP or T-DM1 after local therapy in patients with isolated brain relapse or progression. A total of 48 patients at 9 U.S. sites as part of the Hoosier Cancer Research Network (HCRN) with metastatic HER2+ breast cancer will be enrolled after 1st or 2nd BrM relapse or progression within 8 weeks of local therapy. Patients must currently be receiving standard of care treatment with TP or T-DM1 in the metastatic setting, or adjuvant trastuzumab-

based on T-DM1 therapy with isolated brain recurrence. Extracranial disease must be stable per RECISTv1.1 or absent. Patients may not have leptomeningeal disease or untreated brain lesions over 5 mm. Patients will receive continuous tucatinib added to their current therapy (TP or T-DM1). The primary objective is intracranial PFS compared to a historical control (H_0 : PFS < 5 months (mos), H_A : PFS > 8 mos) of the HER2CLIMB clinical trial where patients could continue on trial with isolated brain progression. In these patients, median time from brain progression to second progression or death was 7.6 mos (95% CI, 3.9 to 11.3 mos) in the tucatinib arm versus 3.1 mos (95% CI, 1.2 to 4.1 mos) in the control arm (Lin et al., J Clin Onc 2020). Secondary endpoints include PFS by RECISTv1.1, PFS of extracranial disease, locally treated versus new distant intracranial metastasis PFS, site of first progression (brain versus non-brain), OS, and toxicity in patients with BrM. Collection of correlative specimens including archival tissue, cerebrospinal fluid (optional), whole blood for ctDNA are planned. Patient-reported outcomes surveyed utilizing the FACT-BR and FACIT-Fatigue questionnaires are also included for future analyses. As of 7/06/23, accrual is 5 patients of the anticipated 48 patients overall, across 5 sites (Duke University, Dana Farber Cancer Institute, Ohio State University, Providence Portland Medical Center, and Washington University in St. Louis) currently open. An additional 4 sites are pending opening. Those interested in this trial can reach out to the study Principal Investigators, Carey Anders, MD (carey.anders@duke.edu) or Sarah Sammons, MD (sarahl_sammons@dfci.harvard.edu).

PO5-20-03

Phase I/II study of stereotactic radiosurgery with concurrent olaparib followed by adjuvant durvalumab and physician's choice systemic therapy in subjects with breast cancer brain metastases

Presenting Author(s) and Co-Author(s):

C. Shen. UNC Lineberger Comprehensive Cancer Center, United States

Y. Abdou. University of North Carolina, Chapel Hill, North Carolina, United States

L. Chen. Memorial Sloan Kettering Cancer Center, United States

X. Tan. UNC Lineberger Comprehensive Cancer Center, United States

G. Gupta. University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

M. Lobbous. Cleveland Clinic Brain Tumor and Neuro-Oncology Center, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

E. Stringer-Reasor. University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, Alabama, United States

C. Anders. Duke Cancer Institute, Durham, North Carolina, United States

BACKGROUND: Despite progress in the treatment of brain metastasis for HER2+ breast cancer, outcomes for patients with HER2-negative breast cancer brain metastases remain poor. Current standard of care consists of local therapies, including surgery and radiotherapy, followed by systemic therapy. Preclinical studies show inhibitors of poly(ADP-ribose) polymerase (PARP) are effective in combination with radiation therapy as a DNA damage response inhibitor. Triple-negative breast cancer (TNBC) has higher rates of homologous recombination deficiency compared to other breast cancer subtypes, and together with HER2-negative, BRCA-mutated breast cancer would be particularly sensitive to PARP inhibition. PARP inhibition has also demonstrated promising efficacy combined with immunotherapy in patients with germline BRCA-mutant and metastatic TNBC in clinical trials (MEDIOLA, TOPACIO). In addition, immunotherapy with stereotactic radiosurgery (SRS) is associated with favorable intracranial control and survival in patients with brain metastases. We hypothesize that this biologically-driven combination will enhance local control of SRS-treated brain metastases through synergy with PARP inhibition, while controlling micrometastatic disease in the brain and extracranial sites via potentiation of the immune response.

METHODS: We are conducting a multi-institution, Phase I/II trial of SRS plus olaparib, followed by durvalumab (with physician's choice systemic therapy), for patients with TNBC (any BRCA status) or HER2-negative with BRCA-mutated (germline or somatic) breast cancer brain metastases [NCT04711824]. A total of 41 patients are planned for enrollment at 8 sites. The primary objectives are to evaluate safety and tolerability (Phase I) and determine intracranial disease control at 6 months (Phase II) of this treatment combination. Secondary objectives include determining clinical activity via intracranial and global progression-free survival, overall survival, and intracranial and extracranial response rate. Exploratory objectives will assess potential biomarkers of treatment response, including changes in circulating tumor cells and DNA in blood and cerebrospinal fluid, germline and tumor mutations in DNA repair pathway genes, and PD-L1 expression, as well as quality of life and patient-reported outcomes. A surgical sub-study (n=5) will evaluate olaparib concentration/distribution in resected brain metastases. As of June 2023, cohort 2 of phase I has been completed without dose-limiting toxicity.

PO5-20-04

A Phase II Study of Ribociclib and Endocrine Treatment of Physician's Choice for Locoregional Recurrent, Resected Hormone Receptor Positive HER2 Negative Breast Cancer (RaPhLRR Study)

Presenting Author(s) and Co-Author(s):

O. Danciu. University of Illinois Cancer Center, Chicago, United States

N. Chan. NYU, United States

K. Wisinski. University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, United States

T. Millard. University of Virginia, United States

K. Kemmer. University of Michigan, United States

S. Phadke. University of Iowa, Iowa city, Iowa, United States

Z. Chen. University of Illinois, United States

A. Cuesta Fernandez. Orlando Health, United States

M. Clark. Parkview, United States

A. Conlin. Providence Cancer Institute, United States

C. Omene. Rutgers Cancer Institute of New Jersey, United States

S. Ehsani. University of Arizona, United States

S. Dublis. University of Michigan Health West, United States

V. Gadi. University of Illinois, United States

Background Hormone receptor positive (HR+) breast cancer (BC) is the most common subtype of BC (70-80%). This subset tends to have good prognosis, therefore most patients with localized disease have excellent long-term survival, approaching 100% 5-year relative survival. However, 10% of patients experience loco-regional recurrence (LRR) within 5 year of final surgical management of the primary disease-well within the typical treatment window of adjuvant endocrine therapy. Few studies exists to guide the systemic treatment of patients who have suffered LRR of HR+ HER2 - BC. The randomized controlled CALOR trial demonstrated no benefit to systemic cytotoxic chemotherapy for this subgroup of patients and persistent high rate of subsequent recurrences (50% within 10 years on LRR event). There is no standard of care for managing this patient population. The combination of ribociclib and endocrine therapy (ET) (fulvestrant and aromatase inhibitors) is FDA approved for management of unresectable recurrences and metastatic HR+HER- BC (MONALEESA trials). CDK4/6 inhibitors have been investigated in early BC setting too, several trials showing positive results (monarchE, NATALEE). Data is needed to investigate their use in patients with LRR. Trial design This is a multicenter, single arm phase II study to evaluate efficacy and safety of ribociclib and ET in patients with LRR of HR+HER2- BC. Treatment includes ribociclib for 36 months, 600 mg daily for 21 days, 28-day cycle plus physician's choice ET for 60 months (fulvestrant or AIs). Ribociclib dose was chosen based on approved dose in metastatic BC. Eligibility Criteria Patients ≥ 18 of age, with LRR of BC (ipsilateral breast, axilla, regional lymph nodes, chest wall), histologically confirmed estrogen receptor positive and/or progesterone receptor positive, HER 2 negative. Patients must have adequate local treatment for LRR (surgery and/or radiation) with negative microscopic margins, no evidence of distant metastatic disease. Prior treatment with neo-adjuvant and adjuvant chemotherapy and ET is allowed, no prior CDK 4/6 inhibitor in the last 12 months. Pre and post-menopausal women are allowed. Patient must

enroll within 6 months of the last local therapy. Specific aims Primary objective: to estimate subsequent recurrence-free survival (RFS) at 3 years for ribociclib when administered with ET in patients with HR + HER2- BC with adequately resected local recurrence. Secondary objectives: to estimate distant metastasis-free survival and overall survival, to evaluate safety and tolerability, to identify predictors of LRR. Correlative analysis will explore prognostic and predictive biomarkers of treatment with ribociclib and ET and potential molecular mechanisms of resistance to treatment. Statistical Methods From previous published data (J Clin Oncol. 2018 Apr 10;36(11):1073-1079), we assume that patients receiving standard of-care management following recurrence would have a recurrence free survival (RFS) rate of 80% at 3 years and that treatment with ribociclib + ET will increase it by 7%. We wish to have at least 80% power at that significance level of 0.0487 to correctly detect that improvement in RFS rate at 3 years from 80 to 87%. Because only an improvement in RFS rate is of clinical interest, we have a directional hypothesis, and have used a 1-sided alpha. Using a one-sample survival study design, with assumed accrual duration of 3-years and additional follow-up time of 3 years, the minimum sample size requirement is N=180 patients. Target accrual The minimum sample size requirement is N=180 patients. A bigger sample size of N=200 patients will achieve a power of at least 84%. Current accrual is 6/200. This study will be open at up to 35 sites. Contact information The study is being administered through the HCRN, it can be identified as BRE20-468, NCT05467891, ocdanciu@uic.edu

PO5-20-05

The FOR ME (Fostering Opportunities in Research through Messaging and Education) study: Using multiple qualitative methods to develop a culturally sensitive narrative intervention to promote equity in clinical trials.

Presenting Author(s) and Co-Author(s):

N. Hippalgaonkar. University of Illinois Chicago, United States

R. Nguyen. University of Illinois Chicago, United States

L. Carnahan. The University of Illinois at Chicago, United States

V. Henderson. Fred Hutchinson Cancer Center, United States

T. Mersha. University of Illinois at Chicago, United States

E. Cohn. Fred Hutchinson Cancer Center, United States

K. Salum. Fred Hutchinson Cancer Center, United States

A. Williams. University of Illinois at Chicago, United States

L. Coleman. Sisters Working It Out, United States

B. Brent. Sisters Working It Out, United States

A. Murphy. Equal Hope, United States

P. Thomas. Equal Hope, United States

P. Khosla. Mt. Sinai Hospital, United States

K. Hoskins. University of Illinois Chicago, United States

Background: Black women are more likely to present with advanced stage disease and to die following a breast cancer (BC) diagnosis compared to women from other racial/ethnic groups. In 2020, only 7.2% of enrollees in clinical trials that led to the approval of 3 novel drugs for breast cancer were Black. While there are many contributing factors to this inequity (i.e., tumor biology, social and structural health determinants, racial injustice, and differential access to and utilization of high-quality mammography, diagnostics, and therapies), persistent underrepresentation of Black patients in cancer clinical trials (CTs) slows scientific advancements.

Objective: The aim of this study is to develop, optimize, and test a narrative decision aid intervention (web-based video) for Black women diagnosed with BC to promote shared decision making and CT participation. The first aim is to conduct multiple qualitative methods with multi-level stakeholders to identify barriers, facilitators, and intervention priorities that would assist Black breast cancer patients to make informed decisions about participating in clinical trials. The second aim is to create a culturally sensitive, narrative intervention designed to support decision making and motivate Black breast cancer patients to participate in clinical trials. Aim 3 will then pilot a study to determine acceptability of the intervention among patients and assess whether it increases clinical trial participation in a safety net oncology practice.

Methods: Guided by community-based participatory research approaches, we used multiple qualitative methods (key informant interviews (KIIs) and story circles) to identify barriers and facilitators that support decision-making and CT participation. The KIIs, completed in-person, via phone, or video conferencing, were recorded and professionally transcribed. The research team used thematic analysis and inductive coding approaches. Next, interviews and focus groups will invite feedback on the educational/motivational content of the intervention and will

be used to develop a culturally sensitive script and story boards. A video production company will produce the narrative intervention. Finally, focus groups and interviews with participant cohorts will provide feedback on the completed intervention. Black women diagnosed with BC will view the intervention in an oncology clinic. Using a pretest/posttest design, we will analyze the acceptability of the intervention and its effect on intention to participate in clinical trials. We will then conduct a quasi-experimental study in a safety net oncology practice to determine whether the rate of clinical trial participation among Black breast cancer patients increases following implementation of the intervention as a standard component of new patient education.

Progress: Recruitment started in July 2022 and currently 30 of 30 interviews with patients are completed, 20 of 20 interviews with clinical stakeholders (oncologists and clinical trial staff) are completed, and 14 of 20 interviews with advocates and community partners are completed. Data collection and the analysis of the interviews and story circles is ongoing.

PO5-20-06

Paraneoplastic cerebellar degeneration in anti-Yo antibody and HER2-positive metastatic breast carcinoma

Presenting Author(s) and Co-Author(s):

Y. Kim. Rush University Medical Center, United States

A. Coogan. Rush University Medical Center, United States

A. Madrigrano. Rush University Medical Center, United States

Paraneoplastic cerebellar degeneration (PCD) in the context of breast carcinoma affects less than 1% of patients. In most cases, breast cancer diagnosis follows several months or even years after the onset of neurological symptoms. The first association between PCD and occult gynecologic cancers (breast or ovarian) was identified in 1938 with the discovery of antibodies directed against cytoplasmic antigens of Purkinje cells ("anti-Yo antibodies"). Since then, evidence has grown significantly to support anti-Yo antibodies as excellent diagnostic markers of PCD with underlying gynecologic and breast carcinoma.

This case study evaluates a 57-year-old female who initially presented with headache and subacute cerebellar ataxia. Her symptoms progressed over a period of three months with multiple falls, onset of speech difficulties, and diplopia. She also reported 30-pound weight loss, which she attributed to dieting and starting semaglutide. Magnetic resonance imaging (MRI) of the brain and spine were unremarkable and autoimmune workup was normal. Cerebral spinal fluid (CSF) and serum studies demonstrated positive anti-Yo antibodies. Computed tomography (CT) of the abdomen and pelvis showed an enlarged left axillary lymph node concerning for metastatic disease with a 1.2cm focus of asymmetric density in the central inferior left breast parenchyma. Diagnostic mammogram one year prior was reportedly normal. Ataxia symptoms improved after a course of empiric intravenous immunoglobulins and steroids.

Ultrasound-guided biopsy of the left axillary lymph node revealed metastatic mammary carcinoma: estrogen and progesterone receptor negative and human epidermal growth factor receptor 2 (HER2)-positive, cT0N2aM0, ypTxN1aM0, stage IIIa (AJCC 8th edition). She underwent further metastatic workup, including repeat CSF studies and MRI. MRI of the spine was remarkable for multiple hemangiomas throughout the cervical, thoracic, and lumbar spine, with subsequent unremarkable bone scan. MRI of the abdomen was remarkable for right hepatic lobe hemangioma and a right adrenal nodule. CSF studies showed no sign of metastases. After multidisciplinary discussion, TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) neoadjuvant therapy was initiated and repeat imaging demonstrated favorable treatment response with a shrinking axillary mass; no primary breast mass was identified. The patient underwent left sentinel lymph node biopsy with a positive frozen section intraoperative for invasive cancer, therefore proceeded with left axillary lymph node dissection. She was offered a mastectomy but elected for only axillary surgery. Pathology revealed 1 of 14 lymph nodes were positive for metastatic ductal carcinoma. She remains in a rehabilitation center and her ataxia is improving, but her functional status remains below baseline. She is undergoing radiation to whole breast and regional lymph nodes.

With this case, we aim to continue to build upon the limited base of the exceedingly rare presentation of breast cancer-associated paraneoplastic syndrome. In addition, several studies and case reports have demonstrated a strong correlation between HER2 overexpression and anti-Yo associated PCD. As we continue to diagnose and monitor breast cancer patients, we

could consider starting to screen for anti-Yo antibodies in HER2-positive patients to gain insight into a patient's prognosis and development of PCD.

PO5-20-07

A Case of Metastatic Breast Cancer to Soft Tissue of the Thigh

Presenting Author(s) and Co-Author(s):

R. Melissa. Rush University Medical Center, United States

J. Alexieva. Rush University Medical Center, United States

A. Coogan. Rush University Medical Center, United States

L. Hussein. John H. Stroger, Jr. Hospital of Cook County, United States

E. Marcus. John H. Stroger, Jr. Hospital of Cook County, United States

J. Wechsler. John H. Stroger, Jr. Hospital of Cook County, United States

Breast cancer is the most diagnosed cancer in women worldwide. The predominant cause of breast cancer mortality is metastatic disease with bone, lung, liver and brain being most common sites of metastasis. After melanoma, breast cancer is the most common cancer to have cutaneous metastatic disease and this presentation represents half of all cutaneous metastases. We are presenting a case of a 70-year-old female with distant recurrence of breast cancer to the left thigh.

A 70-year-old female presented to clinic with a palpable left breast mass noted July 2022. Her medical history was notable for right sided upper lobe stage IIIB squamous cell lung cancer diagnosed in 2013 treated with chemotherapy and chest radiation (RT), menopause at 25 years old following TAH/BSO for fibroids. Family history included prostate cancer and genetic testing was negative for pathogenic mutation. Diagnostic mammogram showed a lesion in the left breast at 9:00 of 1.4 cm x 1.2 cm x 1.4 cm, and biopsy showed grade 3 triple negative invasive ductal carcinoma (IDC). Her nodes were clinically and radiologically negative. She opted for breast conservation. In September of 2020 the patient had a left lumpectomy with sentinel lymph node biopsy. Final pathology (path) was pT1cN0 with two foci of IDC, grade 3, measuring 1.9x1.9x1.1 cm and 0.4x0.2x0.2 cm with negative margins. Two sentinel lymph nodes were negative for carcinoma. She received 4 cycles of doxorubicin and cyclophosphamide and started paclitaxel, but only completed 5/12 planned cycles. During these treatment cycles she was admitted twice for shortness of breath and found to have an exudative pleural effusion, repeat cytology was negative for malignancy at which point fluid did not recur. There was no CT evidence of lung nodules or plural thickening. Echocardiogram showed normal ejection fraction of 45%. PET scan was negative. Chemotherapy was stopped in February of 2021. Initial pre-operative discussion with radiation oncology indicated no contraindication to adjuvant RT. However, after simulation, it was deemed by radiation oncology that the patient was no longer a candidate for RT as during her lung cancer treatment, she had received RT of 69.4 Gy including the area of the current lumpectomy cavity. She then opted for bilateral mastectomy with immediate reconstruction in June 2021. Final path from both breasts showed no carcinoma.

In November of 2021 she was admitted for shortness of breath and on CT scan was noted to have a left sided lung nodule. The patient declined biopsy and underwent a left wedge resection in January of 2022. Final path showed a 2.2. cm carcinoma consistent with breast primary that was ER 0, PR 0, and Her 2 neu 1+. She was started on capecitabine with plan for 6 months of treatment but stopped taking this after one month due to severe pain in her hands and feet.

In November 2022 the patient noted a left thigh mass. Exam showed a firm, palpable thigh mass without overlying skin changes and core needle biopsy showed adenocarcinoma, favoring breast primary, ER 0, PR 0, HER 2 neu 2+ and FISH negative. PET scan showed no uptake in the chest abdomen or pelvis, however a 2.6x2.3x3.1 cm round mass in the left thigh was seen with SUV max of 8.6. She was started on trastuzumab-deruxtecan by medical oncology in December of 2022. The thigh tumor shrank significantly, however, patient discontinued after two infusions, citing intolerable hand weakness. She then received RT to the thigh. She was treated using 3D technique and 6 MV photons for a total dose of 5400 cGY, from February to March of 2023. Repeat PET June 2023 showed no avid uptake in the thigh. She has declined any additional systemic therapy.

Soft tissue metastasis in distant recurrent breast cancer is uncommon and little guidance exists on clinical management. In cases of metastatic disease to the skin, hormone positive lesions can be managed with hormonal therapy. Early detection and biopsy for receptor studies may help guide therapy in cases of distant soft tissue recurrence.

PO5-20-08

A Case of Multifocal Ductal Breast Carcinoma with Extension into Lobules and Concurrent Primary Colon Adenocarcinoma

Presenting Author(s) and Co-Author(s):

R. Jafry. Aga Khan Medical University, United States

H. Khan. The University Health Science Center at Houston, United States

J. Jones. UT Health Houston, Houston, Texas, United States

Background Multifocal (MF) multicentric breast cancer is a form of breast cancer that consists of disease independently developing at various locations due to a tumor clone spreading within the ductal complex. Multifocal breast cancer is associated with increased local recurrence. Our case highlights an example of multifocal breast cancer and addresses treatment challenges. **Case presentation** The patient is a 52-year-old African American female with a history of HCV cirrhosis, diabetes mellitus, and hypertension who presented with a palpable 4 cm right breast mass, without adenopathy, clinically Stage II, T2N0. Mammogram revealed a 2.5 cm right breast mass and three right level 1 axillary nodes with biopsy confirming invasive ductal carcinoma with extension into the lobules, ER positive (3%)/PR-/HER2-, Ki-67 95%.

Neoadjuvant paclitaxel, carboplatin, and pembrolizumab was initiated but she incurred complications of decompensated liver cirrhosis after the second cycle and treatment was held. After 2 cycles her tumor was not palpable, and surgery was recommended, but due to COVID infection and concurrent decompensated liver failure surgery management was delayed. She underwent staged surgery with partial mastectomy without lymph node exploration. Histopathology showed DCIS grade 3 with extension into lobules and invasive ductal carcinoma with no lymphovascular invasion and all margins were negative, pathological stage ypT3NxM0. Immunohistochemistry demonstrated partial ER+ (50%)/PR-/HER2-, Ki-67 80%.

She was given 4 cycles of adjuvant cyclophosphamide, adriamycin, pembrolizumab and continued on maintenance pembrolizumab. The patient was found with anemia out of proportion to chemotherapy and underwent colonoscopy that showed a colonic mass. Biopsy showed a primary moderately differentiated colonic adenocarcinoma. Her re-excision with new margins for partial mastectomy had negative margins, and 2 negative sentinel lymph nodes for ypN0.

Genetic testing was negative. She continued on adjuvant immunotherapy with pembrolizumab for breast cancer. She is planned to start on adjuvant anastrozole. Patient has completed adjuvant radiation treatment and has no new complaints. She is pending curative intent completion colectomy for colon cancer.

Discussion This case of MF breast cancer is significant, as one foci was ER negative, which responded to neoadjuvant chemoimmunotherapy and other ER positive that did not respond to treatment and was surgically excised. The pathology report from the surgical specimen revealed DCIS with extension into the lobules. Due to her tenuous clinical condition, she had staged surgeries for breast cancer, and now colon cancer. Genetic testing is negative.

Currently, there is insufficient data to suggest which surgical approach is preferred in MF breast cancer. Based on the literature, breast conservation therapy (BCT) is a feasible option and is oncologically safe. Due to the patients' medical condition and infections, it was felt a less invasive surgery could offer cure and minimize complications. Our patient underwent

neoadjuvant chemoimmunotherapy, followed by partial mastectomy, adjuvant chemoimmunotherapy, second staged completion breast surgery, radiation therapy, and anti-estrogen therapy.

MF breast cancer is associated with increased lymph node involvement. A 2022 meta-analysis found that multifocal and multicentric breast cancer has a slightly increased risk of death as compared to unifocal tumors. Lastly, our patient is African American, and multifocal tumors occur with a higher incidence in African Americans (43.4%) and Asian patients (37%) as compared to whites (28.9%). This case of breast cancer highlights treatment challenges in a case of multifocal multicentric breast cancer occurring concurrently with a secondary primary colonic cancer.

PO5-20-09

LOCOREGIONAL MANAGEMENT OF DE NOVO STAGE IV HORMONE-POSITIVE BREAST CARCINOMA AFTER CDK 4/6 INHIBITOR TREATMENT

Presenting Author(s) and Co-Author(s):

R. Abella. St. Luke's Medical Center, Quezon City, National Capital Region, Philippines

R. Li. St. Luke's Medical Center, Quezon City, National Capital Region, Philippines

Systemic therapy remains the backbone for treatment of metastatic breast carcinoma. Locoregional treatment of the primary tumor remains controversial. While it has an established role in the palliative setting, its survival benefit remains unclear. The rationale behind locoregional approach is the reduction of tumor burden and the removal of cancer stem cells which may propagate the disease. In previous literature, hormone-positive breast cancer seems to be the best candidate for locoregional treatment in the presence of synchronous metastases. We present a case of a 43 year-old, female, with no known comorbidities, who sought consult due to note of a hard lump on her right breast. Core needle biopsy of the right breast mass was performed which showed invasive breast carcinoma, no special type, Nottingham histologic grade 2. On immunohistochemistry, tumor was ER +8, PR +8, Ki 67 90%, Her-2 neu negative. Baseline positron emission tomography/CT (PET/CT) scan showed hypermetabolic, heterogeneously-enhancing lobulated right breast mass, 3 x 6.7 x 7.7 cm, with smaller hypermetabolic adjacent nodules. There was also note of multiple enhancing, hypermetabolic lung and pleural nodules, and lymphadenopathies in the mediastinal, right axillary, right cardiophrenic and perigastric areas. Well-defined, hypermetabolic heterogeneously hypoenhancing masses were also seen in segments II and VII of the liver. There was also note of right-sided pleural effusion. Ultrasound-guided thoracentesis was done which turned positive for malignant cells on pleural fluid analysis. She underwent 4 cycles of chemotherapy with Doxorubicin and Paclitaxel. Reevaluation PET-CT scan revealed partial response. Patient was then started on Ribociclib plus Letrozole with ovarian function suppression for 18 months. On latest reevaluation PET/CT scan, there was no evidence of hypermetabolic metastatic disease, with demonstration of hypermetabolic activity only in the right breast. The patient then underwent right total mastectomy, with histopathologic findings of residual invasive carcinoma, Nottingham histologic grade 3, residual tumor size of 3.5 cm, with 95% tumor cellularity and lymphovascular invasion identified, ypT2. All surgical margins were negative for tumor. Currently, the patient has no evidence of disease, with ribociclib and letrozole continued until disease progression or unacceptable toxicity. In this case, surgery of the primary tumor was performed in the presence of a responsive metastatic disease, with the primary tumor being the only evidence of disease. With the advent of newer therapy options like cyclin-dependent kinase 4/6 inhibitors offering outstanding survival benefit for metastatic disease, a more aggressive and synergistic approach with locoregional therapy may be done to eradicate the tumor burden, translating to better long-term survival. Locoregional management of the primary tumor should be discussed in the context of a multidisciplinary team approach and should be individualized based on the individual patient's need.

PO5-20-10

Treatment with CDK4/6 Inhibitor in a Patient with Metastatic Breast Cancer Causing Myelophthisis

Presenting Author(s) and Co-Author(s):

N. Dahake. Temple University, Philadelphia, Pennsylvania, United States

J. Senchak. Fox Chase Cancer Center, United States

J. Nasibli. Fox Chase Cancer Center, United States

J. Incorvati. Fox Chase Cancer Center, United States

Background: Symptomatic bone marrow metastasis causing myelophthisis is a rare manifestation of metastatic breast cancer, indicating a poor prognosis due to significant cytopenias. CDK4/6 inhibitors are first-line therapies for metastatic hormone-positive breast cancer but remain an unclear choice in breast cancer patients with significant cytopenias due to associated hematological adverse effects. We present a case of biopsy-proven hormone-positive breast cancer with bone marrow infiltration causing profound pancytopenia. CDK4/6 inhibitors were safely administered despite their cytopenic effects. Case Presentation: A 59-year-old female presented after an abnormal annual mammogram and biopsy showed calcifications stromal fibrosis, cyst formation, and usual ductal hyperplasia in the right upper outer quadrant. One month later, she presented to an outside hospital with gingival bleeding, epistaxis, progressive dyspnea on exertion, and generalized weakness. Labs showed severe anemia with a hemoglobin of 4.8 g/dL (baseline 12.1 g/dL), thrombocytopenia with platelets of 5 K/mm (baseline 215 K/mm), LDH of 879, reticulocyte count of 5%, and negative direct Coombs test. Peripheral smear showed no schistocytes, but showed nucleated RBCs, severely reduced platelets, and occasional giant platelets. The patient was treated for presumed ITP, and the presence of nucleated RBCs prompted bone marrow biopsy which confirmed metastatic invasive lobular carcinoma breast cancer (ER 90-95%, PR 90-95%, HER2 1+). She was discharged on letrozole 2.5 mg daily with close outpatient oncologic follow-up. One week later, she presented to our institution with persistent symptomatic anemia and thrombocytopenia. Inpatient systemic therapy was begun using dose-reduced Palbociclib (75mg) and letrozole with close CBC monitoring while also receiving packed red blood cells (goal >6.5) and platelet transfusions (goal >10). Repeat bone marrow biopsy showed extensive marrow fibrosis, but no significant hematopoietic elements. ADAMTS13 was 134%, ruling out TTP, and she was treated again for presumed ITP with dexamethasone and IVIG. Throughout the 4-week admission, her right breast mass decreased in size and she was discharged after completing 3 weeks of Palbociclib with biweekly outpatient transfusions. During follow-up, the patient's hemoglobin and platelets slowly started to respond allowing her to become transfusion-independent and allowing dose escalation. Restaging scans 2 months after hospitalization showed an overall improvement of disease burden. The patient continued to do well for almost 18 months, however, later redeveloped visceral crisis and is responding to chemotherapy. Discussion: There is limited data on the management of breast cancer with bone marrow infiltration at presentation. A wide range of survival data in different case reports exists, ranging from 5 to 44 months. However, chemotherapy was used in these studies rather than CDK4/6 inhibitors. By far, cytopenias are the most concerning grade 3 and 4 side effect of Palbociclib. Data from the PALOMA-1 trial suggest that hematologic toxicities, specifically neutropenia, were different from those associated with cytotoxic chemotherapies and are more transient and reversible in nature. Studies have examined the in vitro mechanism of bone marrow suppression in Palbociclib versus cytotoxic chemotherapy, and its cytostatic effect on neutrophil precursors allows for hematological toxicities to be transient. With strong supportive care

measures, patients in bone marrow visceral crisis can be safely treated with cytopenic CDK4/6 inhibitors.

PO5-20-11

Synchronous Breast Cancer and Pheochromocytoma: A Case Series

Presenting Author(s) and Co-Author(s):

N. Dahake. Temple University, Philadelphia, Pennsylvania, United States

A. Tushir. Temple University, United States

A. Padmanabhan. Fox Chase Cancer Center, United States

Background:

Pheochromocytomas are rare, although literature suggests a rising incidence due to the widespread use of sensitive imaging modalities. Synchronous presentation of breast cancer with a pheochromocytoma is exceedingly rare with only one case documented in the literature. We present two cases of malignancy in the breast in which pheochromocytomas were incidentally detected during workup and management with vastly different presentations.

Case Presentation:

Two patients presented with breast cancer and were secondarily diagnosed with pheochromocytoma.

Patient 1 is a 48-year-old postmenopausal female with a history of intraductal papilloma four years prior, who presented with right breast nipple discharge. Diagnostic mammogram showed a right breast mass and biopsy confirmed an intraductal papilloma with intermediate-grade DCIS, ER+/PR-. She had no family history of cancer or PGL/PPC. During a scheduled lumpectomy, she developed hypoxia, hypotension, and flash pulmonary edema requiring intubation and ECMO with prolonged ICU stay and long recovery with tracheostomy for four months. Contrast-enhanced CT of her abdomen showed a 9 cm right adrenal mass. Serum and urine metanephrines were markedly elevated, and it was determined that she had an adrenal crisis secondary to undiagnosed pheochromocytoma. She completed treatment for DCIS with lumpectomy and radiation and is currently on adjuvant anastrozole. She additionally had an adrenalectomy for pheochromocytoma, which was found to be stage PASS 2. Subsequent genetic testing confirmed the absence of germline mutations associated with hereditary PGL/PPC or breast cancer.

Patient 2 is a 57-year-old female presenting with a history of left breast mass she first noted a year ago, with newly found nipple retraction and skin changes. Biopsy showed invasive ductal carcinoma of the breast, G3, Stage IIIA, pT3N2aM0, ER 95%/PR-/Her2- (IHC 0). Staging PET scan showed a 3.4 cm hypermetabolic left adrenal mass in addition to the breast mass and left axillary adenopathy. Serum and urine metanephrines were elevated, and pheochromocytoma was diagnosed. Family history was positive only for pancreatic cancer in a maternal aunt. Comprehensive genotype testing was negative for hereditary breast cancer and PGL/PCC syndromes. She was concomitantly treated with a radical mastectomy for breast cancer and a left adrenalectomy and tolerated the procedure well as she received perioperative alpha-adrenergic blockade with doxazosin. She has received chemotherapy and radiation for breast cancer treatment and is currently on adjuvant anastrozole. The adrenal mass was confirmed to be a pheochromocytoma PASS 2-3.

Discussion:

We present two unique cases of breast cancer and pheochromocytomas discovered in tandem with variable clinical manifestations. It is extremely uncommon to have a presentation of

primary breast malignancy concomitantly with pheochromocytoma, and we demonstrate two cases that occurred within months of one another at our facility.

During the first case, metastatic workup was not indicated for DCIS. However, during the seemingly benign lumpectomy procedure, the patient experienced significant complications, leading to intense ICU management, intubation, and tracheostomy. In the second case, a metastatic workup was completed due to locally advanced breast cancer where the adrenal mass was detected and a pheochromocytoma was diagnosed prior to surgery. This allowed both cancers to be resected simultaneously and safely. This series demonstrates the importance of keeping pheochromocytomas in the differential during the workup of adrenal masses prior to surgical interventions. Additionally, they demonstrate how the usual workup and management of breast cancer does not take into account these rare but significant diagnoses, and that can result in fatal consequences.

PO5-20-12

A Case of Bilateral Breast Cancer in a patient on Ocrelizumab

Presenting Author(s) and Co-Author(s):

K. Mehra. Saint Vincent Hospital, Worcester, Massachusetts, United States

M. Hejazi. Hartford Healthcare Medical Group, United States

Background: Ocrelizumab is an anti-CD20 B cell depleting monoclonal antibodies that was FDA approved in 2017 for Relapsing-remitting multiple sclerosis and primary progressive multiple sclerosis based on two large phase III trials (OPERA I and ORATORIO)¹. In these trials, patients being treated with Ocrelizumab developed more malignancies compared to placebo. Among these cancers, breast cancer was prominent occurring in about 0.5-0.8% of the patients in the Ocrelizumab group as opposed to 0% in the placebo group. Here we present a case of bilateral breast cancer in a patient with Multiple Sclerosis (MS) treated with Ocrelizumab. Case Presentation A 66-year-old woman with a long-standing history of relapsing-remitting multiple sclerosis (MS) presented to us with concerns of bilateral masses on a screening mammogram. She was diagnosed with MS 30 years prior to presentation and was initially treated with multiple immunomodulators. However, she had progression of disease and was started on Ocrelizumab two years prior to presentation. She was up to date with her screening mammograms which had been unrevealing till now. Family history was significant for breast cancer in her grandmother in her 70s. Her annual mammogram screening showed bilateral irregular masses. A subsequent right breast ultrasound showed three breast masses (1cm, 0.5cm and 0.5cm respectively) and her left breast showed a 0.5 cm mass. Biopsy from the right breast showed invasive ductal and lobular carcinoma (ER+, PR+, HER2-) and that from the left breast showed invasive lobular carcinoma (ER+, PR+, HER2-). She underwent bilateral mastectomies and sentinel lymph node biopsies. The surgical margins and lymph nodes were negative for malignancy hence radiation was not warranted. Genetic testing revealed one pathogenic variant in MSH3 but was negative for BRCA1 and 2. Since her Oncotype dx score was low, adjuvant chemotherapy was not offered. She was started on aromatase inhibitor and her Ocrelizumab was permanently discontinued.

Discussion Ocrelizumab is one of the immunomodulator drugs for MS with a probable mechanism being B-cell depletion. The mechanism of how it causes breast cancer is unknown. However, suggested theory is that B cell inhibitors can increase the risk of breast cancer by inhibiting the potentially protective role of the B cells. The B cells are thought to play a role in the tumor micro-environments as antigen presenting cells and activators of natural killer and cytolytic T cells targeted toward lysis of tumors. Also, B cell presence, specifically CD20 B cells, is linked to a better prognosis in breast cancer. One study has also pointed out the importance of timing of anti-b cell therapy in relation to cancer morbidity. Treatment of mice with Anti-CD20 therapy prior to tumor challenge did not result in cancer metastasis. Whereas post tumor challenge, there was increased tumor cell survival and metastasis.

Our patient although had a family history of breast cancer, did not have a genetic mutation that could have contributed to her breast cancer. Her breast cancer developed after her therapy with Ocrelizumab hence raising suspicion for causation. With rise in the use of immunosuppressive therapies, further data is needed to delineate pathogenesis. Women with MS have lower all-cause survival after breast cancer diagnosis than women without MS. Hence it is important to identify any risk factors or therapies that might be associated with increased risk of cancer.

PO5-21-01

Carcinoma en cuirasse- a rare, but striking, cutaneous manifestation of metastatic breast cancer

Presenting Author(s) and Co-Author(s):

M. Godbole. Henry Ford Cancer Institute, Henry Ford Health System, Detroit, Michigan, United States

K. Wani. Henry Ford Health, United States

S. Zia. Henry Ford Health, United States

V. Dabak. Henry Ford Cancer Institute, Henry Ford Health System, Detroit, Michigan, United States

Introduction:

Carcinoma en cuirasse is a rare cutaneous metastatic presentation most commonly arising from primary breast cancers, typically after mastectomy. It appears like cellulitis and later develops into thickened rough patches of skin and even nodules. Carcinoma en cuirasse holds a poor prognosis, and treatment is difficult. Chemotherapeutic agents are unable to reach the tumor cells necessary, and radiation is ineffective because of skin curvature.

Case Presentation:

We report a female in her 70s with prior history of left breast ductal carcinoma in situ status post-radiation and lumpectomy, who presented with skin thickening of the left breast and solid masses in bilateral breasts 10 years later. Biopsy showed invasive ductal carcinoma of left breast (estrogen receptor [ER]/progesterone receptor positive [PR], human epidermal growth factor receptor-2 [HER2] negative) and ductal carcinoma in situ of right breast (ER/PR positive). She underwent right breast lumpectomy; however, the left breast mastectomy was aborted due to worsening of her skin findings on preoperative examination. An excisional skin biopsy revealed poorly differentiated invasive ductal carcinoma involving the dermis, deep dermis and focally involving the epidermis. Her diagnosis changed to stage 4 breast cancer, specifically carcinoma en cuirasse. Systemic treatment was initiated with palbociclib and letrozole and subsequently, she underwent left breast mastectomy given an excellent response to initial therapy. Surgical biopsy interestingly was HER2 positive and therefore her regimen was changed to taxotere, trastuzumab and pertuzumab. She completed adjuvant treatment and has been on maintenance trastuzumab along with letrozole currently and is doing well 5 years later with negative PET scans.

Discussion:

Our case is unique due to diagnosis of carcinoma en cuirasse before mastectomy, change in HER2 receptor status during treatment and excellent response to therapy with ongoing response to date. We think that an early diagnosis as well as targeted treatment could be the possible reasons for prolonged survival of more than 5 years.

Conclusion:

Any unexplained skin findings in breast cancer patients should prompt consideration of carcinoma en cuirasse. With ongoing treatment advances, many newer therapy options are available for metastatic breast cancer. Based on our case, we think that patients with this disease can have better outcomes.

PO5-21-02

Breast cancer screening based on physical breast examination: ITABERAÍ randomized trial

Presenting Author(s) and Co-Author(s):

R. Freitas-Junior. Federal University of Goiás & Araujo Jorge Cancer Hospital, Goiânia, Goiás, Brazil

D. Rodrigues. Federal University of Goiás, Brazil

R. Corrêa. Federal University of Goiás, Brazil

L. Soares. Federal University of Goiás, Seoul, Brazil

Introduction: Approximately 70% of the Brazilian population depends on the public healthcare system (Sistema Único de Saúde - SUS). However, only 16% of SUS users have access to mammography for breast cancer screening, which necessitates the evaluation of new strategies to reduce mortality from the disease, including expanding physical breast examination (PBE) by non-medical professionals. Within the primary healthcare network, the Community Health Agent (CHA) is a technical-level professional who performs activities through home visits. The primary objective of this study is to evaluate the effectiveness of screening actions based on PBE performed by CHA in reducing advanced tumors (Stage III and IV) and breast cancer mortality rates. Secondary objectives include comparing the number of breast cancer diagnoses between the groups, establishing the overdiagnosis rate, comparing cancer-specific survival, comparing overall survival, comparing the number of diagnostic procedures, assessing the interval between the first symptom and diagnosis, evaluating the interval between diagnosis and the start of treatment, and comparing the financial cost of diagnosis and treatment for breast cancer patients. **Trial design:** Multicenter, phase III, prospective, randomized clinical trial. The target population comprises women aged 40 years or older and users of SUS. The randomization process will be carried out based on the spatial analysis of each participating center, using sociodemographic information on women from each macroregion to verify the homogeneity of data between groups. **Intervention:** After randomization, CHA in each group underwent training at different times. CHA in the CG received guidance on breast cancer screening and prevention according to Ministry of Health recommendations, while CHA in the IG received the same guidance and participated in theoretical and practical training for PBE (only female professionals). **Variables and data collection:** An application was developed to be installed on mobile devices, which the CHA used during home visits. The graphical interface of the application was developed in Dart/Flutter. For the backend, Python programming language was used along with the Flask framework to create the Application Programming Interface (API) responsible for the communication between the database and the application. The MySQL software was used for the relational database. The variables used for building the application included sociodemographic data, lifestyle habits, medical history, information on previous examinations, and physical breast examination. **Statistical analysis:** For the analyses, the database will be exported to the REDCap (Research Electronic Data Capture) platform. The calculations were defined to detect a reduction in severe cases and mortality (10% and 20%, respectively). For this purpose, a sample power of 80% and a Type I error of 5% were adopted after adjusting for intraclass correlation and sampling effect (0.032 and 1.892, respectively). The calculations were estimated using nQuery software (version 9.1). For the city of Itaberaí, a population of 1,894 women was estimated in each group, resulting in a total of 3,788. **Present and target accrual:** The trial was activated in December 2022, and as of June 30th, 2023, 2,467 patients had been accrued. The study will last for 16 years, and the first data analyses will be conducted in 2024. Registration and ethical

aspects: The trial is registered in ReBEC (Brazilian register): RBR-39vm2nd. Contact information: Prof. Dr. Ruffo Freitas-Junior, Federal University of Goiás, ruffojr@terra.com.br.

PO5-21-03

Cosmetic assessment in the UNICANCER HypoG-01 trial: a deep learning approach

Presenting Author(s) and Co-Author(s):

- A. Cafaro. TheraPanacea, Paris, France, United States
- A. Ruffier. Centre Jean Bernard - Clinique Victor Hugo - Institut inter-régional de Cancérologie (ILC) - CCS, 64 Rue de Degré, 72000 Le Mans, France, United States
- G. Bielinyte. Institut Gustave-Roussy, Département d'oncologie radiothérapie, Villejuif, France, United States
- Y. Kirova. Institut Curie, Paris, Ile-de-France, France
- S. Racadot. Centre Léon Bérard, Lyon, France, United States
- M. Benchalal. Centre Eugène Marquis, Rennes, France, United States
- J. Clavier. ICANS - Institut de cancérologie Strasbourg Europe, Strasbourg, France, United States
- c. charra-brunaud. Institut de Cancérologie de Lorraine, vandoeuvre les nancy, France
- M. Chand-Fouche. Département de radiothérapie, Centre Antoine Lacassagne, Nice, France, United States
- D. Argo-Leignel. Hôpital du Scorff, Lorient, France, United States
- K. Peignaux. Centre Régional De Lutte Contre Le Cancer Georges-François Leclerc C.G.F.L, Dijon, France, United States
- A. Benyoucef. Centre Henri Becquerel, Rouen, France, United States
- D. Pasquier. Centre Oscar Lambret, Lille, France, United States
- P. Guilbert. Institut Godinot, United States
- J. Blanchecotte. Institut de Cancérologie de l'Ouest (ICO) - Site d'Angers, Angers, France, United States
- A. Tallet. Paoli-Calmettes Institute, Marseille (France), United States
- A. Petit. Institut Bergonié, United States
- G. Bernadou. CORT37, Chambray-lès-Tours, France, United States
- X. Zasadny. Site Chénieux - Polyclinique de Limoges, Limoges, France, United States
- C. Lemanski. ICM - Montpellier, Montpellier, France, United States
- J. Fourquet. C.H. de Lens, Lens, France, United States
- E. Malaurie. C.H. Intercommunal Créteil, Créteil, France, United States
- H. Kouto. Centre Galilée, Lille, France, United States
- C. Massabeau. Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France, United States
- A. Henni. Institut de cancerologie des haut de France, Beuvry, France, United States
- P. Regnault. Clinique Bordeaux Tivoli-Ducos, Bordeaux, France, United States
- A. Belliere. Centre Jean Perrin, Clermont-Ferrand, France, United States
- Y. Belkacemi. Henri Mondor University Hospital, France
- M. Le Blanc-Onfroy. Institut de Cancérologie de l'Ouest, ICO - René Gauducheau, Nantes, France, United States

J. Geffrelot. Centre Francois Baclesse, United States
J. Prevost. Centre Pierre Curie, Beuvry, France, United States
E. Karamouza. Gustave Roussy, Bureau Biostatistique and Epidémiologie, F-94805, VILLEJUIF France/Oncostat U1018, Inserm, Université Paris-Saclay, Ligue Contre le Cancer, F-94805, VILLEJUIF France, United States
S. Michiels. Gustave Roussy, Villejuif, France, United States
M. Bergeaud. UNICANCER, Unitrad, Paris, France, United States
A. Lamrani-Ghaouti. UNICANCER, Unitrad, Paris, France, United States
S. Romdhani. TheraPanacea, Paris, France, United States
A. Bombezin-Domino. TheraPanacea, Paris, France, United States
N. Paragios. CentraleSupélec. University of Paris-Saclay., United States
S. Rivera. Gustave Roussy, villejuif, United States

Introduction

Cosmetic evaluation after breast cancer treatment is a clinical indicator of toxicity. User bias and inter-subject variability hamper this objective. To address this limitation, a deep learning approach was developed on the basis of the HYPOG-01 trial (NCT03127995), a phase III trial comparing hypo to normo-fractionated radiotherapy (RT) in breast cancer patients requiring nodal irradiation.

Material and Methods

Cosmetic outcomes using the Harris scale were assessed by a radiation oncologist using a 4-level rating system from excellent to poor. This evaluation involved photographs from 581 female patients included in the intention-to-treat population of the HYPOG-01 study analysis (mastectomy/pamectomy and non-usable cases excluded). Front images were taken with the arms along the body at baseline, 3-weeks after radiotherapy start, end of treatment, then 6 months and every year after randomization up to 5 years.

Comparing manual landmark annotation with the semi-automated software BCCT.core©, the agreement rate was moderate, with an intra-class correlation coefficient (ICC) of 0.66 (95%CI 0.57-0.73). The dataset consisted of 2,348 images, which were divided into exclusive patient-based training (1,661), validation (308), and testing (377) datasets. The distribution of Harris scores in the dataset was highly imbalanced: 7% excellent, 33% good, 45% fair, and 15% poor.

Nipple landmarks were used as landmarks to address picture acquisition variations by cropping and resizing images to 224x224 resolution. Feature extraction was performed using a Swin-TransformerV2, an advanced attention-based vision model initially trained on ImageNet. Newly integrated fully connected layers categorized the extracted features.

The model was trained for 300 epochs, and the highest F1-score model was selected. Asymmetry in texture, marks, and breast geometry played a crucial role in Harris scoring. To improve the model's performance, we generated symmetrical images from the region of interest, averaging them with the original images, and we incorporated the timestamps from image captures as an additional influencing factor. We employed techniques such as contrast modulation, lighting adjustments, and geometric transformations to augment the dataset, introducing additional variations and enhancing the model's generalization and accuracy.

Results

The performance of our model was evaluated using balanced binary classification, multi-class

accuracy, and F1-score. Comparatively, our model performed similarly to BCCT in terms of overall accuracy but demonstrated better performance in separating multiple classes, as indicated in Table 1. In Table 2, we present a confusion matrix that provides insights into the model's performance

Conclusion

The proposed solution simplifies and accelerates the evaluation process by utilizing only two nipple landmarks, surpassing manual and semi-automated tools. This advancement opens doors for automated, large-scale cosmetic toxicity evaluation. Continuous improvement and validation contribute to its robustness and reinforce its significant impact in assessing cosmetic outcomes after breast cancer treatment.

Evaluation of performance on the test set (only on cases with evaluation by BCCT (327 images)).

	F1 score (4 classes)	Balanced Multi-class Accuracy (4 classes)	Balanced Binary Accuracy (Excellent & Good vs Fair & Poor)
BCCT	0.41	0.49	0.69
Tested model	0.42	0.54	0.68

Confusion matrix between our predictions and the labels on the test set (only on cases with evaluation by BCCT (327 images)).

Prediction \ True	Excellent (12)	Good (109)	Fair (167)	Poor (39)
Excellent	50%	24%	12%	0%
Good	50%	49%	32%	5%
Fair	0%	26%	43%	18%
Poor	0%	1%	13%	77%

PO5-21-04

Leveraging Digital Twins for Patient Stratification and Treatment Optimization in geriatric oncology: A Breast Cancer Multivariate Clustering Analysis

Presenting Author(s) and Co-Author(s):

P. HEUDEL. centre leon berard, United States

M. Ahmed. Geodaisics, United States

F. Renard. Geodaisics, United States

Context: Geriatric oncology necessitates an accurate evaluation of a patient's health status and cancer characteristics. Digital twins, virtual replicas of a patient and their cancer, can aid in predicting real-world behaviors and support therapeutic decision-making. Objectives: This study aims to demonstrate how digital twins can optimize treatments by simulating various scenarios based on the individual characteristics of patients and their cancers. Methods: Creation of a digital twin relies on the use of advanced manifold learning technologies. A model is built to represent the variability present in the reference cohort, capturing complex relationships and inherent data structures. A reference digital twin is generated by drawing samples from this model, thus reflecting the characteristics distribution of the reference population. Stratification (MeanShift algorithm) enables cohort structure visualization and classical statistics estimation for each stratum. Multivariate analysis was performed on a French monocentric population of 1345 patients aged over 70 years who underwent surgery for HER2-negative early breast cancer. Results: 8 cluster, created by manifold learning based on biological, demographic, and tumoral variables, exhibits unique five-year survival rates and influential factors. The clusters represent specific patient subgroups, each with its distinct set of characteristics and prognostic indicators. Table 1 provides a summary of these variables' averages within each cluster. we can thus see that the variables of clusters 3 and 6 (including only HR+ cancers) do not show statistically significant differences, unlike their 5-year survival rates (cluster 3 : 80,9% (CI95 :70-88.5) and 63.9% (CI95 :47.6-77.5) for cluster 6, $p = 0,04$). Provided with model results, the relative importance of these variables varies from one cluster to another, underscoring the heterogeneity among patient subgroups. Interestingly, Hormonal receptor status, nodal involvement and tumoral grade were not the predominant variables in these clusters, which challenges traditional perspectives. Table 1 : Mean value of variables per cluster (SBR grade 0=grade 1 and 2 ; 1= grade 3) Discussion: The findings underscore the vast variability of individual variable importance across clusters. Digital twins enabled the modeling of these complex interactions, providing valuable insights for clinical decision-making. Conclusion: Digital twins offer a valuable tool for personalizing care in oncogeriatrics, facilitating the identification of patient subgroups, yielding more accurate treatment outcomes, and guiding future research directions. The results affirm that incorporating digital twins into oncogeriatric care could potentially lead to the enhanced personalization of therapeutic approaches, ultimately improving patient outcomes.

Cluster	0	1	2	3	4	5	6	7
Age	78,8	76,4	76,8	76	76,5	77,6	75	80,4
Body mass index	34,5	27	25,9	25,7	26,1	24,2	25,3	26,3
Antecedents/comorbidity	0,5	1	0	0	0,4	0,4	0	0,8
Hemoglobin (g/dL)	13,3	13,3	13,5	12,7	13,1	12,9	14	12,1
Lymphocytes (G/L)	1,7	2	2,5	2	3	1,8	1,7	1,7
Tumor size	51	21,4	25,1	17,7	44,9	25,2	19,4	24
Axillary lymph nodes involvement	1,5	0,4	0,6	0,9	10,2	0,8	0,3	0,6
Hormone receptor status	0,6	1	1	1	0,7	0	1	1
SBR grade	0,3	0	0,9	0	0,4	0,8	0	0,8

Table 1 : Mean value of variables per cluster (SBR grade 0=grade 1 and 2 ; 1= grade 3)

PO5-21-05

An Endocrine Resistant-Related Gene Signature Revealing the Tumor Microenvironment to Predict the Prognosis of Hormone Receptor-Positive Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

X. Kang. Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China., United States

J. Liu. Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China., United States

X. Wang. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, United States

Key words: breast cancer; hormone receptor-positive; predictive model; prognosis; endocrine therapy; drug resistance

Hormone receptor positive (HR+) breast cancer is the most common type of breast cancer, accounting for approximately 70% of all breast cancer, in whom endocrine therapy plays a vital role. However, the limited effectiveness of endocrine therapy due to intricate mechanisms of drug resistance poses a significant challenge in treating certain patients. Therefore, it is imperative to identify novel indicators of endocrine resistance and develop new models for predicting recurrence-free survival (RFS) in patients with HR+ breast cancer. In this study, we successfully established an endocrine resistance-related risk model based on multicenter RNA sequencing data. This model could represent tumor microenvironment characteristics and provide valuable insights into predicting the prognosis of HR+ breast cancer patients. A seven gene risk model reflecting endocrine therapy resistance in 208 early HR+ breast cancer patients from two centers was constructed by LASSO analysis and multivariate cox regression. Based on the median value of risk score, patients were divided into high-risk group and low-risk group. Compared with the low-risk group, the high-risk group exhibited a significantly worse prognosis, which showed consistent across two external validation cohorts (TCGA-BRCA and METABRIC cohort). Time dependent ROC curve showed excellent capacity of gene model in predicting 1,3 and 5-year RFS. The IC50 analysis revealed that patients in low-risk group exhibited greater sensitivity to endocrine drugs, such as tamoxifen, fulvestrant and palbociclib, which strongly suggested that the identified gene signature can effectively differentiate between endocrine-resistant and -sensitive status. Gene-set enrichment analysis revealed regulation of cell killing, positive regulation of inflammatory response and T cell mediated cytotoxicity were enriched in low risk group, suggesting immune activation and a higher immune infiltration status. Conversely, the high-risk group demonstrated associations with collagen metabolic process, extracellular matrix structural constituent and collagen fibril organization, which were the indicative of the location and function of cancer-associated fibroblasts (CAFs). As expected, ssGSEA results revealed elevated expression levels of immune cells (e.g., natural killer cells, tumor-infiltrating lymphocytes, CD8+ T cells) and immune functions (e.g., T cell co-stimulation, inflammation-promoting, cytolytic activity) in the low-risk group. However, three diverse acknowledged methods (TIDE, EPIC and MCP-counter) consistently identified CAFs as predominantly content in the high-risk groups. Furthermore, considering that CD8+ T cell is the primary cell type responsible for exerting cytotoxic effects, we observed a negative correlation between CD8+ T cells and CAFs. This suggests that CAFs may inhibit the infiltration of CD8+ T cells, thereby weakening their cytotoxic capabilities, leading to a shorter RFS in high-risk

patient groups. In conclusion, a novel gene signature constructed with 7 endocrine resistance response-related genes can be used for prognostic prediction and reflecting the tumor microenvironment status in HR+ early breast cancer. The low-risk group exhibited enhanced anti-tumor immunity, resulting in a favorable prognosis. In contrast, the high-risk group displayed pronounced infiltration of CAFs, indicating their potential to impede immune cell infiltration and impact the efficacy of endocrine drugs through the formation of physical barriers and recruitment of immunosuppressive factors. Consequently, patients in the high-risk group experienced a worse prognosis. Therefore, inhibiting these genes may be a therapeutic option for overcoming endocrine therapy resistance in HR+ breast cancer patients.

PO5-21-06

Pathway profiling for prediction of response to neoadjuvant Letrozole therapy in ER positive postmenopausal breast cancer: gaining new insights for targeted treatment

Presenting Author(s) and Co-Author(s):

N. de Gruij. Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands

A. de Groot. Leiden University Medical Center, United States

Y. Wesseling-Rozendaal. InnoSIGN, Netherlands

D. Keizer. InnoSIGN, Eindhoven, Netherlands

S. Neerken. InnoSIGN, Eindhoven, Netherlands

J. Kroep. Leiden University Medical Center, United States

Introduction: The NEOLBC (NCT03283384) study included postmenopausal patients with hormone receptor positive (ER \geq 50%, PR any), HER2 negative, stage II/III breast cancer. A baseline biopsy was taken prior to start letrozole treatment and after two weeks of treatment. Based on the two week Ki67-IHC, patients were randomized (Ki67 \geq 1%) to receive either Letrozole + Ribociclib or standard chemotherapy until surgery, or continued (Ki67 < 1%) Letrozole mono therapy. Here we describe the signal transduction pathway profiles to better understand the molecular mechanisms of response to neoadjuvant letrozole. Methods: Signal transduction pathway activities for the ER, AR, MAPK, PI3K, HH, TGF β and Notch pathways were measured on baseline and two weeks samples using the OncoSIGNal qPCR test (InnoSIGN). High pathway activity in a tumor sample was defined as pathway activity value above the 95th percentile of reference normal epithelial breast tissue. The pathway activity patterns of the Ki67 < 1% (n=30) and Ki67 > 1% (n=63) groups were compared between baseline and two weeks of treatment. Results: Although all measured baseline samples (n=93) were ER IHC staining positive (\geq 50%), there is a large range in baseline ER signal transduction pathway activity (32 to 78 on a scale from 0 – 100) and 20% of the samples show an ER-activity range (32 - 45) that normally falls in the range of ER IHC stained negative breast tissue. The group with Ki67 > 1% after 2 weeks Letrozole treatment showed non elevated ER pathway activity at baseline more often (25%) compared to the Ki67 < 1% group (10%). 92% of the patients showed a decrease in ER pathway (11.6 \pm 8.6) activity after 2 week letrozole treatment compared to baseline (p=8.5e-13). Interestingly, baseline AR pathway activity has a good differentiating predictive value for the two week response to letrozole treatment and the overall AR pathway activity score was higher in the low Ki67 group (51.4 \pm 7.4) than in the Ki67 \geq 1% group (46.7 \pm 6.4; p=0.0053) and more often classified as high in 30% of the low Ki67 group vs. 13% of the Ki67 \geq 1% group. The Ki67 > 1% group showed activation of non-hormonal pathways (PI3K, MAPK and/or HH) more frequent (38%) at baseline compared to the < 1% Ki67 group (19%). Conclusion: Positive ER staining does not always relate to a high ER pathway activity, possibly explaining that not all patients respond equally well to ER inhibition therapy. Activation of hormonal pathways (ER, but also AR) appear to be predictive for early (2 weeks) response towards Letrozole as assessed by Ki67 staining. Involvement of non-hormonal pathways is associated with less effective response towards Letrozole alone. Pathway activity patterns could improve insight to underlying hormonal treatment escape mechanisms which could lead to alternative treatment options in patients with ER-positive breast cancer.

PO5-21-07

Mitomycin: its developmental role in the treatment of patients with BRCA - associated triple-negative early and locally advanced breast cancer

Presenting Author(s) and Co-Author(s):

P. Krivorotko. N.N. Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russia

E. Imyanitov, NMRC of Oncology named after N.N.Petrov of MoH of Russia, Saint Petersburg, Saint Petersburg City, Russia

D. Enaldieva. N.N. Petrov National Medical Research Center of Oncology, United States

E. Zhiltsova. N.N. Petrov National Medical Research Center of Oncology, United States

R. Donskih. NMRC of Oncology named after N.N.Petrov of MoH of Russia, Saint Petersburg City, Russia

A. Sokolenko. NMRC of Oncology named after N.N.Petrov of MoH of Russia, Saint Petersburg City, Russia

L. Shaikhelislamova, NMRC of Oncology named after N.N.Petrov of MoH of Russia, Saint Petersburg, Russia

L. Gigolaeva. N.N. Petrov National Medical Research Center of Oncology, United States

T. Tabagua. N.N. Petrov National Medical Research Center of Oncology, United States

A. Komyakhov. N.N. Petrov National Medical Research Center of Oncology, United States

K. Nikolaev. N.N. Petrov National Medical Research Center of Oncology, United States

K. Zernov. N.N. Petrov National Medical Research Center of Oncology, United States

S. Yerechshenko. N.N. Petrov National Medical Research Center of Oncology, United States

R. Pesotsky. N.N. Petrov National Medical Research Center of Oncology, United States

N. Amirov. N.N. Petrov National Medical Research Center of Oncology, United States

A. Emelyanov. N.N. Petrov National Medical Research Center of Oncology, United States

V. Mortada. N.N. Petrov National Medical Research Center of Oncology, United States

Y. Bondarchuk. N.N. Petrov National Medical Research Center of Oncology, United States

V. Semiglazov. N.N. Petrov National Medical Research Center of Oncology, United States

Rationale. BRCA-associated triple-negative breast cancer (TNBC) is one of the most aggressive subtypes of breast cancer with high sensitivity to chemotherapy, which leads to increased interest in the development of new strategies for neoadjuvant treatment of patients with a triple-negative tumor phenotype. The aim of the study is to determine the role of adding platinum to standard neoadjuvant systemic therapy in patients with primary BRCA-associated TNBC, to evaluate the effect of platinum preparations on relapse-free survival in patients of this category, to determine the role of adding mitomycin to platinum in patients with primary BRCA-associated TNBC. Materials and methods. The study included 80 patients diagnosed with primary BRCA - associated TNBC, divided into 3 groups according to the treatment. Each group was subdivided depending on the final pathomorphological result and the presence of relapses. Results. 80 patients with primary BRCA-associated TNBC were divided into 3 groups depending on the ongoing neoadjuvant chemotherapy (NACT). Group I included 48 (60%) patients who received the AC-T regimen, in group II — NAC according to the AC-TCarb regimen, 27 (33.75%) patients, in group III — NAC with mitomycin in combination with cisplatin,

5 (6.25%) of patients. A comparative analysis of the results of the frequency of achieving complete pathomorphological regression (pCR), depending on the addition of a platinum drug to standard NAC, showed the advantage of group II compared to group I (73.7% vs. 41.2%, respectively, $p = 0.0433$). Taking into account the ongoing NAC regimens, with a median follow-up of 20.7 months, patients of group I had a slightly higher risk of relapse compared to patients of group II ($p = 0.099$). Patients of group III demonstrated the achievement of pCR in 66.6% of cases (2/3) during the full course of NAC, 2 patients of group III did not complete the planned course of NAC for medical reasons, due to the development of a pronounced nephrotoxic effect. During the observation period of group III, no cases of relapse were recorded. Conclusions. The addition of platinum drugs to the standard anthracycline/taxane NAPCT regimen in patients with primary BRCA-associated TNBC, results in a higher pCR rate, which entails a reduced risk of disease recurrence. The use of the new NAC regimen with mitomycin in combination with platinum compounds has promising results in patients with this oncopathology, which deserves a more detailed clinical evaluation. Performing a full course of planned NAC has a positive tendency in achieving pCR in patients of this category. Keywords: BRCA1/2 mutation; triple negative breast cancer; platinum preparations; mitomycin; neoadjuvant chemotherapy.

PO5-21-08

Real world experience with Carboplatin plus Nab-paclitaxel as neoadjuvant therapy in patients with early triple negative breast cancer.

Presenting Author(s) and Co-Author(s):

M. Alva. Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain, United States

P. Tolosa. SOLTI Cancer Research Group, Barcelona, Spain/Medical Oncology Department, Hospital 12 de Octubre, Madrid., Madrid, Madrid, Spain

R. Sánchez-Bayona. Medical Oncology Department, Hospital 12 de Octubre, Madrid. SOLTI Cancer Research Group, Barcelona, Spain

L. Lema. Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain, United States

A. Madariaga. 12 de Octubre University Hospital, Spain

C. González Deza. Hospital 12 de Octubre, United States

L. Parrilla. Pathology department, Hospital Universitario 12 de Octubre, Madrid Spain, United States

C. Martín-Arriscado. Instituto de investigación Biomédica del Hospital Universitario 12 de Octubre I+12, United States

L. Manso. Hospital Universitario 12 de Octubre, Madrid, Spain

E. Ciruelos. SOLTI Breast Cancer Research Group, Barcelona, Spain / Medical Oncology, Hospital Universitario, Madrid, Spain

Background:

Neoadjuvant therapy (NA) is the base treatment for the majority of patients with early triple negative breast cancer (TNBC). The achievement of pathological complete response (pCR) after neoadjuvant treatment translates into improvements in long term outcomes. In the last decade, the arrival of new components or formulations have been assessed in clinical trials, such as carboplatin and nab-paclitaxel showing improvements in pCR rates or adverse events profiles. The aim of this study is to provide updated information on the efficacy of Carboplatin plus Nab-paclitaxel combined with other combinations (anthracyclines and immunotherapy) as neoadjuvant therapy in patients with TNBC in the real-world setting.

Methods:

We analyzed a cohort of patients treated with neoadjuvant therapy diagnosed with stage I-III TNBC and ER/PR-low status in a single tertiary hospital in Spain from June 2015 to February 2023. TNBC was defined as ER and PR < 1% and HER-2 negative. ER/PR-low was defined as an expression of estrogen or progesterone receptors \leq 10% by immunohistochemistry (IHC). Both Carboplatin (AUC 2) and Nab-paclitaxel (125 mg/m²) were administered on days 1 and 8 every 21 days. Anthracyclines (Doxorubicin or Liposomal Doxorubicin) were administered every 2 or 3 weeks, at the physician's discretion. Pembrolizumab 200 mg was administered every 21 days concomitantly with chemotherapy. The response to NA was classified according to the residual cancer burden (RCB). pCR was defined as ypT0/is/ypN0. Cox's stratified proportional hazard model was used for event free survival analysis. Event free survival was define disease progression that prevented definitive surgery, local or distant recurrence or death from any cause.

Results:A total of 103 patients were included in the analysis. The median age at diagnosis was 53.1 years. The baseline characteristics of the patients are in table 1. Regarding the systemic

treatment, 91.2% of the patients were treated with anthracyclines sequentially and in 23% of these (n=30) a liposomal formulation was used. Dose-dense anthracyclines were used in the 23.7% of patients. Concomitant pembrolizumab was used in 27.1%(n=28) of the patients, 60.7% (n=17) of these were stage III at diagnosis. Only one patient did not undergo surgery due to intra-treatment systemic progression. The pCR rate (RCB-0) in the total population was 54.3%. Patients with residual disease after NA (n=47) were classified as RCB-I (17.4%), RCB-II (18.4%) and RCB-III (8.7%). The pCR rates according to different features is reported in Table1. The germline mutation carriers in HRD genes (n=14) obtained a pCR rate of 71,4%. In patients with concomitant use of pembrolizumab, the pCR rate was 60.7%. The pCR rate in TNBC and ER/PR-low groups were 54.2% and 55% respectively. The median follow-up time was 27.7 months. The hazard ratio for event of progression between pCR vs residual disease groups was 0.21, 95%CI: 0.06 to 0.76; (p=0.018), with 3 events in the RCB-0 group (n=53) and 12 events in the residual disease group (n=47).

Conclusion:

In the real world setting, the use of carboplatin-nabpaclitaxel plus other combinations, such as anthracyclines and immunotherapy obtain a higher rate of pathological complete response translating to improvements in long term outcomes.

Baseline characteristics

Table 1	Cohort n=103
BMI	
<25	51 (49.51%)
26-30	32 (31.07%)
>30	20 (19.42%)
Tumor size	
0	1 (0.97%)
1	9 (8.74%)
2	67 (65.05%)
3	15 (14.56%)
4	11 (10.68%)
Nodal status	
NO	54 (52.43%)
N+	49 (47.57%)
Clinical Stage	
I	9 (8.74%)
II	60 (58.25%)
III	34 (33.01%)
HER-2 (IHC)	
0	49 (47.57%)
1/2	54 (52.43%)
ER/PR status	
ER/PR <1%	83 (80.58%)
ER or PR ≤ 10%	20 (19.42%)
Grade	
1	1 (0.97%)
2	18 (17.48%)
3	84 (81.55%)
Ki67 (median)	60% (40-75)
Androgen receptor (IHC)	
No	96 (93.20%)
Yes	7 (6.80%)
Germ line HRD status	
Carriers	14 (13.59%)
Non-carriers or unknown	89 (86.41%)

PO5-21-09

Clinical outcomes by age subgroups in the phase 3 TROPiCS-02 study of sacituzumab govitecan vs treatment of physician's choice in HR+/HER2– metastatic breast cancer

Presenting Author(s) and Co-Author(s):

A. Bardia. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States

P. Schmid. Barts Cancer Institute, Queen Mary University London, London, England, United Kingdom

S. Tolaney. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

F. Marmé. Med. Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany

J. Cortés. International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Madrid and Barcelona, Spain & Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Madrid, Spain

T. Valdez. Gilead, United States

H. Wang. Gilead Sciences Inc, Foster City, CA, United States

W. Verret. Gilead Sciences Inc, Foster City, CA, United States

H. Rugo. Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States

Background

Sacituzumab govitecan (SG) is a Trop-2-directed antibody-drug conjugate approved for second-line or later (2L+) treatment of metastatic triple-negative breast cancer in multiple countries and for 2L+ treatment of HR+/HER2– (IHC 0, 1+, or 2+/ISH) metastatic breast cancer (mBC) in the US. SG significantly improved progression-free survival (PFS) and overall survival (OS) vs treatment of physician's choice (TPC) in patients (pts) with pretreated, endocrine-resistant HR+/HER2– mBC in the TROPiCS-02 study. The incidence of HR+/HER2– mBC increases with age, especially after 65, and older pts often have poorer prognosis due to comorbidities, increased toxicity, and reduced efficacy of chemotherapy. In TROPiCS-02, pts aged ≥ 65 years (yr) derived consistent PFS benefit and clinically meaningful improved OS with SG vs TPC. In this analysis, we present additional efficacy and safety outcomes by age subgroup.

Methods

Pts with HR+/HER2– mBC who had received at least 1 endocrine therapy, taxane, and CDK4/6 inhibitor, and 2 to 4 prior lines of chemotherapy for mBC, were randomized to either SG (10 mg/kg IV days 1 and 8, Q3W) or TPC. The primary end point was PFS, and secondary end points included OS, objective response rate (ORR), and safety. A post hoc analysis was conducted by age subgroups (< 65 vs ≥ 65 , < 75 vs ≥ 75).

Results

In total, 543 pts were randomized to the SG (n = 272; 73 [27%] ≥ 65 , 16 [6%] ≥ 75) and TPC (n = 271; 67 [25%] ≥ 65 , 8 [3%] ≥ 75) groups. Baseline characteristics were generally similar across treatment arms in each age subgroup, but a higher proportion of pts had performance status 1 vs 0 in the ≥ 65 vs < 65 and ≥ 75 vs < 75 subgroups, respectively. The data cutoff date was July 1, 2022. SG demonstrated longer median PFS and OS vs TPC across age subgroups. Hazard ratios (HR) for PFS with SG vs TPC were 0.69, 0.59, 0.70, and 0.30 for the < 65 , ≥ 65 ,

< 75, and ≥ 75 subgroups, respectively (Table). The HR for OS were 0.81, 0.80, 0.82, and 0.56 in these subgroups, respectively (Table). Median duration of response (DoR) was also longer with SG vs TPC across age subgroups, although median DoR was not estimable in the ≥ 75 subgroup (Table). ORR was higher with SG vs TPC, except in the ≥ 75 subgroup (Table). Safety was generally similar with SG vs TPC across subgroups with the following differences. Grade ≥ 3 treatment-emergent adverse events were more common in the ≥ 75 subgroup than the other subgroups (SG, 81% in ≥ 75 vs 68%-73% for all others; TPC, 71% in ≥ 75 vs 60%-61% for all others). TEAEs leading to dose reduction were also more common in pts treated with SG in the ≥ 75 subgroup, but were consistent across other subgroups (Table). However, sample sizes in the ≥ 75 subgroup were small, which limits interpretation (Table). TEAEs leading to treatment discontinuation were more common in older pts, irrespective of treatment group (Table).

Conclusions

SG showed benefit in PFS and OS vs TPC in pts with HR+/HER2- mBC across age subgroups, consistent with the intent to treat population. SG was associated with a slight increase in toxicity for elderly pts, as expected. SG demonstrated a favorable benefit/risk profile, with efficacy benefit and acceptable toxicity, for elderly pts.

Table

Efficacy, ITT	< 65 yr		≥ 65		< 75 yr		≥ 75	
	SG (n = 199)	TPC (n = 204)	SG (n = 73)	TPC (n = 67)	SG (n = 256)	TPC (n = 263)	SG (n = 16)	TPC (n = 8)
Median PFS^a (95% CI), mo	5.5 (4.1-6.9)	4.1 (3.0-4.4)	6.7 (4.2-9.0)	3.5 (1.7-5.6)	5.5 (4.1-6.9)	4.0 (3.1-4.4)	9.0 (3.8-NE)	5.5 (0.3-NE)
HR (95% CI)	0.69 (0.53-0.89)		0.59 (0.38-0.93)		0.70 (0.56-0.87)		0.30 (0.08-1.12)	
Median OS (95% CI), mo	14.1 (12.7-16.4)	11.5 (10.3-13.3)	14.9 (12.0-17.5)	10.1 (7.6-14.2)	14.6 (13.0-16.0)	11.2 (10.1-12.9)	12.3 (6.4-NE)	11.6 (5.6-NE)
HR (95% CI)	0.81 (0.64-1.02)		0.80 (0.54-1.19)		0.82 (0.67-1.01)		0.56 (0.20-1.56)	
ORR^a (95% CI), %	21 (16-27)	14 (9-19)	21 (12-32)	15 (7-26)	21 (16-27)	14 (10-18)	19 (4-46)	25 (3-65)
Median DoR^{a,b} (95% CI), mo	8.3 (6.5-9.7)	5.6 (3.8-7.9)	6.9 (5.8-NE)	4.3 (2.3-NE)	7.4 (6.5-8.9)	5.6 (4.1-7.9)	NE	2.5 (2.3-NE)
Safety, all treated, n (%)	SG (n = 196)	TPC (n = 188)	SG (n = 72)	TPC (n = 61)	SG (n = 252)	TPC (n = 242)	SG (n = 16)	TPC (n = 7)
Any grade TEAEs	196 (100)	178 (95)	72 (100)	61 (100)	252 (100)	232 (96)	16 (100)	7 (100)
Grade 3/4	143 (73)	113 (60)	49 (68)	37 (61)	179 (71)	145 (60)	13 (81)	5 (71)
TEAEs leading to dose reduction	63 (32)	65 (35)	27 (38)	17 (28)	82 (33)	80 (33)	8 (50)	2 (29)
TEAEs leading to treatment discontinuation	5 (3)	8 (4)	12 (17)	3 (5)	15 (6)	10 (4)	2 (13)	1 (14)

^aPer independent central review. ^bMeasured in pts with response. ITT, intent-to-treat; NE, not evaluable; TEAEs, treatment-emergent adverse events.

PO5-21-10

Efficacy and Safety of Alpelisib in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor: An Open-label, Multi-centre, Prospective, Single Arm Clinical Trial

Presenting Author(s) and Co-Author(s):

R. Van Severen. Catholic University of Leuven, Brugge, Belgium

A. De Crem. University of Ghent, United States

H. Izci. KU Leuven, United States

I. Slembrouck. Catholic University of Leuven, United States

I. Vanden Bempt. University Hospitals Leuven, United States

H. Wildiers. University Hospitals Leuven, United States

K. Punie. Leuven Cancer Institute, University Hospitals Leuven, United States

E. Naert. University of Ghent, United States

I. Hilderson. Medical Doctor, United States

A. Smeets. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, United States

I. Nevelsteen. Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium, Leuven, Belgium

A. Deblander. University Hospitals Leuven, United States

N. Willers. Catholic University of Leuven, United States

P. Berteloot. University Hospitals Leuven, United States

I. Vergote. Catholic University of Leuven, United States

S. Han. University Hospitals Leuven, Leuven, Vlaams-Brabant, Belgium

A. Vanderstichele. Catholic University of Leuven, United States

G. Floris. University Hospitals Leuven, United States

C. Desmedt. Laboratory for Translation Breast Cancer Research/KU Leuven, Leuven, Vlaams-Brabant, Belgium

H. Denys. Department of Internal Medicine and Pediatrics, Ghent University Hospital, Ghent, Belgium, United States

P. Neven. Universitair Ziekenhuis Leuven, Leuven, Leuven, Vlaams-Brabant, Belgium

SABCS abstract: Monday, July 10, 2023 at 11:59 PM EST (Tuesday 11/07 06:59 AM Belgium) Efficacy and Safety of Alpelisib in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor: An Open-label, Multi-centre, Prospective, Single Arm Clinical Trial Authors: Rik Van Severen¹, Anne-Sofie De Crem², Hava Izci³, Laurence Slembrouck³, Isabelle Vanden Bempt⁴, Hans Wildiers^{3,7}, Kevin Punie^{3,7}, Eline Naert⁵, Ingeborg Hilderson⁵, Ann Smeets^{3,6}, Ines Nevelsteen^{3,6}, Anne Deblander¹, Nynke Willers¹, Patrick Berteloot¹, Ignace Vergote^{1,3}, Sileny Han^{1,3}, Adriaan Vanderstichele¹, Giuseppe Floris^{8,9}, Christine Desmedt³, Hannelore Denys⁵, Patrick Neven^{1,3} Introduction: Currently, patients with luminal metastatic breast cancer receive a CDK4/6 inhibitor in combination with endocrine therapy as a first or second line of treatment. When tumors become resistant to the CDK4/6 inhibitors, treatment with alpelisib (PI3K inhibitor) in combination with

an endocrine agent can be a next treatment option if an activating PIK3CA mutation is confirmed (cfr. SOLAR-1 trial). However, limited data is available after treatment with CDK4/6 inhibitors (cfr. BYLieve trial) and even less about alpelisib in later lines of therapy. Therefore, we aim to investigate the therapeutic efficacy and safety of alpelisib in combination with an endocrine agent in PIK3CA-mutated advanced breast cancer patients in later lines after prior CDK4/6i treatment. Methods: This is an open-label, prospective, multi-centre, single arm clinical trial enrolling patients from both the University Hospital of Leuven (UHL) and Ghent University Hospital (GUH). For each patient, metastatic tumor was tested for PIK3CA mutations using the UHL 96 gene panel. Our endpoints are clinical benefit rate, progression-free survival, time to treatment discontinuation (defined as the date of starting alpelisib to the date of treatment discontinuation or death) and safety. Descriptive statistics were used. Results: Between June 18th 2019 and August 23rd 2021, 38 patients have been included with confirmed PIK3CA hotspot mutations. All patients had CDK4/6 inhibitor in an earlier treatment line. Median age at alpelisib initiation was 64 years (range: 39-82 years). Included patients had a median of four lines of systemic therapy for advanced disease prior to starting alpelisib (range: 1- 11). Clinical benefit rate (patients receiving ³ 6 months of treatment) was 26.3% (10/38). The median progression-free-survival as well as time to treatment discontinuation were 3 months (range: 1 – 18). Dose reduction due to toxicity occurred in 11 patients (29%), of which 7 due to hyperglycemia grade 3, 2 due to diarrhea grade 3, 1 due to rash grade 2 and 1 due to anorexia. Finally, 84% of patients (32/38) stopped alpelisib treatment because of progressive disease, 8% (3/38) because of intolerance, one patient died because of cerebral hemorrhage during treatment, one patient withdrew their informed consent and one patient is still ongoing with the treatment. Conclusion: Our trial demonstrates activity of alpelisib in patients with PIK3CA mutated advanced breast cancer in later lines of treatment after treatment with CDK4/6 inhibitors with a clinical benefit rate of 26.3%. Discontinuation of therapy due to toxicity was seen in only 8% of patients, although toxicity induced dose reduction was needed in 29% of patients. These findings support the results of the BYLieve trial and additionally show efficacy of alpelisib in later lines of treatment for hormone receptor-positive advanced breast cancer.

PO5-22-02

Evaluation of a surface-guided and tattoo-less approach to setup for whole breast radiotherapy

Presenting Author(s) and Co-Author(s):

X. Zhang. Rutgers RWJ/CINJ, United States

S. Mamidanna. Rutgers RWJ/CINJ, United States

Y. Zhang. Rutgers RWJ/CINJ, United States

X. Wang. Rutgers RWJ/CINJ, United States

N. Yue. Rutgers RWJ/CINJ, United States

S. Kumar. Rutgers Cancer Institute of New Jersey, United States

L. Potdevin. CINJ, United States

M. Kowzun. CINJ, United States

M. George. Rutgers Cancer Institute of New Jersey, United States

L. Hathout. RWJ/CINJ, New Jersey, United States

B. Haffty. Rutgers Cancer Institute of New Jersey, United States

N. Ohri. Rutgers Cancer Institute of New Jersey, United States

Background: In preparation for adjuvant breast radiation therapy (RT), several small but permanent skin tattoo marks are often placed to assist with surface alignment for treatment setup and delivery. With advancements in surface-guided technologies, it may be possible to achieve setup accuracy with a “tattoo-less” approach, which can improve cosmetic and quality of life outcomes. This study evaluates the feasibility, accuracy, and potential dosimetric implications of a tattoo-less setup technique. Method: A retrospective analysis of 10 patients diagnosed with right-sided breast cancer who received adjuvant whole breast RT using a tattoo-less approach were included in this study. All patients received an initial whole breast dose of 42.56 Gray (Gy) in 16 daily fractions using a tangential three-dimensional conformal planning technique. This was followed by a 10Gy boost to the lumpectomy site delivered in 4 daily fractions. Daily setup for whole breast treatment was performed by aligning each patient to their individual reference breast surface generated from the planning computed tomography (CT) images via the Vision RT system. Bony landmarks were then verified via daily kV imaging, and translational shifts were recorded for each fraction. The kV imaging was performed to confirm the treatment positioning since the tattoo-less approach was new to the department. For 5 patients, dosimetric differences between initial surface alignment and shifts performed based on bony landmarks were evaluated by recalculating the original clinical plan with a new isocenter position using kV image shifts for each of their 16 treatment fractions. A plan sum of the 16 recalculated plans for each patient was used in further dosimetric analysis. Boost fractions were not included in this study, as setup was verified using surgical clips instead of bony anatomy. Results: Translational shifts for 158 fractions were reviewed as no kV imaging was performed for the other 2 fractions. The mean absolute kV imaging shift was 0.29 cm (CI (95%): 0.25, 0.32; range: 0 to 1.25) in the vertical axis, 0.28 cm (0.23, 0.32; 0 to 1.27) in the longitudinal axis, and 0.24 cm (0.20, 0.28; 0 to 1.98) in the lateral axis. Clinical plans for 5 patients were evaluated with a mean absolute kV shift of 0.27 cm (range: 0.15 to 0.39) in the vertical, 0.32 cm (0.13 to 0.77) in the longitudinal, and 0.29 cm (0.18 to 0.38) in the lateral directions. Dosimetric analysis revealed a slight increase in mean heart dose from the original clinical plan, with an average difference of 4.12 cGy (range: 0.7 to 10.5 cGy). The maximum

increase in $V_{20\text{Gy}}$ of the ipsilateral lung was 2.7%. Less than 1% of change was observed in the maximum plan dose, as well as in the $V_{95\%}$ coverage, except for one patient, whose $V_{95\%}$ was decreased from 99.6% to 94.6%. This difference was caused by a large longitudinal shift which could be attributed to possible patient movement. Conclusions: These findings demonstrate the feasibility and accuracy of a tattoo-less treatment approach in a small cohort of breast cancer patients receiving whole breast RT. Further investigation with larger cohorts is warranted.

PO5-22-03

Influence of the surgical clip concerning the dose and volume of irradiated surrounding tissues including lung and heart in the planning of radiotherapy boost with conservative breast surgery with and without oncoplasty.

Presenting Author(s) and Co-Author(s):

N. Freitas. ARAUJO JORGE CANCER HOSPITAL & CEBROM, Goiania, Goias, Brazil

P. WATANABE. Federal University of Goias, Brazil

J. Paiva. ARAUJO JORGE CANCER HOSPITAL & CEBROM, Brazil

C. BEZERRIL. ARAUJO JORGE CANCER HOSPITAL & CEBROM, Brazil

M. VALENTIM. CEBROM, United States

T. Gontijo. ARAUJO JORGE CANCER HOSPITAL, United States

F. Araujo. ARAUJO JORGE CANCER HOSPITAL, United States

R. Freitas-Junior. Federal University of Goias & Araujo Jorge Cancer Hospital, Goiânia, Goias, Brazil

Introduction: Patients with the highest risk of breast cancer undergoing conservative surgery receive an additional boost dose of radiotherapy in the tumor bed during treatment planning, which is known to bring benefits in local control. **Objectives:** To evaluate the influence of the surgical clip concerning the volume of surrounding tissues irradiated during radiotherapy, in patients submitted to conservative breast surgery with and without oncoplasty.

Materials/Methods. The analyzed variables were defined as: the volume of the boost (V100 Boost) and breast tissue (V100 Breast) that received 100% of the prescribed dose during the radiotherapy planning and the volume of the heart (V40 Heart) and lung (V40 Lung) that received 40% of the prescribed dose during the boost phase in patients undergoing treatment with breast conservation. The variables were compared about the insertion or not of the surgical clip and the influence of oncoplastic surgery on the volume of irradiated tissues of the breast, boost, heart and lung during radiotherapy planning. Student's t-test (95%CI; $p < 0.05$) was used to compare mean volumes as a function of the presence or not of surgical clips and oncoplastic surgery. **Results:** Retrospective study included 183 women with breast cancer who underwent treatment with conservative breast surgery and radiotherapy of the whole breast, followed by sequential boost, between January 2011 and January 2021. Boost, breast, heart, and lung volumes were evaluated during planning for conformational radiotherapy. The results showed a significant difference between the average boost volumes when the patient was clipped. The average boost volume that received 100% of the prescribed dose was V100 Boost=244.22cm³ (SD±158) in the absence of the clip. In the presence of 1 or 2 clips, this average was V100 Boost= 94.87cm³ (SD±37) and with 3 or more clips it was V100 Boost= 96.99cm³ (SD±39) ($p < 0.001$). There was also a significant difference in mean breast volumes that received 100% of the prescribed dose. In the absence of the clip, the V100 Breast=373.16 cm³ (SD±222) and when 1 or 2 clips were present, the V100 Breast=235.28 cm³ (SD±125) ($p=0.01$). The analyzes of the mean volumes of the heart (V40 Heart) and lung (V40 Lung) that received 40% of the prescribed boost dose were not statistically significant, regardless of the presence and number of clips. For the oncoplasty group, there was no statistical difference between the means of boost, breast, heart and lung volumes. **Conclusion:** The presence of the surgical clip reduced the volume of the boost and the breast that received 100% of the dose in the radiotherapy planning. The volume of the boost (V100 Boost), which received 100% of the dose prescribed during radiotherapy planning, was smaller in patients with a surgical clip, as was the volume of irradiated breast tissue (V100 Breast) in clipped patients. The volume of

irradiated tissue in the heart (V40 Heart) and lung (V40 Lung) that received 40% of the prescribed dose during the boost phase in radiotherapy planning did not suffer statistical differences in insertion or not of the surgical clip. Oncoplastic surgery and the presence of surgical clips did not influence the volumes of irradiated boost, breast, heart and lung tissues during the radiotherapy planning of patients undergoing conservative surgical treatment of the breast. Table: Means of boost, breast, heart and lung irradiated volumes according to the presence or absence of clips and oncoplastic surgery

Variable (cm ³)	Clip		p valor	Oncoplasty		p valor
	With	Without		With	Without	
	Means	Means	Means	Means		
V100% Boost	94	244	< 0,001	102	118	0,906
V100% Breast	235	373	0,01	271	272	0,816
V40% Heart	1,10	4,52	0,33	1,96	1,39	0,903
V40% Lung	56,66	56,10	0,93	51,63	52,53	0,796

Means of boost, breast, heart and lung irradiated volumes according to the presence or absence of clips and oncoplasty surgery

Table: Means of boost, breast, heart and lung irradiated volumes according to the presence or absence of clips and oncoplasty surgery

Variable (cm ³)	Clip		p*	Oncoplasty		p*
	With	Without		With	Without	
	Means	Means	Means	Means		
V100% Boost	94	244	<0,001	102	118	0,906
V100% Breast	235	373	0,01	271	272	0,816
V40% Heart	1,10	4,52	0,33	1,96	1,39	0,903
V40% Lung	56,66	56,10	0,93	51,63	52,53	0,796

PO5-22-04

Genomic analysis of local recurrences following risk adapted breast radiotherapy in the IMPORT trials defines 'true recurrences' and 'new primaries'

Presenting Author(s) and Co-Author(s):

S. Lightowers. University of Cambridge, Cambridge, England, United Kingdom

M. Roman-Escorza. Kings College London, United Kingdom

E. Provenzano. Cambridge University Hospitals NHS Trust, UK and Cambridge Biomedical Research Centre (NIHR), United Kingdom

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

J. Carroll. CRUK Cambridge Institute and Precision Breast Cancer Institute, University of Cambridge, United Kingdom

H. Chan. Department of Breast Surgery, Nuffield Health Cheltenham Hospital, United Kingdom

C. Griffin. Clinical Trials and Statistics Unit, Institute of Cancer Research, London, England, United Kingdom

J. Haviland. Queen Mary University of London, United Kingdom

M. Jefford. Independent Cancer Patient's Voice, United Kingdom

A. Kirby. The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, United States

N. Somaiah. The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, United Kingdom

M. Sydenham. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

J. Tittley. Institute of Cancer Research, United Kingdom

J. Yarnold. Institute of Cancer Research, United Kingdom

C. Coles. University of Cambridge, United Kingdom

E. Sawyer. Guy's and St.Thomas' NHS Foundation Trust/King's College London, United States

Background: Most ipsilateral breast tumor recurrences (IBTR) following breast conserving surgery occur near the tumor bed (Veronisi et al, Ann Oncol 2001) and are considered to represent 'true recurrence' (derived from residual malignant cells of the index cancer). A smaller number occur elsewhere in the breast and are thought to be 'new primaries' (independently occurring cancer). The IMPORT LOW (Coles et al, The Lancet 2017) and IMPORT HIGH (Coles et al, The Lancet 2023) trials investigated adaptation of radiotherapy dose-volume to this spatially varying risk, testing partial breast irradiation and simultaneous integrated boost in patients with tumors at low and high risk of IBTR respectively. We analysed genomic relationships between index cancers and recurrences in these trials, to ascertain the frequency of true recurrences and unrelated new primaries, and their spatial distribution.

Methodology: FFPE blocks were obtained from 137 patients who developed subsequent ipsi- or contralateral breast cancer: 66 from IMPORT HIGH and 71 from IMPORT LOW (4 with bilateral second cancers). DNA extracted from index and subsequent cancers underwent shallow whole genome sequencing (sWGS) using the Illumina NovaSeq 6000 system. Copy number profiles were derived from sWGS data using the R package QDNAseq(Scheinin et al, Genome Res

2014); those that failed QC criteria were removed. Relatedness of tumor pairs was determined using the R package Breakclone (Lips et al, Nat Genet 2022). This approach uses individual copy number aberration breakpoint position rather than events at chromosomal arm level. The p value cutoff for relatedness was 0.01; values between 0.01 and 0.05 were considered ambiguous. Researchers were blinded to clinical information prior to results.

Results: In 80/137 tumor pairs both copy number profiles met QC criteria and clonal relationship could be ascertained. In total 26/80 were considered related, 20/80 ambiguous and 34/40 non-related (Table 1).

16/26 ipsilateral subsequent cancers in IMPORT HIGH were clonally related to the primary tumor and could be considered true recurrences. In 5/26 it was impossible to accurately call clonality as pairs shared only common copy number changes such as 1q or 8q gain and 16q loss. 5/26 were considered new primaries. In the lower risk IMPORT LOW cohort, subsequent cancers appear to have similar chances of being related or independent.

As expected, most contralateral tumors in IMPORT LOW showed no evidence of a clonal relationship to the index tumors. In both trials an ambiguous subgroup of pairs shared some common copy number changes suggesting similar phenotype. 5/14 contralateral tumors in IMPORT HIGH, in which some women were also at high risk of systemic relapse, shared very similar copy number profiles to the index tumor and may be metastases rather than new primaries.

Discussion: A considerable number of tumors classed as IBTR appear genomically unrelated to the index cancer particularly in low risk cancer; this biology is relevant to clinical management both initially and at 'recurrence'. The finding that 5/14 contralateral cancers in the high risk group appear to be clonally related suggests that some may be metastases. Results are being confirmed by targeted sequencing and will be correlated with recorded spatial and clinicopathological data and patient outcome. Future work will analyse spatial relationships more precisely using deformable image registration.

PIK3CA and ESR1 alterations detected in circulating tumor DNA at baseline and post abemaciclib treatment

Table: PIK3CA and ESR1 alterations detected in circulating tumor DNA at baseline and post abemaciclib treatment

PIK3CA variants	Detected at baseline (n = 75)*, n (%)	Detected post treatment (n = 33), n (%)
H1047R	10 (13.3)	6 (18.2)
E545K	9 (12.0)	5 (15.2)
E542K	5 (6.7)	3 (9.1)
N345K	2 (2.7)	1 (3.0)
C420R	1 (1.3)	1 (3.0)
K111N	1 (1.3)	1 (3.0)
Q546P	1 (1.3)	Not detected
R88Q	1 (1.3)	1 (3.0)
R108H	1 (1.3)	Not detected
L452_G460del	1 (1.3)	Not detected
G914A	Not detected	1 (3.0)
Amplification	Not detected	1 (3.0)
ESR1 variants	Detected at baseline (n = 75)*, n (%)	Detected post treatment (n = 33), n (%)
D538G	6 (8.0)	5 (15.2)
Y537N	4 (5.3)	1 (3.0)
Y537S	3 (4.0)	4 (12.1)
Y537C	2 (2.7)	Not detected
L536H	2 (2.7)	1 (3.0)
L536R	2 (2.7)	Not detected
S463P	1 (1.3)	Not detected
E380Q	1 (1.3)	1 (3.0)

*From the 77 patients with baseline circulating tumor DNA samples, 2 patients were excluded because their samples failed during assay quality control.

*From the 77 patients with baseline circulating tumor DNA samples, 2 patients were excluded because their samples failed during assay quality control.

PO5-22-05

ULTRA-HYPOFRACTIONATED ADJUVANT RADIATION THERAPY FOR BREAST CANCER (UK FAST FORWARD TRIAL): A REAL LIFE SCENARIO ANALYSIS IN A DEVELOPING COUNTRY

Presenting Author(s) and Co-Author(s):

R. Bart. Radioserra - Radioterapia Petrópolis, Petrópolis, Rio de Janeiro, Brazil

D. Przybysz. Radioserra - Radioterapia Petrópolis, Macaé, Rio de Janeiro, Brazil

R. Ferrari. Radioserra - Radioterapia Petrópolis, Orlando, Brazil

L. Franco. Radioserra - Radioterapia Petrópolis, Petrópolis, Rio de Janeiro, Brazil

C. Almeida. Radioserra - Radioterapia Petrópolis, Macaé, Rio de Janeiro, Brazil

P. Canary. Radioserra - Radioterapia Petrópolis, Macaé, Rio de Janeiro, Brazil

Introduction: Selected patients showed non-inferior outcomes after conservative surgery for early breast cancer in the FAST-Forward UK (26Gy in 5 fractions) when compared to standard to date treatment. This study triggered an important change in radiation therapy routines across the world. We aimed to establish a pattern of treatment related events at a third-world country cancer center. Methods: We retrospectively analyzed all patients treated with 26Gy in 5 fractions (1 week) from January 2020 to June 2023. All data was exported and analyzed for demographics. A clinical profile was traced, dosimetric parameters and side effects assessed based on individual inquiries to each patient, per and post treatment. A strict medical record was kept in order to understand patterns of side effects and results. Results: 101 individuals were identified. Mean age was 64 years, 48 (47%) patients experienced radiation dermatitis of any grade, 33 (32%) grade 1, 9 (8%) grade 2, 6 grade 3 or 4 (5%). Patients older than 60 years showed to be a significant factor for dermatitis development (34 over a total of 48 - 70%) and 8 (53%) over 15 had grade 2 or higher dermatitis. 27 (26%) developed radiation dermatitis during sessions. 21 (20%) took 7 or less days to heal; 27 (26%) had a recovery longer than one week at an average age of 65 years - being the majority of dermatitis grade 1. Reported toxicities were sharp pain 31 (30%), burning pain 24 (23%), edema 17 (16%) and pruritus 5 (4%). At the time of this study was completed, 3 reported deaths (2%) were reported - with a 97% rate of survival. Conclusions: The fast forward trial regimen has 3 years since its publication. Our study shows that in a selected group of breast cancer patients, this novel model has shown to be a safe alternative for adjuvant radiation therapy following breast conservative surgery, results corroborating with published data. To the best of our knowledge, this is the largest single center group analyzed and published.

PO5-22-08

Comparison of long-term oncological outcomes in young women with breast cancer between BRCA-mutation carriers versus non-carriers: How genetic risk factors and tumor characteristics influence the prognosis.

Presenting Author(s) and Co-Author(s):

D. Gentile. IRCCS Humanitas Research Hospital, Milan, Lombardia, Italy
S. Di Maria Grimaldi. IRCCS Humanitas Research Hospital, United States
A. Sagona. IRCCS Humanitas Research Hospital, United States
E. Barbieri. IRCCS Humanitas Research Hospital, United States
A. Bottini. IRCCS Humanitas Research Hospital, United States
G. Canavese. IRCCS Humanitas Research Hospital, United States
G. Caraceni. IRCCS Humanitas Research Hospital, United States
S. Darwish. IRCCS Humanitas Research Hospital, United States
C. Tinterri. IRCCS Humanitas Research Hospital, United States

Objectives and rationale: Breast cancer (BC) arising at a young age is relatively uncommon; however, approximately 6 to 10% of women diagnosed with BC are younger than the age 40. This subgroup of young women presents different risk factors, tumor biology, and clinical outcomes. Moreover, the interpretation of the effects of inherited genetic factors on the prognosis of young patients with BC remains a subject of debate. The primary aim of this study was to evaluate the characteristics of young patients with BC and to compare the long-term oncological results between BRCA-mutation carriers and non-carriers.

We retrospectively reviewed all the consecutive young (≤ 40 years old) BC patients treated at the Breast Unit of IRCCS Humanitas Research Hospital (Milan, Italy). All young patients underwent BRCA-mutation analysis. For further analysis young BC patients were divided into two groups: BRCA-mutation carriers versus non-carriers. Tumor, surgical treatment, and post-operative data were compared between the two groups. Primary end-points were: disease-free survival (DFS), distant disease-free survival (DDFS), and overall survival (OS). The Kaplan-Meier method was used to generate the recurrence and survival curves. Multivariate analyses were performed using the Cox proportional hazards model to identify independent risk and protective factors for DFS, DDFS, and OS.

Results: The characteristics of 63 young BC patients with BRCA-mutation were compared with 339 young BC patients without BRCA-mutation. BRCA-mutation carriers tend to be younger (60.3% versus 34.8% if age ≤ 35 years, odds ratio (OR) = 17.699, 95% confidence interval (95%CI) = 33.871-35.568, $p = 0.001$) and present more aggressive tumors (66.7% versus 40.7% if G3, OR = 17.119, 95%CI = 2.549-2.828, $p = 0.001$; 57.2% versus 12.4% if biological subtype triple negative, OR = 52.727, 95%CI = 2.042-2.417, $p = 0.001$; 73.0% versus 39.2% if Ki67 $\geq 25\%$, OR = 58.981, 95%CI = 47.135-58.505, $p = 0.001$). Young BC patients without BRCA-mutation presented significantly better long-term oncological results in terms of DFS, DDFS, and OS compared with young BRCA-mutation carriers (10-years DFS rate 91.1% versus 58.1%, $p < 0.001$; 10-year DDFS rate 91.2% versus 76.1%, $p = 0.003$; 10-year OS rate 98.0% versus 87.8%, $p = 0.002$, respectively). Neo-adjuvant chemotherapy was found to be an independent protective factor for OS in young BRCA-mutated BC patients (hazard ratio = 14.885, 95%CI = 2.343-94.566, $p = 0.004$).

Conclusions: Breast cancer is more likely to present at a younger age (≤ 35 years) and with more aggressive characteristics (G3, triple negative, Ki67 $\geq 25\%$) in patients with BRCA-mutation compared with their non-mutated counterpart. Young BRCA-mutation carriers show a poorer prognosis in terms of recurrence and survival compared with non-carriers. The implementation of neo-adjuvant chemotherapy may improve survival in young BC patients with BRCA-mutation.

PO5-22-09

Positive pegulicianine fluorescence rate in the lumpectomy cavity correlates with tumor distance to margins in excised tissue

Presenting Author(s) and Co-Author(s):

I. Wapnir. Stanford Cancer Institute/Stanford University, Stanford, California, United States

E. Hwang. Duke University, Durham, North Carolina, United States

K. Hunt. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

D. Carr. Novant Health, Winston-Salem NC, United States

P. Blumencranz. Baycare Medical Group, United States

M. Chang. Lumicell, United States

K. Smith. Lumicell, Inc, United States

J. Ferrer. Lumicell, Inc, United States

B. Smith. Massachusetts General Hospital, United States

Title: Positive pegulicianine fluorescence rate in the lumpectomy cavity correlates with tumor distance to margins in excised tissue

Background: A randomized, two-arm pivotal study of pegulicianine fluorescence guided surgery (pFGS) at 14 US sites was conducted using the Lumicell Direct Visualization System (DVS) to identify residual cancer in the lumpectomy cavity after the standard of care (SoC) tumor excision. We reported that the Lumicell DVS detects residual cancer in the lumpectomy cavity, including in orientations pathologically negative on the SoC specimen. In addition, 15% (9 of 62) of patients with positive SoC margins were converted to final negative margins by taking Lumicell DVS directed cavity margins, avoiding a second unnecessary surgery. Interestingly, 8 of these 9 patients had no tumor found in the Lumicell DVS guided specimens. We hypothesize that fluorescence decreases as the distance from the tumor boundary increases. We analyzed data from the pivotal study (NCT03686215) to assess correlation of pegulicianine signal with tumor-to-margin distance, and its potential clinical value.

Methods: The pivotal study enrolled 406 patients undergoing breast conserving surgery (BCS) for stage 0-III breast cancers. Patients received an IV injection of pegulicianine 2-6 hours prior to surgery. After the standard of care lumpectomy was completed, additional Lumicell DVS-guided cavity margins were excised at sites of positive pegulicianine fluorescence signal in the lumpectomy cavity walls using a hand-held imaging device and patient-calibrated cancer detection software. The positive fluorescence rate, that is, the rate at which the Lumicell DVS indicates areas suspected to contain cancer, was calculated as the ratio of orientations with positive pegulicianine signal to the total number of orientations with (1) negative margins, (2) positive margins and (3) positive margins with ink on tumor, on the initial SoC lumpectomy specimen. Calculations were made on a per-margin basis. Positive margins were defined as ink on tumor for invasive cancer and tumor less than 2 mm from the margin for ductal carcinoma in situ (DCIS) alone.

Results: Results are presented in Table 1. We found a statistically significant higher positive fluorescence rate in orientations with positive margins ($p=0.044$). The positive fluorescence rate was even higher (21.1%) when only considering cases with ink on tumor (a subset of the positive margin group).

Discussion: By design, pegulicianine is activated by enzymes within the tumor and in stromal cells at the invasive front surrounding the tumor. Thus, when tumor is closer to the edge of the lumpectomy specimen, the rate of positive pegulicianine fluorescence in the cavity increases, being highest when there is tumor present at the inked margin. This feature of pegulicianine fluorescence guides the surgeon to resect more tissue in these areas in order to achieve a negative margin of the required width. The conversion of positive margins after the SoC lumpectomy to appropriately wide final negative margins prevents a second surgery, even when there is no tumor in the DVS guided margins. These findings have strengthened our understanding of the utility of this technology.

Table 1

SoC Lumpectomy Margin	Matched Cavity Orientation Positive Fluorescence Rate
Negative SoC Margins	11.0% (226/2048) 95% CI [9.7%, 12.5%]
Positive SoC Margins	17.5% (18/103) 95% CI [10.7%, 26.2%]
Only Ink on Tumor SoC Margins	21.1% (12/57) 95% CI [11.4%, 33.9%]

Positive cavity wall fluorescence rate for SoC lumpectomy positive margins, SoC lumpectomy negative margins and SoC lumpectomy ink on tumor margins

PO5-22-10

Are contralateral prophylactic mastectomy rates impacted by ASBrS guidelines to offer germline genetic testing to all patients with breast cancer? Results from a large, prospective, single-institution cohort

Presenting Author(s) and Co-Author(s):

A. Weiss. Division of Surgical Oncology, University of Rochester School of Medicine and Dentistry, Rochester, New York, United States

S. Knapp. Dana-Farber Cancer Institute, United States

D. Braun. Dana-Farber Cancer Institute, United States

B. Barton. Brigham and Women's Hospital, United States

M. McGrath. Brigham and Women's Hospital, United States

S. Stokes. Dana-Farber Cancer Institute, United States

A. Laws. Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, United States

L. Warren. Brigham and Women's Hospital, United States

S. Morganti. Dana-Farber Cancer Institute; Harvard Medical School; Broad Institute of MIT and Harvard, United States

F. Lynce. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

B. Bychkovsky. Comprehensive Breast Health Center, Brigham and Women's Hospital; Breast Oncology Program, Dana-Farber Brigham Cancer Center Division of Cancer Genetics and Prevention; Dana-Farber Cancer Institute; Harvard Medical School, United States

H. Rana. Dana Farber Cancer Institute, United States

D. Davis. Dana-Farber Cancer Institute, United States

J. Stopfer. Dana Farber Cancer Institute, United States

J. Garber. Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Division of Cancer Genetics and Prevention, Dana-Farber Cancer Institute, United States

T. King. Division of Breast Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana-Farber/Brigham Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

Background: It is unclear whether the release of the American Society of Breast Surgeons' (ASBrS) guideline to offer germline genetic testing to all patients with breast cancer impacted contralateral prophylactic mastectomy (CPM) rates. The objective of this study was to describe trends of germline testing and CPM rates, and to determine predictors of CPM uptake.

Methods: This is a retrospective review of two prospectively maintained single institutional databases: Dana-Farber/Brigham Cancer Center's surgical database, merged with Dana-Farber Cancer Institute's Genetics and Prevention database. Trends in germline testing and CPM rates were described, in relation to the February 2019 ASBrS guideline release, and a multivariable logistic regression model was used to determine factors associated with CPM utilization. Patients with unilateral stage 0-III breast cancer who underwent surgery between January 2016 and July 2020 were included. Patients were considered "tested" if they

underwent germline genetic testing and results were disclosed before their index operation. CPM was defined as contralateral mastectomy performed at index operation or anytime thereafter, excluding mastectomy for a new contralateral breast cancer event.

Results: Among 6,064 women in the cohort, 2,455 (40.5%) had germline genetic testing before their index surgery. Rates of testing significantly increased over the study period from 33.7% in 2016 to 64.9% in 2020 ($p < 0.001$). A total of 783/6,064 (12.9%) patients underwent CPM which was 40.7% (783/1,926) of the patients who underwent mastectomy. The CPM rate was 13.3% before the guideline release (2016 – January 2019) and 12.5% after (February 2019 – 2020). There was no significant change in CPM rate over time ($p = 0.527$), including before ($p = 0.380$) and after ($p = 0.220$) the 2019 guideline release. The following factors were associated with increased CPM rates on multivariable logistic regression: identification of a pathogenic/likely pathogenic variant in a breast cancer predisposition gene (Adjusted Odds Ratio [Adj. OR] 24.43), genetic testing with a negative test result (Adj. OR 1.52), number of relatives with breast/ovarian cancer (Adj. OR 1.18 and 1.39, respectively for each additional relative), younger age (Adj. OR 0.97 if pre-menopausal, 0.91 if post-menopausal, for each year decrement), and cT2-3 tumors (Adj. OR 1.53 and 1.94, respectively as compared to other cT stages); all $p < 0.05$.

Conclusions: Despite increasing germline genetic testing rates, CPM rates were stable over time, indicating that offering genetic testing to more patients does not increase CPM rates in our experience. Selection bias is most certainly contributing to the apparent association between CPM and genetic testing, even if there is a negative test result, as the classic indications for genetic testing are similar to those for CPM.

PO5-22-11

Radiotherapy-associated Complications in Breast Cancer patients treated with Nipple-Sparing Mastectomy: Results of the Reconstruction-after-Mastectomy AGO R02 Registry.

Presenting Author(s) and Co-Author(s):

F. Peintinger. Univ.Prof. Priv.Doiz. Dr. Florentia Peintinger, Austria

E. Sieghartsleitner. Universitätsklinik für Frauenheilkunde und Geburtshilfe, Graz, Austria, United States

B. Pfeifer. Private University for Health Sciences and Health Technology, Hall in Tirol, Austria & Tyrolean Federal Institute for Integrated Care, Tirol Kliniken GmbH, Austria, United States

G. Pristauz-Telsnigg. Department of Gynecology, Medizinische Universität Graz, Austria, United States

G. Tsangarakis. Department of Gynecology, Medizinische Universität Graz, Austria, United States

R. Hochstätter. Abteilung für Gynäkologie und Geburtshilfe, Barmherzige Brüder Linz, United States

R. Koller. Abteilung für Plastische, Ästhetische und Rekonstruktive Chirurgie, Wiener Krankenanstaltenverbund, Austria, United States

U. Denison. Institute for Gynaecological Oncology and Senology, Karl Landsteiner Society, Hietzing Hospital, Vienna, Austria, United States

C. Hager. Department of Gynecology and Obstetrics, City Hospital, Dornbirn, Austria, United States

R. Reitsamer. Breast Center, Paracelsus Medical University of Salzburg, Salzburg, Austria, United States

Nipple-Sparing mastectomy (NSM) followed by implant-based breast reconstruction is an oncologically safe procedure increasingly used in patients with breast cancer. A proportion of patients treated with NSM will be receiving adjuvant radiotherapy according to contributing factors indicating radiotherapy use.

Methods

Data from six breast centers in Austria were entered in the AGO R02 Registry from women who underwent breast reconstruction after mastectomy between 2012 and 2022 to evaluate complications associated with surgical techniques and selection of patients. Univariate analysis was used to identify factors that may impact surgical outcome.

Results

The registry included a total of 744 female patients. Of 913 NSMs, 730 NSMs were followed by implant-based reconstruction. Adjuvant radiotherapy was administered in 132/730 patients (18%).

In this group minor complications (infection, hematoma) were observed in 6 patients (4.5%) and major complications requiring additional surgery (wound breakdown, skin and/or nipple necrosis) were observed in 16 patients (12.1%) in a short term follow up of 4 months (mean).

In the group of patients without adjuvant radiotherapy minor complications (infection,

hematoma) were observed in 33 patients (4.5%) and major complications (wound breakdown, skin and/or nipple necrosis) were observed in 75 patients (10.3%). In both groups no statistically significant association was observed between complications and age, body mass index, diabetes, preoperative chemotherapy, implant position (pre/subpectoral), use of mesh. Smoking and chemotherapy were the only factors associated with higher proportion of minor complications in patients not receiving radiotherapy.

Conclusions

Women treated with adjuvant radiotherapy after NSM followed by implant-based reconstruction have a higher incidence of major complications requiring additional surgery in comparison with women treated without radiotherapy in a short term follow up. Considering new radiotherapy techniques/volumes and early multidisciplinary planning may optimize multimodal treatment in these patients.

Supported by AGO Österreich

PO5-22-12

Development and Validation of a Genomic Test to Predict Tumor Response of the Axillary Nodes after Neoadjuvant Chemotherapy (NAC) in Patients with HER2-negative Breast Cancer: Results of the AGO-35 trial

Presenting Author(s) and Co-Author(s):

F. Peintinger. Univ.Prof. Priv.Do. Dr. Florentia Peintinger, Austria

T. Kühn. Department of Gynecology, Hospital Esslingen, Esslingen, Germany

H. Kolberg. Klinik für Gynäkologie und Geburtshilfe, Bottrop, Germany, United States

R. Reitsamer. Breast Center, Paracelsus Medical University of Salzburg, Salzburg, Austria, United States

S. Schmatloch. Brustzentrum Elisabeth-Krankenhaus Kassel, Germany, United States

E. Sieghartsleitner. Universitätsklinik für Frauenheilkunde und Geburtshilfe, Graz, Austria, United States

L. Du. Department of Translational Molecular Pathology University of Texas MD Anderson Cancer Center, United States

A. Berghold. Institut für Medizinische Informatik, Statistik und Dokumentation, Medizinische Universität Graz, Austria, United States

W. Symmans. UT MD Anderson Cancer Center, United States

Background: De-escalation of axillary surgery in patients with lymph node-positive breast cancer is currently being tested in ongoing trials for patients with downstaged nodes after neoadjuvant chemotherapy (NAC). A proportion of such patients will achieve an excellent axillary node response to NAC, i.e. conversion to pathologic node-negative status after chemotherapy. Genomic prediction of tumor chemosensitivity before final surgery may identify which patients could safely undergo conservative surgical management of their regional lymph nodes.

Methods: The AGO-35 (NCT0203274) is a prospective trial for patients with HER2 negative breast cancer scheduled for neoadjuvant chemotherapy that includes an anthracycline- based regimen followed by 3-4 cycles of taxanes. The LN predictor is a newly developed model for predicting the probability of pathological lymph node-positivity after NAC in triple-negative (TNBC) or hormone-receptor positive (HR+) breast cancer. To calculate the LN predictor, which is developed in microarray, we calibrated the normalized individual gene module and SET ER/PR from RNAseq to the Affymetrix U133A platform using independently combined total of 220 pairs of TNBC samples with both RNAseq and U133A microarray results. The logistic regression model is applied for the prediction of the binary outcome, pathological lymph node-positive or negative after NAC. The cut-points of LN predictor in TNBC and HR+ samples were pre-determined for each subtype of breast cancer and then, independent, blinded evaluation in the AGO-35 trial samples.

Results: A total of 251 patients with HER2 negative breast treated with neoadjuvant chemotherapy were included. The LN predictor was validated on 189 qualified samples with wtRNA sequence. Statistical analysis of 181 samples is shown in Table 1.

Conclusion: Preliminary results of the AGO-35 trial show that the newly developed molecular LN predictor may accurately predict chemosensitivity response to NAC, in high proportion of

patients with TNBC.

Supported by: Wissenschaftsfonds (FWF) KLI 406

EUBREAST study group

AGO Österreich

Breast Cancer Research Foundation (BCRF-0158)

Table 1. Genomic prediction of chemosensitivity

	LN+		LN-	
	TNBC	HR+	TNBC	HR+
Genomic LN Predictor of Response	29/39 74%	14/56 25%	42/43 98%	17/43 40%
Overall	43/95 45%		59/86 69%	
Frequency of ypNO	20/29 69%	6/14 43%	36/42 86%	16/17 94%
Overall	26/43 61%		52/59 88%	

PO5-23-01

SentiNeo: A feasibility study on a magnetic approach to targeted axillary dissection and sentinel lymph node biopsy after neoadjuvant chemotherapy

Presenting Author(s) and Co-Author(s):

K. Chin. Dept of Surgery, Sahlgrenska Academy, Gothenburg University, United States

R. Olofsson Bagge. Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden

N. Mirzaei. Sahlgrenska Univeristy Hospital, United States

A. Kovács. Department of Clinical Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden, Vastra Gotaland, Sweden

H. Leonhardt. Dept of radiology, Sahlgrenska Academy, Gothenburg University, United States

P. Zaar. Dept of radiology, Sahlgrenska Academy, Gothenburg University, United States

A. Karakatsanis. Department for Surgical Sciences, Uppsala University, Uppsala, Sweden

E. Pantiora. Department of Surgical Sciences, Uppsala University, United States

S. Eriksson. Department of Surgery, Västmanland County Hospital, Västerås, Sweden, United States

M. Ekholm. Department of Oncology, Ryhov County Hospital, Jönköping, Sweden
Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden, United States

A. Thompson. Baylor College of Medicine, Houston, Texas, United States

P. Barry. Department of Surgery, The Royal Marsden Hospital NHS Trust, London, United Kingdom, United States

M. Boland. Department of Breast Surgery, St Vincent's University Hospital, Dublin 4, Ireland, United States

V. Man. Department of Surgery, University of Hong Kong, Hong Kong SAR, United States

A. Kwong. Department of Surgery, The University of Hong, Kong-Shen Zhen Hospital, China, United States

F. Wärnberg. Gothenburg University, Gothenburg, Sweden

Background Neoadjuvant chemotherapy (NAC) is increasingly used to treat certain breast cancer subtypes, and often, with good axillary response. Axillary management after NAC has become a contentious topic. Low detection rates and high false negative rates for sentinel lymph node biopsies (SLNB) could be due to the chemotherapy-induced fibrosis and blockage of the lymphatic drainage. Complete axillary response raises the dilemma of whether axillary clearance is still necessary after NAC in node positive patients. Targeted axillary dissection (TAD) is a safe alternative but the optimal method for index metastatic lymph node marking and lymphatic mapping of additional SLNs is largely undetermined. In SentiNeo, we study the feasibility and accuracy of using superparamagnetic iron oxides nanoparticles (SPIO) and magnetic seeds for axillary staging after NAC. Methods: Patients from two hospitals undergoing NAC were included: 40 without (cN0) and 40 with (cN+) axillary metastases. For cN0, SPIO was injected before and Technetium (Tc^{99}) after NAC. For cN+, a magnetic clip was inserted into the index metastatic node together with SPIO injection before and Tc^{99} after NAC. Endpoints were 1) Index node detection and 2) SLN detection and concordance rates. Detection rate was defined as the proportion of patients who had SLNs detected as per tracer

(using both magnetometer and gamma probe). Concordance was defined as the number of nodes marked by both SPIO and Tc⁹⁹, divided by the total number of Tc⁹⁹ marked nodes. As this is a feasibility study, no calculations for statistical significance were done. Results: All 80 patients have been included and 60 have completed NAC and surgery: 35 cN0 with SLNB and 25 cN+ with TAD. Overall, SLN detection rates (excluding the index nodes) were 83.3% (50/60) for SPIO and 76.7% (46/60) for Tc⁹⁹. In cN0, SLN detection rate was 85.7% (30/35) for SPIO and 88.6% (31/35) for Tc⁹⁹. In cN+, the index node was found in 24 of 25 patients. One patient did not receive a magnetic clip due to administrative error. The SLN detection rate (excluding index nodes) was 80% (20/25) for SPIO and 60% (15/25) for Tc⁹⁹. In total, 142 lymph nodes were retrieved, of which 71 contained both tracers. The concordance was 84% (out of 84 nodes detected with Tc⁹⁹, 71 were also detected with SPIO). However, the reversed concordance was only 55% (out of 129 nodes detected with SPIO, 71 were radioactive). The overall mean (median) number of retrieved nodes were 2.2 (2) for SPIO and 1.4 (1) for Tc⁹⁹. Conclusions: In this pilot study we have shown that injecting SPIO before NAC is feasible with detection rates comparable to Tc⁹⁹ injected after NAC. More nodes were retrieved with SPIO and furthermore, we hypothesize that these nodes might be more representative than nodes detected with a tracer injected after NAC. Finding the index node using the SentiMag probe was easy. For SLN detection with SPIO the same probe was used, making the magnetic approach to axillary staging an appealing alternative with no need for an extra localisation before surgery or access to nuclear medicine facilities. These findings justify a larger study which is in planning.

Table: Preliminary data on SentiNeo study: Sentinel lymph node biopsy and targeted axillary dissection after neoadjuvant chemotherapy.

	All completed NAC & Surgery	cN0	cN+
Number of patients	60	35	25
Average age	53.5 (30-79)	51.5 (30-76)	55.6 (30-79)
BMI	26 (17-41)	26 (19-41)	27 (17-39)
Cancer subtypes			
Luminal	23% (14)	0% (0)	56% (14)
HER2 amplified	45% (27)	54% (19)	32% (8)
TNBC	32% (19)	46% (16)	12% (3)
Detection rate (per patient)			
SPIO (index node excluded)	83.3% (50/60)	85.7% (30/35)	80% (20/25)
Tc ⁹⁹ (index node excluded)	76.7% (46/60)	88.6% (31/35)	60% (15/25)
Index node Magsced	-	-	96% (24/25)
Concordance (per node)			
Nodes containing SPIO and Tc ⁹⁹	71	43	28
Nodes containing SPIO only	58	29	29
Nodes containing Tc ⁹⁹ only	13	9	4
Concordance (SPIO vs. Tc ⁹⁹)	84.5%	82.7%	87.5%
Reverse concordance (Tc ⁹⁹ vs. SPIO)	55%	59.7%	49.1%

PO5-23-02

Targeted Axillary Dissection with Paramagnetic Marker Localization

Presenting Author(s) and Co-Author(s):

R. Reitsamer. Breast Center, Paracelsus Medical University of Salzburg, Salzburg, Austria, United States

A. Sir. University Hospital Salzburg, Department of Senology, Paracelsus Medical University Salzburg, Salzburg, Austria

E. Forsthuber. University Hospital Salzburg, Department of Senology, Paracelsus Medical University Salzburg, Salzburg, Austria

F. Peintinger. Institute of Pathology, Medical University of Graz, Graz, Austria / Universitätsklinik für Frauenheilkunde und Geburtshilfe, Graz, Austria, United States

Background: Targeted axillary dissection (TAD), the combination of sentinel lymph node biopsy (SLNB) and targeted lymph node biopsy (TLNB), can reduce the false negative rates of SLNB alone dramatically in breast cancer patients, who received neoadjuvant chemotherapy (NACT). However optimal methods for TAD are still under investigation. A paramagnetic marker Magseed® was used for the identification of the TLN in this study. Methods: 80 patients eligible to receive NACT were included. All patients had positive axillary lymph nodes verified by core biopsy. Six patients did not receive NACT for any reason. After NACT the targeted lymph nodes (TLNs) were marked with Magseed®, a non-radioactive paramagnetic marker. The SLNs were marked with dual tracer method. The SLNB and the selective TLNB were performed in 74 patients. The Magseed® marked TLNs were identified with the Sentimag® probe and excised. Specimen x-ray was performed to confirm the Magseed® within the prior to NACT biopsied and clipped lymph node. The identification rates of TLNs and SLNs, and the concordance rates were calculated. Results: The TLN identification rate was 100% (74/74), the SLN identification rate was 81.1% (60/74), the concordance rate of TLN and SLN was 58.1% (43/74). In 66.2% (49/74) of the patients the TLN converted to negative, and no ALND was performed. When the TLN converted to negative, a SLN could not be identified in 18.4% (9/49) of the patients. In 33.8% (25/74) of the patients the TLN remained positive after NACT and ALND was performed. When the TLN remained positive, a SLN could not be identified in 40% (10/25) of the patients. Complications according Magseed® deployment or identification could not be observed. Conclusion: Magseed® is a reliable and feasible marker for the identification of TLNs after NACT.

PO5-23-03

Impact of prosthetic nipple reconstruction after mastectomy on quality of life

Presenting Author(s) and Co-Author(s):

O. Buonomo. 1Breast Unit Policlinico Tor Vergata, Department of Surgical Science, Tor Vergata University, Viale Oxford 81, 00133, Rome (RM), Italy; 2 Ars Biomedica, Via Luigi Bodio, 58, 00191 Roma, Italy, Lazio, Italy

J. Caspi. 1Breast Unit Policlinico Tor Vergata, Department of Surgical Science, Tor Vergata University, Viale Oxford 81, 00133, Rome (RM), Italy; Tel Aviv, Israel

M. Materazzo. 1Breast Unit Policlinico Tor Vergata, Department of Surgical Science, Tor Vergata University, Viale Oxford 81, 00133, Rome (RM), Italy; 2PhD Program in Applied Medical-Surgical Sciences, Department of Surgical Science, Tor Vergata University, Rome, RM, Italy; United States

M. Pellicciaro. 1Breast Unit Policlinico Tor Vergata, Department of Surgical Science, Tor Vergata University, Viale Oxford 81, 00133, Rome (RM), Italy; 2PhD Program in Applied Medical-Surgical Sciences, Department of Surgical Science, Tor Vergata University, Rome, RM, Italy; United States

g. Vanni. 1Breast Unit Policlinico Tor Vergata, Department of Surgical Science, Tor Vergata University, Viale Oxford 81, 00133, Rome (RM), Italy; 2PhD Program in Applied Medical-Surgical Sciences, Department of Surgical Science, Tor Vergata University, Rome, RM, Italy; United States

Introduction

Post-mastectomy breast reconstruction (PMBR) is considered complete after nipple-areola complex (NAC) restoration, which is pivotal in restoring body image, and enhancing the psychosocial and sexual well-being of women treated for Breast Cancer (BC). Various methods, including nipple sharing, skin grafts, and local flaps with or without augmenting materials, have been proposed to achieve optimal aesthetic results. Despite these strategies, NAC flattening remains a common complication, leading to diminished aesthetic outcomes. To address this issue, a nipple reconstruction implant (NRI) (FixNip NRI™) has been developed. This study aims to assess patient quality of life (QoL) following prosthetic nipple reconstruction.

Materials and Methods

A multinational (Tor Vergata University and Israel) multicentric retrospective study with a prospectively maintained database was designed. The primary outcome was the comparative analysis of patients who underwent NRI with patients who received PMBR without NAC reconstruction. The Nipple Reconstruction (NR) group included patients with grade I and II capsular contracture, no active BC, and NAC reconstruction with NRI between 2019 and 2022. All patients were assessed post-surgery at 1-week, 3-months, 6-months, and 1-year intervals to measure NAC projection. In addition, satisfaction with Breasts, Physical Well-being, Psychosocial Well-being, and Sexual Well-being were evaluated using the Breast-Q score at each time interval. The NR group was compared using a propensity match score (PMS) from a prospectively maintained database of patients undergoing mastectomy without NAC reconstruction in the same time frame in Tor Vergata University. Breast Q score Within group and Between group analysis were performed with Wilcoxon-Mann-Whitney test.

Results

Eleven patients were enrolled in the NR group. A total of 53 female patients were considered for the NN group. Following a PMS analysis, 11 patients were included in this study group to

achieve a 1:1 ratio with the NR Group, accounting for confounding variables (Table I). In the NR group, the mean procedure time was 21 minutes. Mean NAC projections were 3.4 mm, 3.5 mm, 3.6 mm, and 3.6 mm at 1 week, 3 months, 6 months, and 1 year, respectively. No statistically significant difference in nipple projection over time was observed. Table II presents the Breast Q score among groups at 1 week and 1 year. In the between group analysis NR group showed a statistically significant difference in all the descriptors analyzed. Within-group analysis revealed a higher value of sexual well-being in the NR group at 1 year.

Conclusion

Despite the small sample size, the NRI offers a promising solution for NAC reconstruction, maintaining nipple projection, and enhancing patients' quality of life.

Table I: Confounding Variable

Variable	NN (n=11)	NR (n=11)	P-value
Mean Age (years), Range	50.2 [Range 32-64]	51.8 [Range 38-66]	>0.05
Mean BMI, Range	23.9 [19.4-26.1]	23.6 [19.8-25.6]	>0.05
Hypertension (n / %)	2/11 (18%)	2/11 (18%)	>0.05
Diabetes Mellitus (n / %)	1/11 (9%)	1/11 (9%)	>0.05
Marital status (married=n / %)	8/11 (72%)	9/11 (81%)	>0.05

Table II: Breast Q score analysis

Breast-Q Parameter	NN Group		NR Group		p-Value Between Groups		p-Value Within Groups (between 1-week and 1-year)	
	1-week (6-months from BR) (means)	1-year (18-months from BR) (means)	1-week (means)	1-year (means)	1-week	1-year	NN Group	NR Group
Satisfaction with Breasts	5	5.2	7.1	7.4	<0.001	<0.001	0.82	0.552
Physical Well-being	6.4	7.3	8	8.4	<0.001	0.002	<0.001	0.184
Psychosocial Well-being	4.6	5.1	6.9	8.1	<0.001	<0.001	0.704	0.106
Sexual Well-being	4	4.2	5.2	7.1	0.042	<0.001	0.794	0.009

PO5-23-04

Clinical utility of sentinel lymph node biopsy in women \geq 70 years with early breast cancer – an international, retrospective multi-center cohort study

Presenting Author(s) and Co-Author(s):

R. Merh. The Royal Marsden NHS Foundation Trust, Worcester Park, England, United Kingdom

D. Vorburger. Breast Cancer Unit, Comprehensive Cancer Center Zurich, University Hospital Zurich, Zurich, Switzerland

J. Jung. Seoul National Univ. Hospital, Surgery, Korea, United States

H. Lee. Seoul National University Hospital, United States

M. Tasoulis. The Royal Marsden NHS Foundation Trust, London, England, United Kingdom

Introduction

Traditionally, sentinel lymph node biopsy (SLNB) has been used to stage the axilla in early breast cancer (EBC) to guide adjuvant treatment recommendations. Following advances in tumor biology understanding, targeted systemic therapies and genomic testing, with increasing de-escalation of axillary surgery, its role may be less critical especially in selected groups of women.

Aims

Evaluate clinical utility of SLNB in adjuvant treatment recommendations for women \geq 70 years with EBC.

Methods

Retrospective cohort study of women \geq 70 years with cT1-2N0 EBC undergoing primary surgery and SLNB between 01/2017-12/2022 at The Royal Marsden Hospital (RMH), University Hospital Zurich (USZ) and Seoul National University Hospital (SNUH) in the United Kingdom, Switzerland and South Korea respectively. Simple descriptive statistics and non-parametric tests were performed as appropriate.

Results

A total of 884 patients were included in the analysis, with 584 patients from RMH, 148 from USZ and 152 from SNUH. The median age was 75 (IQR 72-79) years. Most cancers were invasive ductal (82.9%), grade 2 (61.4%), hormone receptor (HR) positive/HER2 negative (82.9%) with a median tumor size of 17 (IQR 4-50) mm. SLNB was positive in 116 (13.1%) patients. Of these 116 patients, 20 (17.2%) had completion ALND; 7/20 had further RT up to levels 3&4 of the axilla. Of these 116 patients, 96 patients (82.8%) avoided ALND; 25/96 had no further treatment, and 71/96 patients had loco-regional axillary RT (8/71 had RT to levels 1&2 and 63/71 had RT up to levels 3&4). As per international guidelines for patients with EBC with 1-2 positive macrometastases on SLNB treated with breast conserving surgery and breast RT, 5/20 could have been spared ALND, and 50/71 axillary RT. Completion ALND was more likely to be performed at SNUH compared to the other 2 units ($p < 0.0001$). Axillary RT was more likely to be administered at SNUH and less likely at RMH ($p < 0.0001$).

The multidisciplinary team (MDT) recommended adjuvant chemotherapy (AC) in 146 (16.5%) patients and 100 received it. Of those with a positive SLNB ($n=116$), AC was recommended in 35, and received by 29. Recommendation for AC was significantly associated with younger age

($p=0.021$), fewer comorbidities ($p=0.003$), higher tumor grade ($p< 0.0001$), increased tumor size ($p< 0.0001$), HR negative status ($p< 0.0001$), high genomic risk profile ($p< 0.0001$) and positive SLNB status ($p< 0.0001$), but not center ($p=0.497$).

A subgroup analysis of 505 patients with cT1N0, HR+/HER2- EBC, representing a more favorable prognosis group, was performed. Here, 52/505 (10.3%) patients had positive SLNB, of whom 11 had no further axillary treatment, 9 underwent ALND and 32 axillary RT, where 4/9 could have been spared ALND and 28/32 axillary RT as per international guidelines mentioned above. AC was recommended in 26/505 (5.15%) women and 23 received it. AC was not recommended in 39/52 (75%) cases, despite a positive SLNB. MDT recommendation for AC was associated with grade 3 ($p< 0.0001$), multifocal disease ($p=0.021$), positive SLNB status ($p< 0.0001$), high genomic risk profile ($p< 0.0001$), lower age ($p=0.044$), fewer co-morbidities ($p=0.001$) and center ($p=0.007$) with SNUH being more likely than the other 2, but not ethnicity ($p=0.130$); AC receipt was associated with the same factors except age ($p=0.347$).

Conclusions

Real-world data demonstrates axillary overtreatment despite evidence of the safety of de-escalation of axillary management in EBC. Only a small proportion of women ≥ 70 years with EBC had positive SLNB that may influence adjuvant treatment recommendations, especially with favorable prognosis tumors. In such cases, where clinical morbidity and financial burden of SLNB may outweigh the benefits, a nuanced discussion for opting in SLNB rather than routine performance should be considered.

PO5-23-05

The Impact of Bi-Annual Diagnostic Imaging on Detecting Ipsilateral Breast Recurrence in Patients Undergoing Breast Conserving Surgery for Breast Cancer

Presenting Author(s) and Co-Author(s):

P. Miah. NYU Langone Health, United States

L. Fiedler. NYU Langone Health, United States

A. Baez. NYU Langone Health, United States

A. Sevdalis. NYU Langone Health, United States

A. Marmer. NYU Langone Health, United States

C. DiMaggio. NYU Langone Health, United States

L. Pak. NYU Langone Health, United States

R. Shapiro. NYU Langone Health, United States

K. Hiotis. NYU Langone Health, United States

D. Axelrod. NYU Langone Health, United States

A. Guth. NYU Langone Health, United States

F. Schnabel. NYU Grossman School of Medicine, New York, New York, United States

Introduction: Breast conserving surgery (BCS) represents the preferred option for surgical treatment for a majority of patients with early-stage breast cancer who are eligible for this approach. When compared with mastectomy approaches, BCS provides patients with equivalent survival while preserving the affected breast. It is necessary to achieve clear surgical margins as positive lumpectomy margins are associated with an increased risk for ipsilateral breast tumor recurrence. With advances in imaging techniques, as well as effective systemic therapy and contemporary radiation therapy, local recurrence after BCS has decreased and overall survival for patients has improved. Retrospective studies have quantified the recurrence rate in unifocal breast cancer as 8 - 15% at 20 years. The NCCN recommends annual mammography at least 6 months after post-lumpectomy radiation therapy, but there is little data regarding more frequent surveillance after lumpectomy in the early post-operative setting. The purpose of this study was to evaluate the impact of short interval surveillance mammography on the detection of early in-breast recurrence in patients undergoing BCS. Methods: Our IRB-approved Breast Cancer Database was queried for patients enrolled from 11/2009 to 6/2023 who underwent breast conservation surgery for a diagnosis of in situ or invasive breast cancer in this retrospective analysis. Per our institutional protocol, patients were recommended to undergo diagnostic mammography of the treated breast(s) every 6 months for 2 years after BCS. After the initial 2 year period, bilateral mammography was performed annually in the absence of other indications. Additional supplemental imaging such as breast ultrasound and MRI were performed at physician discretion and based on patient risk and breast density. Variables of interest included the presence of pathogenic germline mutations, family history of breast cancer, and disease characteristics. Our primary endpoint was ipsilateral breast tumor recurrence. Results: Of 2491 patients who underwent breast conservation surgery for in situ or invasive breast cancer, 191 (7.7%) developed recurrent disease, including ipsilateral and contralateral recurrence, and distant disease, in the study period. A total of 83 (3.2%) patients developed ipsilateral breast recurrence during the entire study period. Of those, 19 (22.9%) were detected within the first two years after surgery. Six of the 19 patients (31.6%) had their recurrences detected on yearly diagnostic mammography while 6 (31.6%) patients had their recurrences detected on interval 6-month unilateral diagnostic imaging. In both groups, 5/6

recurrences were invasive disease after an original diagnosis of invasive cancer, and the remaining patient had recurrent DCIS. The remaining 7/19 patients (36.8%) had their ipsilateral recurrences detected on palpation or other diagnostic imaging. In this group as well, there was one case of recurrent DCIS, with the remaining 6 cases representing recurrent invasive cancer. Of the 19 patients with ipsilateral recurrences, none had pathogenic germline mutations. 4 of the 19 patients (21%) had positive margins after their initial lumpectomy surgery with re-excisions required to achieve clear margins. Conclusion: Interval diagnostic surveillance imaging every 6 months after breast conserving surgery identified almost one-third of the ipsilateral breast tumor recurrences that occurred within the first 2 years after surgery in our population. While our numbers are small, the relationship of re-excision lumpectomy surgery to subsequent risk for local recurrence has been described by others, and bears further study. Particularly in view of our observation that the majority of in-breast recurrences were invasive, our data supports the practice of more frequent imaging follow up in the first 2 years after breast conserving surgery.

PO5-23-06

Predictive Factors for Reconstructive Method and Outcomes in Mutation-Positive Breast Cancer Patients

Presenting Author(s) and Co-Author(s):

S. Sortur. Georgetown Univ SOM, United States

J. Gupta. Georgetown Univ SOM, United States

C. Lava. MedStar Georgetown University Hospital, United States

L. Berger. MedStar Georgetown University Hospital, United States

V. Harish. Georgetown University, United States

Z. Khan. Georgetown Univ SOM, United States

D. Spoer. MedStar Georgetown University Hospital, United States

L. Rosal. MedStar Georgetown University Hospital, United States

I. Greenwalt. MedStar Georgetown University Hospital, United States

L. De La Cruz. Medstar Georgetown University Hospital, Department of Breast Surgery, United States

D. Song. Georgetown University, United States

K. Fan. Georgetown University, United States

Background: BRCA1 and BRCA2 mutations significantly increase the risk of breast cancer, and prophylactic mastectomy reduces the risk by around 90% in these patients. Previous studies have explored predictors of mastectomy type in high-risk genetic mutation patients, but further characterization is needed. This study aims to identify factors associated with resection and reconstruction methods and predictors of postoperative complications in mutation-positive (M+) patients. Methods: A multicenter retrospective cohort study included patients with a genetic predisposition for breast cancer undergoing breast surgery, seen between January 2016 and October 2022. Patient demographics, comorbidities, oncologic history, operative details, and postoperative outcomes were collected. Descriptive statistics and multivariate logistic regression were performed. Results: Among the 176 patients analyzed, 75 (42.6%) had BRCA1, 71 (40.3%) had BRCA2, 11 (6.3%) had PALB2, and 8 (4.5%) had CHEK2 mutations. Mean age and body mass index (BMI) were 41.0 ± 17 years and 24.9 ± 6.9 kg/m², respectively. Among patients with prior breast reconstruction (n=86, 48.9%), augmentation mammoplasty (n=31, 17.6%) was the most common procedure, followed by oncologic resection (n=21, 11.9%) and reduction mammoplasty (n=15, 8.5%). Nipple-sparing mastectomy (NSM) (n=107, 60.8%) was the most frequent surgical approach, followed by skin-sparing mastectomy (SSM) (n=43, 24.4%), simple mastectomy (n=14, 8.0%), lumpectomy (n=4, 2.3%), and radical mastectomy (n=4, 2.3%). Tissue expander (n=77, 43.8%) was the most common reconstruction method. By a median follow-up duration of 23.9 months, 66 (37.5%) of patients experienced postsurgical complications. Operative complications recorded within 30 days included seroma (n=9, 5.1%), hematoma (n=8, 4.5%), cellulitis (n=10, 5.7%), dehiscence (n=13, 7.4%), surgical site infection (n=11, 6.3%), and delayed wound healing (DWH) (n=24, 13.6%). Other long-term complications included mastectomy flap necrosis (n=22, 12.5%), total reconstructive failure (n=9, 5.1%), red breast syndrome (n=2, 1.1%), and capsular contracture (n=12, 6.8%). The choice of autologous breast reconstruction was correlated with younger age (OR 0.81, 95% CI: 0.69-0.95, p = 0.012) and Hispanic or Latino race (OR 0.01, 95% CI: 0.001-0.25, p=0.007). BMI was significantly correlated with incidence of hematoma (OR 1.17, 95% CI: 1.02-1.33, p=0.024), DWH (OR=1.1, 95% CI: 1.01-1.20, p=0.030), and dehiscence (OR 1.25, 95% CI:

1.09-1.43, $p=0.001$). Choice of autologous reconstruction was positively correlated with DWH (OR 8.86, 95% CI: 2.25-34.86, $p=0.002$) and dehiscence (OR 18.24, 95% CI: 2.58-129.158, $p=0.004$). Conclusion: In this macroscopic study, the most common breast reconstruction method for M+ patients was tissue expander-based. However, only autologous reconstruction was found to have positive correlates, specifically younger age and Hispanic or Latino origin. Younger patients may pursue this method given less concern for short term complications, which are historically increased in autologous reconstruction. Minority distrust of foreign medical material implantation may play a role in Hispanic or Latino choice. Additionally, autologous reconstruction and BMI were associated with certain postoperative complications, particularly dehiscence, DWH, and hematoma, results consistent with general breast cancer surgery cohorts. This study helps better characterize the M+ population and contributes insight into the resection and reconstructive choice in this patient population.

PO5-23-08

Adenylosuccinate lyase is essential for proliferation and mitochondrial function of endocrine therapy resistant breast cancer cells

Presenting Author(s) and Co-Author(s):

A. Yadav. The Hormel Institute, United States

L. Jin. Hormel Institute/University of Minnesota, United States

R. Clarke. The Hormel Institute, United States

S. Sengupta. The Hormel Institute, United States

Eighty percent of breast cancers express estrogen receptor alpha (ER α , ESR1) at the time of diagnosis. Endocrine therapy (ET) is the standard treatment that either block estrogen mediated ER activation (such as tamoxifen, fulvestrant) or suppress estrogen synthesis (such as exemestane, letrozole, or anastrozole). While ET is initially effective, emergence of ET-resistance is common and possess a major clinical challenge. Hence, there is an ongoing need to develop new treatments for ET-resistant-ER α positive breast cancer. In this study we investigated the role of adenylosuccinate lyase (ADSL), an enzyme of the de-novo purine biosynthesis pathway as a potential target of ET-resistant breast cancer. The protein level of ADSL in two independent ET-resistant cell line model LCC9 and T47D-4HT cells were significantly higher in comparison to its parental ET-sensitive cell lines, MCF7 and T47D cells, respectively. Transient knockdown of ADSL using two independent siRNA in both LCC9 and T47D-4HT cells results in a significant decrease of cell growth, colony, and spheroid formation. Notably, reduced ADSL levels in LCC9 cells prevented the cells from progressing from G1 to S phase of cell cycle with concurrent elevation of cyclin D1/D3, CDK2/4, and cyclin E. On the other hand, in T47D-4HT cells, ADSL reduction caused cells to accumulate in S-phase of cell cycle and showed lower levels of total cyclin D1 protein. Mechanistically, in LCC9 cells (but not in T47D-4HT cells), ADSL depletion induced DNA replication stress which activates (phosphorylate) ataxia-telangiectasia-mutated-and-Rad3-related kinase (ATR) and its major downstream effector checkpoint kinase 1 (Chk1) that in turn failed to de-phosphorylate the inhibitory-phospho-groups of cyclin-dependent kinase 2 (CDK2). In addition, ADSL depletion perturbed the mitochondrial function in both LCC9 and T47D-4HT cells. Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) was lower in both the cells along with the mitochondrial membrane potential. Pertinently, lower concentration of AICAR (5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside), a product of ADSL enzyme function, partially rescued the cell growth and restored mitochondrial membrane potential in ADSL-depleted LCC9 cells. To further understand the global effects of ADSL depletion we performed RNA-sequencing of LCC9 and T47D-4HT cells after ADSL depletion and compared with respective control siRNA transfected cells followed by gene set enrichment analysis. Intriguingly, diverse effect was observed in LCC9 and T47D-4HT cells as very few genes were found to be commonly regulated between these two cell lines. Analysis of clinical data sets revealed high level of ADSL transcript was associated with adverse progression free survival and overall survival in breast cancer patients treated with endocrine therapies. Overall, our findings demonstrate that ADSL-mediated de novo purine synthesis is critical for cellular growth, proliferation, and mitochondrial function of endocrine therapy-resistant breast cancer cells. Therefore, targeting ADSL is a novel potential therapeutic approach for ER α positive ET-resistant breast cancer.

PO5-23-09

Metabolic alterations in Estrogen Receptor-positive breast cancer contributing to CDK4/6 resistance.

Presenting Author(s) and Co-Author(s):

M. Allam. Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, United States

A. Coskun. Georgia Institute of Technology & Emory University, United States

T. Hu. Georgia Institute of Technology, United States

Y. Gu. Department of Pathology&Laboratory Medicine, Emory University School of Medicine, United States

S. Badve. Emory University School of Medicine, United States

Y. Gokmen-Polar. Emory University School of Medicine, United States

Background CDK4/6 inhibitors (CDK4/6i) are potent FDA-approved agents for the treatment of metastatic and for high-risk early estrogen receptor positive (ER+) breast cancer. However, significant proportion of patients continue to develop disease progression. Response does not correlate well with expression of CDK4/6 or key cell cycle proteins. Ki67, a proliferation marker, is prognostic, but NOT predictive of response. Resistance to CDK4/6i is mediated by multiple mechanisms including metabolic alterations. Herein, we explore the metabolic alterations associated with development of CDK4/6i resistance.

Methods To understand the key metabolic alterations associated with resistance, we first developed abemaciclib-resistant ER+ cell lines and compared their metabolic profile with their parental/sensitive counterparts. Seahorse metabolic profiles were performed on parental cells (MCF-7, LCC2, LCC9, T47D and ZR-75.1) and their resistant derivatives. In addition, spatial proteomics analysis was performed using multiplex cyclic immunofluorescence (CyclIF) assay for 27 markers including 14 metabolic regulators (MCT1, GLUT1, G6PD, VDAC1/3, LDHA, GAPDH, PGC1A, HK2, ATP5A, GLUD12, CPT1A, CS, C6 Ceramide, COXIV), 9 signaling (CD36, CCND1, CCNE1, pRB, MKI67, pERK, CDH1, GPNMB and MET) and 4 segmentation markers (pan-cytokeratin for epithelial cells, concanavalin A for endoplasmic reticulum, phalloidin for actin, and wheat germ agglutinin (WGA) for Golgi and plasma membrane) in sensitive and resistant cells. Following the image registration (hiPlex) and cell segmentation (CellProfiler), multiplex protein images were clustered for cell phenotypes (HistoCAT).

Results Cells resistant to abemaciclib showed G1 phase arrest, but a dramatic increase in invasive capacity. The Seahorse XFp Cell Energy Phenotype Assay demonstrated altered metabolic profiles including decreased extracellular acidification rate (ECAR) and oxygen consumption rate (OCAR) indicative of glycolysis, and mitochondrial respiration, respectively, in resistant cells. Multiplex CyclIF utilized a panel of 11 cycles resulting in a total of 27 markers. We demonstrated that three metabolic enzymes, mitochondrial voltage-dependent anion channel protein (VDAC1/3), lactate Dehydrogenase A (LDHA) and PPAR γ coactivator 1 α (PGC1 α) are significantly overexpressed in CDK4/6 resistant cells compared to the control parental sensitive cells. Further analyses are ongoing to better characterize these changes in human samples treated with CDK4/6i.

Conclusion Our findings highlight the importance of metabolic pathways in development of resistance to CDK4/6i treatment. Understanding the mechanisms by which these pathways

contribute to therapeutic failure will further provide with novel intervention strategies and new avenues for prevent recurrence/resistance in ER+ breast cancer.

PO5-23-10

Development of a long-term in vitro assay able to identify compounds that can overcome resistance to CDK4/6 inhibitor plus endocrine therapy in ER+ HER2- breast cancer

Presenting Author(s) and Co-Author(s):

S. Kronstadt. Novartis Institutes for BioMedical Research, United States

N. Umbreit. Novartis Institutes for BioMedical Research, United States

M. Niederst. Novartis Institutes for BioMedical Research, United States

R. Janssens. Novartis Institutes for BioMedical Research, United States

CDK4/6 inhibitor plus endocrine therapy (ET) has emerged as the standard of care first line therapy in ER+ HER2- breast cancer. While this combination has shown the ability to extend overall survival, nearly all patients acquire resistance and progress after 2-3 years. Subsequently, interest has turned to identifying a third partner compound that can be integrated into the CDK4/6i plus ET backbone regimen with the goal of overcoming resistance and driving a deeper response. However, a comprehensive assay-based workflow proficient in identifying compounds with the most promising potential is lacking. To fill this need, we set out to develop a high-throughput in vitro assay with relevant multi-faceted readouts to assess the efficacy of potential triplet combinations using 12 human ER+ breast cancer lines. For this assay, cells were engineered to express nuclear RFP to enable accurate cell counting using basic imaging techniques in 384 well plates. Each third partner compound was tested at two different doses and, in addition to the triplet combination (CDK4/6i + ET + third partner), single agent as well as double agent combinations were investigated. The assay was imaged and re-dosed every 5 days until day 15. On day 15, the compounds were washed out and the cells underwent a 25-day drug holiday to monitor relapse. Duplicate plates of all conditions were monitored and imaged every two hours for 24 hours for live cell staining of apoptosis markers. Additional duplicate plates were fixed and stained on days 5 and 15 for markers of senescence and cell cycle. Images were subsequently fed into a python-based algorithm to determine the percentage of cell population expressing the various markers and phenotypic correlates were extracted. We are looking for triplet combinations that induce a deeper cell cycle arrest, senescence, and/or cell death compared with the CDK4/6 inhibitor plus ET only treatment. Our drug holiday results will help elucidate the treatments able to continue to induce suppression once washed out, indicating treatment options that may induce long-lasting, possibly irreversible effects on the cells. Finally, by extracting phenotypic correlates from brightfield images we hope to cluster the various compounds in their effects across cell lines of diverse backgrounds to help understand the best way to benefit multiple patient populations. Overall, the assay will be able to identify and differentiate various therapeutic combinations based on cell count, senescence, and cell death. The format of this assay enables depth of analysis not accessible using other techniques such as FACS, including full dose-response curves, combination matrices, and longitudinal analyses. Additionally, the assay can be modified to evaluate any number of cellular markers and can be useful across a number of applications. The approach developed here will be foundational in discovering next-step strategies for patients with therapy resistance.

PO5-23-11

Elevated linoleic acid levels in red blood cells membrane predicts response to neoadjuvant chemotherapy in breast cancer patients

Presenting Author(s) and Co-Author(s):

B. Walbaum. Pontificia Universidad Catolica de Chile, United States

C. SÁNCHEZ. Pontificia Universidad Catolica de Chile, United States

F. ACEVEDO. Pontificia Universidad Catolica de Chile, United States

Introduction: Fatty acids (FA) consumed in the diet have been implicated in increasing the risk of breast cancer (BC). Humans have a wide variety of FAs, including saturated (SFA), monounsaturated (MUFA), and polyunsaturated (PUFA) FAs. PUFAs can be further classified into omega-3 (n-3) and omega-6 (n-6) PUFAs. While n-3 has been associated with reducing inflammation and promoting apoptosis in BC cells, n-6 has been linked to increased inflammation, oxidative stress, and the promotion of BC cell proliferation and treatment resistance. In healthy women, the n-3 content in mammary tissue correlates with n-3 content in red blood cells (RBCs). The FA profile of the RBC membrane provides an unbiased option to assess lipid intake and composition, reflecting long-term FA intake and providing an objective and sensitive measure of lipid intake and body fat deposits. Notably, BC patients have been found to display a high n-6:n-3 ratio in RBCs, which is associated with inflammatory and oxidative stress biomarkers.

The neoadjuvant chemotherapy treatment (NACT) model presents a unique opportunity to study resistance mechanisms in non-metastatic BC patients. In this approach, the absence of tumor (pathologic complete response: pCR, or Residual Cancer Burden (RCB) = 0) after NACT indicates treatment sensitivity and better overall survival (OS).

Objective: The objective of this study is to determine whether differences in FA profiles determined in the RBC membrane and plasma are associated with the response to NACT in non-metastatic BC patients.

Methods: A prospective study was conducted, including non-metastatic BC patients scheduled to receive NACT. Blood samples were collected before the first cycle of NACT to measure plasma and RBC FA derivatives, SFAs, MUFAs, and PUFAs. The pathological complete response (pCR) and residual cancer burden (RCB) were assessed.

Results: A total of twenty-eight BC patients were included in the study. When comparing pCR vs. no-pCR using total SFA, MUFA, and PUFA plasma samples, no significant differences were observed. However, in RBC, an increase in PUFA was associated with a higher rate of no-pCR (** $p < 0.01$). Furthermore, comparing omega-6 and omega-3 (both PUFA) levels, an increase in omega-6 was associated with no-pCR (** $p < 0.01$), while no significant differences were observed with omega-3. No differences were obtained in plasma samples for either omega-6 and omega-3. To determine which specific omega-6 PUFAs were responsible for the association with no-pCR, elevated levels of linoleic acid (LA) in RBC were found to be associated with no-pCR (** $p < 0.01$). Other omega-6 PUFAs, including gamma-linolenic acid (GLA), eicosadienoic acid (EDA), dihomo-gamma linolenic acid (DGLA), and arachidonic acid (ARA), showed no significant associations. Multivariate and regression analysis confirmed LA (C18:2 n-6, LA) as the most relevant FA when assessing RCB (0-1 vs. 2-3) in RBC membranes, but not in plasma. The receiver operating characteristic (ROC) curve analyzing LA

levels in RBC showed an area under the curve (AUC) of 0.855 for RCB (sensitivity: 76.9%, specificity: 92.3%).

Conclusions: To the best of our knowledge, this is the first study demonstrating a clear connection between RBC membrane FA composition, specifically LA concentration, and the pathological response in BC patients after NACT. The measurements taken in plasma did not show significant associations, suggesting that RBC membrane FA profile of could serve as a relevant prognostic biomarker for studying resistance mechanisms to NACT in early BC patients

Measured FAs in RBC membrane and plasma by pathologic complete response

FA name/ FA type	Formula	RBC membrane				plasma					
		pCR	SD	No pCR	SD	p-value	pCR	SD	No pCR	SD	p-value
Total SFA	--	37,73	2,73	37,90	2,39	0,87	36,93	2,24	35,53	2,71	0,19
Caprylic acid	C8:0	0,07	0,13	0,03	0,00	0,19	0,06	0,02	0,06	0,02	0,41
Capric acid	C10:0	0,06	0,02	0,13	0,21	0,32	0,13	0,21	0,07	0,01	0,24
Lauric acid	C12:0	0,12	0,02	0,12	0,02	0,96	0,12	0,02	0,14	0,03	0,08
Myristic acid	C14:0	2,13	0,43	2,05	0,27	0,53	2,10	0,21	2,15	0,27	0,62
Palmitic acid	C16:0	22,22	2,32	23,27	2,55	0,31	22,62	1,20	22,06	2,22	0,48
Stearic acid	C18:0	11,61	1,08	10,65	2,88	0,35	10,66	1,11	9,78	1,21	0,08
Arachidic acid	C20:0	0,15	0,03	0,17	0,03	0,06	0,12	0,02	0,10	0,02	0,039*
Behenic acid	C22:0	0,49	0,08	0,55	0,12	0,18	0,38	0,12	0,39	0,11	0,72
Lignoceric acid	C24:0	0,88	0,12	0,92	0,08	0,35	0,73	0,11	0,77	0,09	0,31
Caprylic acid	C8:0	37,73	2,73	37,90	2,39	0,87	36,93	2,24	35,53	2,71	0,19
Total MUFA	--	29,28	3,36	28,16	3,16	0,40	27,32	3,11	27,30	3,16	0,99
Myristoleic acid	C14:1	0,09	0,02	0,08	0,02	0,26	0,07	0,02	0,07	0,02	0,59
Palmitoleic acid	C16:1	2,65	0,36	2,62	0,45	0,86	2,23	0,34	2,31	0,45	0,66
Oleic acid	C18:1	25,10	3,09	24,10	3,08	0,44	23,69	2,91	23,72	3,10	0,97
Gondoic acid	C20:1n-9	0,66	0,13	0,60	0,10	0,17	0,47	0,11	0,48	0,12	0,87
Erucic acid	C22:1n-9	0,31	0,12	0,28	0,12	0,48	0,28	0,08	0,24	0,09	0,30
Nervonic acid	C24:1	0,48	0,13	0,48	0,16	0,93	0,57	0,14	0,47	0,12	0,07
Total PUFA	--	34,91	1,20	39,34	3,87	0,0028*	37,89	3,11	39,55	3,61	0,25
Linoleic acid	C18:2n-6	20,02	1,86	23,65	3,01	0,0029*	22,57	3,37	23,25	3,02	0,59
γ -linolenic acid	C18:3n-6	0,10	0,04	0,10	0,04	0,84	0,08	0,03	0,10	0,02	0,0150*
α -linolenic acid	C18:3n-3	0,83	0,26	1,08	0,29	0,034*	0,82	0,19	0,97	0,29	0,16
Eicosadienoic acid	C20:2n-6	1,01	0,29	1,13	0,34	0,34	0,92	0,13	1,03	0,24	0,23
Dihomo γ linoleic acid	C20:3n-6	0,95	0,05	1,11	0,40	0,25	1,12	0,27	1,21	0,34	0,47
Eicosatrienoic acid	C20:3n-3	0,02	0,01	0,03	0,01	0,24	0,03	0,01	0,03	0,01	0,44
Arachidonic acid	C20:4n-6	9,30	1,25	9,47	1,34	0,75	9,91	1,25	10,30	1,72	0,54
Eicosapentaenoic acid	C20:5n-3	1,49	0,42	1,54	0,51	0,81	1,37	0,41	1,50	0,49	0,52
Docosapentaenoic acid	C22:5n-3	0,22	0,08	0,23	0,08	0,80	0,17	0,09	0,19	0,06	0,44
Docosahexanoic acid	C22:6n-3	0,99	0,20	1,01	0,22	0,84	0,91	0,14	0,96	0,28	0,61
Total n-6	--	31,36	1,24	35,46	3,76	0,0041*	34,59	3,04	35,91	3,51	0,35
Total n-3	--	3,55	0,70	3,88	0,47	0,15	3,30	0,40	3,65	0,57	0,11
n-6:n-3 ratio	--	9,15	1,81	9,22	1,26	0,90	10,59	1,46	10,06	1,95	0,48

*Indicates p<0.05; abbreviations: pCR: pathological complete response; SD: standard deviation; yr: years; BMI: body mass index; HR: hormone receptor; HER2: human epidermal growth factor receptor type-2; NLR: neutrophil to lymphocyte ratio; HG: histological grade; RCB: residual cancer burden; NA: not applicable

PO5-24-01

Narazaciclib's differential targets and kinase inhibitory activity contribute to the enhanced inhibition of tumor growth in preclinical models

Presenting Author(s) and Co-Author(s):

P. Kechagioglou. Johannes Gutenberg University Medical Centre Mainz, United States

D. Chakraborty. Johannes Gutenberg University Medical Centre Mainz, United States

C. Dupont. Johannes Gutenberg University Medical Centre Mainz, United States

H. Yurugi. Johannes Gutenberg University Medical Centre Mainz, United States

U. Distler. Institute of Immunology, University Medical Center Mainz, United States

S. Tenzer. Institute of Immunology, University Medical Center Mainz, United States

A. Chernobrovkin. Pelago Bioscience, United States

K. Riegel. Johannes Gutenberg University Medical Centre Mainz, United States

J. Mooz. Johannes Gutenberg University Medical Centre Mainz, United States

M. Lamber. Goethe University, Frankfurt, United States

V. Dötsch. Goethe University, Frankfurt, United States

S. Cosenza. Onconova Therapeutics Inc, United States

S. Fruchtman. Onconova Therapeutics Inc, United States

K. Rajalingam. Johannes Gutenberg University Medical Centre Mainz, United States

Despite improvement of outcomes for HR+, HER2- metastatic breast cancer by cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors, safety concerns and disease progression raise a critical need to identify novel approaches. Narazaciclib (ON123300), a novel CDK4/6i, designed to enhance efficacy and safety by its multi-targeted kinase inhibitor activity. Narazaciclib is in Ph I trials; NCT04739293 and CXHL1900340; studying different administration regimens and in endometrial cancer in combination with letrozole (NCT05705505). Our study explored the activity of narazaciclib and its metabolite ON1232580 in comparisons to the FDA approved CDK4/6i and identify additional targets engaged by narazaciclib.

To identify direct and secondary targets engaged by narazaciclib and palbociclib, proteome wide Cellular Thermal Shift Assay (CETSA) and Integrative Inferred Kinase Activity (INKA) analysis were performed. Both CETSA and INKA analysis identified additional targets engaged by narazaciclib compared to palbociclib in both MDA-MB-231 lysates and intact cells such as BUB1, CHEK1, AURKA, GSK3 α and GSK3 β . In TNBC patients with BUB1 overexpression, bioinformatics analysis indicates a low survival correlation. Molecular docking data showed a higher affinity of narazaciclib with BUB1 compared to palbociclib and abemaciclib.

The differential activity of narazaciclib was explored by using cohorts of human and mouse breast cancer cell lines and cell based assays. Comparison of narazaciclib's in vitro IC₅₀ profile to other CDK4/6i was studied against a panel of 370 kinases (HotSpot) and K_d values were determined by KINOMEscan. Intracellular IC₅₀ kinase values were determined by NanoBret technology. Narazaciclib and abemaciclib were found to be the most promiscuous in vitro kinase inhibitors and ribociclib the most specific. Abemaciclib and narazaciclib had similar profiles against the CDK family members. K_d values of CDK4/cyclinD1 binding show similar trends; abemaciclib (0.08 nM), narazaciclib (0.18 nM), palbociclib (0.75 nM) and ribociclib (1.3

nM). Although narazaciclib displayed nM IC₅₀ values in the in vitro assays against many CDKs, narazaciclib was very specific in cellular kinase assays with highest activity against CDK4/6, CSF1R and NUAK1.

A stronger inhibition of cell proliferation, as well as induction of apoptosis and senescence were detected in narazaciclib and its metabolite ON1232580 treated PYMT cells, a murine mammary carcinoma model which recapitulates luminal BC subtype, compared to the other CDK4/6i. Both narazaciclib and ON1232580 enhanced CCL5 and CXCL10 mRNA levels, while a higher reduction of PD-L1 and pRb protein levels and a promoting effect on the H2D1 and B2M mRNA levels was shown in narazaciclib and its metabolite treated PYMT cells. Narazaciclib showed significant synergy with anti-PD1 in the EMT-6 syngeneic breast cancer model. A differential effect of narazaciclib on the expression levels of 62 cytokines was detected compared to abemaciclib and palbociclib. Lastly, inhibition of autophagy sensitizes cancer cells to both ON123300 and ON1232580, and induces irreversible cell proliferation inhibition, providing a novel therapeutic approach.

Our findings identify important differences generated from assay models studying kinase inhibition, binding and pathway engagement. Understanding the role of the differential targets engaged by narazaciclib, the potential enhanced antitumor immunity and the sensitization by autophagy inhibitors to cell death, will guide future clinical studies.

PO5-24-02

Interferon-induced bone marrow stromal antigen 2 (BST2) is a functional tumor-initiating cell marker in triple-negative breast cancer

Presenting Author(s) and Co-Author(s):

E. Souto. Baylor College of Medicine, Houston, Texas, United States

P. Gong. Baylor College of Medicine, United States

J. Landua. Baylor College of Medicine, United States

R. Srinivasan. Baylor College of Medicine, United States

L. Dobrolecki. Baylor College of Medicine, United States

A. Ganesan. Baylor College of Medicine, United States

M. Lewis. Baylor College of Medicine, Houston, Texas, United States

Background: A subpopulation of tumor cells known to have intrinsic resistance to therapies and contribute to metastasis function as “cancer stem”, or tumor-initiating, cells (TICs). TICs can be identified by various biomarkers, including fluorescent reporters for signaling pathways that regulate TIC function such as STAT signaling. However, standard TIC reporters have limitations. Their expression is unstable and there is no established method to follow TICs as they undergo cell state changes. Furthermore, we do not completely understand the transcriptional features of TICs. Improved methods of identifying TICs as well as the development of high-resolution transcriptional signatures are essential to understand TIC biology. An improved understanding of TIC biology can inform the development of novel therapeutics to selectively ablate the TIC compartment, thus improving response to standard cancer therapies.

Methods: We screened a panel of PDX models to determine whether a STAT reporter identifies TICs in patient-derived xenograft (PDX) models. To augment existing STAT TIC reporters, we developed a two-component STAT signaling-specific lineage-tracing (LT) system. The first component labels active STAT signaling cells by expression of enhanced green fluorescent protein (EGFP⁺), followed by a self-cleaving P2A peptide and a TAM-inducible Cre-recombinase (4M67-EGFP-P2A-CreER^{T2}). The second component is a constitutively expressed dual-color switching Cre-dependent reporter vector (EFS-*loxPdsRed_{loxP}*-mNeptune2). We determined which LT cell populations (EGFP⁺/mNeptune2⁺, EGFP⁺/dsRed⁺, EGFP⁻/mNeptune2⁺, and EGFP⁻/dsRed⁺) from SUM159 xenografts functioned as TICs. To probe TIC transcriptional features, we performed scRNA seq on the two tumor models with STAT TICs and a PDX model that did not have STAT TICs. We performed lineage trajectory analysis and differential gene expression analysis to characterize candidate TIC transcriptional signatures. To confirm whether these transcriptional features are associated with TICs, we identified a biomarker of this cell state (bone marrow stromal antigen 2 [BST2]) and explored the relationship between this biomarker and TICs.

Results: We identified four PDX models with STAT reporter activity, one of which had STAT TICs. We validated our LT system in several models both in vitro and in vivo, then demonstrated EGFP⁺/mNeptune2⁺ from SUM159 xenografts are enriched for TICs and that lineage-tagged cells (mNeptune2⁺) function as proliferative early progenitor cells. scRNA seq of three xenograft models uncovered a distinct antiviral cell state in all three models that represent

a more highly enriched TIC subpopulation. Critically, transcriptional features were shared between the antiviral cell states across xenograft models. To determine whether cells in this antiviral state represent TICs, we FACS-enriched BST2 cells (an IFN-stimulated cell surface protein that was a marker of the antiviral cell state) and demonstrated enrichment of the TIC population by mammosphere formation assays and limiting dilution transplantation. We demonstrated that BST2 expression is increased in residual PDX tumors following chemotherapy. Furthermore, we demonstrated similar antiviral cell states are present in human breast cancer scRNA seq datasets.

Conclusions: These data demonstrate TICs adopt an antiviral cell state in some triple-negative breast cancers, and BST2 is a function marker of TICs in this cell state. Therefore, targeting genes associated with this cell state or associated antiviral pathways may represent a therapeutic vulnerability to eliminate TICs in some breast cancers.

PO5-24-03

Breast cancer intrinsic subtypes predict outcomes in primary and metastatic samples

Presenting Author(s) and Co-Author(s):

T. Ahmed. Tempus Labs Inc., Edison, New Jersey, United States

M. Carty. Tempus Labs Inc., New York City, New York, United States

K. Nadhamuni. Tempus Labs Inc., New York City, New York, United States

R. Pelossof. Tempus Labs Inc., New York City, New York, United States

Background: The prognostic and predictive value of the PAM50 intrinsic subtypes, namely Luminal A, Luminal B, Her2, and Basal-like subtypes, is well-studied in primary as well as metastatic breast cancer settings. Prosigna has emerged as a rapid PAM50 subtype predictor based on the NanoString nCounter assay. However, assay reproducibility across various RNASeq or qRT-PCR platforms can be challenging, especially when applying the predictor on metastatic breast cancer tumors. Here, we used SpinAdapt to create an intrinsic subtype predictor that works on RNA sequencing data, and validates on multiple tumor-sites. We evaluate real-world outcomes for our intrinsic subtype predictions across various immunohistochemical (IHC) labels and metastatic sites.

Methods: We trained the subtype predictor on a cohort of 2,497 breast cancer patients using the PAM50 genes, profiled using Nanostring RNA nCounter assay (GSE148426). Approximately 5,423 de-identified records of breast cancer patients sequenced using whole-exome capture RNA-seq were included in our reference dataset. The reference dataset contained samples collected from various sites including breast (n=2440), liver (n=936), lymph node (n=577), lung (n=540), and bone (n=304). For subtype classification, we first batch-corrected the external dataset to Tempus RNA-seq reference dataset using SpinAdapt, then trained a Support-Vector Classifier (SVC) on the corrected data. A 10-fold CV experiment was performed on the corrected dataset to analytically validate the intrinsic subtype predictions. We retrospectively analyzed 7,021 de-identified breast cancer patients with known hormone receptor (HR) or HER2 status and a matched RNASeq sample. The concordance between HR/HER2 status and PAM50 prediction was analyzed, and these patients were excluded from training. Real-world overall survival (rwOS) was evaluated from the time of first diagnosis. The outcomes across intrinsic subtypes were further assessed according to tumor collection site and HR/HER2 IHC status.

Results: The 10-fold CV experiment on the Tempus-adapted GSE148426 dataset achieved F-1 scores of 0.97, 0.86, 0.94, and 0.87 on Basal, HER2-like, Luminal A, and Luminal B PAM50 subtypes, respectively. On the Tempus evaluation dataset, 85.3% of HR+/HER2- patients (n=4,366), 65.4% of HR-/HER2+ patients (n=240), and 75.4% of HR-/HER2- patients (n=1,930) were classified as Luminal, HER2-like, and Basal, respectively. Evaluating outcomes on Tempus patients for each PAM50 group, the rwOS for the basal group was significantly shorter than patients not predicted to be basal (n=5,845, $p < 2e-90$). The rwOS for the predicted PAM50 basal patients remained significantly shorter than non-basal patients even when stratified by site of metastasis: breast (n=2,405; $p < 1e-27$), lymph node (n=577, $p < 1e-7$), liver (n=936; $p < 1e-25$), lung (n=540, $p < 1e-13$), and bone (n=304, $p < 1e-3$). Interestingly, within both HR+/HER2- (n=3,653) and HR-/HER2- (n=1,664) IHC cohorts with available outcomes data, the predicted PAM50 basal subtype could further stratify each of these populations with basal-subtype showing significantly worse prognosis than the non-basal subtype ($p < 1e-27$ and $p < 1e-7$, respectively).

Conclusions: We retrospectively analyzed Tempus multimodal RWD to validate an in-house breast intrinsic subtype predictor that is agnostic to the site of metastasis. The prognostic value of the basal subtype was significant for breast cancer patients across various sites of metastasis including lymph node, liver, lung, and bones and IHC groups. For patients in each of the HR+/HER2- and triple negative IHC groups, the intrinsic molecular subtypes provided an additional level of prognostic detail with statistical significance. These data emphasize the importance of combining molecular subtypes with IHC-based diagnostics to fully characterize clinically relevant subpopulations and risk.

PO5-24-04

Fibronectin, DHPS and SLC3A2 Signaling Cooperate to Control Tumor Spheroid Growth, Subcellular eIF5A1/2 Distribution and CDK4/6 Inhibitor Resistance

Presenting Author(s) and Co-Author(s):

C. Geller. California State University Northridge, United States

J. Maddela. California State University Northridge, United States

G. Ortiz-Soto. California State University Northridge/Baylor University, United States

R. Tuplano. California State University Northridge, United States

F. Runa. California State University Northridge, United States

Y. Adamian. California State University Northridge, United States

R. Güth. California State University Northridge, United States

L. Tomaneng. California State University Northridge, United States

J. Cantor. BD Biosciences, United States

J. Kelber. California State University Northridge/Baylor University, United States

Extracellular matrix (ECM) protein expression/deposition within and stiffening of the breast cancer (BC) microenvironment, facilitates disease progression and correlates with poor patient survival. However, the mechanisms by which ECM components control tumorigenic behaviors and responses to therapeutic intervention remain poorly understood. Fibronectin (FN) is a major ECM protein controlling multiple processes related to cancer metastasis. In this regard, we previously reported that DHPS-dependent hypusination of eIF5A1/2 is necessary for fibronectin-mediated BC metastasis and epithelial to mesenchymal transition (EMT). Here, we explored the clinical significance of an interactome generated using hypusination pathway components and markers of intratumoral heterogeneity. Solute carrier 3A2 (SLC3A2 or CD98hc) stood out as an indicator of poor overall survival among patients with basal-like BCs that express elevated levels of DHPS. We subsequently discovered that blockade or knockdown (KD) of DHPS or SLC3A2 reduced BC spheroid growth. Interestingly, spheroids stimulated with exogenous fibronectin were less sensitive to inhibition of either DHPS or SLC3A2 – an effect that could be abrogated by dual DHPS/SLC3A2 blockade or KD. In this regard, we observed that inhibition of both SLC3A2 and DHPS reduced total and hypusinated eIF5A1/2 levels most effectively. We further discovered that a subset of BC cells responded to fibronectin by increasing cytoplasmic localization of eIF5A1/2. Notably, these fibronectin-induced subcellular localization phenotypes correlated with a G0/G1 cell cycle arrest. Fibronectin-treated BC cells responded to dual DHPS/SLC3A2 blockade by shifting eIF5A1/2 localization back to a nucleus-dominant state, suppressing proliferation and further arresting cells in the G2/M phase of the cell cycle. Finally, we observed that dual DHPS/SLC3A2 inhibition increased the sensitivity of both Rb-negative and -positive BC cells to the CDK4/6 inhibitor palbociclib. Taken together, these data identify an uncharacterized mechanism through which extracellular fibronectin controls cancer cell tumorigenicity by modulating subcellular eIF5A1/2 localization. These findings provide prognostic/therapeutic utility for targeting the cooperative DHPS/SLC3A2 signaling axis to improve BC treatment responses.

PO5-24-05

The Metabolic and Epigenetic Contributions of Fibroblast Growth Factor Receptor-Mediated Breast Cancer Progression

Presenting Author(s) and Co-Author(s):

J. Tuokkola. University of Minnesota, United States

L. Reese. University of Minnesota, United States

K. Schwertfeger. University of Minnesota, United States

Despite recent improvements in treatment options, breast cancer remains the second leading cause of cancer-related deaths among women, with metastasis of the primary tumor accounting for most of these deaths. Signaling by fibroblast growth factor receptors (FGFRs) is active in 85% of breast cancers and results in enhanced proliferation, migration, invasion, and therapeutic resistance of tumor cells. A common feature of breast cancer is altered cholesterol metabolism including an increase in cholesterol stored intracellularly as cholesteryl esters (CEs). In breast cancer cells, high levels of CEs are associated with aggressive disease and CEs are essential for growth and migration of cancer cells. Furthermore, there is mounting evidence that modifications to metabolic pathways impact epigenetic processes including DNA methylation and histone post-translational modifications. These epigenetic changes support tumor progression and metastasis through oncogene activation and silencing of tumor suppressors. While there have been numerous studies focused on the role of metabolic and epigenetic changes in breast cancer, none have attempted to connect these altered pathways to upstream growth factor receptor pathways, such as the FGFR pathway, in cancer cells. We hypothesize that FGFR signaling promotes changes to cholesterol metabolism and epigenetic regulation which lead to breast cancer progression. To study the proposed roles of FGFR signaling, we utilized murine mammary cells of differing metastatic abilities with inducible, oncogenic FGFR1 signaling. We also included the FGFR-dependent murine mammary tumor lines 4T1 and 4T07 which demonstrate differing metastatic capabilities. Through gene expression studies, we found an FGFR-mediated increase in cholesterol metabolic processes including cholesterol storage, uptake, and synthesis. Along with this, we found an FGFR-mediated increase in CE content in our models. Interestingly, these changes were exclusive to our highly metastatic models. Additionally, we have identified FGFR-mediated changes in the expression of histone modifying enzymes in our cell lines. Many of the enzymes modified by FGFR have been previously reported to play a role in breast cancer metastasis. To further elucidate the role of enhanced cholesterol storage in breast cancer progression, we treated cells with pharmacological inhibitors of cholesterol storage. Using in vitro assays, we demonstrate that cell survival, migration, and invasion all decrease when cholesterol storage is inhibited. Again, we observe that our highly metastatic cell line models are more sensitive to this inhibition. Taken together, these data suggest a role for FGFR signaling in promoting breast cancer progression and metastasis. With further studies, this connection may inform the development of novel therapeutic strategies to combat therapeutic resistance in breast cancer.

PO5-24-06

Genomic findings in metastatic breast cancer

Presenting Author(s) and Co-Author(s):

K. Cole. University of Chicago, Chicago, Illinois, United States

M. Tjota. University of Chicago, United States

J. Segal. University of Chicago, United States

P. Wang. University of Chicago, United States

S. Crespo-Ramos. University of Chicago, United States

Introduction: Although metastatic breast cancer is the second leading cause of cancer death in women, the genomic findings in metastatic breast cancer are not as well characterized as those of primary breast cancers. Metastatic tumors are genetically heterogeneous, enriched for resistance mutations, and often lack targetable alterations. Improved understanding of the molecular mechanisms that drive metastatic disease of all receptor subtypes is required to identify possible molecular targets and to develop new targeted therapies in an effort to reduce the mortality.

Methods: A cohort of 50 metastatic breast cancer cases (n=33 ER+/PR+, n=3 ER+/HER2+, n=3 ER-/HER2+ n=11 TNBC) sequenced at our medical center between 2018-2023 was evaluated, and the molecular findings of the major subtypes were analyzed. Genomic data included mutations, copy number alterations, tumor mutation burden and microsatellite instability.

Results: The most frequent somatic alteration were PIK3CA mutations, involving 17/33 of ER+/PR+/HER- tumors, 5/11 TNBC tumors and 5/6 HER+ cases. TP53 mutations (frameshift and missense) were more frequently identified in TNBC and HER2+ cases ($p < 0.05$). Recurrent CCND1, FGFR1 and MYC copy number amplifications were seen almost exclusively in hormone receptor positive/HER2- tumors ($p > 0.05$). ESR1 mutations involved 15% of the ER positive cancers and were frequently associated with co-occurring CCND1 and FGFR1 copy number gains. Significant genomic losses that drive tumorigenesis were also detected. Both CDKN2a and PTEN deletions were found in ER/PR positive disease, as well as triple negative tumors. Genomic deletions associated with worse outcomes such as TP53 and DICER1 were also detected. ERBB2 amplification was 100% concordant with our immunohistochemical and FISH results for the 6 HER2 positive cases. All 50 cases demonstrated a low tumor mutation burden and were microsatellite stable.

Conclusion: We detected driver alterations that involve multiple pathways including estrogen receptor signaling, PI3K/AKT/MTOR, the cell cycle, and receptor tyrosine kinases. The genomic alterations are enriched for resistance mechanisms, like ESR1 mutations and FGFR1 gains that mediate resistance to endocrine treatment, as well as PIK3CA, also implicated in both endocrine and HER2-targeting therapy resistance. Of particular interest, were the amplifications detected in the ER+/PR+ tumors, such as CCND1 on chromosome 11q, FGFR1 on 8p and MYC on 8q, which were detected in almost half (45%) of our hormone receptor positive cohort. Some of the identified driver amplifications also define a subset of the Integrated Molecular Subtypes (Curtis et al., *Nature*; 486(7403): 346–352), i.e., Clusters 2, 6 and 9 that are typically hormone receptor positive but associated with either a very poor prognosis (Cluster 2) or an intermediate prognosis (Clusters 6 and 9), unlike the copy neutral ER positive tumors or those with the classic 1p and 16q alterations. Therefore, copy number

profiling of advanced-stage breast cancers may be a useful tool for determining prognosis, identifying possible targetable driver pathways and selecting appropriate patients for molecularly guided clinical trials.

PO5-24-07

HER2 EXPRESSION HETEROGENEITY PATTERN IN INVASIVE BREAST CARCINOMAS: FREQUENCY, DISTRIBUTION AND RELATION TO MORPHOLOGICAL VARIABLES

Presenting Author(s) and Co-Author(s):

A. Waitzberg. Universidade Federal de São Paulo, São Paulo, Sao Paulo, Brazil

L. Barbosa. São Paulo Federal University, United States

A. Filho. São Paulo Federal University, United States

A. da Cruz. São Paulo Federal University, United States

L. Gonzalez Porta Nova. São Paulo Federal University, United States

K. Prigenzi. São Paulo Federal University, United States

Human epidermal growth factor receptor 2 (HER2), a critical contributor to breast cancer development, is found to be amplified and overexpressed in approximately 15-20% of cases, making it a significant factor in carcinogenesis. This scenario was targeted by anti-HER2 drugs approved by several regulatory agencies in the past 15 years. Recently, novel anti-HER2 antibody-drug conjugates (ADCs) were approved to metastatic breast cancer with some HER2 expression albeit not due to amplification of the gene. Despite being classified as HER2 negative, most of these tumors exhibit detectable amounts of HER2 protein, reinforcing the challenging task of HER2 expression evaluation. In this scenario, it is very important to evaluate the spectrum of HER2 expression within a tumor due to its heterogeneity. We designed a retrospective linear study to reanalyze all HER2 immunohistochemical core biopsy slides of patients with primary invasive breast carcinomas (IBC) diagnosed and treated at São Paulo Federal University Hospital between 2019 and 2023. Pathological variables (histological subtype, histological grading, and hormonal receptors expression) were collected in pathology reports. Only patients with available slides and blocks were enrolled. HER2 slides were evaluated by three observers in consensus to access ASCO-CAP 2018 guidelines HER2 expression; presence or absence of HER2 expression heterogeneity; pattern of heterogeneity; frequency of the primary and secondary HER2 score in heterogeneous cases; and frequency of HER2 score in cases with homogeneous expression. Statistical analyses were performed with Chi-Square and Mann-Whitney U test using SSPS (26.0) program. 353 cases were included in this study. 104 (29,5%) were under 50 years and 249 (70,5%) over 50 years. 54,1% cases were left sided and 45,9% right sided. IBC of no special type comprehended 324 cases (91,8%) and invasive lobular carcinomas (ILC) were represented by 26 cases (7,4%); less than 1% of the cases were rare subtypes. Overall, HER2 results was negative in 296 (83,9%) cases and positive in 42 (11,9%) cases; HER2 2+ accounted by 15 cases (4,2%). Out of the negative cases, 235 (79,4%) were classified as 0+ and 61 (20,6%) were classified as 1+. Homogenous HER2 expression was observed in 287 cases (81,3%) with predominance of 0+ expression (80,8% - 232 cases), followed by 1+ (9,4% - 27 cases). ITH was present in 66 cases (18,7%), in which the subtyping was represented by 39 scattered (59,1%), 25 clustered (37,9%) and 2 mosaic (3%). The most prevalent score in this group was 1+ (51,5% - 34 cases), followed by 3+ (25,8% - 17 cases); the secondary score was predominantly categorized as 0+ (58,3%), followed by 1+ (20%) and 2+ (20%); only one case showed as 3+ expression. In the ILC group, 24 cases (92,3%) exhibited homogeneous HER2 expression, with predominant 0+ score (75% - 18 cases), while 2 cases (7,7%) showed heterogeneous expression. Out of the cases with heterogeneous HER2 expression, one exhibited a clustered heterogeneity pattern, with a primary HER2 score of 1+ and a secondary score of 0+. The other case displayed a scattered heterogeneity pattern, with a primary HER2 score of 3+ and a secondary score of 2+. There

was a statistically significant association between HER2 expression heterogeneity and histologic grade ($p = 0.005$), and a marginal association with estrogen ($p = 0.060$) and progesterone ($p = 0.060$) expression. Tumor size wasn't associated with heterogeneity ($p = 0,071$). We conclude that heterogeneity is prevalent in HER2 expression, especially in IBC, and should be addressed in pathology reports, especially in the ADCs scenario.

PO5-24-08

Differential exploitation of Cation Transport Regulator homolog 1 (CHAC1) by Wild-type and mutant p53

Presenting Author(s) and Co-Author(s):

V. MEHTA. CENTRAL UNIVERSITY OF PUNJAB, San Antonio, Texas, United States

H. CHANDER. National Institute of Biologicals, NOIDA, Uttar Pradesh, India

Background: Cancer cells are constantly exposed to harsh conditions like nutrient deprivation, hypoxia, and calcium imbalance leading to the induction of UPR. In its early phase, UPR aims to restore homeostasis while prolonged stress leads to induction of apoptosis. Thus, it is not surprising to observe that expression of the UPR components has been reported to both promote as well as suppress tumorigenesis. Studies have shown that Cation transport regulator homolog 1 (CHAC1) plays a dual role in cancer progression. The objective of the present study is to investigate the p53 mediated regulation of CHAC1 in breast cancer. Methods: We initially subjected a breast cancer tissue microarray (TMA) to immunohistochemistry (IHC) with p53 and CHAC1 specific antibody. We further did in vitro experiments like western blotting, qRT-PCR to see the expression of CHAC1 when wild type (WT) p53 was either induced using camptothecin (CPT) and Nutlin-3 in WT p53 expressing breast cancer cells or by the ectopic WT and mutant p53 transfection in null p53 breast cancer cells (MDA-MB-157). The Chromatin immunoprecipitation (ChIP) assay was done to find a potential binding site of p53 on CHAC1 promoter. Further, in vitro study was done to elucidate a potential role of CHAC1 in cell proliferation. Results: The IHC staining analysis revealed that there was no significant difference in the CHAC1 expression between high and low p53 staining tissue cores as high CHAC1 staining was observed in both cases. Further, in vitro analysis reinforced the findings of CHAC1 in TMAs as cell line studies showed that both forms of p53 had enhancing effect on CHAC1 levels. Upon induction of WT p53 and/or ectopic transfection of WT and mutant p53, we observed that CHAC1 levels were upregulated in a dose dependent manner. ChIP assay revealed that while WT p53 occupies the promoter region of the CHAC1 gene to induce its expression, mutant p53 may be inducing CHAC1 expression through an unknown mediator. These observations provide the basis that CHAC1 may be a novel transcriptional target of p53. Ectopic transfection of WT and mutant 53 showed opposite effect on cellular proliferation as evident from BrdU cellular proliferation assay in MDA-MB-157 cells. Further, we showed that CHAC1 enhanced breast cancer cell proliferation possibly via upregulation of PI3K/Akt/mTOR pathway and may likely be a player in angiogenesis as shown by in vitro angiogenesis assay. Conclusion: Taken together, the data from present study suggests that the effect of CHAC1 on cellular proliferation was associated with the status of p53 in breast cancer cells. The results suggest a plausible explanation for the differential behavior of CHAC1 in tumorigenesis.

PO5-24-09

Optimizing the Therapeutic Treatment of Breast Cancer Through a Dual Data-driven Theoretical Model

Presenting Author(s) and Co-Author(s):

A. Najafi. Texas A&M University, United States

M. Jolly. Indian Institute of Science, United States

J. George. Texas A&M University, United States

Despite rapid advancements in treatments and technology, breast cancer remains the second leading cause of cancer related morbidity in women in the US. As a heterogeneous disease, the unique genetic and phenotypic profile of each tumor complicates the prediction of treatment responses and optimized treatment strategies. One primary manifestation of phenotypic plasticity and concomitant intra-tumoral heterogeneity is the Epithelial-Mesenchymal Transition (EMT). The acquisition of migratory and invasive properties through EMT facilitates tumor metastasis and results in worse patient outcomes. As a result, the EMT and its reverse process (MET) often influence treatment response. However, the different mechanisms through which these therapeutic drugs affect the EMT-related phenotypic switching rates as well as each phenotype's replication rates are unclear, and further investigation is required for better understanding their precise effect for directing optimal treatment strategies and improved patient outcomes. Here, we compile an atlas of publicly available metastatic and non-metastatic RNA sequencing data of breast cancer cell lines treated with therapeutic and chemotherapeutic drugs and propose a dual data-driven theoretical framework for understanding the effects of each drug on breast cancer treatment response. We infer the cell fractions, EMT phenotypic transition rates and phenotypic replication rates of each case through an extension of our previously developed hybrid data-driven and theoretical model, COMET. We infer single-cell RNA sequencing-derived EMT-related trajectories and apply a continuous time Markov chain model to infer inter-state transition rates. By analyzing the atlas of RNA sequencing data and integration with our framework, we gain novel insights into the context-specific mechanisms by which therapeutic drugs affect the phenotypic transition rates. This comprehensive understanding will contribute to optimizing breast cancer therapy and ultimately improving patient outcomes.

PO5-24-10

Clinical significance and immune landscape analyses of the immune related genes based prognostic signature for HER2 positive breast cancer

Presenting Author(s) and Co-Author(s):

X. Li. Fujian Cancer Hospital, United States

W. Fu. Fujian Medical University Union Hospital, United States

Y. Yu. Fujian Cancer Hospital, United States

J. Zhang. Fujian Medical University Union Hospital, United States

C. Song. Fujian Provincial Cancer Hospital, United States

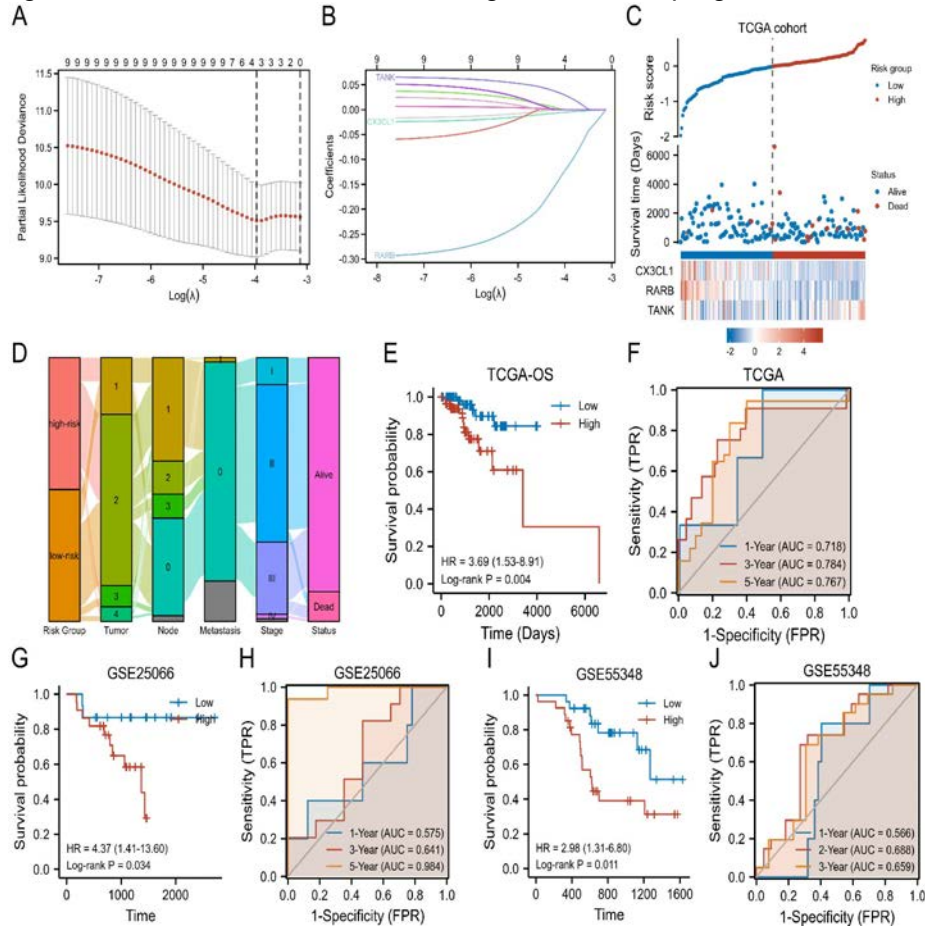
Objective: To date, significant breakthrough has yet to be achieved in immunotherapy for HER2-positive breast cancer (HPBC). In this study, we aimed to construct a risk model for predicting prognosis and therapy response and evaluating the tumor immune landscape in HPBC patients.

Methods: Differentially expressed immune-related genes (IRGs) were used as input to weighted correlation network analysis (WGCNA) to identify modules of highly correlated gene. An optimal prognostic TPBC-IRGs signature were constructed by least absolute shrinkage and selection operator (LASSO) cox regression. Survival analysis and ROC curves were analyzed to identify the predictive value in a training cohort and external validation cohorts. With three GEO datasets and samples from our center, the anti-HER2 therapeutic efficacy in HPBC patients was predicted through this prognostic model. Additionally, the immunotherapy outcome was forecasted using IMvigor210 dataset. We also investigated the connection between high and low-risk populations and immune checkpoints and analyzed immune infiltration levels of these populations with several algorithms. Ultimately, we develop a combined model and nomogram by integrating the risk score with clinical factors.

Results: 11 key genes associated with overall survival (OS) in the blue module were selected for further analysis. A 3-gene signature (CX3CL1, RARB, TANK) based prognostic risk model was developed. The Kaplan-Meier survival curve revealed that patients with high-risk score had shorter OS compared with the low-risk group. The AUC of the training cohort at 1-, 3- and 5-year were 0.718, 0.784 and 0.767. The performance of the risk model was validated with GSE25066 and GSE55348. It's showed that the risk scores of HPBC who were resistant to trastuzumab were significantly higher than those of patients who were sensitive to trastuzumab. The results indicated that the levels of immune checkpoints expression (such as PD-1, CTLA4 and TIGIT) and immune infiltration were higher in low-risk group than in high-risk group. The combined model showed better prognostic prediction accuracy compared to the clinical model or gene signature alone (1-year AUC=0.910 ; 3-year AUC=0.832 ; 5-year AUC=0.882).

Conclusion: The immune gene-based risk profile and combined prognostic model in this study may hold promise for clinical use in predicting the prognosis and treatment efficacy of HPBC patients.

figure3. Construction of HPBC-IRGs signature based prognostic model.



PO5-24-11

An integrated approach for comprehensive molecular and tumor microenvironment characterization of invasive lobular carcinoma

Presenting Author(s) and Co-Author(s):

J. Mouabbi. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

K. Chernyshov. BostonGene, Corp., United States

O. Baranov. BostonGene, Corp., United States

V. Kushnarev. BostonGene, Corp, United States

P. Turova. BostonGene, Corp., United States

A. Butusova. BostonGene, United States

S. Menshikova. BostonGene Corp., United States

J. Brown. BostonGene, Corp, United States

N. Kotlov. BostonGene Corp., United States

P. Clayton. BostonGene, Corp., United States

K. Nomie. BostonGene Corp., United States

N. Fowler. BostonGene Corp., United States

D. Tripathy. The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Introduction: Although recent studies have shown that invasive lobular carcinoma (ILC) is associated with worse long-term outcomes compared to invasive breast cancer of no special type (NST), they are treated in a similar manner. Therefore, classification approaches to help understand the molecular characteristics associated with the different BC subtypes are needed to personalize therapy. Here, we describe an integrated analytical approach to comprehensively characterize ILC samples.

Methods: We collected genomic and transcriptomic data for 16,087 ILC and NST samples, with clinical and pathological annotation, from 59 datasets and used an internally developed algorithm based on clustering performed after gene expression analysis to classify them into 5 intrinsic subtypes: Basal, Luminal A (LumA), Luminal B (LumB), HER2 high, and HER2 low. We performed gene set enrichment analyses and utilized the DESeq2 algorithm to perform differential expression analysis of RNA-seq data. We performed molecular grade subtyping using methods described by Antysheva et al. (Cancer Res., 2022). Samples that were listed as ILC or had an inactivated CDH1 gene by mutation, deletion or low expression (< -2.5 MAD after median scaling) were defined as having an ILC histomolecular subtype. Using methods described by Bagaev et. al. (Cancer Cell, 2021), 29 functional gene expression signatures were selected, and unsupervised dense Louvain clustering was performed to identify TME subtypes. The Mann-Whitney U test was used for statistical analysis. The tertiary lymphoid structures (TLS) gene signature was evaluated using methods described by Sautès-Fridman et al. (Nat. Rev. Cancer, 2019).

Results: In the ILC samples (n=1,887), we identified LumA (46%), LumB (40%), Basal (8%), HER2 high (3%), and HER2 low (3%) subtypes. In contrast, the NST samples were classified as LumB (41%), LumA (25%), Basal (19%), HER2 high (9%), and HER2 low (5%). Molecular

grade subtyping revealed that 67% of ILC samples were low grade and 33% were high grade, compared to NST where 55% were high grade and 45% were low grade. Notably, among high-grade ILC, LumB (64%) and Basal (23%) subtypes were predominant. Key differentially expressed genes included downregulated CDH1 and upregulated MMP23B, IGF1, and TFAP2B across LumA and LumB ILC samples. Further analysis revealed downregulation of TACSTD2 and CDH3 in the Basal subtype for ILC samples compared to NST samples. Transcriptomic-based TME subtyping revealed distinct TME distributions across the BC subtypes and molecular grades for ILC samples (Table 1). In high-grade ILC LumB samples, 38% had a Desert (D; predictive of poor immunotherapy response) and 39% had an Immune-Enriched (IE; predictive of favorable immunotherapy response) TME. In low-grade ILC LumB samples we found that while 51% had a D TME, only 14% had an IE TME. We found an overrepresentation of the TLS signature [Solid TLS] in ILC compared to NST samples, and higher matrix remodeling and CAF signatures in LumA compared to the LumB subtype among low-grade ILC samples. Samples with high CD274 expression levels had higher percentages of T cells and M1 macrophages, and LumA samples had significantly higher ($p < 0.001$) CD274 expression compared to the other BC subtypes.

Conclusion: These results provide in-depth molecular and tumor microenvironment characterization of ILC. Further optimization of this analytical approach could lead to the development of more effective therapeutic strategies.

Table 1. ILC subtypes classification

Molecular Grade Subtypes	TME Subtypes	Breast Cancer Subtypes				
		Luminal A	Luminal B	Basal	HER2 high	HER2 low
High Grade	<i>Immune-Enriched (IE)</i>	39%	39%	23%	35%	42%
	<i>Immune-Enriched, Fibrotic (IE/F)</i>	23%	12%	16%	16%	19%
	<i>Fibrotic (F)</i>	38%	11%	24%	23%	20%
	<i>Desert (D)</i>	0%	38%	37%	26%	19%
Low Grade	<i>Immune-Enriched (IE)</i>	9%	14%	16%	19%	6%
	<i>Immune-Enriched, Fibrotic (IE/F)</i>	31%	17%	32%	29%	23%
	<i>Fibrotic (F)</i>	43%	18%	47%	43%	59%
	<i>Desert (D)</i>	17%	51%	5%	9%	12%

PO5-24-12

IRX5010, a Highly Selective RAR γ Nuclear Receptor Agonist Compound Inhibits In Vivo Growth of Murine EMT-6 Triple Negative Breast Cancer and Human JIMT-1Her2+ Breast Cancer By Induction of Tumor-Infiltrating Effector Memory T-cells

Presenting Author(s) and Co-Author(s):

M. Sanders. Io Therapeutics, Inc., The Woodlands, Texas, United States

M. Topalovski. Champions Oncology, United States

V. Vuligonda. Io Therapeutics, Inc., The Woodlands, Texas, United States

Research Objectives and Rationale: Previously, RAR γ agonism has been shown to play an essential role in CD8 T-cell-mediated immunity to infectious pathogens. However, we found no previous reports on effects of RAR γ agonists on in vivo tumor growth of triple negative or Her2+ breast cancers. Here we explored whether RAR γ could play a critical role in T-cell-mediated immunity in these breast cancers, using potent highly selective novel RAR γ agonist compounds.

Experimental methods and results: We synthesized and screened compounds for selective transactivation of RAR γ in reporter assays. Three highly potent compounds, demonstrating highly selective RAR γ transactivation at less than one nanomolar concentrations, were selected for further evaluation of potential anti-cancer activities in vitro. None of the three evaluated compounds demonstrated significant inhibitory effects on in vitro growth of EMT-6 triple negative breast cancer cells at concentrations of 20-100 millimolar, indicating that the three compounds have insignificant direct inhibitory effects on EMT-6 cancer cell growth in vitro. We then examined the effects of one of the compounds in vivo in a syngeneic mouse model of EMT-6 triple negative breast cancer. Treatment with the most potent of the three compounds, IRX5010, demonstrated dose response inhibition of in vivo growth of EMT-6 tumors. Inhibition of tumor growth at day 17 relative to vehicle was 59% and 69% respectively in mice treated with IRX5010 at 10 or 25 mg/kg/day. A cohort treated with 50 mg/kg/day was sacrificed early on day 12 due to excessive weight loss and deaths of some of the animals. This cohort experienced a 73% inhibition of tumor growth relative to vehicle. Gross necropsies of animals in the 25 and 50 mg/kg/day dose groups did not show observable pathologic findings in any major organ. Flow cytometry was performed on freshly excised tumors on the day of termination of the in-life portion of the study in the 10 and 25 mg/kg/day dose groups. Tumors from mice treated with IRX5010 had increased intratumoral numbers of Total CD45+ cells; Total CD3+, Total CD4+, and Total CD8+ T-cells per mg of tumor tissue, relative to vehicle controls. IRX5010 treated mice also had increased intratumoral CD4+IL-17+ T-helper cells; and increased CD4+CD62L- and CD8+CD62L- T-effector memory T-cells per mg of tumor tissue relative to vehicle-treated control mice.

We also conducted an experiment of treatment with IRX5010 in mice transplanted with human immune cells (to provide a human immune system) to examine its effects on xenografted human Her2+ JIMT-1 cancer cells. In this model, treatment with IRX5010 at 10 mg/kg/day resulted in a 17% inhibition of tumor growth relative to vehicle control over 26 days of treatment. Flow cytometric analysis showed that tumors from the IRX5010 treated mice contained increased numbers per mg of tumor tissue of intratumoral human CD8+ T-cells, most of which were CD8+ CD7- CD45RA+ terminally differentiated effector memory phenotype T-cells.

Conclusions: Treatment with IRX5010, a potent and highly selective RAR γ nuclear receptor agonist compound demonstrated substantial treatment effects relative to vehicle control on inhibition of growth of murine triple negative breast cancer in vivo, despite having essentially no growth inhibitory effect on these cells in vitro. Treatment of xenografted human Her2+ tumors in mice with humanized immune systems resulted in a moderate inhibition of Her2+ breast cancer growth relative to vehicle controls. In both models, treatment with IRX5010 induced tumor infiltrating T-lymphocytes of largely effector memory phenotypes, demonstrating an effect on the tumor immune microenvironment. These data identify RAR γ and RAR γ agonists as a new treatment target and novel treatment modality for breast cancers, especially for the highly unmet need for new and better treatments for triple negative breast cancer.

PO5-25-01

Treating liver metastases by reversing cell competition between metastatic cancer cells and hepatocytes

Presenting Author(s) and Co-Author(s):

K. Lake. UT Southwestern, United States

S. Mohta. UT Southwestern, United States

C. Smith. UT Southwestern, United States

V. Repaka. UT Southwestern, United States

L. Xu. UT Southwestern, United States

K. Saunders. UT Southwestern, University of Texas at Dallas, United States

V. Pandit. UT Southwestern, United States

E. Goff. UT Southwestern, United States

C. Zhang. UT Southwestern, United States

J. Pena. UT Southwestern, United States

C. Hodgdon. Grasp Cancer, United States

J. Maues. GRASP, Washington, District of Columbia, United States

E. Chen. UT Southwestern, United States

I. Chan. University of Texas Southwestern Medical Center, United States

Background: Although breast cancer liver metastases (BCLM) are common events, with 40-50% of patients with metastatic breast cancer developing liver metastases, their development indicates poor prognosis. Patients with BCLM have a 5-year survival rate of 8%. Specific treatments for liver metastases are virtually non-existent, partly because the key events of early liver metastasis formation remain unknown. The liver is a dense organ, and metastatic breast cancer cells (MCC) must clear space among hepatocytes, the primary cell population in the liver, during metastatic formation. Cell competition is a developmentally conserved process that explains how organs or primary tumors form when cells within those tissues have varying fitness and compete with one another. This competition can result in the survival and expansion of one cell population, and the induction of cell death through apoptosis in the other. We hypothesized that MCC use cell competition with hepatocytes to create space and expand within the liver. **Objectives:** In this study, we tested the hypothesis that MCC use cell competition with hepatocytes to create space and expand within the liver, resulting in hepatocyte apoptosis. **Methods:** We develop new in-vitro and mouse lineage-traced models to assay cell competition between MCC and hepatocytes, initially using balb/c derived breast cancer (4T1) and hepatocyte (H2.35) cells and syngeneic mouse models of liver metastasis. These models directly capture MCC and hepatocyte interactions, and we can assess modes of cell competition, including apoptosis, through immunostaining. Because prior literature suggests that the developing mammary gland informs both cell competition and metastasis, we next performed a bioinformatics screen to identify potential signals that contribute to cell competition between MCC and hepatocytes. We generated a new single-cell RNA-seq dataset that incorporates information from the developing mammary gland and breast cancer cells. This dataset includes 3264 primary breast cancer cells across 3 models of aggressive breast cancers, encompassing HER2+ and TNBC subtypes, as well as 526 embryonic mammary gland cells. Using this platform, we identify genes enriched in both breast cancer and the developing mammary gland. Next, we validate genes by testing for their high expression in

MCC when compared to hepatocytes. Then, we determine the impact of target genes on cell competition in our models. Results/Discussion: Our models demonstrate that MCC use cell competition to create space in the liver by inducing apoptosis in neighboring hepatocytes. MCC induce apoptosis in neighboring hepatocytes through cell competition in in-vitro co-cultures by 11.7-fold compared to MCC apoptosis. Hydrodynamic tail-vein engraftment in NOD-scid-gamma mice livers with MCC also resulted in increased neighboring hepatocyte apoptosis. Using our bioinformatics screen, we identified 5 potential targets that could drive breast cancer metastasis and cell competition. Using our competition models, perturbation of SerpinE2, a protease inhibitor which was one of the top gene targets, successfully modulated competition between MCC and hepatocytes. Knock-out of SerpinE2 in MCC did not affect their viability or growth but resulted in MCC apoptosis adjacent to hepatocyte neighbors by 16.9-fold when compared to wild type conditions. Further, co-culture of MCC that lacked SerpinE2 with hepatocytes resulted in decreased hepatocyte apoptosis by 2.3-fold compared to hepatocytes co-cultured with wild-type (WT) MCC. These findings suggest that hepatocytes cannot outcompete or kill WT MCC, but they can outcompete and kill MCC that lack SerpinE2. Future work focused on the perturbation of SerpinE2 may lead to novel therapies for patients at risk for or with BCLM. Our findings suggest that restoring the competitiveness of the liver parenchyma could be a new treatment modality for treating liver metastases.

PO5-25-02

Microenvironment based co-culture dependence of breast cancer and immune cell interactions on functional outcomes

Presenting Author(s) and Co-Author(s):

K. Norek. Syantra inc., United States

J. Kennard. Syantra inc., Alberta, Canada

K. Fuh. Syantra inc., United States

R. Shepherd. Syantra inc., United States

K. Rinker. University of Calgary, Calgary, Alberta, Canada

O. Kharenko. Syantra inc., Calgary, Alberta, Canada

The tumour microenvironment (TME) includes physical forces from interstitial fluid flow and cell-cell interactions that modulate cancer development and progression through activation of multiple oncogenic pathways leading to tumor growth and metastatic spreading. We previously reported on the role of physical forces on epithelial to mesenchymal transition (EMT) and S100 gene family expression and cell to cell adhesion properties with implications to normal breast development and cancer. Signals from the tumor exit the local tumor environment through interstitial fluid transport and cell migration where they can be found in the blood stream. We developed a whole blood RNA gene expression biomarker panel coupled with proprietary software capable of identifying the presence of an active breast cancer signature at early stages of disease with clinical study results previously reported. Here we report on results from transcriptomic and function studies with cell interaction models. Cancer cells can influence immune cells through direct contact or via secreted molecules causing the immune cells to undergo functional changes. To investigate mechanisms involved in the induction of these alterations in a model system, we performed co-culture studies with human monocytic cells and breast cancer cells. Interaction of human monocytic cells with the breast cancer cells caused significant changes in both behavior and transcriptomes. Moreover, using RNAseq and pathway analysis we demonstrated that the changes induced through the exposure to the more aggressive triple negative (TNBC) phenotype were distinct from the alterations triggered upon contact with an ER+ breast cancer cell line. We also show that cancer-immune crosstalk triggers EMT as well as activation of multiple oncogenic pathways associated with cell migration and invasion, cell chemotaxis and cell-to-cell interactions. As the interplay between cancer and immune cells plays an important role in cancer progression, these findings provide important insight into key mechanisms controlling these outcomes.

PO5-25-03

Immune cell infiltrate profiles in primary Triple Negative Breast Cancer and co-relation with treatment response and survival outcomes.

Presenting Author(s) and Co-Author(s):

P. Vaid. CTCR and Ashoka University, United States

D. Kelkar. CTCR and PCCM, United States

L. Shashidhara. CTCR, Ashoka University and IISER Pune, United States

C. Koppiker. PCCM and CTCR, United States

M. Kulkarni. CTCR and PCCM, United States

Introduction

Tumor microenvironment (TME) in breast cancer is a heterogeneous landscape with multiple cell types, each modulating the tumor progression and the disease prognosis. These cell types include lymphocytes, RBCs, stromal cells, macrophages, cancer-associated fibroblasts (CAFs), and cancer stem cells. Each cell type in the TME influences tumor progression and clinical outcomes for patients in a good or bad way, depending on the interaction with tumor cells. Tumor-infiltrating lymphocytes (TILs) are shown to be prognostic for therapy response in many cancers in the western cohorts. Our recent study showed that a higher proportion of Indian TNBC patients had intra-tumoral TILs compared to Western cohorts, and these are predictive of better response to NACT and longer disease-free survival in patients, making it a distinct finding from Western reports.

In the follow-up study, we are characterizing infiltrating immune cell subtypes and their comparative association with treatment response in TNBC patients. Results from preliminary analysis and comparative analysis between responders and non-responders will be presented here. We speculate that the pro- and anti-tumorigenic immune cell population and its spatial information would help us understand TME and its precise role in response to therapy.

Methods

A retrospective cohort of breast cancer patients from a single one-surgeon breast cancer clinic with a uniform treatment strategy was evaluated for this study. FFPE primary tissue samples with variable TILs scores (moderate to high), taken from patients who showed complete response to the NACT treatment (n=6) and non-responding group (n=8) determined by H&E stained slides from our cohort, were further stained for immune cells (Pan-B cell, Pan-T cells, Pan-macrophages) and T cells (CD4; Helper T cell marker, CD8; Cytotoxic T cell marker), FOXP3 (Regularly CD4+ cell marker) and PanCK (Pan-tumor marker) and counterstained with DAPI for multiplex imaging. Multispectral images for these slides were obtained using the Leica Aperio Versa system. Parameters such as individual cell types of identification and scoring, spatial proximity to tumor cells, and individual cell types will be determined by HALO software using the High plex module.

Results

A total of 14 TNBC samples were stained for the T-cell subtypes panel and Immune cell subtype s panel to determine the TIME. DAPI stain was used for nuclear counting based the parameters such as threshold intensity, nuclear size, roundness, and aggressiveness. The cytoplasmic size was selected as 2um beyond the outside nuclear boundary. Using Halo-Indica software, around 50000-300000 cells/tissue were evaluated across all samples from mIF whole slide scans of biopsy samples. Cell count was validated by cross-checking individual ROIs and

manual cell count using Fiji. A Highplex module was used to identify individual signal positivity for each marker based on threshold intensity and cell completeness percent. Preliminary data showed a higher proportion of CD8+ cells and macrophages population are spatially closer to the tumor cells in Responders compared to non-responders.

Conclusion

Immune profiles are distinct among responding and non-responding patients in the Indian TNBC cohort. The association of these profiles with long-term survival in patients and various clinical and pathological parameters will help us determine the clinical relevance of these profiles and identify distinct immune subgroups as prognostic in Indian TNBCs.

PO5-25-04

Predictive value of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in patients with triple negative breast cancer treated with pembrolizumab

Presenting Author(s) and Co-Author(s):

A. Schreier. Weill Cornell Medical College, New York, United States

R. Zappasodi. Weill Cornell/New York Presbyterian, United States

I. Serganova. Weill Cornell/New York Presbyterian, United States

L. Munoz Arcos. Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, New York, United States

X. Zhou. Weill Cornell/New York Presbyterian, United States

M. Cristofanilli. Weill Cornell Medicine, United States

E. Andreopolu. New York Presbyterian/Weill Cornell Medical Center/Columbia University, New York, NY, United States

Background: Immune checkpoint inhibitors (ICIs) offer new treatment possibilities for women with triple-negative breast cancer (TNBC) – one of the most challenging breast cancer subtypes. The PD-1 inhibitor pembrolizumab (pembro; Keytruda®) is approved in metastatic TNBC (mTNBC) patients with PD-L1(+) tumors, and for neoadjuvant treatment (NAT) in stage II/III TNBC [1, 2]. Residual cancer burden (RCB) after NAT is highly prognostic, with pathologic complete response (pCR, RCB 0) anticipating long-term survival [3]. In mTNBC, pembro plus chemotherapy in the 1st-line improves progression free survival (PFS), but durable responses are rare. Optimizing ICI use in TNBC thus remains an unmet need, and defining easily assessable markers of response is crucial. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are peripheral blood surrogates of tumor inflammation and have prognostic and predictive value in TNBC [4-8]. Elevated NLR (≥ 5) and PLR (≥ 200) correlate with worse outcomes upon ICIs in melanoma and non-small-cell lung cancer [9, 11-14]; however, this has not been studied in breast cancer [9, 10]. We evaluated the relationship of baseline NLR and PLR with pembro responses in TNBC patients. Methods: We retrospectively reviewed data from TNBC patients who completed pembro between 10/2/20 - 6/1/23 at Weill Cornell. Patients on NAT who did not complete treatment were excluded. RCB score (pCR/0, 1, 2, 3) was calculated from surgical resection pathology reports using the MD Anderson RCB Calculator [15, 16]. Baseline laboratory data were obtained from clinical records. Associations between NLR and PLR with RCB levels were examined using the non-parametric Kruskal-Wallis test (if >2 levels), the Wilcoxon rank sum test (if 2 levels), or the Spearman's rank correlation. NLR and PLR were also correlated with PFS (measured from pembro start date to date of progression) in metastatic patients. PFS data for metastatic patients without interval imaging since pembro initiation were censored at the date of data analysis, and PFS was not calculated for patients who received only 1 cycle of pembro. Results: We identified 63 eligible patients: 24 were excluded due to lack of TNBC diagnosis (n=20), or because they only received adjuvant pembro (n=4). Of the 39 remaining patients, 5 did not complete NAT and 2 had missing data, leaving 32 evaluable patients (17 in the NAT cohort and 15 in the mTNBC cohort). Overall, the median age was 51 years, and 16% were Hispanic, 11% Asian, 57% non-Hispanic, 24% Black, and 65% Non-Black. Neoadjuvant cohort: The pCR rate was 30%. Patients with both NLR ≥ 5 and PLR ≥ 200 , had a pCR rate of 0%; in patients with NLR < 5 or PLR < 200 , pCR rate was 43%. Median NLR in pCR vs. non-pCR groups was 1.91 [IQR: 1.72-2.73] vs. 2.44 [IQR: 1.97- 5.24] ($p=0.3$), with trends towards significance when NLR was compared between RCB levels >1 (2.67; IQR: 2.05, 6.49) vs. RCB levels ≤ 1 (1.91; IQR: 1.63,

2.58) ($p=0.14$). Mean PLR was higher in patients with RCB 2-3 (409) compared to those with pCR or RCB 1 (167) ($p=0.146$). Metastatic cohort: The overall mean PFS was 7.8 months. Visceral metastases were seen in 80% of patients (17% liver, 33% brain). In patients with brain mets, baseline NLR and PLR were higher than in the overall cohort (NLR, 4.86 vs. 2.78; PLR, 429 vs. 186). Conclusions: Our study is the first to evaluate NLR and PLR as response biomarkers in TNBC patients receiving pembro and is the first report of our real-world data of TNBC patients on pembro. In our neoadjuvant cohort, higher baseline NLR and PLR correlated with higher RCB levels, with a trend towards statistical significance. Further investigation and correlation of NLR and PLR with tumor microenvironment features will help to clarify these relationships.

PO5-25-05

Crosstalk between adipocyte and tumor cells with ESR1 mutations via adipsin enhances tumor growth

Presenting Author(s) and Co-Author(s):

A. Belyakov. Albany College of Pharmacy and Health Sciences, United States

K. Jin. Albany College of Pharmacy and Health Sciences, Albany, New York, United States

While endocrine therapies have shown clinical benefits for breast cancer with ESR1 mutations, resistance development is a significant challenge. Evidence suggests that the complement system is critical to tumor development, and recent studies highlight the role of adipsin in breast cancer growth. In a previous study, we characterized the role of complement pathway-mediated adipsin in ESR1 mutant cell lines (Y537S and D538G), identifying the upregulation of adipsin, C3, and C3aR in ESR1 mutant cells. The interaction between C3a and C3aR enhanced ESR1 mutant cell growth, and inhibiting C3aR abolished cell growth and increased apoptosis. Combining C3aR inhibitors with fulvestrant or CDK4/6 inhibitors had a synergistic inhibitory effect on ESR1 mutant cells. Our findings suggest that the complement pathway plays a role in ESR1 mutant cell proliferation and that C3aR is a potential target to mitigate ESR1 mutant breast cancer growth and metastasis. Additionally, we demonstrated the critical role of the feedback loop of adipsin in ESR1 mutant cell growth in adipocyte crosstalk. Using differentiated mouse 3T3-L1 adipocytes induced with tumor-conditioned media from ESR1 mutant cells, we observed the upregulation of adipsin, C3, and C3a in the adipocyte secretome, which enhanced C3a levels. Blocking the interaction between C3a and C3aR in ESR1 mutant cells using a C3aR inhibitor significantly inhibited ESR1 mutant cell growth compared to wild-type cells and enhanced apoptosis. Our findings suggest that upregulation of adipsin from ESR1 mutant cells and adipocytes in crosstalk increases tumor cell growth. Future studies will investigate the critical role of adipsin's auto- and paracrine effects in breast cancer with ESR1 mutations.

PO5-25-06

S100A4 blocking antibody suppresses metastasis through immune modulation

Presenting Author(s) and Co-Author(s):

J. Leu. Houston Methodist Research Institute, United States

H. Deng. Texas Therapeutics Institute, Brown Foundation Institute of Molecular Medicine, The University of Texas Health Science Center, United States

X. Wei. Texas Therapeutics Institute, Brown Foundation Institute of Molecular Medicine, The University of Texas Health Science Center, United States

H. Tran. Houston Methodist Research Institute, United States

N. Abdelfattah. Houston Methodist Research Institute, United States

J. Salazar. Houston Methodist Research Institute, United States

J. Maldonado. Houston Methodist Hospital, United States

C. Cristobal. Baylor College of Medicine, United States

H. Lee. Baylor College of Medicine, United States

Z. An. Texas Therapeutics Institute, Brown Foundation Institute of Molecular Medicine, The University of Texas Health Science Center, United States

N. Zhang. Texas Therapeutics Institute, Brown Foundation Institute of Molecular Medicine, The University of Texas Health Science Center, United States

K. Yun. Houston Methodist Research Institute, United States

Introduction Cancer metastasis poses a major clinical challenge and is responsible for ~90% of cancer-associated deaths. However, progress in treating metastatic disease has been slow. Triple-negative breast cancer, for example, has only one FDA-approved treatment for metastatic disease in the upfront setting, chemo plus Pembrolizumab. This suggests that modulating the immune system may be an effective approach. High S100A4 expression is associated worse survival in multiple cancer types, and it promotes epithelial-mesenchymal transition, angiogenesis, cancer metastasis, and stemness in multiple cancer types. Recently, we published that S100A4 is highly expressed in immune suppressive myeloid and T cells in human gliomas, and S100a4-deletion in stromal cells only is sufficient to increase survival in mouse models of GBM. **Hypothesis** We hypothesize that S100A4 plays a critical role in the TME in multiple cancer types and blocking S100A4 function in the TME is an effective strategy to suppress tumor growth, immune evasion, and metastasis. **Methods** To investigate whether S100A4 inhibition in tumor microenvironment (TME) is a generalizable therapeutic approach, we first analyzed S100A4 expression pattern in 20 human cancer types at the single-cell level. In addition, we analyzed whether loss of S100a4 expression in the host stroma provides survival advantage in non-glioma mouse models: B16 melanoma and MC38 colorectal cancer models. To translate our findings and to block S100A4 function systemically, we developed blocking antibodies against human S100A4 protein. A total of 114 monoclonal antibodies targeting S100A4 were tested, and 7 clones suppressed S100A4 function ex vivo. To further characterize their function in vivo, two different mouse models of breast cancer metastasis were utilized: 1) MMTV-PyMT spontaneous and 2) 4T1 transplanted tumor models. Flow cytometry analyses were performed from blood, primary tumor, and lung metastatic nodules to compare the immunophenotypes of mice treated with IgG and S100A4 antibodies. **Result** Our findings indicate that S100A4, a protein involved in cell signaling and migration, exhibits highly conserved expression in monocytes and myeloid-derived suppressor cells (MDSCs) across various human cancers. Consistently, S100a4 deletion in the stroma (host mouse) blocked

tumor formation in other cancer types, such as B16-F10 melanoma and MC38 colorectal cancer models. Flow cytometry analyses of immune cells in these models revealed that myeloid cells (CD11b+) constitute the majority of immune cells (CD45+) in both MC38 (77.6%) and B16-F10 (52.6%) tumors in B6 mice. In both spontaneous breast cancer metastasis model, MMTV-PyMT, and transplanted 4T1 breast cancer model, S100A4 antibody treatment significantly reduced breast cancer metastasis to the lung. Mechanistically, anti-S100A4 antibody treatment prevents PMN-MDSC/neutrophil infiltration into the lung, resulting in reduced expression of S100A8/9 and other chemokine/cytokines, such as MMP9 that prime the premetastatic niche. Furthermore, anti-S100A4 treatment reduced the number of circulating M-MDSC in the blood and CD163+ macrophages in the primary tumor. Conclusion We have identified a functionally blocking antibody of human S100A4 protein. Our results indicate that soluble S100A4 protein promotes cancer-associated M-MDSC and PMN-MDSC/neutrophils frequencies in the peripheral blood and lung tissue, respectively, to prime the lung metastatic niche. Notably our anti-S100A4 monoclonal antibody has ~10-fold higher affinity for human S100A4 protein compared to mouse S100A4 protein, suggesting that it is a highly promising drug candidate for future clinical development.

PO5-25-07

A research impact assessment method to evaluate Susan G. Komen's research funding impact on drugs approved for breast cancer treatment

Presenting Author(s) and Co-Author(s):

D. Brantley-Sieders. Susan G. Komen, Mebane, North Carolina, United States

L. Leslie. Susan G. Komen, United States

A. Dworkin. Susan G. Komen, United States

K. Sabelko. Susan G. Komen, Dallas, Texas, United States

K. Wojtanik. Susan G. Komen®, United States

Susan G. Komen (Komen) is the largest private funder of breast cancer research, having invested nearly \$1.1 billion in cutting edge breast cancer research with a focus on conquering deadly metastatic and aggressive breast cancers, advancing precision medicine, and addressing disparities in breast cancer care and outcomes. There is a growing demand on Komen and other research funders from patients, donors, and other constituents to understand how investments in biomedical research translate into clinical impact that is meaningful to patients, the public, and others beyond academic publications and other bibliometrics. Komen uses a variety of approaches to evaluate the impact of our research investments, including a recently developed method to determine how Komen's funding has impacted discovery and development of breast cancer drugs approved by the FDA from 2012-2022. Utilizing bibliometric analysis derived from the Dimensions for Funders platform, we systematically identified links between Komen-funded research, Komen-funded researchers, and FDA approved drugs. First, we identified fundamental clinical trials that led to initial and expanded FDA approval of each drug from prescribing information labels and press releases. Using API technology, we then performed a bibliometric linkage analysis and analyzed citation results from fundamental clinical trial studies, working backwards to capture fundamental pre-clinical and basic research studies that identified each drug's target and its functions in the context of breast cancer biology. After collecting and curating publications in an unbiased manner, we evaluated each published study and contributing authors for Komen support. We identified specific "touchpoints" for fundamental studies including direct Komen funding for the published study and/or Komen support of key personnel. Early results revealed direct and indirect Komen research touchpoints across the research pipeline for several drugs, including direct touchpoints for basic, pre-clinical, and clinical trial studies that led to FDA approval of the PI3K inhibitor alpelisib, basic research and pre-clinical studies that led to FDA approval of CDK4/6 inhibitors, and basic research studies that led to FDA approval of PARP inhibitors olaparib and talazoparib. By adopting this approach, we can demonstrate the impact of Komen's research investment across the full development timeline for each drug. This will allow us to measure and communicate how Komen's investment in innovative research from discovery to clinical development is driving advances in breast cancer clinical care that improves outcomes.

PO5-25-09

rs2242652 POLYMORPHISM OF THE hTERT GENE IN WOMEN WITH BREAST CANCER

Presenting Author(s) and Co-Author(s):

M. Alvares. OncoClinicas, Brasilia, Distrito Federal, Brazil

E. Mascarenhas. OncoClinicas, Brasilia, Distrito Federal, Brazil

J. Matos. OncoClinicas, Brasilia, Brazil

Introduction: Breast cancer is the most common neoplasm in women around the world. There are several risk factors for this cancer: sex, age, body mass index (BMI), hormone therapy, family history, genetic mutations, among several others.

The vast majority of breast tumors are characterized as carcinomas and may originate from ducts or lobules. Immunohistochemistry is related to the expressions of the estrogen receptor (ER) and progesterone receptor (PR), as well as the expression of the human epidermal growth factor receptor 2 (HER2), cell proliferation or the absence of any expression from receptors on the tumor membrane.

The telomeres protect the chromosomes natural endings from suffering DNA loss. Telomerase is a ribonuclear protein complex (RNA and protein) that neutralizes telomeres' shortening.

Recurrent point mutations in the TERT telomerase promoter have been identified in several cancers, and the rs2242652 polymorphism is a single nucleotide change, and has been described as associated with breast cancer risk. Objective: The objective of this study is to analyze the TERT rs2242652 polymorphism in breast cancer women and to test the correlation of such data with the prognosis and various clinical variables. Methods: The study was conducted as an observational clinical study of women with breast cancer. A blood sample was collected from the patient and PCR was performed to extract the DNA and to analyze the telomerase polymorphisms in this population. To ensure a more descriptive analysis, the data was used in the construction of tables and graphs, that were then studied in a qualitative manner. The associations were analyzed through direct correlation tests and were followed by comparisons of categorization groups. Results and discussion: Fifty-four women presented polymorphism of the telomerase hTERT gene rs2242652. They were divided into two groups according to the A or G allele that confer the GA / AA and GG gene variants.

It was found that the GA / AA group had a trend towards more aggressive tumors, presenting 33% triple negative and 22% of tumors with HER2 overexpression, different from the GG group: 19% triple negative and 10% HER2 overexpression. More aggressive T4 tumors, were more expressive in the GA / AA gene variant group representing 20% of the patients, whereas in the GG group they represented only 8%. Conclusion: The data found in this study on the telomerase TERT gene polymorphism rs2242652 with breast cancer refers to a tendency found in tumors that have a more severe prognosis, to associate with the gene variant linked to the A allele of this gene, however a larger sample number is required for statistical confirmation.

PO5-25-10

Clinical and Epidemiologic Significance of HER2-Low Expression in Breast Cancer in the Pathways Study

Presenting Author(s) and Co-Author(s):

T. Khoury. Department of Pathology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

R. Payne Ondracek. Roswell Park Comprehensive Cancer Center, United States

S. Yao. Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

L. Mendocino. Roswell Park Comprehensive Cancer Center, United States

W. Davis. Roswell Park Comprehensive Cancer Center, United States

A. Omilian. Roswell Park Comprehensive Cancer Center, United States

M. Kwan. Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States

J. Roh. Division of Research, Kaiser Permanente Northern California, United States

L. D'Addario. Kaiser Permanente Division of Research, United States

E. Valice. Division of Research, Kaiser Permanente Northern California, United States

D. Fernandez. Kaiser Permanente Division of Research, United States

I. Ergas. Division of Research, Kaiser Permanente Northern California, United States

C. Ambrosone. Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

L. Kushi. Division of Research, Kaiser Permanente Northern California, United States

Background: A subset of breast cancers (BC) typically classified as HER2-negative do express low levels of the protein and can be responsive to targeted therapy trastuzumab-deruxtecan. It is unclear if HER2-low tumors have a biology distinct from that in HER2 negative BC. The goal of this study was to evaluate the clinical and epidemiologic features of tumors with HER2-low expression compared with those classified as HER2-negative in a large population study.

Material and methods: The Pathways Study is a prospective multi-ethnic cohort study of women with BC enrolled between 2006-2013 within Kaiser Permanente Northern California (KPNC). Breast biomarker results were extracted from pathology reports and underwent centralized pathology review. HER2-low was defined as 1+ or 2+ (negative by in situ hybridization); HER2-negative was defined as 0+. Other data were collected by self-report or extraction from electronic health records at the KPNC cancer registry, including BC risk factors, tumor characteristics [AJCC stage, ER/PR positive or negative status], treatment modality (chemotherapy, radiation therapy, hormonal therapy, and type of surgery), and survival outcomes [recurrence free survival (RFS), breast cancer specific mortality (BCSM), and overall survival (OS)]. The clinical and epidemiologic variables were tested in association with HER2 status (low/negative) by t-tests. Associations of HER2-low with survival outcomes were calculated by proportional hazards regression. Women were included in this analysis if they had a documented HER2 value that was not classified as HER2-positive.

Results: Of the 2,200 eligible cases, 1,295 (57.2%) had tumors that were HER2-low. Hormone receptors (HR) were positive in 1,956 (88.9%) cases. HER2-low expression was observed more often in HR-positive cases than in HR-negative, 1,144 (58.4%) vs. 115 (47.1%),

respectively ($p=.0005$). Patients with HER2-low tumors were less likely than those with HER2-negative BC to have family history: 232 of 1259 (18.6%) vs. 214 of 941 (22.8%), respectively ($p=.015$). This difference was true for patients with HR-positive tumors but not for HR-negative. HER2-low expression appeared to be more common in Asian patients in the HR-negative group than in patients from any other race or ethnicity group. In the HR-negative group, patients with HER2-low had better OS, BCSM, and RFS ($p=.019$, $.014$, and $.034$, respectively) than those with HER2-negative disease. Multivariable analyses were performed for the HR-negative group and adjusted for age at diagnosis, tumor AJCC stage, and type of treatment. Compared with patients with HER2-negative status, patients with HER2-low tumors had lower risk for OS (hazard ratio=0.48, 95% confidence interval: 0.28 to 0.81, $p=.006$); for RFS (hazard ratio=0.49, 95% confidence interval: 0.27 to 0.90, $p=.021$); and for BCSM (hazard ratio=0.36, 95% confidence interval: 0.17 to 0.76, $p=.007$). In analyses stratified by race and ethnicity and controlled for age at diagnosis, AJCC stage and treatment type, Black patients with HER2-low tumors had lower risk for RFS (hazard ratio=0.44, 95% confidence interval: 0.21 to 0.94, $p=.035$) compared with patients with HER2-negative tumors.

Conclusions: In this large prospective study with well annotated epidemiologic, clinical, and outcome data, we observed some clinical and epidemiologic differences between HER2-low and HER2-negative patients, raising the possibility that HER2-low might be a unique biologic entity.

PO5-25-11

Appropriate use of interventional cohort studies with threshold-crossing designs for de-escalation trials in breast cancer

Presenting Author(s) and Co-Author(s):

H. Tovey. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

L. Finneran. The Institute of Cancer Research, Clinical Trials and Statistics Unit, United States

L. Kilburn. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

I. Macpherson. University of Glasgow - Institute of Cancer Sciences, United Kingdom

A. Wardley. Outreach Research & Innovation Group Ltd, Manchester, England, United Kingdom

H. Stobart. Independent Cancer Patients' Voice, United States

L. Turner. Independent Cancer Patients' Voice, United States

M. MacKenzie. Independent Cancer Patients' Voice, United States

C. Coles. Cambridge University Hospitals NHS Foundation Trust, United States

C. Kirwan. The University of Manchester, United States

J. Bliss. Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, England, United Kingdom

For some populations of patients with early breast cancer (BC), clinical outcomes have improved such that the focus has shifted to identifying aspects of therapy that can be reduced or omitted to spare patients toxicity without compromising outcomes. For example, in patients with HER2+ disease, introduction of HER2-targetted therapy significantly reduced event rates but at increased exposure to toxicity. For those with a pathological complete response (pCR) to neo-adjuvant anti-HER2 therapy, the absolute gain from continued adjuvant therapy is likely to be small and the event rate sufficiently low such that any deviation from the expected prognosis would be sufficient to infer failure of a reduced treatment strategy.

Previous studies would usually adopt a non-inferiority (NI) trial randomising patients between standard of care (SOC) and reduced therapy. The reduced therapy would be declared non-inferior if the difference between the groups does not exceed a pre-agreed NI margin. Some populations, such as those described, have a very low rate of recurrence and thus large sample sizes are required to gain sufficient power resulting in several issues.

In these situations, threshold-crossing designs, also known as interventional cohort studies (ICS), provide an alternative to traditional NI trials. In ICS, a single cohort is recruited and receives the reduced therapy. The event rate is compared to a pre-defined fixed threshold, above which recurrence rates would be considered unacceptable. When conducted appropriately, such studies are statistically and logistically efficient, and should be considered definitive. ICS can be used when

1. A stable background of SOC exists with robust data from which an appropriate crossing-boundary can be defined. Critically, the historical control population used to define the boundary must closely reflect the study population and those seen in clinical practice.

2. The event rate is sufficiently low and consequently has low variability, so a concurrent control group is not required because an accurate estimate of the event rate with SOC already exists.

3. The primary endpoint of interest is reliable, sensitive to treatment and timely to allow early stopping if interim analyses indicate an issue.

The well-defined excellent prognosis of patients with HER2+ BC who have a pCR to contemporary neo-adjuvant therapy, coupled with the pattern of relapse rates dropping off rapidly after 3 years, makes this an appropriate setting for implementing such designs. Three recently initiated studies testing reduced therapy in this patient population, HER2-RADiCAL (NIHR131362), CompassHER2 (NCT04266249) and DECRESCENDO (NCT04675827), all have an ICS design. An ICS approach is also valid for trials testing avoidance of radiotherapy in very low-risk populations, where the absolute benefit is likely low and occurrence of late local events is salvageable so as not to impact on overall survival, such as in PRIMETIME (ISRCTN 41579286).

In contrast, there are several settings where these designs should not be used. For example, in the assessment of systemic therapy in ER+ HER2- BC the recurrence rate is constant beyond 3 years meaning events cannot be picked up in a timely manner and a fixed threshold defined at 3/5 years would not allow preclusion of a later drop-off in efficacy. It would also be premature to use ICS in TNBC following immunotherapy as outcome data is not yet sufficiently mature to accurately define a suitable threshold. Finally, if relapse rates are not sufficiently low, natural variation in control group incidence rates would prevent setting a suitable fixed threshold.

We will discuss the key requirements and design features for using ICS to efficiently evaluate avoidance of treatment in BC and highlight the importance of patient involvement in the development of such trials.

PO5-25-12

CDH1 mutations predict resistance to neoadjuvant taxane therapy

Presenting Author(s) and Co-Author(s):

S. Knappskog. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Norway

R. Helwa. KG Jebsen Center for Genome-directed therapy in Cancer, University of Bergen, Norway, United States

S. Rachakonda. German Breast Group, Neu-Isenburg, United States

L. Gansmo. KG Jebsen Center for Genome-directed therapy in Cancer, University of Bergen, Norway, United States

C. Denkert. Institut für Pathologie, Philipps Universität Marburg und Universitätsklinikum Marburg (UKGM), Germany

L. Yates. Wellcome Genome Campus, Hinxton, Cambridgeshire, UK, United States

C. Solbach. University Hospital Frankfurt, Frankfurt, Germany

M. Untch. AGO-B and HELIOS Klinikum Berlin Buch, Berlin, Germany, Berlin, United States

B. Sinn. Institut für Pathologie, Charité Berlin, Germany

A. Litmeyer. Institute of Pathology, Philipps-University Marburg (UKGM), Germany, United States

B. Ataseven. Breastcenter, Hospital Detmold/Ostwestfalen-Lippe, Germany, United States

J. Huober. Kantonsspital St.Gallen, Brustzentrum, Departement Interdisziplinäre medizinische Dienste, St. Gallen, Switzerland

D. Wedge. Manchester Cancer Research Centre, University of Manchester, UK, United States

T. Karn. Universitätsklinikum Frankfurt, Frankfurt am Main, Germany

O. Nikolaienko. KG Jebsen Center for Genome-directed therapy in Cancer, University of Bergen, Norway, United States

F. Marmé. Med. Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany

P. Fasching. Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany

H. Eikesdal. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Hordaland, Norway

E. Stickeler. Klinik für Gynäkologie und Geburtsmedizin, Uniklinik RWTH Aachen, Germany, United States

C. Schem. Mammazentrum am Krankenhaus Jerusalem, Hamburg, Germany

P. Jank. Institut für Pathologie, Philipps Universität Marburg und Universitätsklinikum Marburg (UKGM), Germany, United States

M. van Mackelenbergh. Universitätsklinikum Schleswig-Holstein, Klinik für Gynäkologie und Geburtshilfe, Schleswig-Holstein, Germany, United States

V. Müller. Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

B. Felder. German Breast Group, Neu-Isenburg, Germany, United States

J. Holtschmidt. German Breast Group, Neu-Isenburg, Germany

P. Campbell. Wellcome Genome Campus, Hinxton, Cambridgeshire, UK, United States

S. Loibl. German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany, Neu-Isenburg, Hessen, Germany

P. Lonning. Department of Oncology, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Bergen, Hordaland, Norway

CDH1 mutations predict resistance to neoadjuvant taxane therapy

Background:

Despite recent advances in personalized medicine, conventional chemotherapy remains a backbone in breast cancer therapy. Thus, identifying markers predicting sensitivity or resistance to individual chemotherapeutics is of great importance.

Methods:

In the EpiTax neoadjuvant trial, enrolling patients between 1997-2003, patients with primary breast cancers (T2 >4cm, T3/T4 and/or N2/N3) were randomized to epirubicin 90mg/m²/3W or paclitaxel 200mg/m²/3W monotherapy, with cross-over in case of inferior response. Pre-treatment snap-frozen tumor biopsies from 223 patients were analyzed by targeted NGS of a 360 gene panel. Endpoint for comparison was clinical response to the first regimen, since pCR was rare due to the large tumor sizes at inclusion. For validation purposes we performed targeted sequencing of tumor samples from a total of 478 patients included in the Gepar Trio (n=132), Quattro (n=171) and Quinto (n=175) trials, in which patients with >2cm tumors received neoadjuvant anthracycline / taxane combination regimens. Here, the primary endpoint was clinical response to combined treatment, but since these tumors were smaller than in the EpiTax-trial, pCR was included as a secondary endpoint. In addition, experimental validations were performed -by CDH1 knock-down and CRISPR/Cas9 knock-out in cell line models.

Results:

In samples from the EpiTax-trial, CDH1 mutations predicted an inferior response (trend across response groups; cPD, cSD, cPR and cCR) in the paclitaxel arm (p=0.01) as well as the epirubicin arm (p=0.04). The predictive value was observed within the subgroup of ER-positive cases (both for paclitaxel (p=0.005) and epirubicin (p=0.003)) but not among ER-negative tumors. The majority of CDH1 mutations (24/34=71%) were observed in lobular cancers. While lobular histology predicted resistance to paclitaxel (but not epirubicin), CDH1 mutations predicted resistance also within the subgroup of lobular cases (p=0.002), demonstrating CDH1 mutations to be an independent predictor and not only a co-variate to lobular histology. As assessing functionally linked genes, mutations in GATA3, a transcriptional regulator of CDH1, were predominantly observed in ductal cancers, and were not predictive of resistance to any compound. Yet, combining GATA3 and CDH1 mutations into a composite biomarker predicted resistance to both paclitaxel (p=0.007) and epirubicin (p=0.01), especially in ER-positive cases (p=0.002 and p=0.0004, respectively). While EMT-signatures had predictive value, this effect was largely dominated by CDH1, while other EMT-related genes had limited impact on response.

In the independent validation cohort from the Gepar trials, selected with enrichment for lobular cancers (34%), CDH1 mutations were not significantly associated with resistance to therapy (p=0.19) although predicted lack of pCR (p=0.01). Combining GATA3 and CDH1 mutations predicted lack of clinical response (p=0.05) and lack of pCR (p=0.0007) respectively in this cohort.

In the in vitro analyses, resistance to paclitaxel was observed in three different breast cancer cell lines upon siRNA mediated knock-down of CDH1, as well as in a CRISPR/Cas9 mediated

CDH1 knock-out model, as measured by growth rate, induction of apoptosis, G2 arrest, mitochondrial respiration and tubulin stability. For anthracyclines, similar effects were observed for mitochondrial respiration.

Conclusions:

In conclusion, mutations in CDH1 predicted resistance to paclitaxel and epirubicin. Our data suggest that CDH1 mutations should be explored further as a predictive biomarker for potential application.

PO5-26-01

Assessing the effect of multimodal therapy in massive fungating breast cancers without distant metastasis

Presenting Author(s) and Co-Author(s):

T. Tamanuki. Breast Surgical Oncology, Funabashi Municipal Medical Center, United States

M. Namura. Breast Surgical Oncology, Funabashi Municipal Medical Center, United States

T. Aoyagi. Breast Surgical Oncology, Funabashi Municipal Medical Center, United States

H. Sakata. Breast Surgical Oncology, Funabashi Municipal Medical Center, United States

M. Iwai. Breast Surgical Oncology, Funabashi Municipal Medical Center, United States

S. Shimizu. Pathology, Funabashi Municipal Medical Center, United States

H. Matsuzaki. Breast Surgical Oncology, Funabashi Municipal Medical Center, United States

Background: Massive fungating breast cancers (MFBCs), which comprise exudative, foul-smelling tumors, the size of a child's head or involve extensive ulceration are classified as locally advanced breast cancers. The National Comprehensive Cancer Network guidelines recommend preoperative neoadjuvant chemotherapy in patients with locally advanced breast cancer without distant metastases. However, limited evidence is available regarding the successful treatment of fungating breast cancers. In clinical practice, many fungating breast cancer cases are treated as stage IV tumors. This study aimed to investigate whether multimodal therapy, including surgery for giant breast cancers, can improve survival rates and whether the survival rates are comparable to those of other stage III breast cancers.

Subjects and methods: Out of 1480 cases of primary breast cancer diagnosed at our hospital between June 2012 and March 2020, 123 patients with clinical stages IIIA–IIIC were chosen for analysis. Furthermore, 29 of these patients with MFBC were selected. During multimodal therapy for selected patients with fungating breast cancer, difficulties were encountered in some patients with single-stage skin suturing and closure after standard neoadjuvant chemotherapy. These patients underwent surgery with an additional skin flap or skin grafting. Furthermore, radiation therapy was added as needed. We compared the survival rates of these patients with those of patients who received drug therapy only according to the therapeutic protocol for Stage IV. Survival rates of patients with MFBC and other stage III breast cancers were also compared. Statistical analyses were conducted using the Kaplan–Meier curve and the log-rank test.

Results: Of the 29 patients with MFBC, 22 (75.9%) and seven (24.1%) were treated with multimodal and palliative therapies, respectively. The median age and follow-up period of the multimodal therapy group were 62 (range: 43–94) years and 67 (range, 32–131) months, respectively. The corresponding values for the palliative therapy group were 79 (range: 42–88) years and 31 (range: 2–96) months. All patients in the palliative treatment group were hormone receptor positive and HER2 negative, and treatment with hormone therapy was initiated. The 7-year survival rate was significantly higher in the multimodal therapy group than in the palliative treatment group (92.3% vs. 68.6%, $p = 0.0317$). Furthermore, the 5-year distant recurrence-free rate was higher in the multimodal treatment group (79.3% vs. 63.5%). Local recurrence did not occur in any patient in the multimodal treatment group. There was no significant difference in the 7-year survival rates between patients with MFBC and those with other stage III breast cancers (86.8% vs. 75.3%; $p = 0.239$). Triple-negative breast cancer accounted for 20.8% (20/96) of the other stage III breast cancers, but none of these were MFBCs.

Conclusions: Clinically, MFBCs are often palliatively treated as stage IV tumors, even in the absence of distant metastasis. However, the survival rate was significantly higher in the multimodal therapy group than in the palliative treatment group. Furthermore, the survival and distant recurrence-free rates for MFBC were higher than those for other stage III breast cancers. Therefore, patients with MFBCs should be actively treated using curative treatments.

PO5-26-02

Changes in Breast Cancer Optoacoustic Imaging Features During Neoadjuvant Therapy and Correlation with Pathologic Response: A feasibility study

Presenting Author(s) and Co-Author(s):

B. Dogan. UT Southwestern Medical Center, Dallas, Texas, United States

B. Ozcan. University of Texas Southwestern, Dallas, Texas, United States

H. McArthur. UT Southwestern, Dallas, Texas, United States

Y. Peng. UT Southwestern Medical Center, United States

Purpose: To evaluate the association of optoacoustic imaging (OA/US) feature changes with neoadjuvant therapy response and compare with volumetric changes.

Methods and Materials: In an IRB approved, HIPAA compliant single arm, single-institution study, 20 breast cancer patients scheduled to undergo neoadjuvant systemic chemotherapy (NAC) were prospectively enrolled to undergo optoacoustic imaging (OA/US) at baseline, prior to cycle 2(Postcycle 1), mid-therapy (mid-chemo) and pre-operative(pre-op) timepoints using a standardized scan protocol. % change in volume was recorded for each timepoint. OA/US features: internal vessels (OAint), total internal hemoglobin (OAHb), internal deoxyHb, external peripheral zone (OApz), boundary zone (OAbz) scored using a previously validated schema. Pathology was collected from standardized reports using residual cancer burden (RCB) and pathologic complete response (pCR) as end points. RCB0-II were classified as responders, RCB-III as non-responders. Descriptive statistics displayed as mean and standard deviation and compared using Wilcoxon Rank-Sum test. Association of volume change was performed using odds ratio (OR) generated from univariate logistic regressions (P-Value < 0.05 for significance).

Results: Mean patient age was 50.4 years (SD± 9.5), index cancer size: 26.3mm (SD±9.7). Surgical pathology showed pCR in 6(30%), partial response in 11(55%), no response in 3(15%) cancers, with mean overall residual cellularity of 32.7%(SD±33.5). Mean % residual volume was not significantly different between responders vs nonresponders. [PostCycle 1 (43.7 ± 25.3 vs 38.5 ± 24.8, p=0.7), mid-chemo (64.2 ± 30.9 vs. 65.8 ± 24.6, p=0.8), pre-op (82.9 ± 23.5 vs 89.3 ± 8.4, p=0.9) timepoints. Regression analysis did not show significant correlation of %vol change with pCR at any timepoint (p >0.05). Postcycle 1, OAHb change was significantly higher in patients who had pCR (76.4% vs 108.8%; p=0.02). At pre-op scan, greater decreases were seen in all OA/US scores in cancers that achieved pCR compared to non-pCR [OAbz (25.0% vs. 84.7% P = 0.03; OAint (40.0% vs. 90.3% P = 0.03);OAHb (18.3% vs. 91.8%; P = 0.03); deoxyHb (26.7% vs. 104.8%; P = 0.02), total OAext (25.8% vs. 88.1%; P = 0.03); total internal (16.2% vs. 91.6%; P = 0.03)].

Conclusions: OA/US feature changes demonstrate higher correlation with pCR than volumetric shrinkage in this feasibility study and show promise as a potential tool to non-invasively identify pCR.

Percentage Change in Optoacoustic Ultrasound (OA/US) Feature Scores from Baseline, Stratified by (pathologic complete response (pCR)).

Scan timepoint	pCR Mean ± Std Dev (N)	Non-pCR Mean ± Std Dev (N)	P-value
Cycle 1 (Feature score assessed)			
External Peripheral Zone Radiating Vessel (OApz) Score	121.7 ± 87.65 (6)	96.2 ± 22.11 (14)	0.582
External Capsular/Boundary Zone Vessel (OAbz) Score	80.2 ± 17.10 (6)	91.3 ± 17.49 (14)	0.215
Internal Vessel (OAint) Score	88.3 ± 25.82 (6)	98.0 ± 20.34 (14)	0.453
Internal Total Hemoglobin (OAHb) Score	76.4 ± 19.79 (6)	108.8 ± 32.14 (14)	0.015
Internal Deoxygenated Blush (deoxyHb) Score	88.6 ± 47.31 (6)	99.3 ± 60.81 (14)	0.561
Total External Feature (OAext) Score	93.8 ± 37.48 (6)	92.5 ± 19.42 (14)	0.362
Total Internal Feature Score	78.7 ± 26.23 (6)	100.1 ± 33.29 (14)	0.172
Total Feature Score	76.9 ± 23.76 (6)	95.7 ± 17.32 (14)	0.107
Pre-Surgery (Feature score assessed)			
External Peripheral Zone Radiating Vessel (OApz) Score	66.7 ± 47.14 (2)	94.2 ± 25.21 (11)	0.357
External Capsular/Boundary Zone Vessel (OAbz) Score	25.0 ± 11.79 (2)	84.7 ± 20.65 (11)	0.027
Internal Vessel (OAint) Score	40.0 ± 0.00 (2)	90.3 ± 26.89 (11)	0.028
Internal Total Hemoglobin (OAHb) Score	18.3 ± 2.36 (2)	91.8 ± 42.49 (11)	0.029
Internal Deoxygenated Blush (deoxyHb) Score	26.7 ± 9.43 (2)	104.8 ± 68.20 (11)	0.022
Total External Feature (OAext) Score	25.8 ± 10.71 (2)	88.1 ± 22.91 (11)	0.029
Total Internal Feature Score	16.2 ± 2.75 (2)	91.6 ± 41.58 (11)	0.030
Total Feature Score	13.4 ± 1.26 (2)	88.3 ± 25.46 (11)	0.030

PO5-26-03

Evaluation of cardiotoxicity in Mexican patients with Breast Cancer under neoadjuvant treatment by two-dimension speckle echocardiography

Presenting Author(s) and Co-Author(s):

H. Williams-Sanchez. National Institute of Cancer, Ciudad de Mexico, Distrito Federal, Mexico

J. Espinosa-Fernandez. INSTITUTO NACIONAL DE CANCEROLOGIA, United States

S. Ruiz-Cruz. Instituto Nacional de Cancerologia, Distrito Federal, Mexico

A. Velazquez-Martinez. Instituto Nacional de Cancerología, United States

N. Espinola-Zavaleta. National Institute of Cardiology Ignacio Chavez, United States

E. C. Guerra. National Institute of Cardiology Ignacio Chavez, United States

A. Aparicio-Ortiz. National Institute of Cardiology Ignacio Chavez, United States

A. Cabello-Ganem. National Institute of Cardiology Ignacio Chavez, United States

S. Luna-Alcalá. National Institute of Cardiology Ignacio Chavez, United States

L. Proaño-Bernal. National Institute of Cardiology Ignacio Chavez, United States

N. Antonio-Villa. National Institute of Cardiology Ignacio Chavez, United States

Background

Cardiotoxicity is a major concern in breast cancer patients treated with anthracyclines or anti-HER-2 therapy. The assessment of left ventricular ejection fraction (LVEF) by transthoracic echocardiogram (TTE) has been the most common method to evaluate cardiotoxicity. Different TTE parameters have been studied to assess cardiotoxicity, we aimed to evaluate left atrial strain (LAS) as a parameter of diastolic cardiotoxicity in Mexican patients under neoadjuvant treatment.

Methods

We prospectively recruited patients with breast cancer under neoadjuvant treatment with anthracyclines and/or anti-HER-2 from March 2022 to present. The evaluation includes TTE, and troponin measurements before chemotherapy, and respective follow-ups at 3 and 6 months from the baseline. We enrolled 187 patients, 172 and 131 had completed the three and six-month follow-ups, respectively. We limited the analysis to patients we could assess cardiotoxicity status, defined according to the ESC 2022 guidelines. Clinical and echocardiographic parameters were compared according to cardiotoxicity status using Chi-squared, two-tailed t-tests or Wilcoxon tests, as appropriate.

Results

The mean time of follow-up at second assessment was 213 days. The patients are divided into cardiotoxicity and no cardiotoxicity group. We reported 81 events of cardiotoxicity if we include troponin measurement or 36 events if we only evaluate TTE measurements. The incidence of cardiotoxicity in this study was not related with common risk factors as high BMI, presence of hypertension/diabetes or smoking status, but it was statistically associated with the presence of elevated LDL cholesterol ($p = 0.026$). Fourteen percent (14%) were HR-/HER-2 (+), 44% HR+/HER-2 (-), 25% HR+/HER-2 (+), and 17% triple negative subtype. Eightyfive percent (85%) of patients received anthracyclines, 28% in combination with anti-HER-2 treatment, 12% received double anti-HER-2 blockade anthracycline free. The accumulated dose of anthracycline didn't differ between groups. The use of anthracyclines and double anti/HER blockade was statically associated with development of CTRCD ($p < 0.01$ and $p < 0.01$),

respectively, but not with a single anti-HER-2 treatment.

In troponin-based cardiotoxicity definition, at the three-month follow-up, those who developed cancer therapy-related cardiac dysfunction (CTRCD) had only statically significant lower LVEF (Table 1) with respect to basal assessment. LASr baseline, three months and six months was similar between groups. In the cardiotoxicity group without troponin measurement, we observed statically significant decreased LVEF and LV GLS at 3 months and six months, and tendency to decreased LASr with respect to basal evaluation.

Conclusions

In our cohort the only modifiable risk factor with impact in the development of CTRCD was dyslipidemia, specifically high LDL. The traditional chemotherapy schemas as anthracyclines and doble anti HER-2 blockade correlate with the development of cardiotoxicity, but not the use of anti-HER-2 as single agent. The addition of troponin measurement to cardiotoxicity definition detected a greater number of events in this study, but doesn't reflect changes in ETT parameters as LV- GLS and LVEF at this time of follow up, which means structural changes induced by treatment take time and serological measurement of troponin can enhance sensitivity and allows early detection. Further follow up and ETT assessment are needed.

Table1. Cardiotoxicity events including or not troponin levels and TTE parameters.

Characteristic	All N = 172	No Cardiotoxicity No troponin N = 136	Cardiotoxicity No troponin N = 36	p-value ¹	No cardiotoxicity Troponin N = 91	Cardiotoxicity Troponin N = 81	p-value ¹
LVEF	63.3 ± 5.5	63.4 ± 5.5	63.0 ± 5.5	0.6	63.5 ± 5.5	63.2 ± 5.6	0.6
Unknown	3	3	0		2	1	
LV GLS	-23.42 ± 2.73	-23.00 ± 2.45	-24.99 ± 3.18	-0.001	-22.80 ± 2.50	-24.11 ± 2.83	0.002
Unknown	0	0	0		-31.9 ± 8.8	-31.7 ± 5.4	0.5
RV FWS	-31.8 ± 7.3	-31.9 ± 7.9	-31.5 ± 4.8	0.7	53 ± 18	58 ± 21	0.3
Unknown	0	0	0		24 ± 9	24 ± 12	0.5
LASr	56 ± 19	55 ± 19	58 ± 19	0.3	1	0	
Unknown	0	0	0				
3 months					63.9 ± 4.7	62.0 ± 6.6	0.088
LVEF	63.0 ± 5.8	63.8 ± 4.9	59.7 ± 7.4	0.001	1	0	
Unknown	1	1	0		-22.96 ± 2.44	-22.76 ± 2.90	0.9
LV GLS	-22.86 ± 2.66	-23.16 ± 2.48	-21.76 ± 3.03	0.019	2	0	
Unknown	2	2	0		-26 ± 17	-28 ± 13	0.8
RV FWS	-27 ± 15	-27 ± 15	-25 ± 16	0.062	4	0	
Unknown	4	4	0		50 ± 16	52 ± 14	0.12
LASr	51 ± 15	51 ± 15	49 ± 14	0.5	8	0	
Unknown	8	8	0		22 ± 9	21 ± 8	0.6
6 months					9	0	
LVEF	63.1 ± 6.2	63.8 ± 5.1	61.3 ± 8.3	0.2			
Unknown	44	41	3		64.0 ± 5.1	62.5 ± 6.8	0.2
LV GLS	-22.83 ± 2.82	-23.30 ± 2.54	-21.47 ± 3.18	0.004	35	9	
Unknown	43	40	3		-22.99 ± 2.45	-22.71 ± 3.09	0.7
RV FWS	-29.3 ± 10.8	-28.5 ± 12.1	-31.4 ± 6.3	0.2	34	9	
Unknown	81	70	11		-29.2 ± 5.1	-29.4 ± 13.5	0.078
LASr	53 ± 17	54 ± 18	51 ± 13	0.8	54	27	
Unknown	127	100	27		51 ± 12	55 ± 19	0.7

LVEF (Left Ventricular Ejection Fraction); LV GLS (Left Ventricular Global Longitudinal Strain); RV FWS (Right Ventricular Free Wall Strain); LASr (Left Atrial Reservoir Strain)

¹Wilcoxon rank sum test; Wilcoxon rank sum exact test

PO5-26-04

The value of skin involvement in achieving of pCR in patients with locally advanced breast cancer

Presenting Author(s) and Co-Author(s):

V. Amosova. N.N. Blokhin National Cancer Research Center, United States

A. Petrovskiy. Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Blochin" Ministry of Healthcare of Russian Federation, Moscow, Russia

O. Trofimova. N.N. Blokhin National Cancer Research Center, United States

M. Frolova. N.N. Blokhin National Cancer Research Center, United States

A. Rumyantsev. N.N. Blokhin National Cancer Research Center, United States

Objective: The management of patients with locally advanced breast cancer (LABC) with skin involvement (edema or thickening) continues to be one of the most controversial topics in mammology. The most recommended conventional treatment strategies include systemic therapy (chemotherapy/ hormone therapy/ biological agents) followed by local therapy (surgery and/or radiation therapy). However, approximately 1/3 of patients with locally advanced breast cancer are "resistant" to neoadjuvant chemotherapy (which is manifested by the persistence of skin involvement/edema/ thickening). In this study, we aimed to identify the relationship between skin involvement and clinicopathological features of LABC patients. In particular, we sought to develop the algorithm for skin involvement measurement and examine the impact of skin involvement on the rate of pCR.

Materials and methods: We performed a retrospective analysis of 182 patients diagnosed with LABC from 2010 to 2018 at N.N. Blokhin National Cancer Research Center. All patients were treated with neoadjuvant hormone- or chemotherapy and were considered as borderline for surgical resection because of partial skin edema. Ninety one women received surgery with consecutive radiotherapy (first group) and 50 women (second group) received radiotherapy (total dose 50 Gy) with consecutive surgery after systemic treatment. We developed the algorithm for skin involvement measurement, using a series of formulas. We further interrogated the impact of skin involvement on the rate of breast and lymph node pathological response in every group.

Results: The median percentage of skin edema before systemic therapy was 76.3% in the first group and 70.1% in the second group. The median percentage of skin edema after systemic therapy was 62.3% in the first group and 69.1% in the second group. There wasn't a statistically significant difference between the two groups ($p=0,675$ and $p = 0,286$, respectively).

Breast pCR was seen in 19,7% ($n=18$) of the first group patients and partial response was seen in 72.6% ($n=66$). Breast pCR was seen in 30% ($n=15$) of the second group patients and partial response was seen in 70% ($n=35$). Results showed no significant differences between groups, $p=0,342$ and $p = 0,12$, respectively. Nodal pCR was reported in 23,9% ($n=16$) and partial response in 50,8% ($n=34$) of the 67 node-positive patients. Nodal pCR was reported in 31,6% ($n=12$) and partial response in 65,8% ($n=29$) of the 38 node-positive patients of the second group. There was no statistical difference in the groups, $p >0,05$.

Conclusion: Increasing attention has been paid to LABC patients due to the clinical commonness and the complexity of treatment. Our study showed that LABC patients with incomplete clinical response to neoadjuvant systemic therapy can achieve pCR or partial

response of tumor despite partial skin edema. In this study we developed the algorithm for skin involvement measurement. We hope that knowledge about volume of skin involvement revealed by this study might shed light on individualized therapies for these patients. In future, it allows to evaluate criteria of tumor resectability to improve patient selection. Therefore, prospective randomized trials are needed to improve optimization of the local treatment.

PO5-26-05

Machine learning-based risk prediction for late distant recurrence in young women with estrogen receptor-positive/human epidermal growth factor 2-negative breast cancer

Presenting Author(s) and Co-Author(s):

D. Shin. Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Seoul, Republic of Korea

J. Lee. Sacred Heart Hospital, Hallym University, Dongtan, United States

J. Cheun. Seoul Metropolitan Government Seoul National University Boramae Medical Center, United States

J. Lee. Soonchunhyang University Seoul Hospital, United States

Y. Shin. Dept. of Information Convergence Engineering, College of Information and Biomedical Engineering, Pusan National University, Busan, Republic of Korea, United States

S. Bae. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

E. Kang. Seoul National Univ. Hospital, Surgery, Republic of Korea

S. Kwon. School of Biomedical Convergence Engineering, College of Information and Biomedical Engineering, Pusan National University, Yangsan, Republic of Korea, United States

H. Lee. Seoul National University Hospital, United States

J. Ryu. Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam, Ulsan-gwangyoksi, Republic of Korea

S. Ahn. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, Seoul, United States

Background

There is a clinical unmet need to predict the risk of late recurrence in premenopausal women with estrogen receptor (ER)-positive/human epidermal growth factor 2 (HER2)-negative breast cancer (BC) who completed endocrine treatment (ET). Previous studies suggest that the CTS5 model, developed using data from cohorts with postmenopausal women and predicts a likelihood of late recurrence after five years of ET, is not highly predictive in premenopausal women. We developed a machine learning-based model predicting the chance of late distant recurrence (DR) using multi-institutional cohorts of premenopausal women with ER-positive/HER2-negative BC who have had no DR for five years from the surgery.

Methods

The study conducted a retrospective review of patients who underwent primary surgery between 2000 and 2011 at Samsung Medical Center, Gangnam Severance Hospital, and Seoul National University Hospital. The study included premenopausal women with ER-positive/HER2-negative BC aged 45 years or younger, who were treated over two years of ET with or without ovarian function suppression and had not experienced distant recurrence for at least five years following the surgery. Patients who had received neoadjuvant chemotherapy were excluded from the study. The primary endpoint is the area under the curve (AUC) and sensitivity (Recall) of the model predicting late DR after five years from primary operation. A total of nine clinical features, including age, tumor size, the number of positive lymph nodes, nuclear grade (NG), histologic grade (HG), progesterone receptor (PR) status, chemotherapy, extension of ET, and addition of OFS, were utilized for supervised machine learning classification.

Results

A total of 2,555 patients were included in this study. The median age was 41 (range, 21-45) years. During a median follow-up duration of 130.3 (range, 60.0-257.6) months, 157 women (6.1%) had late DR after five years of breast cancer surgery. Age, NG, HG, tumor size, and the number of positive LNs were important clinicopathologic variables for late recurrence. The treatment variables included chemotherapy, extension of ET, and the addition of OFS. There were 1,951 patients (76.4%) who had adjuvant chemotherapy, 650 patients (25.4%) with extension of ET over 5 years, and 529 patients (20.7%) who underwent addition of OFS. To develop the model, we performed repeated 5-fold cross-validation using a Balanced Random Forest classifier. The AUC and sensitivity of the model with six features, including age, tumor size, the number of positive lymph nodes, NG, HG, and PR status, were 0.705 and 0.768, respectively. When chemotherapy was added to this model, the AUC and sensitivity of the model increased to 0.713 and 0.771, respectively. When two more treatment features, such as ET extension and addition of OFS, were added to the model, the AUC and sensitivity were 0.714 and 0.752, respectively.

Conclusions

Demographic and clinical characteristics of the patients in this study

Characteristic	All patients (n = 2,555) (%)	
Age, years		
Median	41	
Range	21-45	
Nodal status (No. of positive nodes)		
Negative	1569	(61.4)
1	409	(16.0)
2-3	284	(11.1)
4-9	212	(8.3)
9+	81	(3.2)
Nuclear grade		
Well	401	(15.7)
Intermediate	1550	(60.7)
Poor	604	(23.6)
Histologic grade		
I	664	(26.0)
II	1377	(53.9)
III	514	(20.1)
Tumor size, mm		
<10	360	(14.1)
10-20	994	(38.9)
20-30	804	(31.5)
>30	397	(15.5)
Progesterone receptor		
Positive	2338	(91.5)
Negative	217	(8.5)
Chemotherapy		
No	604	(23.6)
Yes	1951	(76.4)
Endocrine therapy extension		
No	1905	(74.6)
Yes	650	(25.4)
Ovarian function suppression		
No	2026	(79.3)
Yes	529	(20.7)
Distant recurrence (> 5 years)	157	(6.1)

PO5-26-06

Understanding patient experiences to inform future studies to reduce treatment burden in breast cancer

Presenting Author(s) and Co-Author(s):

S. Potter. Bristol Medical School, United States

M. MacTier. NHS Greater Glasgow and Clyde NHS Trust, United States

K. Fairhurst. Bristol Medical School, United States

J. Gath. NA, United States

H. Stobart. Independent Cancer Patients' Voice, United States

S. McIntosh. Queen's University Belfast, United States

Background Most patients with early breast cancer receive multimodality therapy, including surgery, chemotherapy, radiotherapy and endocrine therapy. Currently, not all patients benefit from the treatments they receive but many experience significant morbidities that substantially impact their quality of life. Personalised approaches to treatment offer the opportunity for patients to avoid treatments that do not offer oncological benefit without compromising breast cancer outcomes. Further studies are needed to evaluate these approaches; it is vital that future research is designed to optimise treatment benefit while remaining acceptable to patients. This survey aimed to understand experiences of patients who have received treatment for early breast cancer to inform future risk-adapted studies. **Methods** An online survey was co-developed with patient advocates to explore respondents' experiences of treatments. Questions included simple demographics, treatments received and views about omitting therapies if it was safe to do so. Free-text boxes were provided for respondents to explain their decision. The survey was circulated via social media platforms from April-July 2023. Responses were summarised using simple descriptive statistics and free text was analysed thematically. **Results** 112 responses were received. Respondents were mostly aged 40-60 (n=88, 72.7%) and diagnosed with breast cancer between 1995 - 2023 (median 2017). Treatments received included surgery (n=107, 95.5%), radiotherapy (n=85, 75.9%), chemotherapy (n=69, 61.6%) and endocrine therapy (n=82, 73.2%). Of the 106 (94.6%) respondents who expressed a preference, 38 (35.8%) would omit chemotherapy; 34 (32.1%) would choose not to have endocrine therapy; 19 (17.9%) would prefer to avoid surgery and 11 (10.4%) would omit radiotherapy if safe to do so. Respondents opting to avoid chemotherapy highlighted the 'brutal' short-term side effects and their profound impact on their ability to continue with their daily lives. Hair loss was a common concern and chemotherapy was considered 'very visible', making them a 'cancer patient' in the eyes of others. Long-term effects of treatment such as peripheral neuropathy had lasting effects on respondents' activities of daily living. Almost all respondents who would omit endocrine therapy cited the profound impact of side effects including joint/muscle pains, fatigue, hair loss, sleep disturbance and loss of libido on quality of life. Some respondents commented that the treatment itself was a daily reminder of their diagnosis. Surgery was identified as having long-term impacts on respondents' physical and psychological well-being. Many expressed a desire to avoid 'disfiguring' procedures which had affected their relationships and quality of life. Respondents highlighted specific procedures they would choose to avoid including mastectomy due to the 'trauma' of losing a breast and axillary node clearance due to complications such as lymphoedema. Fewer women chose to avoid radiotherapy. Reasons to do so included both short and long-term side effects of treatment including chronic pain, difficulties travelling and attending for treatment over 5 weeks. Although there was generally a positive response to the concept of reducing unnecessary treatments,

safety was a key concern. Several respondents commented that they would have any treatments considered necessary as survival was their 'absolute priority'. Respondents felt that patients would need to be reassured that any reduction in treatment would not impact long-term outcomes. Conclusions This survey suggests patients would support studies aiming to reduce the burden of breast cancer treatment, and that different patients may wish to de-escalate different components of therapy. Studies developing an evidence base to allow treatment personalisation with a particular emphasis on reducing chemotherapy and endocrine therapy are research priorities.

PO5-26-07

Surgery for Invasive Lobular Carcinoma: A Patient Experience Survey from the Lobular Breast Cancer Alliance

Presenting Author(s) and Co-Author(s):

L. Hutcheson. Lobular Breast Cancer Alliance Inc., Massachusetts, United States
J. Axelrod. Lobular Breast Cancer Alliance Inc., United States
T. Cushing. University of Colorado, Aurora CO, United States
C. Fitzwater. Lobular Breast Cancer Alliance Inc., United States
R. Jeselsohn. Dana-Farber Cancer Institute, Boston, Massachusetts, United States
G. Joergensen. Lobular Breast Cancer Alliance Inc., United States
M. Karsten. Charité, Berlin, United States
M. Kimm. Williams College, United States
M. Kruse. Cleveland Clinic, Cleveland, Ohio, United States
T. Langdon. Lobular Breast Cancer Alliance Inc., United States
J. Levine. Lobular Breast Cancer Alliance Inc., California, United States
M. Mitchell-Daniels. Lobular Breast Cancer Alliance Inc., United States
R. Mukhtar. University of California, San Francisco, United States
B. Neilsen. Lobular Breast Cancer Alliance Inc., United States
S. Paluch-Shimon. Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, and Faculty of Medicine, Hebrew University, Jerusalem, Israel
T. Pross. Charité - Universitätsmedizin Berlin, Germany, United States

The Lobular Breast Cancer Alliance (LBCA) is a nonprofit, patient advocacy organization committed to raising awareness and promoting research into invasive lobular carcinoma (ILC). While ILC accounts for 15% of breast cancers, knowledge about ILC remains limited.

ILC's hallmark is lack of E-cadherin, which results in non-cohesive formation and impacts accuracy of imaging tests and staging. Consequently, patients with ILC have higher rates of positive surgical margins, mastectomies, and axillary lymph node (LN) dissections.

To understand the surgery experience of individuals with ILC, LBCA conducted an anonymous online survey from 6/21-7/2/23, distributed via the LBCA newsletter, social media, and partner organizations. Questions addressed pre-operative imaging, type of surgery, surgical margins, LN status, decision making about and patient experience with surgery. Analyses were limited to those respondents who had surgery. Study limitations include potential recall and selection bias. Results 1,482 individuals with a diagnosis of ILC completed the survey and 1,426 had undergone surgery. 76% were from North America, 11% from England, and 4% from Australia. Average age at diagnosis was 56 (range 31-86). At diagnosis, 38% were clinically stage 1; 37% stage 2; 17% stage 3; and 4% de novo metastatic. 75% had a mammogram that indicated dense breasts.

Of 1,426 surgery respondents (SR), 95% reported that ILC was identified in only one breast at diagnosis. 80% had a pre-surgical MRI. MRI revealed larger tumors than seen on other imaging for 43% and revealed previously unseen contralateral ILC for 3%.

375 (26%) of SRs were diagnosed with ipsilateral disease and had a pre-surgical MRI that did not reveal new information about their ILC. Of these, post-surgical pathology reports indicated 16% had additional ipsilateral foci, 2% contralateral disease, and 40% had larger tumors than seen on pre-surgical imaging.

614 (43%) of SRs had one or more lumpectomy (L), 560 (39%) of SRs had a double mastectomy (DM), and 451 (32%) of SRs had a single mastectomy (SM). 123 (20%) of SRs who had one or more Ls, had a subsequent SM or DM.

For those undergoing L (614), reasons for this choice included: recommendation from their care team (83%), wanted to keep their breast (25%), thought it was better for their overall survival (OS) (14%), and 13% indicated they wanted breasts but did not want reconstruction.

Of the 560 women who had a DM, 60% indicated that they thought a DM would improve their OS, 50% were concerned about the risk of local recurrence, 47% doubted that imaging would detect future ILC tumors, and 45% noted concern that ILC is more likely to be bilateral. Of note, only 9% had ILC or ILC and another invasive breast cancer in both breasts at initial diagnosis and 31% who had a pre-surgical MRI changed their initial surgical treatment plan. Post surgery, pathology for DM group revealed larger tumors than seen on imaging (57%), and 6% had tumors found in a second breast that were not seen on imaging.

For those 451 who had an SM, reasons for this choice included: 75% said it was what their care team recommended, 35% thought it would improve OS, 20% feared risk for local recurrence, and 15% doubted imaging would detect future ILC.

Of 614 respondents who had L, 33% had positive margins at first surgery. Of those, 17% reported multiple Ls and M; and 24% reported clear margins were never achieved. Of the 1011 SM or DMs reported, 10% did not achieve clear margins after these surgeries. Conclusion The survey demonstrates the experience of a large cohort of women with ILC, reporting high rates of uncertainty about accuracy of imaging, high rates of repeat surgery, bilateral mastectomies, and positive margins. Patients are factoring concerns about potential extent of disease and future recurrence in their surgical decision making. These results support the need for improved pre-operative staging and imaging modalities specific to ILC.

PO5-26-08

Caveats behind the improved outcomes observed in recent clinical trials for women with breast cancer : Korean breast cancer consensus meeting 2023

Presenting Author(s) and Co-Author(s):

A. Han. Yonsei University Wonju college of Medicine, United States

Y. Kang. Incheon St. Mary's Hospital, United States

S. Kim. Seoul National University, United States

E. Chae. Kyong Pook University, United States

H. Kim. Soon Cheon Hyang University, United States

K. Park. Korea University Anam Hospital, Republic of Korea

Introduction

Korean Breast Cancer Society has organized the biennial Korean Breast Cancer Consensus Conference to find solutions to clinical situations that cannot be answered by randomized clinical trials or other definitive treatment research data.

Unlike guidelines which are designed to apply to the majority of patients with early or advanced breast cancer encountered in daily practice, consensus meetings yield answers from clinicians' perspectives and experiences. Therefore, this meeting aimed to integrate patient preferences, treatment availability, or other individual circumstances upon recent medical advances and available evidence.

Materials and methods.

Panelists were invited from various fields, such as medical oncology, surgical oncology, radiation oncology, pathology, radiology, nuclear medicine, hereditary cancer specialist.

Results.

1. caveats behind optimizing treatment

There had been strong interests in refining thresholds for treatment and it can be more or less than previous standard treatment. Some patients clearly required escalated treatment, such as ovarian function suppression, combined HER2-targeted treatment, and utilization of immunotherapy during neoadjuvant systemic treatment.

However, even same agent which showed great success for high risk patients showed

Disappointing results and even failure. Furthermore, we need more sophisticated decision even for successful stories which introduced above, because of their serious adverse events. AntiPd-1/PD-L1 showed different serious adverse events profiles and Trastuzumab-deruxtecan is related with life-threatening pulmonary complication.

Therefore, there is a clinical equipoise for an appropriate therapeutic threshold not only for low-risk patients but also high-risk patients who can safely forgo recommend treatment escalation in the newly introduced clinical trials.

2. Completely new serious adverse events observed in new drugs.

Unlike chemotherapy, most targeted therapies cause lethal damage that clinicians may not have experienced. Some, such as pulmonary complications from trastuzumab deruxtecan, can be fatal if not treated immediately. Even if patients survive, they may suffer catastrophic outcomes because these agents leave a fatal disability that is too great for the patient's quality of life. Moreover, in South Korea, where government-run health insurance is the only payer and at the same time policy maker, non-medical constraints such as passive reimbursement plans, value-based medicine, and intentional delay or denial of certain drugs, panelist delivered varying opinions on the extent to which new agents can be utilized and which treatment plan could offer equal clinical benefit with less toxicity, or provide for a measurable improvement in outcomes.

3. utilizing genomic signatures

Panelist raised issues genetic assay which analyzed genes currently we do not have treatment options which can modify disease process. Many questions were addressed such as, appropriate sampling time, which sample, liquid or tumor, can yield meaningful information.

Conclusion

Korean Breast Cancer consensus meeting highlighted important caveats behinds new promising findings. Clinical unmet need and uncertainty should be disclosed before patients because what clinician and patients work with is their life. Shared decision making is essential and patients should become well aware of science and medicine. Proactive approach of clinician is critical for these movements.

PO5-26-09

Digital image analysis and a novel set of cell line samples as aids in the development of a quantitative external quality assessment programme for Ki-67.

Presenting Author(s) and Co-Author(s):

A. Dodson. UK NEQAS ICC & ISH, London, United Kingdom

F. Berisha. UK NEQAS ICC & ISH, United States

D. Wilkingson. UK NEQAS ICC & ISH, United States

L. Zabaglo. UK NEQAS ICC & ISH, United States

S. Parry. UK NEQAS ICC & ISH, United States

Background and Aims

Ki-67 is a well-established biomarker of proliferation in breast cancer (BC). However, its value in treatment decision making is hampered by a lack of analytical reproducibility.

Regular participation in external quality assessment (EQA) substantially improves inter-laboratory concordance.

Pre-requisites in establishing a fit-for-purpose EQA for Ki-67 are a well-validated testing substrate and a reproducible method of assessing Ki-67 scores in participants' submitted materials. We report here on the results of work using cell line controls analysed by digital image analysis (DIA) as a first step towards providing such an EQA.

Materials and Methods

A formalin-fixed paraffin embedded (FFPE) cell line microarray (CLMA) was designed and produced in conjunction with Array Sciences LLC (Sausalito, USA). It was comprised of cores taken from a pure population of Sf9 caterpillar cells, which have been shown to be completely unreactive with most commercial antibodies to human Ki-67, together with cores of Sf9 cells mixed with four different human BC cell lines. These were BT-20 (85% BC cells), ZR-75-1 (75%), BT-474 (65%) and BT-483 (55%). Sections from the CLMA were mounted onto glass microscope slides together with sections from a FFPE tonsil sample and two BC samples; one BC showed high (~30%, BC-high) and the second, low proliferation (~5%, BC-low). In both BC samples proliferating cancer cells were distributed homogeneously throughout the the block.

Unstained sections were distributed to laboratories participating in the Scheme's Ki-67 BC programme; after routine IHC-staining for Ki-67 returned slides were centrally visually assessed for stain quality and subjected to DIA using an in-house application developed on Visiopharm software (Visiopharm A/S, Hoersholm, Denmark).

Results

Slides were returned by 37 laboratories.

Analysis of Ki-67 scores obtained on the Sf9 core identified two distinct groups. The first (n = 27) were negative or showed low Ki-67 scores (mean = 1.1%, 95% CIs: 0.2-1.9%), the second (n = 10) displayed a step-change in scores (mean = 49.9%, 95% CIs: 33.2-66.7%); the means of the two groups were significantly different (P < 0.0001). When Ki-67 scores for each of the tissue samples were dichotomized into similar groups, the means of those groups differed significantly for the two BC samples (P < 0.001), but not for tonsil.

Quality scores generated by visual assessment did not differ significantly between the two groups. However, when slides bearing Sf9 cores demonstrating aberrant Ki-67 scores were visually examined nuclear staining was clearly visible, and non-specific nuclear staining could also be identified in the matched BC tissue samples, but not in the tonsil sections.

Correlation of Ki-67 scores between the four BC cell line cores and each of the BC tissue samples was examined using Pearson's correlation statistics. The r statistic range was 0.57-0.71 in comparisons between BC cell line cores and the BC-high sample, and 0.53-0.70 for those with BC-low; in each case BT-483 showed the highest correlation score and BT-20 the lowest. A similar analysis was undertaken between the tonsil and the two BC tissues. The r statistic for correlation between tonsil and BC-high scores was 0.72; it was 0.64 for those between tonsil and BC-low.

Conclusions

By using a pure population of Sf9 cells we have developed a sensitive indicator of non-specific nuclear staining in IHC preparations stained for Ki-67 which identifies the presence of the artefact quantifiably.

Cores made from Sf9/BC cell line mixtures (especially BT-483) produce Ki-67 scores which correlate with those obtained in breast cancer samples at a similar level to those achieved between tonsil and BC samples; this is true for both high and the low proliferation ranges. Cell line mixtures can be adjusted to show Ki-67 scores in the clinically relevant ranges, and they do not show the inherent biological variations seen in tissue controls such as tonsil.

PO5-26-11

The Breast Cancer Research Foundation Drug Research Collaborative – A unique and innovative model for industry-funded, academically driven research to advance the field of breast cancer.

Presenting Author(s) and Co-Author(s):

U. Jariwala. BCRF, Phoenix, Arizona, United States

D. El-Ashry. BCRF, United States

J. Garber. Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Division of Cancer Genetics and Prevention, Dana-Farber Cancer Institute, United States

L. Norton. Memorial Sloan Kettering Cancer Center, United States

The Breast Cancer Research Foundation (BCRF) is committed to preventing and curing breast cancer through groundbreaking research. In pursuit of this mission, the BCRF launched the Drug Research Collaborative (DRC) in 2016—a pioneering program designed to bridge the gap between academic investigators and access to investigational therapies, thereby fostering greater academic-driven research in breast cancer. The DRC's primary objective is to fund independent, innovative, and high-quality investigator-initiated trials (IITs) and pre-clinical/translational research projects. In conventional drug development, industry-sponsored registration trials play a crucial role, leaving limited resources and scope for exploratory and translational IITs that fall outside the industry's drug approval strategy. Additionally, industry-funded IIT research faces challenges such as reputational risks, perceived influence during internal review processes, intellectual property (IP) concerns, and logistics/program management burdens. The BCRF-DRC program addresses these challenges by issuing requests for proposals to generate creative and unbiased ideas, which are then vetted through an academic review process involving leading breast cancer experts. The most promising research projects are selected for further advancement. The BCRF-DRC program is facilitated by the BCRF research staff, providing project management, while the Translational Breast Cancer Research Consortium (TBCRC), founded by the BCRF and also supported by Susan G. Komen, supports the clinical trial aspects of the program. Since its inception, the BCRF-DRC has expanded from one to three industry partners, securing a total funding of \$25 million for 15 projects, including seven clinical trials and eight pre-clinical projects. This abstract reports on the ongoing progress and outcomes achieved by these three programs. The BCRF-DRC represents a revolutionary paradigm in research funding and collaboration by harnessing the collective power of industry partners, philanthropic organizations, and academic institutions. Through this collaborative effort, the BCRF-DRC provides a unique platform for researchers to accelerate the translation of scientific discoveries into effective clinical interventions, thus making significant strides in the field of breast cancer in the coming decades. By empowering academic investigators, fostering unbiased research, and addressing the limitations of industry-funded IITs, the BCRF-DRC is revolutionizing breast cancer research and driving the development of novel interventions. This abstract highlights the transformative potential of the BCRF-DRC program and its contribution to advancing breast cancer treatments and ultimately improving patient outcomes. The success of this collaborative model serves as a testament to the power of multi-sector partnerships and the pivotal role they play in shaping the future of breast cancer research.

PO5-26-12

Optimizing Treatment Decisions in Microinvasive Ductal Carcinoma in Situ: Evaluating the Need for Surgical Axillary Staging

Presenting Author(s) and Co-Author(s):

C. Lava. MedStar Georgetown University Hospital, United States

K. Li. MedStar Georgetown University Hospital, United States

L. Berger. MedStar Georgetown University Hospital, United States

D. Spoer. MedStar Georgetown University Hospital, United States

L. Rosal. MedStar Georgetown University Hospital, United States

A. Williams. Fox Chase Cancer Center, Philadelphia, Pennsylvania, United States

M. Masanam. Medstar Georgetown University Hospital, United States

I. Greenwalt. MedStar Georgetown University Hospital, United States

J. Son. MedStar Georgetown/MedStar Montgomery, North Bethesda, Maryland, United States

L. De La Cruz. Medstar Georgetown University Hospital, Department of Breast Surgery, United States

Background: Surgical axillary staging is often debated in patients with microinvasive ductal carcinoma in situ (T1mi) due to the low occurrence of nodal metastasis. Axillary surgery (ASx) is associated with risks like seroma, wound complications, lymphedema, and sensory deficits. This study aims to assess the utility of surgical axillary staging in clinically node-negative (cN0) T1mi breast cancer patients and provide insights for optimizing high value surgical treatment and subsequent decision-making. Methods: This retrospective cohort study analyzed data from the National Cancer Database (NCDB) to investigate axillary status of patients with cT1mi breast cancer between 2012 and 2019. Patient demographics, clinical characteristics, treatment methods and pathologic findings were collected. Comparisons were made between those who did and did not undergo ASx, and of those who did, between patients who were pathologically node-positive (pN+) vs. node-negative (pN-). Results: Of 10,843 patients analyzed, 9,220 (85.0%) underwent ASx while 1,623 (15.0%) did not. Mean age of patients undergoing ASx and those who did not was 59.2±11.2 and 66.3±12.8 years, respectively ($p < 0.001$). On univariate analysis, other factors associated with undergoing ASx were having private insurance, fewer medical comorbidities, having a HER2+ or triple negative phenotype, higher grade, presence of lymphovascular invasion and undergoing mastectomy (all $p < 0.05$). Sentinel lymphadenectomy was performed in 83% of patients while axillary lymph node dissection (ALND) was performed in 17% of patients. Final pathology demonstrated an upgrade to a true invasive cancer (T1 or greater) in 29.3% of cases. Of 9,069 patients who underwent ASx with known pathologic nodal status, 8,512 (93.9%) were pN- and 557 (6.1%) were pN+. Factors independently associated with increased odds of having positive nodes were younger age (OR 1.02, 95% CI 1.01-1.03, $p < 0.001$), Black race (OR 1.51, 95% CI 1.12-2.10, $p = 0.007$), lymphovascular invasion (OR 13.72, 95% CI 10.25-18.36, $p < 0.001$), and undergoing mastectomy (OR 1.98, 95% CI 1.57-2.51, $p < 0.001$). Among the pN+ patients, only 64 (0.7%) had ≥ 3 total positive nodes and would require ALND. On subset analysis of the 4,190 patients undergoing mastectomy, 244 (5.8%) did not undergo ASx, while 3,946 (94.2%) did, of whom 373 (9%) were pN+. Regarding adjuvant treatments in this group, more patients who underwent ASx received chemotherapy (12% v. 8%, $p < 0.001$), and among those who did undergo surgery those who were pN+ were much more likely to receive chemotherapy (58% v. 12%, $p < 0.001$). However, similar proportions of patients who did and did not undergo ASx received adjuvant radiation (5% v. 4%,

p=0.65), while, as expected, among those undergoing ASx, a higher proportion who were pN+ underwent radiation (32% v. 5%, $p < 0.001$). Conclusion: Surgical axillary staging for T1mi breast cancer is common, but many patients are node-negative. More patients are undergoing ALND than necessary based on pathology. Nodal status influences adjuvant therapy decisions. Identifying factors linked to upgrade and higher pN+ probabilities can enable personalized surgical treatments, reducing morbidity for most patients.

PO5-27-01

Comparison between the 7th and the 8th edition of TNM Staging System of American joint committee on Cancer(AJCC) for Breast Cancer Patients, diagnosed and treated at King Abdulaziz Medical City

Presenting Author(s) and Co-Author(s):

N. Abdelhafiez. National Guard Health Affairs, United States

A. Alkushi. National Guard Health Affairs, United States

L. Alriyees. National Guard Health Affairs, United States

M. ARABI. National Guard Health Affairs, United States

F. Alsalamah. National Guard Health Affairs, United States

E. Masuadi. King Abdulaziz University for Health Sciences, United States

A. OMAIR. National Guard Health Affairs, United States

M. Alkaiyat. National Guard Health Affairs, United States

H. Shehata. King Abdulaziz Medical City, Riyadh, Ar Riyadh, Saudi Arabia

Breast cancer is a heterogeneous disease with different biological and molecular characteristics that affect local recurrence, metastases, prognoses, and response to available therapies. The 8th edition of the American Joint Committee on Cancer (AJCC) staging system for breast cancer has incorporated the biological and molecular characteristics, tumor grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor status (Her-2) and tumor grade, into the traditional anatomical 7th edition that only considers tumor size, lymph nodes status, and distant metastases. The aim of this study is to compare the 7th to 8th editions of the AJCC staging system for prognostic impact, assess the effect of the new edition on the treatment and treatment outcome

Method

A retrospective cohort study was performed for all breast cancer patients, diagnosed between (2013 -2019) and underwent upfront surgery at King Abdulaziz Medical City (KAMC). Patients' clinicopathological, immunohistochemical, surgical, therapeutic, and follow-up data were retrieved. Overall survival (OS) and breast cancer-specific survival (BCSS) were estimated using the Kaplan–Meier method. Univariate analysis using Fisher's exact test was used to compare staging systems' prognostic accuracy. Multivariable analysis using Cox proportional hazards regression analysis was performed to identify factors independently associated with disease outcome

Results

A total of 169 female patients were included, the 8th AJCC staging system resulted in a reallocation of 108 (63.9%) of the patients to a different stage group. The majority were downstaged (60.9%) while only 3% were upstaged, most of the upstaged patients had a triple-negative subtype (80%). The change in overall stage for the 8th edition was most significant in stage I (an increase by 140.3%), followed by stage II (downstaged by 74.3%) and stage III (downstaged by 49.7%) compared to the 7th edition. Critically 42.8% of all downstaged patients treated with adjuvant chemotherapy were found to have received unnecessary chemotherapy after applying the 8th AJCC staging system as per National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommendations. The 8th AJCC staging system was a better prognostic predictor of disease survival, patients in 8th AJCC stage 3 had a higher

tendency to develop metastases and die because of their disease (P-value 0.03, 0.051, respectively).

Conclusions:

Our comparison revealed that the AJCC 8th edition staging system is superior and more comprehensive than the 7th, in term of prognostic value, and in defining the precise adjuvant therapy

Figure 1

		8 th AJCC Prognostic Staging System							
		IA	IB	IIA	IIB	IIIA	IIIB	IIIC	Total
7 th AJCC Staging System	IA	46 (27.20%)	4 (2.40%)	0	0	0	0	0	50 (29.60%)
	IB	4 (2.40%)	1 (0.60%)	0	0	0	0	0	5 (3.00%)
	IIA	28 (16.60%)	14 (8.30%)	7 (4.10%)	0	0	0	0	49 (29.00%)
	IIB	5 (3.00%)	18 (10.70%)	6 (3.60%)	4 (2.40%)	0	0	0	33 (19.50%)
	IIIA	0	11 (6.50%)	2 (1.20%)	1 (0.60%)	1 (0.60%)	0	0	15 (8.90%)
	IIIB	1 (0.60%)	0	0	0	1 (0.60%)	1 (0.60%)	1 (0.60%)	4 (2.40%)
	IIIC	0	0	1 (0.60%)	0	7 (4.10%)	4 (2.40%)	1 (0.60%)	13 (7.70%)
	Total	84 (49.70%)	48 (28.40%)	16 (9.50%)	5 (3.00%)	9 (5.30%)	5 (3.00%)	2 (1.20%)	169

Of all cases, 36.1% had the same stage in both 7th and 8th AJCC staging systems while 60.9% were down staged and only 3.0% were upstaged.

Comparison of the 7th AJCC and the 8th AJCC staging system

PO5-27-02

A Tumor Emboli Platform for Morphometric Analysis, Drug screening and for Intravital Optical Imaging in a Murine Model to Simulate Clinicopathological Features of Inflammatory Breast Cancer

Presenting Author(s) and Co-Author(s):

D. Sannareddy. Department of Surgery, Duke University School of Medicine, Durham, North Carolina, United States

T. Charity. Duke University, North Carolina, United States

A. Bennion. Trinity College of Arts and Sciences, Duke University, North Carolina, United States

C. Way. Biomedical Engineering, Duke University, North Carolina, United States

E. Yu. Trinity College of Arts and Sciences, Duke University, North Carolina, United States

R. Erdmann. Mechanical Engineering, Baylor University, United States

G. Palmer. Department of Radiation Oncology, Duke University School of Medicine; Duke Cancer Institute, United States

G. Devi. Department of Surgery, Duke University School of Medicine; Duke Consortium for Inflammatory Breast Cancer, Duke Cancer Institute, Durham, North Carolina, United States

Background: Inflammatory breast cancer (IBC) is distinguished by the presence of tumor emboli, clusters of tumor cells, found within breast parenchyma and dermal lymphatic vessels. These emboli serve as a crucial clinicopathological hallmark, believed to underlie the characteristic diffuse growth pattern and aggressive progression observed in IBC patients, with nearly 30% of patients presenting with metastatic disease at diagnosis. However, the rarity of this cancer and the absence of a solid tumor mass pose challenges in obtaining biospecimens, particularly those with evidence of tumor emboli. To address this pressing need for preclinical models that replicate this distinctive tumor growth pattern, we describe a tumor emboli culture platform that facilitates live imaging, enables compound screening by assessing various phenotypes of the emboli, and permits evaluation of emboli in an in vivo murine model.

Methods: The tumor emboli culture system was evaluated for physiological measurements corresponding to dermal lymphatic vessels and subsequently employed to generate tumor emboli from diverse patient-derived cell lines and PDX. Confocal microscopy was employed to characterize cellular information across multiple slices of the tumor emboli. This provided a comprehensive, multi-parametric analysis of single-cell and spheroid phenotypes, including measurements of number, size, shape, and viability of the organoids. Furthermore, we developed imaging algorithms to evaluate phenotypic changes in tumor emboli in response to anti-cancer drug treatment. We also optimized a technique that allows for in vivo tumor emboli implantation including in a transgenic mice with red fluorescent lymphatic vasculature that were surgically implanted with a dorsal skin window chamber. This allowed for intravital optical imaging of the local tumor microenvironment and adjacent skin. **Results:** Our culture platform enables live imaging of the tumor emboli generated over a span of 7-10 days, maintaining key parameters including kinematic and dynamic viscosity, density along with sheer wall stress within the reported physiological range for lymphatics. Through higher resolution confocal image acquisition and multi-parametric analysis, we conducted particle counting and classification, providing statistically significant insights into the integrity of tumor emboli over time. Additionally, the developed algorithms allowed for quantitative analysis of images from tumor emboli cultures subjected to anti-cancer drugs, revealing disparities in drug efficacy on tumor emboli integrity and dispersion including inter-cluster space within the emboli. Intravital

optical imaging, coupled with quantitative analysis of dispersion characteristics of the tumor emboli implanted in the murine model over 5-6 days, demonstrated a diffuse spread reminiscent of observations in IBC patients. Furthermore, immunohistochemistry staining showed marked Ki67, CD45, F4-80 revealing a proliferative tumor microenvironment with high levels of macrophage infiltration. Conclusions: As of now specific targeted therapies for IBC patients remain elusive. Our culture platform for tumor emboli, when combined with advanced imaging techniques both in vitro and in vivo and traditional approaches like immunohistochemistry and genomic evaluation, forms a powerful toolkit for assessing the phenotype and dispersion characteristics of this unique pathological feature in IBC. This preclinical model offers crucial insights, potentially paving the way for precision medicine strategies in the treatment of this understudied cancer. Funding in part from American Cancer Society Mission Boost MBG-20-141-01-MBG grant (GRD), Department of Defense W81XWH-20-1-0153 (GRD), Duke Consortium for Inflammatory Breast Cancer Education (AB, CW, RE).

PO5-27-03

Mutational impact of APOBEC3A and APOBEC3B in a human cell line

Presenting Author(s) and Co-Author(s):

M. Carpenter. UT Health San Antonio, San Antonio, Texas, United States

N. Temiz. University of Minnesota, United States

M. Ibrahim. UT Health San Antonio, San Antonio, Texas, United States

M. Jarvis. University of Minnesota, Minneapolis, Minnesota, United States

M. Brown. University of Minnesota, Minneapolis, Minnesota, United States

P. Argyris. Ohio State University, Columbus, Ohio, United States

W. Brown. University of Minnesota, Minneapolis, Minnesota, United States

D. Yee. Masonic Cancer Center, University of Minnesota, Minnesota, United States

R. Harris. UT Health San Antonio, San Antonio, Texas, United States

A major source of mutation in cancer is DNA cytosine deamination by APOBEC3 enzymes resulting in C-to-T and C-to-G mutations in TCA and TCT motifs. Here, we develop a selectable system to quantify genomic mutations and compare the mutagenic activities of three leading APOBEC3 candidates - APOBEC3A, APOBEC3B, and APOBEC3H. The human cell line, HAP1, is engineered to express the thymidine kinase (TK) gene of HSV-1, which confers sensitivity to ganciclovir. Expression of APOBEC3A and APOBEC3B, but not catalytic mutant controls or APOBEC3H, triggers increased frequencies of TK mutation and nearly indistinguishable TC-biased cytosine mutation profiles in the selectable TK reporter gene. Whole genome sequences from TK mutant clones enabled an analysis of thousands of single base substitution mutations and extraction of local sequence preferences with APOBEC3A preferring YTCW motifs over 70% of the time and APOBEC3B just under 50% of the time (Y=C/T; W=A/T). Signature comparisons with breast tumor whole genome sequences indicate that most malignancies manifest intermediate percentages of APOBEC3 signature mutations in YTCW motifs, mostly between 50 and 70%, suggesting that both enzymes are contributing in a combinatorial manner to the overall mutation landscape. These studies combine to help resolve a long-standing etiologic debate on the source of APOBEC3 signature mutations in cancer and indicate that future diagnostic and therapeutic efforts should focus on both enzymes.

PO5-27-04

The epidemiological profile and lifestyle of non-village indigenous women from Amazonas, Brazil and the likely impact on breast cancer mortality

Presenting Author(s) and Co-Author(s):

M. VINHOTE DA SILVA. UEA, United States

L. SOUZA GUIMARÃES. Hospital Universitario da Universidade Federal do Amazonas, United States

A. Nazário. Universidade Federal de São Paulo, United States

M. DE OLIVEIRA CASTRO. UFAM, United States

Introduction: The high and growing incidence of breast cancer is a reality in almost every continent. However, the low mortality from this neoplasm among indigenous people of Amazonas, Brazil, is an intriguing fact (table 1). In spite of having a lower life expectancy at birth, the magnitude of low mortality is even greater. Indigenous women have gradually integrated into the non-indigenous community, and the reality of low mortality from breast cancer may be at risk of not existing in the future if the justification is in their reproductive epidemiological profile and lifestyle. **Objective:** This work seeks to find variables that can justify the fact that indigenous women from the Amazon region die less from breast cancer when compared to non-indigenous women. **To achieve this,** we evaluated reproductive epidemiological factors and lifestyle in non-village indigenous women and compared them with the same data in non-indigenous women. **Methods:** This is a cross-sectional study consisting of a convenience sample in which all indigenous people treated at the Mastology Outpatient Clinic of the Getúlio Vargas University Hospital of the Federal University of Amazonas were invited to participate from September 2020 to March 2023. There were 126 women: 39 non-village indigenous people who have lived in Manaus for more than 5 years and are integrated into society, 47 non-village indigenous people who live in riverside and interior populations of Amazonas - or in Manaus for less than 5 years - and 40 non-indigenous individuals. A questionnaire in interview format was administered with the objective of evaluating epidemiological and reproductive aspects such as age, education, BMI, menarche, parity, age at first pregnancy, breastfeeding, use of hormonal medications as well as lifestyle factors including smoking, alcohol consumption, dietary habits, physical activity, use of herbs, roots and seeds for therapeutic purposes and practice of religious devotional habits. **Results:** There was no difference in age, BMI, education, menarche and parity between the interviewed patients, nor in the assessment of the consumption of milk, sugar, fruits, vegetables and legumes, smoking habits, alcohol intake or physical activity between the groups. Indigenous women living in Manaus had a lower age at first pregnancy when compared to non-indigenous women. The variable "breastfeeding time" did not reach statistical significance but demonstrated a very close index ($p = 0.058$) and a tendency to suggest that indigenous people, regardless of their place of residence, breastfeed for a longer duration. Non-indigenous women had a longer history of using hormonal medications when compared to indigenous women living in Manaus. Regarding meat consumption habits, indigenous women living in riverside and interior populations showed higher percentages of sporadic consumption of beef, sporadic consumption of wild animals, and daily consumption of white meat compared to non-indigenous people. On the other hand, non-indigenous women had a higher percentage of never having consumed wild animal meat when compared to the two other groups. Among indigenous women from riverside populations, there was a lower percentage of religious practices. The consumption of herbs, roots or seeds for therapeutic purposes was more commonly observed among indigenous people living in Manaus when compared to non-indigenous people. **Conclusion:** No epidemiological or lifestyle

variables were found in both groups of indigenous people that justify the low mortality from breast cancer in these women. However, although the variable “breastfeeding time” did not reach statistical significance, it demonstrated a very close index (p 0.058) and a tendency to suggest that indigenous people, regardless of their place of residence, breastfed for a longer duration. This could be a potential explanation for the low mortality from this disease among indigenous women.

Table 1: Participation of breast cancer deaths in the total number of deaths in women over 20 years of age in the State of Amazonas Source: prepared by researchers

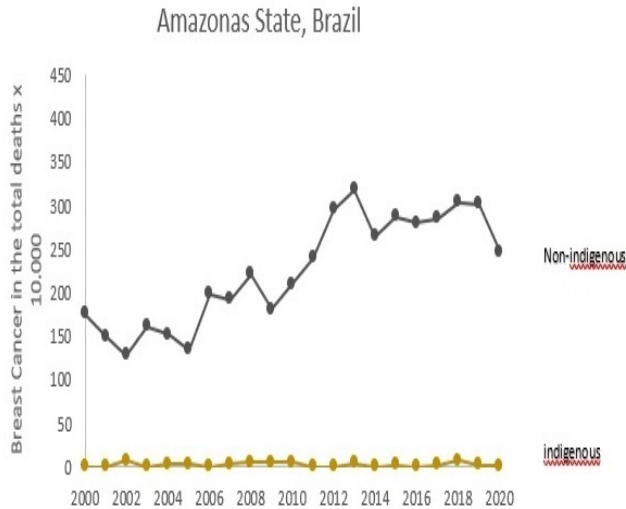
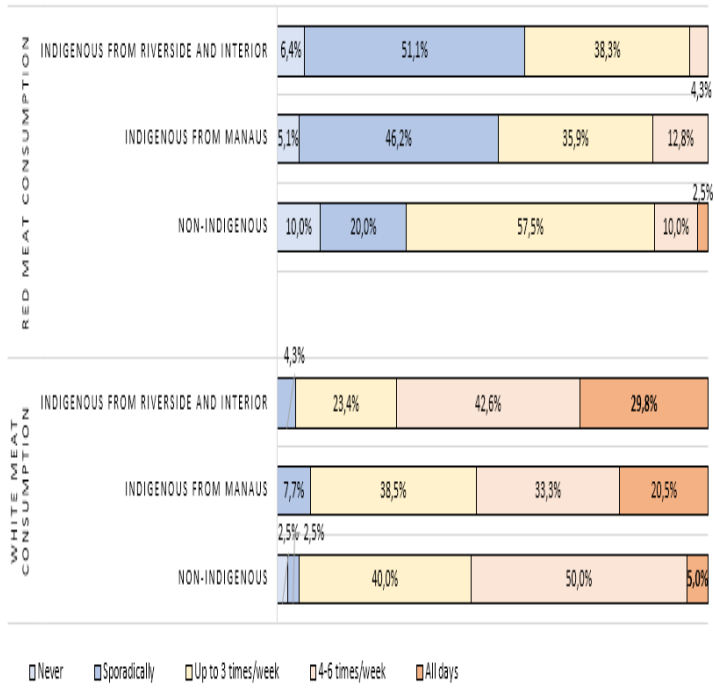


Table 2 - Menarch, parity (childbirth and miscarage), breastfed, Family history of breast cancer, image exam

	Groups			Total	p
	Indigenous from Riverside and interior AM (N=47)	Indigenous from Manaus (N=38)	Non-indigenous (N=40)		
Menarch (years)					0,327
Media ± SD	13,4 ± 1,5	13,1 ± 1,8	13,2 ± 1,8	13,2 ± 1,8	
Mediana (Min - Max)	13,0 (10,0 - 18,0)	13,0 (10,0 - 18,0)	13,0 (10,0 - 18,0)	13,0 (10,0 - 18,0)	
Parity (childbirth and miscarage)					0,128
Media ± SD	3,5 ± 2,1	4,4 ± 2,7	3,2 ± 2,1	3,7 ± 2,4	
Mediana (Min - Max)	3,0 (1,0 - 9,0)	4,0 (1,0 - 11,0)	3,0 (1,0 - 10,0)	3,0 (1,0 - 11,0)	
Age at first pregnancy					0,011
Media ± SD	19,3 ± 3,3	18,1 ± 4,0	22,0 ± 5,8	19,7 ± 4,5	
Mediana (Min - Max)	19,0 (14,0 - 32,0)	18,0 (12,0 - 28,0)	21,0 (16,0 - 34,0)	19,0 (12,0 - 34,0)	
Breastfed					0,537
No	8 (18,2)	7 (17,9)	10 (27,0)	25 (20,8)	
Yes	39 (81,8)	32 (82,1)	27 (73,0)	95 (79,2)	
Breastfeeding during (months)					0,058
Media ± SD	70,6 ± 84,7	63,9 ± 67,1	40,0 ± 44,8	59,8 ± 61,3	
Mediana (Min - Max)	45,5 (7,0 - 300,0)	38,0 (2,0 - 300,0)	24,0 (3,0 - 216,0)	38,0 (2,0 - 300,0)	
Use of hormonal medications					0,120
No	26 (55,3)	21 (53,8)	14 (35,0)	61 (48,4)	
Yes	21 (44,7)	18 (46,2)	28 (65,0)	65 (51,6)	
Time of using hormonal medications					0,041
Media ± SD	37,9 ± 25,8	31,4 ± 38,9	63,0 ± 69,8	45,9 ± 51,6	
Mediana (Min - Max)	36 (7,0 - 120,0)	12,0 (1,0 - 120,0)	48,0 (2,0 - 348,0)	36,0 (1,0 - 348,0)	
Family history of breast cancer					0,778
No	40 (85,1)	35 (89,7)	34 (85,0)	109 (88,5)	
Yes	7 (14,9)	4 (10,3)	6 (15,0)	17 (13,5)	
Breast image exam					0,001
No	21 (45,7)	19 (50,0)	5 (12,8)	45 (36,8)	
Yes	25 (54,3)	19 (50,0)	34 (87,2)	78 (63,4)	
Age at first image exam					0,567
Media ± DP	37,8 ± 12,2	39,3 ± 9,2	35,8 ± 11,9	37,3 ± 11,4	
Mediana (Min - Max)	39 (18,0 - 78,0)	40,0 (20,0 - 80,0)	39,0 (14,0 - 81,0)	39,0 (14,0 - 78,0)	

Table 3: Red and white meat consumption



*P<0,05

PO5-27-05

Computational design and validation of a novel peptide-drug conjugate for treatment of triple negative breast cancer

Presenting Author(s) and Co-Author(s):

F. Liu. ProteinQure, Inc, Ontario, Canada

A. Zhai. ProteinQure, Inc, Ontario, Canada

O. Yoluk. ProteinQure, Inc, Ontario, Canada

A. Broom. ProteinQure, Inc, Ontario, Canada

T. Stone. ProteinQure, Inc, Ontario, Canada

G. Butterfoss. ProteinQure, Inc, Ontario, Canada

S. Popa. ProteinQure, Inc, Ontario, Canada

T. Li. ProteinQure, Inc, Ontario, Canada

L. Siow. ProteinQure, Inc, Ontario, Canada

C. Ing. ProteinQure, Inc, Ontario, Canada

D. White. ProteinQure, Inc, Ontario, Canada

Sortilin (SORT1) is a member of the vacuolar protein sorting 10 protein (Vps10p) family that functions as a receptor regulating peptide and protein trafficking between the plasma membrane, lysosomes, and trans-golgi network. As a cell surface receptor, SORT1 is able to mediate efficient endocytosis of extracellular ligands to the lysosomal compartment. Numerous reports have identified enriched SORT1 expression in a variety of tumor types, including triple-negative breast cancer (TNBC), a subtype of breast cancer associated with aggressive clinical behavior and poor disease outcomes. We sought to exploit SORT1-dependent internalization of peptides as a platform for rapid and specific chemotherapy delivery into TNBC cells. Using ProteinStudio (our proprietary computation-enabled design capabilities), we generated high-affinity SORT1 targeting peptides that exhibit efficient receptor dependent internalization and lysosomal localization. Alternative computational approaches such as AlphaFold2 failed to recapitulate the peptide design. Peptide drug conjugates (PDCs) were generated via a linkage strategy that combines our designed peptides to the antimetabolic agent monomethyl auristatin E (MMAE). Our PDC molecules exhibit potent tumor regression in a MDA-MB-231 TNBC cell derived xenograft model, thereby highlighting the potential of SORT1-engaging PDCs as an efficacious targeted chemotherapeutic delivery strategy.

PO5-27-06

Development of TTX-MC138, a First-In-Class miRNA-10b-Targeted Therapeutic Against Metastatic Cancers of Diverse Primary Disease Origins

Presenting Author(s) and Co-Author(s):

Z. Medarova. TransCode Therapeutics, Inc., United States

N. Robertson. TransCode Therapeutics, Inc., United States

S. Ghosh. TransCode Therapeutics, Inc., United States

A. Varkaris. Massachusetts General Hospital, Boston, Massachusetts, United States

P. Caravan. Athinoula A. Martinos Center for Biomedical Imaging, MGH, HMS, United States

S. Duggan. TransCode Therapeutics, Inc., United States

Conventional therapies targeted towards the primary tumor cell oftentimes do not affect the metastatic cell and, in fact, may promote metastasis. For these reasons, our research has focused on developing therapies specific to unique properties of metastatic tumor cells. In our earlier work, we identified miRNA-10b as a master regulator of the viability of metastatic tumor cells. We determined that miRNA-10b not only promotes the capacity of tumor cells to migrate and invade surrounding tissue, but, importantly, serves as a powerful master regulator of the viability of cancer cells. This knowledge allowed us to develop a therapeutic miR-10b inhibitor, named TTX-MC138, which is effectively delivered to metastatic tumor cells and can elicit complete responses and life-long disease remissions in preclinical models of breast and pancreatic adenocarcinoma. As a critical step towards de-risking further clinical development of TTX-MC138, we have embarked on a Phase 0 clinical trial with Cu64-labeled TTX-MC138. The trial involves microdose injection of Cu64-labeled TTX-MC138 into stage IV breast cancer patients, followed by positron emission tomography-magnetic resonance imaging (PET-MRI). The study seeks to determine the pharmacokinetics of TTX-MC138 and its uptake in metastatic lesions. The impact of this work is three-fold. First it can establish that TTX-MC138, which is so effective in mice, will also accumulate in human metastases. This greatly de-risks the clinical development of the therapeutic because it shows drug delivery is indeed feasible. Second, the Phase 0 studies will reveal the pharmacokinetic behavior of TTX-MC138 which will allow one to establish dosing during therapy. Third, once TTX-MC138 reaches late-stage clinical trials, one can use the radiolabeled therapeutic to select patients for treatment, based on which patients' metastases accumulate the drug. Studies that we present in support of the Phase 0 trial include dosimetry/PK and tissue distribution studies, as well as metabolite analysis in non-human primates. In non-human primates injected with Cu64-labeled TTX-MC138 at a dose of 100 microg, the organs with the highest uptake were the liver, heart, lung and spleen. The mean whole blood half-life was 12.2 ± 2.3 h (mean \pm standard deviation) and the mean plasma blood half-life was 11.5 ± 1.8 h. RadioHPLC analysis of plasma samples showed that the drug is very stable with respect to metabolism. Combined, these studies support first-in-human testing of TTX-MC138 for the treatment of metastatic cancer and, by addressing the issue of drug delivery, enable the clinical development of a wide array of TTX-based therapeutics.

PO5-27-07

A novel ROR1 inhibitor CPD86 suppresses Triple-Negative Breast Cancer cells via regulation of AKT/GSK3 β pathway

Presenting Author(s) and Co-Author(s):

T. Ta. Saint Joseph's University, Philadelphia, Pennsylvania, United States

V. Reed. Saint Joseph's University, United States

N. Chandra. Saint Joseph's University, United States

N. Dwyer. Saint Joseph's University, United States

N. Fultang. University of the Sciences, United States

S. Gupta. University of Dehli, United States

I. Singh. University of Dehli, United States

B. Peethambaran. Saint Joseph's University, United States

Breast cancer is the second most commonly diagnosed cancer in women in the United States. The most aggressive subtype is triple negative breast cancer (TNBC), which accounts for 15-20% of new cases on average each year. Histologically, it is characterized by the absence of estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2), which are typically targeted by hormone therapies such as tamoxifen, fulvestrant, or letrozole. Standard of care for TNBC includes traditional chemotherapy and radiation, which are detrimental to both cancerous and normal cells. Therefore, the lack of all hormone receptors in TNBC calls for the investigation of novel anti-cancer compounds that specifically target TNBC with minimal damage to non-cancerous tissues. Receptor orphan tyrosine kinase-like receptor 1 (ROR1) is an oncoprotein that is overexpressed in several human malignancies such as lung, breast, prostate and pancreatic cancers, but not in normal tissues. Inhibition of ROR1 signaling has shown to repress proliferation and induce apoptosis of cancer cells. Through in-silico docking and isothermal titration calorimetry, we identified a novel compound CPD86 that interacts with and inhibits ROR1. We hypothesize that CPD86 selectively targets TNBC cells by reducing the phosphorylation of AKT/GSK3 β via the inhibition of ROR1. Our in vitro results suggest that CPD86 inhibits cell viability and induces intrinsic apoptosis of TNBC cells at a half-maximal inhibitory concentration of 2-5 μ M, but not in normal breast epithelial cells with minimal ROR1 expression. CPD86 also represses TNBC cell migration and invasion while leaving non-malignant cells unharmed. This study highlights that ROR1 inhibitors could be developed as a potential therapeutic for TNBC and the data would serve as proof-of-concept justification for evaluation in other ROR1-upregulated cancers.

PO5-27-08

Cytotoxicity and motility inhibitory effect of FA-Hep-CuS nanoparticles on breast cancer cells

Presenting Author(s) and Co-Author(s):

D. Arreola. Texas A&M University, United States

In spite of a decreased rate of cancer onset, by about 33%, since 1991, it is still as dreadful and a major cause of death globally. After heart disease, cancer continues to be the second most prevalent cause of death in the US. According to the American Cancer Society, there will be around 2 million new cases of cancer identified in Americans in 2023, along with approximately 610,000 cancer-related deaths. Breast cancer will continue to be the most common invasive cancer diagnosed in women. Each year about 2.3 million women are diagnosed with breast cancer. In consideration of the severity of breast cancer, herein we designed and synthesized a multimode photothermal agent, FA-Hep-CuS, for the advancement of photothermal therapy of cancer. CuS nanoparticles deposited on heparin-conjugated folic acid (FA-Hep-CuS) were prepared by gently heating unfractionated heparin in dimethyl formamide (DMF), then adding N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC), and finally adding the aminated folic acid in DMF and stirring for four days. Further, FA-Hep was dispersed in DI water, then citrated CuS nanoparticles dispersed in DI water were added, and the mixture was stirred for 8 hours to prepare FA-Hep-CuS. Moreover, the activation of the nanoparticles by non-ionizing radiation (NIR; $\lambda = 808$ nm) was also evaluated for increased anti-cancer efficiency. In MDA-MB-231 (Triple-negative or TNBC or ER⁻/PR⁻/Her2⁻) breast cancer cell lines, the cytotoxic effects of FA, CuS, and FA-Hep-CuS, as well as their ability to impede motility, have been investigated. They have also been examined to determine how they affect the expression of mesenchymal indicators and clonogenicity. All these demonstrated significant dose-dependent in-vitro cytotoxicity against MDA-MB-231 breast cancer cells. The cell viability assay showed that the FA-CuS was more effective than FA and CuS. Activation of the nanoparticles with NIR resulted in the significantly enhanced dose-dependent inhibitory potential of the nanoparticles against the migratory properties of the aggressive TNBC cells. In agreement, the clonogenicity of the TNBC cells was also inhibited dose-dependently. We are now focusing on its inhibitory potential on the EMT markers of the TNBC cells. We further aim to investigate the effects of FA-Hep-CuS in in-vivo models of breast cancers.

PO5-27-09

Pharmacological eIF4E inhibition suppresses anti-tumor activity in ER+ breast cancer

Presenting Author(s) and Co-Author(s):

M. Friedersdorf. Ribometrix, United States

D. Blake. Ribometrix, United States

S. Thompson. Ribometrix, United States

K. Marran. Ribometrix, United States

J. Sorrentino. Ribometrix, United States

Elevated levels of eukaryotic initiation factor 4E (eIF4E) are found in a broad range of cancers, including breast, and have been associated with aggressive, drug resistant tumors. Furthermore, elevated eIF4E activity is sufficient to cause transformation in various cancers, while inhibition suppresses tumor growth. eIF4E, the main regulator and rate limiting factor of protein synthesis, is the downstream integrator of several important oncogenic signaling pathways (PI3K/AKT/mTOR, Ras/Raf/MEK, and Myc). Activation of eIF4E results in increased protein levels of key proliferation and metabolism proteins such as Cyclin D1 (CCND1) and Ornithine Decarboxylase 1 (ODC1), as well as an overall increase in cellular synthesis machinery, causing cellular growth and proliferation. Here, we describe the development and characterization of novel, potent, and selective eIF4E inhibitors. Compounds from this chemical series have nanomolar activity in multiple biochemical and biophysical m7G cap-competition assays as well as potent inhibition of translation in cellular and biochemical assays. In cells, these compounds rapidly and reversibly decrease protein levels of several oncogenes, including CCND1, leading to a G1 cell cycle arrest. We demonstrate that eIF4E inhibitors cause growth inhibition in a variety of breast cancer cell lines, including ER+ breast cancer. These inhibitors also inhibit growth of breast cancer lines with acquired resistance to Palbociclib with the same potency as the parental cell lines. Additionally, eIF4E inhibition shows an increased sensitivity in resistant cell lines when combined with standard of care (SOC), including Palbociclib. Select analogs from the series demonstrate favorable ADMET/PK properties with good oral bioavailability and low safety risk. Lastly, these compounds have demonstrated near complete tumor growth inhibition in non-breast cancer in vivo models. Ongoing experiments will address in vivo efficacy in ER+ breast cancer in both monotherapy and in combination with SOC.

PO5-27-10

Next generation antibody drug conjugates: Multi-payload conjugates targeting multiple mechanisms of cell killing

Presenting Author(s) and Co-Author(s):

M. Lobba. CatenaBio, United States

D. Trinter. CatenaBio, United States

M. Nguyen. CatenaBio, United States

D. Gutierrez. CatenaBio, United States

S. Brady. CatenaBio, United States

C. Symister. CatenaBio, United States

A. Lau. CatenaBio, United States

R. Kendall. CatenaBio, United States

S. Johri. CatenaBio, United States

M. Francis. University of California, Berkeley, United States

Background: ADCs have had tremendous impact on patient outcomes in breast cancer and are rapidly moving towards second line use. However, many patients fail to respond or relapse after treatment with ADC therapies due to tumor heterogeneity and resistance to ADC payloads.

Method: CatenaBio has developed a novel Multi-Payload-Conjugate (MPC) system capable of attaching distinct payloads at different sites to the same antibody, enabling the production of single-molecule targeted combination therapies with defined DAR . Results: We screened combinations of different payloads targeting several different mechanisms attached to trastuzumab at different drug-antibody ratios to optimize tumor cell killing. These targeted combination ADCs demonstrated robust killing in both HER2 high and low tumor cell lines.

Conclusion: Antibody Drug Conjugates have revolutionized the treatment of high HER2 positive breast cancer. More recently advances have been made in the design of ADCs to expand indications to include HER2 low as well as HER2 negative patients. These constructs offer the next step in ADC design and allow for the combination of multiple mechanisms of action in a single MPC that are highly effective across multiple breast cancer cell lines. These molecules offer the potential to circumvent tumor resistance pathways and deliver deeper and more durable responses. Disclosures: Marco Lobba, Devin Trinter, Maxwell Nguyen, Daniel Gutierrez, Samantha Brady, Chanez Symister, Andrew Lau, Richard Kendall, and Saurabh Johri are employed by Catena Biosciences. Matthew Francis is a co-founder and advisor to Catena Biosciences.

PO5-27-11

A COMPARATIVE STUDY OF DIAGNOSTICS MADE BY FINE NEEDLE ASPIRATION (FNA) BIOPSY VERSUS TRU-CUT FOR BREAST PATHOLOGY IN A ONE STOP CLINIC PROGRAM IN MEDELLIN, COLOMBIA.

Presenting Author(s) and Co-Author(s):

S. Gil. Ayudas Diagnósticas SURA, Antioquia, Colombia

C. Agudelo. Ayudas Diagnósticas SURA, United States

J. Castaño. Ayudas Diagnósticas SURA, United States

M. Naranjo. Ayudas Diagnósticas SURA, United States

C. Piedrahita. Ayudas Diagnósticas SURA, United States

D. Wilches. Ayudas Diagnósticas SURA, United States

K. Corredor. Ayudas diagnósticas SURA, United States

Breast cancer is the leading cause of morbidity and mortality among women in Colombia due to non-communicable chronic diseases. This has prompted health insurance companies to develop innovative initiatives to mitigate these negative outcomes. Since September 2018, Ayudas Diagnósticas SURA, in alliance with the Gustave Roussy Hospital and General Electric Healthcare has promoted a “One-stop clinic” program called: “TIEMPO PARA TI”. One of the primary challenges was to demonstrate that breast cytology, based on the Yokohama guidelines approved by The International Academy of Cytology has a high sensitivity, specificity, and diagnostic accuracy. The Yokohama system for classifying breast cytology is comprised of five categories: C1 not satisfactory, C2 benign, C3 atypical, C4 malignancy suspected, and C5 malignant. From September 2018 to December 2022, consecutive patients referred for breast biopsy and suspected of having breast cancer underwent triple assessment of breast tumor and were included in this retrospective study. Descriptive analysis was made using STATA v17 software to compare fine needle aspiration (FNA) biopsy versus Tru-cut. A total of 14,501 patients were included, 14.398 FNA and 14.401 trucut biopsies were performed. The comparative analysis showed a 99% concordance between categories 2, which correspond to benign lesions and 96.7% between categories 5, which correspond to malignant lesions. Our findings demonstrate that a well-executed FNA biopsy is not inferior to a trucut biopsy, as revealed by the Yokohama system, and offers significant advantages, such as cost-effectiveness and prompt diagnosis. Both techniques should be used with caution, considering their advantages and disadvantages.

PO5-27-12

TALL CELL CARCINOMA WITH REVERSED POLARITY: A RARE SUBTYPE OF INVASIVE BREAST CARCINOMA WITH UNUSUAL ONCOGENIC DRIVER MUTATION R132C IN IDH1 GENE

Presenting Author(s) and Co-Author(s):

K. Prigenzi. Hospital Israelita Albert Einstein, United States

L. Ferreira Cortes. Hospital Israelita Albert Einstein, United States

P. Campregher. Hospital Israelita Albert Einstein, United States

J. de Oliveira Filho. Hospital Israelita Albert Einstein, United States

N. Andrade Piva. Universidade Federal de São Paulo, United States

Introduction: Tall cell carcinoma with reversed polarity (TCCRP) is a rare subtype of invasive breast carcinoma with a distinguishing morphological feature, which is the predilection of nuclei to polarize to the apical pole of tall columnar epithelial cells. These tumours are most commonly associated with IDH2 p.Arg172 hotspot mutations. All reported cases of TCCRP affected women ranging from 39 to 89 years (mean age of 64 years). The tumours presented as a mammographic or palpable mass, only rarely associated with axillary lymph node metastases. TCCRP are usually associated with an indolent clinical course and a favourable prognosis. Morphologically, TCCRP is composed of circumscribed nests of epithelial cells often exhibiting delicate fibrovascular cores, conveying a solid papillary pattern. True papillae and cystic structures containing colloid-like material may be observed in some cases. The tumour cells are tall and columnar, with abundant eosinophilic cytoplasm, containing bland, round to ovoid nuclei disposed at the apical pole of the columnar epithelial cells. Mitotic figures are rare. Most TCCRPs exhibit a triple-negative phenotype and a low (< 20%) Ki-67 proliferation index. Molecular features of TCCRP comprise IDH2 p.Arg172 hotspot mutations, reported in about 84% of the cases studied, as well as PIK3CA missense mutations, identified in about 68% of these tumours. Only one case of TCCRP was associated with IDH1 gene mutations according to the literature. Case report: A 62 year old woman presented with a palpable mass and no axillary adenopathy was identified. Hematoxylin-eosin (HE) stain showed an invasive breast carcinoma, with epithelial tumour cells arranged in a solid and papillary pattern with thin fibrovascular cores. Neoplastic cells are tall and columnar, with abundant eosinophilic cytoplasm and round to ovoid nuclei, exhibiting no pleomorphism and disposed in the apical pole of the cells. Mitotic figures were not detected. Considering the highly suggestive morphology on HE stain, biopsy sample was sent for molecular analysis by next generation sequencing (NGS). Results and discussion: Molecular analysis by NGS using the TruSight Oncology 500 panel (Illumina) revealed the presence of the oncogenic mutations R132C and H1047R in IDH1 and PIK3CA genes, respectively. Contrary to what occurs in almost all cases of Tall cell carcinoma with reversed polarity (TCCRP), in which an oncogenic mutation is described in codon R172 of the IDH2 gene, in this case a mutation was observed in the IDH1 gene. Such a mutation has been described in only one case diagnosed with TCCRP according to the literature, this being the second reported case. Conclusion: This case report aims to warn of the possibility that other driver mutations may be associated with the diagnosis of TCCRP, such as IDH1 R132 and not just IDH2 R172, and that a comprehensive testing approach of the IDH1/2 genes might be more accurate in these cases.

PO5-28-01

Dynamics of Adipocyte Progenitors in the Mammary Gland during Obesity

Presenting Author(s) and Co-Author(s):

S. Kwende. The University of Texas at Dallas, United States

P. Nuthalapati. The University of Texas at Dallas, United States

D. Ning. The University of Texas at Dallas, United States

J. Sunder Singh. The University of Texas at Dallas, United States

P. Joshi. The University of Texas at Dallas, United States

Being overweight or obese is associated with a higher risk of breast cancer (BC) and worse disease-free and overall survival compared to normal-weight BC patients. The underlying biological basis for this association is attributed to alterations in the endocrine and inflammatory milieu of adipose tissue. However, existing chemotherapy and endocrine therapy are not effective in obese BC patients. There is a critical need to pin down adipose tissue cell types that may govern increased BC risk and adverse outcome in obesity. Adipocyte progenitors are immature mesenchymal cells in adipose tissue that have adipocyte differentiation potential and reported to be dysfunctional in obesity. In previous research, we first reported mammary adipocyte progenitors (MAPs) expressing Platelet-Derived Growth Factor Receptor alpha (PDGFR α) in the stromal microenvironment that transition into epithelial lineages during expansion of the murine mammary epithelium. The contribution of MAPs to shaping a pro-tumorigenic mammary tissue milieu in obesity is not known. Here, using diet-induced obesity MAP reporter and lineage tracing mouse models combined with single-cell RNA sequencing, we reveal elevated PDGFR α ⁺ MAPs in the local mammary stroma in obesity. MAPs in the obese mammary gland manifest alterations in proliferation, cell state and molecular mechanisms, generating an inflammatory, cancer-prone tissue microenvironment. Our findings uncover the MAP lineage as a key contributor to forging an aberrant mammary gland in obesity, providing insight into the potential utility of targeting this cell population for eradicating BC risk related to augmented adiposity.